NON-INTERVENTIONAL (NI) STUDY REPORT

PASS information

Title	BOSEVAL: An observational study - Evaluation of efficacy and safety of Bosulif® under real life conditions of use
Protocol number	B1871047
Version identifier of the study report	Version 1.0
Date	30 May 2024
EU Post Authorization Study (PAS) register number	ENCEPP/SDPP/8231
Active substance	Bosutinib
Medicinal product	Bosulif®
Product reference	BOSULIF 100 mg film-coated tablet, 28 tablets per box, licence number 41566 presentation number 34009 269 935 2 8 (EU no. 1/13/818/001) BOSULIF 400 mg film-coated tablet, 28 tablets per box, licence number 41566 presentation number 34009 301 462 2 4 (EU no. 1/13/818/006)

	BOSULIF 500 mg film-coated tablet, 28 tablets per box, licence number 41566 presentation number 34009 269 937 5 7 (EU no. 1/13/818/003)
Procedure number	EMA/H/C/002373
Marketing Authorization Holder (MAH)	Pfizer Europe MA EEIG Boulevard de la Plaine 17 1050 Brussels Belgium
Joint PASS	No
Research question and objectives	This non-interventional study is designed to evaluate safety, efficacy, as well as modalities of use of Bosulif® under real life conditions of use.
Country(-ies) of study	France
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Marketing Authorization Holder(s)

Marketing Authorization Holder(s)	Pfizer Europe MA EEIG Boulevard de la Plaine 17 1050 Brussels Belgium
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1. ABSTRACT (STAND-ALONE DOCUMENT)

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
(e)CRF	(Electronic) Case Report Form
(S)AE	(Serious) Adverse Events
ANSM	French National Agency for Medicines and Health Products Safety
AP	Accelerated phase
BP	Blast phase
BCR-ABL	Breakpoint Cluster Region - Abelson
CCTIRS	Consultative Committee for Processing of Information in Field of Scientific research
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CML	Chronic Myeloid Leukemia
CNIL	National Commission on Data Processing and Freedoms
CP	Chronic phase
CPP	Ethics Committee
CRA	Clinical Research Associate
CSR	Clinical Study Report
CSSD	Clinical Summary Submission Document
ECOG	Eastern Cooperative Oncology Group
ELN	European Leukemia Net
EMA	European Medicines Agency
ENCEPP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
FACT-leu	Functional Assessment of Cancer Therapy – Leukemia

FISH	Fluorescence In Situ Hybridization
FPFV	First Patient First Visit
GPP	Good Pharmacoepidemiologic Practice
GVP	Guidelines on good pharmacovigilance practices
ICD	Information and Consent Documents
IFNα	Interferon alpha
ISEP	International Society for Pharmacoepidemiology
LPLV	Last Patient Last Visit
MA	Marketing authorization
MedDRA	Medical Dictionary for Regulatory Activities
MCR-C/P/m	Major Cytological Response - Complete/Partial/Minor
MHR-C/P	Major Hematological Response - Complete/Partial
MMR-C/P	Major Molecular Response - Complete/Partial
NMC	National Medical Council
NSAE	Non-Serious Adverse Event
PASS	Post Authorization Safety Study
Ph-	Philadelphia chromosome negative
Ph+	Philadelphia chromosome positive
Ph1	Philadelphia chromosome
PHC	Public Health Code
PV	Pharmacovigilance
QC	Quality Control
RT-PCR	Reverse Transcriptase Polymerase Chain Reaction
SAE	Serious Adverse Event
SmPC	Summary of Product Characteristics
SNP	Safety Narrative Plan
TKI	Tyrosine Kinase Inhibitor
WHO	World Health Organization
WMA	World Medical Association

3. INVESTIGATORS

The names, affiliations, and contact information of the investigators at each study site are listed in Appendix 3.1. **Principal Investigator(s) of the Protocol**

Name, degree(s)	Title	Affiliation
Laurence Jolibois	*Medical and Scientific Hematology Manager*	Pfizer France

Lead Country Investigator(s) of the Protocol

Name, degree(s)	Title	Affiliation
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*Delphine Rea has withdrawn her participation in the study on 16Jun2023

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Name, degree(s)	**Title**	**Affiliation**
Rosamaria Calicchio, PhD	Medical Team Leader	Pfizer France
Laurence Jolibois, MsC	Medical and Scientific Hematology Manager	Pfizer France
Yves Brault, MsC	Statistics Director	Pfizer France
Delphine Berzin, MsC	RWD/EAP Clinical Operations Manager	Pfizer France

4. OTHER RESPONSIBLE PARTIES

Responsible Party Name and Affiliation	Role in the study
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Audrey Halgand (Kraus medical, 3 rue Paul Lafargue, 92800 Puteaux, France)	Translation
Paskëll STEPHAN (Euraxi Pharma, Clinical Research Organization, Tours, France)	Data-manager responsible
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Benoit BERGE (Euraxi Pharma, Clinical Research Organization, Tours, France)	Statistician
Angelina DION (Euraxi Pharma, Clinical Research Organization, Tours, France)	Statistician
Barbara PLANCHEZ (Euraxi Pharma, Clinical Research Organization, Tours, France)	Medical writer
François Montestruc (eXYSTAT, Clinical Research Organization, Montrouge, France)	Statistician / Methodologist
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Pascale Poos (MAJUR Pharma, Cadolive, France)	Clinical Research Associate
Frédéric Feger (idenpendant worker, Lecques, France)	Clinical Research Associate
Christina Schiano (Pro ARC Services, Rognac, France)	Clinical Research Associate
Camille Cathary (Hays, Paris, France)	RWD Clinical Project Manager

5. MILESTONES

Milestone	Planned date	Actual date	Comments
Conduct of evaluation of feasibility	December 2014 – January 2015	03 February 2015 – 26 August 2015	
Independent ethics committee: CCTIRS, approvals of protocol	Not applicable	11 March 2015	Protocol v1 dated on 16 December 2014 approved with comments. Protocol v1.1 dated on _16 March 2015 includes changes requested by CCTIRS comments.
	Not applicable	20 December 2023	Protocol version 2 amendment 1 dated February 15, 2019 was validated and used for this study. It could not be submitted to the CCTIRS because the decree of November 16, 2016 abolished this committee.
Authorization of the CNIL	22 July 2015	22 July 2015	Protocol v1.1 dated on _16 March 2015
	Not applicable	23 April 2019	Protocol v2 Amendment 1_dated on 15 February 2019 notified to CNIL along with updated ICD and eCRF. No approval provided by CNIL as amendment is not considered substantial.

Milestone	Planned date	Actual date	Comments
Start of data collection	22 October 2015	15 October 2015	
End of data collection	December 2023	07 March 2023	Patient 11-25 M36 was delayed from 16 December 2022 to 07 March 2023 and it was decided to recorded this delayed visit in the study.
Registration in the EU PAS register	November 2014	08 January 2015	
Final report of study results	December 2023	08 April 2024	

6. RATIONALE AND BACKGROUND

6.1. Chronic myeloid leukemia

Chronic myeloid leukemia (CML) is a malignant hematological disease which belongs to the group of myeloproliferative syndromes (or myeloproliferative neoplasia according to WHO classification 2008 (Vardiman, Thiele et al. 2009). This hematologic disease is a rare disease, with 600 to 700 new cases per year (the incidence in France is estimated at 1 or 2 cases per 100,000 persons, and increasing with age), accounting for 15% to 20% of all cases of leukemia. Mean age at time of diagnosis is 54 years and the disease affects 1.4 males vs. 1 female patient. The prevalence, on the order of 6000 to 7000 patients in France, is increasing because of a frank decrease in mortality rate, at least during the first 6 years after the diagnosis.

CML results from a specific chromosomal anomaly which occurs in hematopoietic stem cells, although the principal cause of this anomaly is not yet understood. It is characterized by the presence of a chromosomal marker in hematopoietic cells, the Philadelphia chromosome (Ph1 chromosome), which can be detected in 95% of patients with CML (Kalidas, Kantarjian et al. 2001). The chimeric protein BCR-ABL (Breakpoint Cluster Region – Abelson), resulting from translocation t(9; 22) at the origin of the Philadelphia chromosome positive (Ph+), has a high tyrosine kinase activity responsible for leukemic transformation by resulting in excessive and persistent production of white blood cells.

The disease, referred to as chronic, develops gradually and evolves slowly in three successive phases, becoming increasingly resistant to treatments with progression of disease: chronic phase (CP CML), accelerated phase (AP CML) and blast phase (blast crisis) (BP CML). The majority of patients are diagnosed during the chronic phase. Without treatment, patients in chronic phase CML will progress to the accelerated phase in 4 to 6 years. Patients diagnosed during the accelerated phase have a life expectancy estimated at less than 12 months in the absence of treatment. Following the blast phase, patients live on average 2 to 4 months if they are not treated (Kalidas, Kantarjian et al. 2001).

6.2. Therapeutic management of CML

Management of CML has appreciably improved over the last 20 years, in particular since introduction of the oral tyrosine kinase inhibitors BCR-ABL, more than a decade ago. Before the introduction of targeted therapies – tyrosine kinase inhibitors (TKI) – median survival of patients with CML was estimated at 6 years (Hehlmann, Heimpel et al. 1994)

Based on results of the phase III study entitled “IRIS” (International Randomized Interferon versus STI571) published in 2003, imatinib (Glivec®, Novartis, 2001), the first TKI marketed for treatment of CML in 2001, quickly replaced interferon alpha (IFNα) as the 1st line treatment of reference of CML, whether in chronic phase (CP), accelerated phase (AP) or blast phase (BP) with a progression-free survival rate to accelerated phase of 83% at 7 years, and an overall survival rate of 88% during the same period (Kalidas, Kantarjian et al. 2001)

However, imatinib is commonly associated with a certain number of toxicities and resistance. After 8 years follow-up in the IRIS study, only 55% of patients randomized to the imatinib-treatment arm were still under treatment, with discontinuations related to a lack of efficacy (17%), a loss of complete cytogenetic response (15%) or intolerance to imatinib (7%) (O'Brien, Guilhot et al. 2003, Quintas-Cardama, Kantarjian et al. 2009).

Second generation TKIs such as dasatinib (Spyrcel®, Bristol-Myers Squibb, 2006 RCP) and nilotinib (Tasigna®, Novartis, 2007 RCP) subsequently have been developed for 2nd line treatment of CML in patients intolerant or resistant to imatinib. Dasatinib obtained marketing authorization (MA) as 2nd line treatment for all phases of CML: chronic, accelerated and blast phase. Nilotinib obtained MA as 2nd line treatment for patients in chronic and accelerated phase of CML. At the date of the writing of this protocol, these two therapies have obtained MA as 1st line treatment of chronic phase CML. In France, only nilotinib (chronic phase) and imatinib (all phases) are reimbursed as 1st line treatment (Baccarani, Deininger et al. 2013). Like imatinib, resistance or intolerance exist to these treatments, which require changes to treatments (Kantarjian, Hochhaus et al. 2011, Kantarjian, Shah et al. 2012).

Despite recent advances in treatment and management of patients who have CML, an important unmet medical need persists for many patients who are resistant or intolerant to one or more TKI.

Approximately one third of CML patients treated with imatinib do not achieve an optimum response to treatment (Alvarado, Kantarjian et al. 2009). Among patients who are resistant or intolerant to imatinib and who require treatment with dasatinib or nilotinib, approximately half do not maintain a durable cytogenetic response. A clinical study evaluating 2nd line treatment with dasatinib (n=91) or nilotinib (n=25) in 119 patients with CP CML for whom treatment with imatinib has failed, showed that 52% of patients discontinued treatment following development of resistance or intolerance (Milojkovic, Apperley et al. 2012, Cortes, Lipton et al. 2023) .

Treatment with bosutinib (Bosulif®, Pfizer, 2013) offers an additional alternative for patients with CML (all phases) resistant or intolerant to one or more previous therapies with TKI, and in whom imatinib, nilotinib and dasatinib are not considered as appropriate treatments.

6.3. Bosutinib (Bosulif ®, Pfizer)

Bosutinib is a TKI indicated in treatment of adult patients with Philadelphia chromosome positive CML (Ph+ CML) in chronic phase (CP), in accelerated phase (AP) or in blast phase (BP), previously treated with one or more TKI and for whom imatinib, dasatinib and nilotinib are not considered as appropriate treatments. Bosutinib has demonstrated its activity against the majority of mutations in the BCR/ABL domain resistant to imatinib, to dasatinib or to nilotinib, except for the T315I mutation. The European Medicines Agency (EMA) has granted marketing authorization, valid in the entire European Union, for Bosulif® in this indication on 27 March 2013 in the category of an orphan medicinal product (Hanaizi, Unkrig et al. 2014). This approval is based on results of a single-arm, phase II, multicentre clinical trial conducted on 570 patients resistant or intolerant to a previous targeted therapy with TKI (Study 200). Efficacy data observed are listed below (Table 1) according to phase of disease and treatment lines (Cortes, Kantarjian et al. 2011, Khoury, Cortes et al. 2012):

Table 1: Efficacy results of study 200

Phase	Treatments	CHR	MCyR	CCyR
CP CML (n=288)	Imatinib 1st line Bosutinib 2nd line	86%	53% (at 24 weeks: 31%)	41%

CP CML (n=118)	Several TKI and then bosutinib	73%	32%	24%
AP CML (n=76)	One or more TKI and then bosutinib	35%	35%	25%
BP CML (n=76)	One or more TKI and then bosutinib	15%	30%	64%

Concerning the safety profile of bosutinib, the most common grade 1 or 2 non-hematological adverse events (AE) during this trial were diarrhea, nausea, vomiting and rash. 8% and 4% of patients had grade 3 / 4 diarrhea respectively. The most common grade 3 / 4 hematological adverse events were: thrombocytopenia (25%), neutropenia (19%), and anaemia (8%). In addition, bosutinib was associated with a low impact on prolongation of the QT interval, a low incidence of pleural effusions, muscle cramps, musculoskeletal events or cardiac toxicities which can be observed with other TKIs. Approximately 20% of patients in this trial permanently discontinued their treatment with bosutinib following an AE (Cortes, Kantarjian et al. 2011, Khoury, Cortes et al. 2012). Data from this study suggest that bosutinib has a favourable efficacy and safety profile in patients with CML (all phases) pre-treated with one or more TKIs.

In addition, cross-intolerance between bosutinib and a previous targeted therapy with TKI in 570 patients included in the study 200 suggest that patients intolerant to previous treatment with imatinib, dasatinib or nilotinib did not present the same toxicities in treatment with bosutinib. In this study, cross-hematological intolerance between treatment with bosutinib and a previous therapy with imatinib or dasatinib was of relatively low incidence in such patients, although many patients presented with the same grade 3 / 4 cytopenia adverse events during treatment with Bosulif®. Non-hematological cross-intolerance, including diarrhea, remained rare. In conclusion, these results suggest that a CML patient intolerant to previous treatment with a TKI, will not necessarily have a recurrence or enhancement of this intolerance during treatment with Bosulif®. Generally, cross-intolerance between imatinib, dasatinib or nilotinib and bosutinib seems low (Hanaizi, Unkrig et al. 2014).

In 2006, in 2009 and more recently in 2013, the European Leukemia Net (ELN) group developed a series of basic definitions and recommendations which guide the diagnosis, the treatment approach and the follow-up that is appropriate to adopt for patients depending on progression of the disease. Monitoring of response to treatment, successively characterized by a hematological response, a cytogenetic response and then a molecular response should be performed regularly in order to set up appropriate management. Blood sample collection, as well as bone marrow samples collected at regular intervals make it possible to monitor the course of the white blood cell count, the number of cells that are carriers of the Philadelphia chromosome and the BCR-ABL load [Table 2]. Concomitantly, regular consultations with a hematologist and a clinical examination that he/she performs enable to control the patient's overall health condition.

Table 2: Diagnostic tests and monitoring of response to treatment (ELN 2013)

Type of response	Diagnostic test	Type of sample	Monitoring period
HR	Blood cell count	Blood sample	At time of diagnosis, and then every 2 weeks up to obtainment of confirmed CHR, and then at least every 3 months or as needed.
CyR	FISH	Bone marrow blood	At time of diagnosis, at 3 months, at 6 months and at 12 months up to obtainment of a CCyR, and then every 12 months. The karyotype can be replaced with FISH (in blood) only with the CCyR is reached.
	Karyotype	Bone marrow	
MR	RT-PCR	Blood sample	At time of diagnosis, and then every 3 months up to obtainment of an MMR, and then every 3 to 6 months.

6.4. Study rationale

The evolution of treatments and management of patients with CML have made it a treatable chronic disease associated with possible functional cure. In the same capacity as choice of 1st line treatment, the choice of the treatment sequence should take into account previous lines of therapy, comorbidities and individual preferences.

In light of the availability of several targeted therapies for treatment of CP, AP or BC Ph+/CML, each with their own specific safety of use and tolerability profiles and their own concomitant mechanisms of resistance, it is important to evaluate the efficacy, safety, cross intolerance and current modalities for use (dose adjustment, temporary discontinuations, permanent discontinuations of treatment) of these treatments under real life conditions of use in France.

Adherence of patients to their treatment is essential in order to maintain the response to treatment. For the purpose of optimizing adherence to treatment, it is also important to evaluate the strategies used in clinical practice in terms of therapeutic management and management of adverse events related to treatment.

This study will make it possible to obtain data on the real-life conditions of use of bosutinib in treatment of CP, AP or BP Ph+/- CML, in patients previously treated with one or more TKIs and for whom imatinib, dasatinib and nilotinib are not considered as appropriate treatments.

This non-interventional study is designed as a PASS (Post-Authorization Safety Study) and it is conducted voluntarily by Pfizer.

7. RESEARCH QUESTION AND OBJECTIVES

This observational study, whose primary objective was to evaluate the safety and the rate of discontinuation of treatment because of intolerance, made possible to describe management of adverse events (dose adjustment, temporary discontinuation, permanent discontinuation of treatment) under real life conditions of use in France.

7.1. Primary objectives

Under real life conditions of use:

- To determine the proportion of patients with CP, AP or BP Ph+/- CML presenting with AEs considered related to bosutinib by the participating doctor according to:
    - type of adverse event;
    - grade of event: 1, 2, 3, 4 or 3/4.
- To evaluate the proportion of patients who permanently discontinued bosutinib following an AE considered related to bosutinib by the participating doctor.

7.2. Secondary objectives

Under real life conditions of use:

- To determine the safety profile of bosutinib: AEs that occurred during treatment with bosutinib, AEs which required changes to treatment with bosutinib, biological and hematological toxicities that occurred with bosutinib.
- To evaluate adherence of patients to treatment of bosutinib, with the aid of a self-questionnaire completed by patients (Morisky Questionnaire).
- To evaluate quality of life of patients treated with bosutinib, with a self-questionnaire completed by patients (FACT-leu version 4 - Questionnaire specific for leukemia)
- To describe the modalities of treatment with bosutinib under real life conditions of use (dose adjustment and reason for adjustment, dose intensity, relative dose intensity;

duration of treatment, temporary discontinuations/permanent discontinuations and reasons for such discontinuations).

- To evaluate the cumulative response rates: hematological (PHR/CHR), cytogenetic (CCyR / MCyR/ PCyR) and molecular response (MMR/CMR).
- To evaluate efficacy of treatment with bosutinib:
    - Progression-free survival at 1, 2 and 3 years of patients treated with bosutinib
    - Overall survival (OS) at 1, 2 and 3 years in patients treated with bosutinib
    - The percent transformation to AP/BC
- To describe the modalities of hematological, cytogenetic and molecular responses: median time to occurrence of response, median duration of response, type of response according to dose.
- To describe characteristics of patients treated with bosutinib (demographic characteristics; previous medical conditions, comorbidities; duration between time of diagnosis and initiation of treatment; previous treatments and better response under these treatments; duration of previous treatments, reasons for discontinuation of previous treatments; the last hematological, cytogenetic or molecular responses known).
- To evaluate cross intolerance between bosutinib and tyrosine kinase inhibitors prescribed previously.

8. AMENDMENTS AND UPDATES

Table 3. Amendments to the Protocol

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment(s)	Reason
1	22-JAN-2019	Substantial	Liste 2. LIST OF ABBREVIATIONS 3. RESPONSABLE PARTIES 4. RÉSUMÉ 6. ÉVÉNEMENTS IMPORTANTS 9.1. Study design 9.2.1. Criteria for inclusion 9.4.1. Patient data 9.7. Analysis of data 9.8. Quality control 11.MANAGEMENT AND REPORTING OF ADVERSE	The amendment has been written in order to include Ph(-) patients in the analysis. To specify criteria for inclusion in order to facilitate understanding by the investigators and the Clinical Research Associates. The inclusion period has been extended by 24 months. Update of the CRF and precision of data following on-site monitoring. Update of all documents relating to the study following effective application of the GDPR law.	

			EVENTS/ADVERSE REACTIONS	Update the AEM form.	

9. RESEARCH METHODS

This non-interventional study protocol (see Appendix 2) has been submitted to an internal validation committee in conformity with Pfizer standard procedures.

9.1. Study design

This was a national, observational, descriptive, prospective, multicentre study conducted in metropolitan France in adult patients treated for accelerated or blast phase Philadelphia chromosome positive chronic myeloid leukemia, previously treated with one or more TKIs and for whom imatinib, nilotinib and dasatinib were not considered as appropriate treatments. The study was conducted in centres involved in management of CML.

The study was offered to the totality of patients who satisfy criteria for inclusion and for non-inclusion up to the end of the inclusion period defined as 4 years. Patient's therapeutic management was not modified by participation in the study and depended on decisions taken by doctors in agreement with current international recommendations (European Leukemia Net, ELN network [13]). This study did not affect patients' medical care: no supplementary examinations were conducted for the study and no treatments were administered specifically for this study. Furthermore, the study visits, though regular, were in keeping with the usual frequency of follow-up and treatment evaluation for these patients.

This study included 2 main phases:

- Cohort enrolment period and data collection at time of inclusion

Patients have been followed prospectively over a 3-year period starting with their inclusion in the study. The inclusion visit has been performed at time of inclusion of the patient in the study, after

which the patient has been informed and could accept to participate by signing the consent form. The 1st visit of the 1st patient took place on October 15, 2015 and the 1st visit of the final patient was completed on December 19,2019.

The duration of the inclusion period was 50 months.

- Follow-up period and data collection during follow-up

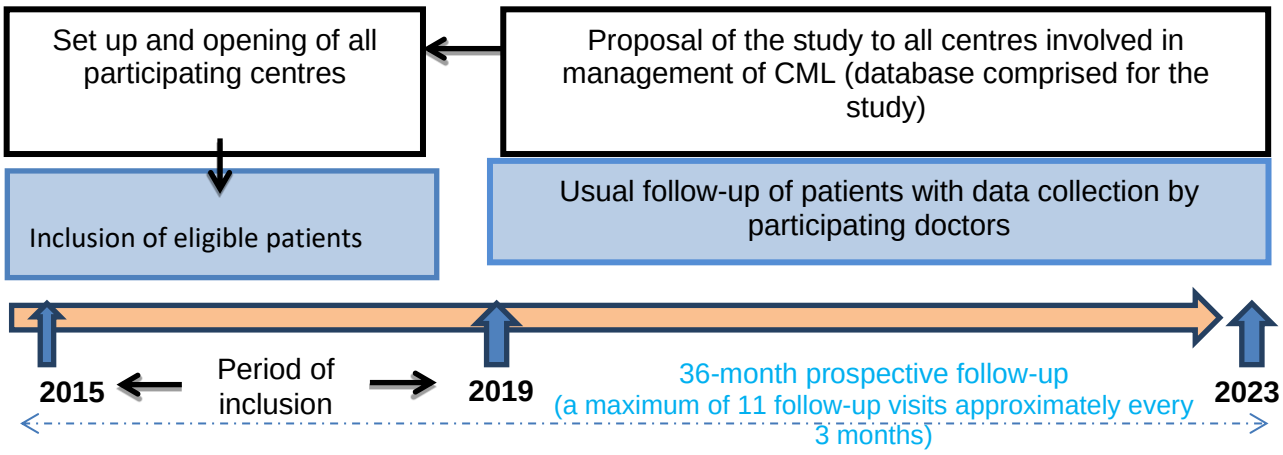
Follow-up began from the date on which the patient signed his/her consent form and ended on the date of the final visit of the final patient, i.e., from October 2017 to March 2023.

The maximum follow-up period for each patient was 36 months. The total duration of the study was 89 months.

Follow-up visits have been performed after usual consultation, estimated at about every 3 months. No visit or additional examination were requested by the protocol: modalities for follow-up and treatment have been left up to the entire judgement of the participating doctor. Data have been recorded during the 3 years of the patient's participation, except in case of withdrawal of consent or death of a patient.

Total duration of the study was 7 years with an inclusion period of 4 years and a follow-up period of 3 years (see Figure 1).

Figure 1: Overall study flowchart



9.2. Setting

9.2.1. Cohort enrolment and data collection at time of inclusion

From October 2015 until December 2019 (i.e., for 50 months), each physician was to include sequentially all volunteer patients followed up in the Department who initiated treatment with bosutinib for treatment of CP, AP or BP phase Ph+ / - CML at the end of the inclusion visit or during the one month prior to it. Furthermore, eligible patients were those who had previously undergone treatment with one or more tyrosine kinase inhibitors (TKIs) such as imatinib, dasatinib, and nilotinib, which were not deemed appropriate treatments. For all patients included, the participating physicians were to complete the electronic case report form (e-CRF) page corresponding to the Inclusion visit (Vi).

9.2.2. Patient follow-up and long-term follow-up

From the 1st inclusion and until the end-of-inclusion date, the participating physicians were to conduct exhaustive data collection on all cases of CP, AP or BP Ph+/- CML treated with bosutinib.

The study collected data from maximum 13 visits: 1 inclusion visit + maximum 12 follow-up visits (a follow-up visit every three months), according to the schedule displayed in Table 4.

Patients who permanently discontinued their treatment with bosutinib were to be followed according to their usual management, estimated at every 3 months in conformity with recommendations of management of CML, until 36 months after the inclusion visit. These visits corresponded to long-term follow-up.

At these visits, the following information had to be provided:

- Outcome of the CML Phase
- Therapeutic management of CML

Table 4: Schedule of data collection

	Inclusion visits		Follow-up visits (every 3 months)		
Type of data	Prior to bosutinib	Bosutinib Initiation	During bosutinib (follow-up)	After bosutinib (long-term follow-up)	Latest news
Data completed by the doctor (questionnaires via eCRF)					
Verification of eligibility criteria		X			
Demographic data	X				
Initial diagnosis of CML	X				
Therapeutic management of CML (previous treatments, best responses to treatment, tests)	X				
Description of pathology at initiation of bosutinib (CML phase, treatment responses and examination, reason for previous line change)		X			
Patient status at baseline (ECOG performance index, history and comorbidities)		X			
Mutational analyses		X			
Biochemical and haematological assessments		X	X		
Description of initiation of bosutinib treatment		X			
Concomitant treatments		X	X		
Description of treatment with bosutinib (changes to terms of use, best answers, reviews)			X		
Modification of concomitant treatments			X		
Pharmacovigilance			X	X	
Evolution of the pathology				X	
Post-bosutinib therapeutic care				X	
Patient status at last new					X
Data completed by the patient (self-questionnaires in paper format)					
Adherence (Morisky 8 items)**			X		

Quality of life (FACT-leu v4)**		X	X*		

* The FACT-leu questionnaire measuring quality of life will only be issued at certain follow-up visits (M3, M6, M12, M18, M24, M36).

** The Quality of Life and Compliance self-questionnaires have been only completed when the patient was on treatment. (The questionnaires were therefore not completed during long-term follow-up visits).

9.2.3. Study withdrawal

Patients could withdraw from the study at any time at their own request or may have been withdrawn at any time based on the judgement of the participating doctor or the sponsor for reasons of safety of use, behavior or administrative reasons. In all circumstances, every effort has been made to document the outcome of the patient whenever applicable. The participating doctor should have collected information on the reason for a patient's withdrawal and follow-up with the patient, concerning all unresolved adverse events.

If a patient withdrawn from the study and also withdrawn his consent for disclosure of future information, no other evaluation has been made and no other data have been collected. The sponsor could keep and continue to use all data collected before the withdrawal of consent.

The reasons for study withdrawal should have been indicated on the e-CRF.

The date of the end-of-study visit should have been recorded.

Study withdrawals before the scheduled end of follow-up were to be classified according to the following categories:

- Lost to follow-up (if yes, the measures taken to contact the patient should have been specified)

- Failure to comply with study procedures (if yes, the cause should have been specified, for example, repeated absence from follow-up visits)

- Study withdrawal requested by the patient (if yes, the reason cited by the patient should have been specified)

- Study withdrawal due to adverse event (if, yes, type of adverse event should have been specified)

- Serious adverse event (if yes, type of serious adverse event should have been specified)

- Death (cause and date should have been specified)

- Other reason (if yes, should have been specified)

9.3. Subjects

The patients included in this study, conducted in metropolitan France, should have satisfied eligibility criteria defined below.

Eligible patients but not included in the study were reported in a registry of non-inclusion with a minimum collection of information (see Table 6).

9.3.1. Criteria for inclusion

Patients should have satisfied all the following criteria for inclusion in order to be eligible.

1. Male or female patient 18 years of age or older;
2. Patient with BCR-ABL Philadelphia chromosome positive or negative CML, in chronic, accelerated or blast phase;
3. Patient resistant or intolerant to previous therapy with TKI for CP, AP or CB CML other than bosutinib;
4. Patient initiating treatment with bosutinib for treatment of CP, AP or BP phase Ph+ / - CML at the end of the inclusion visit or during the one month prior to it;
5. Patient who has been informed that a method of contraception must be used if a risk of pregnancy exists.
6. Patients who have been informed about the study and who signed the informed consent form.

9.3.2. Criteria for non-inclusion

Patients who satisfied one of the following criteria should not have been included in the study:

1. Patient with chronic, accelerated or blast phase BRC-ABL Philadelphia chromosome negative CML;
2. Patient recently diagnosed with CML and who has not received previous treatment with a TKI;
3. ~~3.~~ Patient currently treated with a treatment other than bosutinib~~;~~
4. Patient of childbearing potential not using a method of contraception;
5. Patient treated in the setting of an interventional study for another disease (outside of follow-up period);
6. Patient who refuses computer processing of his/her medical data.

9.4. Variables

Patients were be identified indirectly via a unique number in the study (the centre no., patient no. pair).

The following “patient” data have been collected in the setting of the study at the usual consultation of patients in the centres.

Data	Role	Source
Compliance with criteria for inclusion and non-inclusion	Baseline characteristics	Inclusion visit

Demographic characteristics (year of birth, gender, weight, height, ECOG performance status)	Baseline characteristics	Inclusion visit
Diagnosis of CML (date of diagnosis, phase of CML at time of diagnosis, tests performed for diagnosis)	Baseline characteristics	Inclusion visit
Transcription of BCR-ABL gene at time of diagnosis	Baseline characteristics	Inclusion visit
Previous treatments of CML (type, dose, dosage, duration of previous treatment)	Baseline characteristics	Inclusion visit
Best response to previous treatments	Baseline characteristics	Inclusion visit
Reasons for change of previous treatments (if discontinuation for toxicity, description of the AE: type and grade)	Baseline characteristics	Inclusion visit
Phase of CML in the estimate of the participating doctor, at time of initiation of treatment with bosutinib	Baseline characteristics	Inclusion visit Follow-up visit
Evolution of mutational profile of BCR-ABL gene at time of initiation of treatment with bosutinib	Baseline characteristics	Inclusion visit Follow-up visit
Concomitant treatments at time of inclusion in the setting of management of CML	Baseline characteristics	Inclusion visit
Biological and hematological assessment data	Baseline characteristics Evaluation end point	Inclusion visit Follow-up visit
Hematological, cytogenetic and molecular response at time of inclusion and results	Baseline characteristics	Inclusion visit
Description of initiation of treatment with bosutinib (date of initiation, dose, dosage)	Baseline characteristics	Inclusion visit
Change to concomitant treatments in the setting of management of CML	Evaluation end point	Inclusion visit Follow-up visit

Description of treatment with bosutinib (changes to dose or dosage, temporary or permanent discontinuations of treatment)	Evaluation end point	Follow-up visit
Safety in treatment with bosutinib	Evaluation end point	Follow-up visit
Management of toxicities related to bosutinib (concomitant treatments, additional corrective medical measures)	Evaluation end point	Follow-up visit
Hematologic, cytogenetic and molecular tests performed for monitoring of response to treatment (type and frequency of monitoring, results of tests)	Evaluation end point	Follow-up visit
Compliance with treatment with bosutinib (Morisky Questionnaire) *	Evaluation end point	Follow-up visit
Quality of life (FACT-leu_v4)*	Baseline characteristics Evaluation end point	Inclusion visit Follow-up visit
Patient status and date of last news (date of death if applicable)	Evaluation end point	End of study
Last hematological, cytogenetic and molecular responses known	Evaluation end point	End of study
Status of treatment with bosutinib	Evaluation end point	End of study

* Morisky medication adherence scale and fact leu self-questionnaire are intended solely for patients under treatment with bosutinib.

9.4.1. Effectiveness endpoints

9.4.1.1. Responses

In this section, some endpoints have been deleted or modified compared to the initial protocol in order to be as consistent as possible with the study design.

Cumulative response rate (at least one time)

- Cumulative hematological response, complete (CHR):
    - percent of patients presenting with a CHR at any time during treatment with bosutinib (best response according to the participating doctor's judgement)
- Cumulative cytogenetic response, major (MCyR), complete (CCyR), partial (PCyR), or minor (mCyR):
    - percent of patients presenting with CCyR at any time during treatment with bosutinib (best response according to the participating doctor's judgement)
    - percent of patients presenting with PCyR at any time during treatment with bosutinib (best response according to the participating doctor's judgement)
    - percent of patients presenting with mCyR at any time during treatment with bosutinib (best response according to the participating doctor's judgement)

*Major response (MCyR) percent of patients presenting with MCyR at any time during treatment with bosutinib (best response according to the participating doctor's judgement) will be derived from the complete and partial response.

- Cumulative molecular response, MR3, MR4, MR4.5, MR5:
    - percent of patients presenting with MR3, MR4; MR4.5; MR5 at any time during treatment with bosutinib (best response according to the participating doctor's judgement)

Suboptimal response **(after dose escalation or without dose escalation due to ongoing toxicities):**

- Patient with chronic phase CML, refer to ELN guidelines 2013.
- Patient with accelerated phase or blast phase CML, loss of all hematological response.

Time to response

For each response (hematological, cytogenetic, molecular), the time to response corresponds to the duration between date of initiation of bosutinib and the first date of response.

* if the patient was already in response at initiation, time to response should have been defined as the time between the first date of response to a better response or the maintenance with bosutinib.

Event Date and Outcome for time to response

Scenario	**Date of Event/Censoring**	**Outcome**
Response to bosutinib (all types)	Date of response	Event
Death during bosutinib	Date of death	Censored
Discontinuation of bosutinib	Date of discontinuation	Censored
Lost to follow-up	Date of last contact	Censored

Duration of response

For each response (hematological, cytogenetic, molecular), the duration of response corresponds to the duration between first date of response as defined in the aforementioned and the confirmed loss of response, the progression of disease or death of the patient.

* if the patient was already in response at initiation, duration of response should have been defined as the duration between the first date of response to a better response and the confirmed loss of response, the progression of disease or death of the patient.

Event Date and Outcome for duration of response

Scenario	**Date of Event/Censoring**	**Outcome**
Loss of response	Date of loss of response	Event
Disease progression	Date of disease progression	Event
Death while responding	Date of death	Event
Alive at end of follow-up	Date of last contact	Censored
Lost to follow-up	Date of last contact	Censored

Type of response according to dose

Percent of patients with a response according to mean dose received in period of follow-up to response. Proportions were calculated for each type of response (HR, CyR or MR) and strata of dose a day (strata were ≤ 200, >200 to ≤ 300, >300 to ≤ 400, >400 mg/day)

9.4.1.2. Progression

The proportion of patients with progression of CML defined as passage from CP phase to AP or BP phases. This progression was validated by two consecutive evaluation less than one week apart.

- Patients presenting an increase in leukocyte count in at least one period greater than or equal to one month, with second assay measurement > 20 x 109/L and confirmed at least one week later.
- Patients presenting a loss of major hematological response (with hematological confirmation within a time greater than or equal to 2 weeks after loss of initial response) or non-confirmation of major cytogenetic response (with a Ph+ rate increased by 30%).

The proportion of patients with at least one change in disease phase, and patient progressor from CP to AP, from CP to BP, and from AP to BP.

9.4.1.3. Progression Free Survival (PFS)

PFS was defined as the time from first day of treatment with bosutinib to date of progression estimated by the participating doctor or death of patient (all causes combined). The censoring and event date options to be considered for the PFS analysis are defined as follows:

Event Date and Outcome for PFS

Scenario	Date of Event/Censoring	Outcome
Death during bosutinib	Date of death	Event
Death after treatment discontinuation	Date of death	Event

Disease progression during bosutinib	Date of disease progression	Event
Disease progression after treatment discontinuation	Date of disease progression	Event
Alive without disease progression at end of follow-up	Date of last contact	Censored
Lost to follow-up	Date of last contact	Censored

9.4.1.4. Overall Survival (OS)

OS was defined as the time from first day of treatment with bosutinib to date of death, all causes combined. The censoring and event date options to be considered for the OS analysis are defined as follows:

Event Date and Outcome for OS

Scenario	**Date of Event/Censoring**	**Outcome**
Death during bosutinib	Date of death	Event
Death after treatment discontinuation	Date of death	Event
Alive at end of follow-up	Date of last contact	Censored
Lost to follow-up	Date of last contact	Censored

9.4.2. Safety endpoints

9.4.2.1. Exposure to Bosutinib

Describing treatment modalities for bosutinib under real life conditions of use included:

- *Dosage: mean dosage prescribed at time of initiation and average dosage during treatment.*
- *Change to dose and reasons: percent of patients with dose reduction/percent of patients with a dose increase and if applicable, description of the reason.*

- *Maintenance of dose intensity and relative dose intensity (defined as the result of the ratio of the dose received over the expected dose): percent of patients with a dose intensity/relative dose intensity maintained over time and at different measurement times.*
- *Temporary discontinuation of treatment: percent of patients with temporary discontinuation of treatment and description of the reason; cumulative duration of temporary discontinuations.*
- *Permanent discontinuation of treatment: percent of patients with a permanent discontinuation of treatment and description of reason for discontinuation.*
- *Duration of treatment: duration of initiation up to discontinuation of treatment was calculated for all causes of discontinuation combined and by cause of discontinuation.*

Event Date and Outcome for Duration of treatment

Scenario	**Date of Event/Censoring**	**Outcome**
Bosutinib discontinuation (all causes)	Date of treatment discontinuation	Event
Death during bosutinib	Date of death	Censored
Alive and treated with bosutinib	Date of last news	Censored
Lost to follow-up	Date of last contact	Censored

- Cumulative duration of treatment defined as duration of treatment minus cumulative duration of temporary discontinuations.
- Time to treatment failure (TTF): Duration of treatment from initiation up to permanent discontinuation for all causes

Event Date and Outcome for TTF

Scenario	**Date of Event/Censoring**	**Outcome**
Permanent Bosutinib discontinuation (all causes)	Date of permanent treatment discontinuation	Event
Death during bosutinib	Date of death	Censored
Alive and treated with bosutinib	Date of last news	Censored
Lost to follow-up	Date of last contact	Censored

Average dose during the treatment

The average dose during the treatment is the mean of the doses indicated to the patient during their follow-up (in mg/day):

- If the treatment dose remains unchanged during the follow-up, the average dose is equal to the prescribed dose at initiation.
- If the treatment dose is modified, the average dose is equal to the sum of the products of the prescribed doses (in mg/day) by the number of days treated at those doses, divided by the total number of actual treatment days.

Dose intensity

The dose intensity was defined as the treatment dose received per unit of time. For this study, the received dose was the prescribed dose at initiation (in mg/day) or, in case of treatment modification, the new prescribed dose defined by the physician.

The relative dose intensity is the result of the ratio of the dose received per unit of time (dose intensity) to the expected dose per unit of time (recommended dose according to the bosutinib Summary of Product Characteristics: 500 mg/day). The relative dose intensity was calculated at each timepoints.

9.4.2.2. Adverse Events

All AEs have been coded using the MedDRA dictionary by System Organ Class (SOC) and grade of event according to the CTCAE v4.03 (1, 2, 3, 4 or 3-4). Safety endpoints have been analyzed for the whole study duration from M0 to M36 (overall and by subgroups).

Primary endpoints:

- The proportion of patients presenting with AE considered related to bosutinib by the participating doctor (overall, by types of events and by grade of event)

- The proportion of patients who permanently discontinued bosutinib following an AE considered related to bosutinib by the participating doctor (overall).

Secondary endpoints:

- The proportion of patients presenting AE that occurred during treatment with bosutinib by SOC (overall and by grade of event)
- The proportion of patients presenting AE which required changes to treatment with bosutinib by SOC (overall and by grade of event)
- The proportion of patients presenting biological and hematological toxicities that occurred with bosutinib
- The proportion of patients who permanently discontinued bosutinib because of an AE which had resulted in discontinuation of a previous treatment (imatinib, dasatinib, nilotinib). Cross intolerance has been estimated for all AEs, but also by type of adverse event.
- Measures taken to prevent AE

9.4.2.3. Biological and Hematological Parameters

Biological and hematological parameters were collected as continuous variables.

9.4.3. Other endpoints

9.4.3.1. Characteristics of the Patients Treated with Bosutinib

The description of the population covered presents the characteristics of patients at time of initiation of treatment:

- *demography;*
- *medical history and comorbidities, duration between diagnosis and initiation of Bosutinib treatment and latest hematological, cytogenetic or molecular responses known (cytogenetic and molecular responses have been mentioned only if patient was in chronic phase);*

- *previous treatments: number of lines of treatment, medicinal products, best response during treatment (hematological, cytogenetic or molecular responses), reasons for discontinuation of previous treatments.*

Data at the time of initiation of treatment were data collected at last inclusion visit (M0) or previous inclusion visit before bosutinib initiation. Description have been provided overall and by subgroups.

9.4.3.2. Quality of Life

The quality of life (QoL) of the patient have been assessed with the FACT-leu version 4, a specific questionnaire on Leukemia for Functional Assessment of Cancer Therapy. The questionnaire includes 44 items on a 5-point Likert-type scale scored 0 to 4 (“Not at all”, “A little”, “Moderately”, “Much”, “Enormously”). Items are organized in 5 subscale domains:

- Physical Well-Being or PWB (7 items from 1 to 7): sum score ranges from 0 to 28, Likert-type scale need to be reverse from item 1 to 7.

$$PWB = 7 * \frac{\sum_1^i \mathrm{GP(i)}}{\text{Number of GPi items answered}}$$

- Social/Family Well-Being or SWB (7 items from 8 to 14): sum score ranges from 0 to 28.

$$SWB = 7 * \frac{\sum_1^i \mathrm{GS(i)}}{\text{Number of GSi items answered}}$$

- Emotional Well-Being or EWB (6 items from 15 to 20): sum score ranges from 0 to 24, Likert-type scale need to be reverse for item 15, 17, 18, 19, 20.

$$EWB = 6 * \frac{\sum_1^i \mathrm{GE(i)}}{\text{Number of GEi items answered}}$$

- Functional Well-Being or FWB (7 items from 21 to 27): sum score ranges from 0 to 28.

$$FWB = 7 * \frac{\sum_1^i \mathrm{GF(i)}}{\text{Number of GFi items answered}}$$

- Leukemia Subscale or LeuS (17 items from 28 to 44): sum score ranges from 0 to 68, Likert-type scale need to be reverse for the items from 28 to 37 and from 40 to 44.

$$LEUS = 17 * \frac{\sum \begin{matrix}\text{(BRM3, P2, BRM2, ES3, LEU1, TH1, TH2, HI12,} \\ \text{BMT6, C2, C6, An7, N3, LEU5, LEU6, BRM9, LEU7)}\end{matrix}}{\text{Number of Leus items answered}}$$

Each subscale score (PWB, SWB, EWB, FWB ans LeuS) is computed as the sum score multiply by the number of items in the domain divided by the number of items answered.

Then the following scores have been derived where the higher the score, the better the QoL:

- FACT-Leukemia Trial Outcome Index (TOI) as the sum of PWB, FWB and LeuS range from 0 to 124.

$$TOI = PWB + FWB + LeuS$$

- FACT-G total score as the sum of PWB, SWB, EWB and FWB range from 0 to 108.

$$FACT - G = PWB + SWB + EWB + FWB$$

- FACT-Leukemia total score as the sum of PWB, SWB, EWB, FWB and LeuS range from 0 to 176.

$$FACT - Leukemia = PWB + SWB + EWB + FWB + LeuS$$

Derived scores have been calculated at each measurement time and the change in QoL has been defined by the difference between the best score recorded for a patient during follow-up visits (M3, M6, M12, M18, M24, M36) and his baseline score (M0 = inclusion visit).

9.4.3.3. Adherence to Treatment

The MMAS-8 (Morisky Questionnaire) rating scale consists of eight items added to obtain a total score. Items from 1 to 7 are scored with a “Yes” = 0 and “No” = 1. Item 8 is a 5-point response scored with A = 0 and B, C, D or E = 1. The total score has been described continuously and categorically (0 = high adherence, 1-2 = average adherence, ≥3 = low adherence) at each measurement visit (M3, M6, M9, M12, M15, M18, M21, M24, M27, M30, M33, M36).

9.5. Data sources and measurement

A case report form (CRF) (APPENDIX 5) have been used for recording data. In the setting of this protocol, the CRFs were the reference for collection of medical data in electronic format or in paper format. Data have been collected according to two methods:

- By doctors in an electronic case report form (eCRF),
- By patients in paper format questionnaires.

Questionnaires collected at the different times of measurement were:

- At time of inclusion of patients: a questionnaire at inclusion competed by the doctors; questionnaires on compliance and quality of life completed by patients
- During follow-up of patients: a questionnaire on follow-up completed by the doctor; questionnaires on compliance and quality of life completed by patients
- In case of a premature end of study: end of study questionnaire completed by the doctor for patients lost to follow-up and/or withdrawal of consent.

Considering the non-interventional design of this study, medical data were collected at inclusion during a routine visit scheduled by the participating centers. The study only required the collection of data available in patients' medical files and other items that are routinely evaluated during their disease management. No medical assessment was to be done especially for the study and all medications were prescribed only on participating centers' initiative.

Data of interest were directly collected at inclusion by participating physicians on an eCRF specifically developed by Pfizer for this study. Patients were identified with a number composed with a 2-digit code for the center followed by a 2-digit code for the patient.

In addition, patients completed self-reported questionnaires at timepoints details in Table 4, page 37 et 38 of this document, either on site or at home on "paper" forms, which were returned in secure prepaid T envelopes to the data processing company.

9.6. Bias

9.6.1. Selection bias of patients

Ensuring the sample of the study accurately reflects the target population is crucial for generalizing the study's results to that population. The sample's representativeness is influenced by both internal

validity, which pertains to the precision of estimates and the criteria used to select the study population (i.e., the patients), and external validity, which considers the plan and variations in sampling.

In observational studies, the inclusion of patients introduces the potential for selection bias. The conscious or unconscious choices made by participating doctors during patient selection are inevitable. To mitigate this bias, participating doctors were instructed to sequentially and exhaustively include all patients meeting the study's eligibility criteria until the end of the inclusion period. To monitor the representativeness of the included patients, a registry of non-inclusions has been maintained until the end of the inclusion period, allowing for the control of relevant parameters.

9.6.2. Patients lost to follow-up during follow-up

Special attention has been paid to patients who discontinued the study or those who were not seen in a visit because of the observational characteristic of the study (frequency of visits for follow-up of patients can vary depending on doctors and patients).

For patients lost to follow-up, a questionnaire on the patient’s last news (end of study) will be completed by the participating doctor. Statistical analyses will compare characteristics of patients included and who participated in the entire duration of the study and those who did not complete the entire follow-up (lost to follow-up and/or who discontinued the study before the end of follow-up).

9.7. Study Size

As the primary goal of this study was descriptive and did not entail specific research hypotheses, the calculation of a minimum sample size for participating patients was deemed unnecessary. Furthermore, since CML is a rare disease, a minimum number of patients was not expected.

Based on the number of monthly prescriptions of bosutinib (as per sponsor data) and anticipating the initiation of a competing study in the future, setting a target of one hundred patients for inclusion in

the study seemed reasonable. Participating doctors were expected to include an average of 5 patients each, with no differentiation based on the phase of CML at inclusion. Moreover, one hundred patients would enable to have acceptable precision, defined as half of a 95% confidence interval (CI):

- ≤ 10% to estimate a percent of patients presenting with a given event (Wald asymptotic method without a continuity correction – hypothesis of a 50% rate)
- Of 10% in order to estimate median survival (Greenwood formula under the hypothesis of absence of data censured at the right before median survival and occurrence of a single event at a time.

Consecutive inclusion of patients who satisfied eligibility criteria up to the end of the inclusion period estimated at 2 years ensured the representativeness of patients in the study.

To ensure compliance with this consecutiveness, a registry of non-inclusion has been set up. Patients eligible but not included in the study must have been recorded in this registry and throughout the period of inclusion. A minimum of parameters has been collected.

9.8. Data transformation

Detailed methodology for data transformations, particularly complex transformations (eg, many raw variables used to derive an analytic variable), are documented in the statistical analysis plan (SAP), which is dated, filed and maintained by the sponsor (Appendix 4).

9.9. Statistical methods

This study was a non-interventional and uncontrolled study. In that sense, there was no inferential hypothesis that served for a claim.

The full analysis set (FAS) has been defined as all patients who received at least one dose of bosutinib and who were eligible (compliance with inclusion and exclusion criteria).

The safety analysis set (SAF) has been defined as all patients who received at least one dose of bosutinib.

Eligible patients but not included in the study have been reported in a registry of non-inclusion with a minimum collection of information.

Descriptive statistics have been provided overall and by subgroup defined by treatment lines. Expected treatment lines are:

- 2-L,
- 3L,
- 4L+

A change in dosage or combination of CML treatment did not constitute a change in line.

9.9.1. Main summary measures

Quantitative variables have been described using number of filled and missing data, mean, standard deviation, median, 1st and 3rd quartiles, minimum and maximum.
Qualitative variables have been described using number of filled and missing data and, for each modality, the frequency and percentage (referring to filled data).
Means and percentage have been further described with 95CI% where appropriate.

9.9.2. Main statistical methods

9.9.2.1. Analyses of Time-to-Event Data

Kaplan-Meier estimates (product-limit estimates) have been presented together with a summary of associated statistics including the median survival time with 95%CI at the specified timepoints (yearly).
The CIs for the median have been calculated according to Brookmeyer and Crowley (Brookmeyer, 1982) and the CIs for the survival function estimates at the time points have been derived using the

log-log transformation according to Kalbfleisch and Prentice (Kalbfleisch and Prentice 1980) with back transformation to a CI on the untransformed scale. The estimate of the standard error has been computed using Greenwood's formula(Kalbfleisch and Prentice 2002). Frequency (number and percentage) of participants with each event type and censoring reasons have been presented.
The follow-up duration has also been assessed using a Kaplan-Meier method reversing the censoring and event indicators.

9.9.2.2. Longitudinal Analyses of Continuous Data

Changes from baseline at specified follow-up assessment time points were analyzed using a mixed model for repeated measures (MMRM) under the MAR framework. Analyses included the fixed, categorical visit (including baseline). An unstructured (co)variance structure has been used to model the within-participant errors. If this analysis fails to converge, the following structures have been tested: a heterogeneous Toeplitz covariance structure followed by the heterogeneous first-order autoregressive covariance structure will be considered. The covariance structure converging to the best fit, as determined by Akaike's information criterion, has been used as the primary analysis. The Kenward-Roger approximation has been used to estimate de-nominator degrees of freedom. Mean changes from baseline have been assessed using appropriate contrasts of least-squares means. Two-sided 95% confidence intervals have been provided.

9.9.2.3. Multivariable Analyses of Binary and Categorical Variables

Multivariable logistic regression and multivariable multinomial logistic regressions were used to estimate by maximum likelihood (ML) the association of a qualitative parameters (response to treatment) with predictive factors.
Results were reported in term of ORs with their 95%CI for each categorical and continuous variable implemented in the models.

Predictive factors associated with an outcome of interest were identified through univariable logistic regression models. A distinct logistic regression model was constructed for each factor. If a variable

showed significant association with the outcome at the 10% level, it was included in a multivariable model. Following the completion of the univariable model selection, a backward selection approach was employed to eliminate factors from the multivariable model that did not reach a significant p-value at the 5% level. The covariate with the highest p-value was successively removed until all factors had a p-value less than 0.05.

In cases where a significant interaction was detected, the individual factors involved in the interaction were retained in the model, irrespective of their p-values. The presence of a significant interaction was tested for all variables in the multivariable model. Additionally, a table presenting the 95% confidence intervals and p-values for the odds ratios derived from both univariable and multivariable models was provided.

9.9.3. Main statistical analyses

9.9.3.1. Effectiveness Analyses

All effectiveness analyses have been performed in the FAS (See definition in section **14.1**).

Analyses of the Responses to Bosutinib

Cumulative responses summarized by subgroups for:

- the number and percent of patients presenting with a CHR
- the number and percent of patients presenting with CCyR
- the number and percent of patients presenting with PCyR
- the number and percent of patients presenting with mCyR
- the number and percent of patients presenting with CMR
- the number and percent of patients presenting with an MMR

Time to response and duration of response described using the methodology presented in section 9.9.2.1.

Type of response according to dose described with the number and percentage of each type of response by dose and subgroups.

Predictive factors of the response have been investigated according to the methodology described in section 9.9.2.3. Summary tables with univariable and multivariable estimates of the ORs and 95%CI are provided for each type of response: HR, CyR, MR.

Progression of CML

A summary table is provided with descriptive statistics of the number and percentage of patient which change in disease phase at least one time, and patient progressor from CP to AP, from CP to BP, and from AP to BP (overall and by treatment line)

Progression free and overall survival

PFS and OS is described with a figure and summary table according to the methodology detailed in section 8.1.2 by subgroups.

9.9.3.2. Safety Analyses

All safety analyses have been performed in the SAF (See definition in section **14.2**).

Exposure to Bosutinib

A summary table is provided with the descriptive statistics of the variables which describe the treatment modalities for bosutinib under real life conditions of use by subgroups.

Duration of treatment is described with a figure and summary table according to the methodology detailed in section 9.9.2.3 by subgroups (overall and by cause of discontinuation).

TTF is described with a figure and summary table according to the methodology detailed in section 8.1.2 by subgroups.

Adverse Events

All safety analyses has been performed on the SAF population and reported overall and by subgroups (treatment lines). All AEs have been listed.

Primary analyses

A summary table is provided with the descriptive statistics for the number and proportion of patients presenting with AEs considered related to bosutinib by the participating doctor (overall, by type of adverse event; by grade of event: 1, 2, 3, 4 or 3-4).

A summary table is provided with the descriptive statistics for the number and proportion of patients who permanently discontinued bosutinib following an AE considered related to bosutinib by the participating doctor.

Secondary analyses

A summary table of AEs is provided with the descriptive statistics of the number and percentage for the following categories:

- AEs that occurred during treatment with bosutinib
- AEs which required changes to treatment with bosutinib

A summary table for cross intolerance is provided overall and by type of AE with the descriptive statistics of the number and proportion of patients who permanently discontinued bosutinib because of an AE which had resulted in discontinuation of a previous treatment (imatinib, dasatinib, nilotinib).

A listing of the measures taken to prevent AE is provided.

Biological and Hematological Parameter

Considering the sparsity of biological and hematological data that have been collected in this study, the longitudinal analysis initially planned in the protocol has not been conducted. A summary table with only descriptive statistics is provided at each time point.

9.9.3.3. Other Analyses

Analyses of Quality of Life

A summary table is provided by subgroups with the descriptive statistics of the scores TOI, FACT-G and FACT-Leukemia at each timepoints and descriptive statistics of the maximum absolute positive change from baseline and the absolute change from previous timepoints. A summary table of the LSMeans with 95%CI and LSMeans change from baseline (M0) with 95%CI, is provided at each time point. Estimations is reported overall and by subgroups according to the longitudinal analysis methodology detailed in section 8.1.3.

Analyses of Representativeness of the Study

Representativeness of the study has been assessed with data from registry of non-inclusion, and characteristics of lost to follow-up patient with standardized differences.

Registry of non-inclusion

A summary table with descriptive statistics for age and sex is provided for patients reported in the registry of non-inclusion and patients included.
Number and proportion of patient refusal is provided, other reasons for non-inclusion will be listed.

9.9.4. Missing values

No imputation methods have been used. Restricted maximum likelihood (REML) estimator has been used for the analyses of available longitudinal continuous data and assumed that data were missing at random (MAR).

For time-to-event data, subjects who dropped out or completed the study without meeting the event criteria have been treated as censored at the last visit. Therefore, all subjects have been included in the survival analyses.

Other statistical tests or other statistical models have been performed on complete cases.

9.9.5. Sensitivity analyses

None

9.9.6. Amendments to the statistical analysis plan

Among the patients included only one patient was in AP phase and one in BP phase, consequently, it has been decided to only include the descriptive statistics for these two patients and the inferential analysis were only performed for the CP subgroups.

The representativeness of the participating centres which was originally planned in the PAS was note performed as no database with relevant information about hematologist were available.

9.10. Quality control

9.10.1. Set up of participating doctors

It has been offered to doctors preselected to participate in this study.

The participation was formalized through the signing of the financial agreement. Following the validation of the agreement, a site setup visit was arranged by the Clinical Research Associate to present the study and related documents to the participating doctor and designated members of their staff, if applicable.

9.10.2. Logistics and monitoring of participating centres

Logistics and monitoring of participating centers were actively managed throughout the study. Regular contacts with participating doctors were established to ensure understanding and adherence to the protocol and electronic questionnaire.

Study Monitors took charge of conducting at least one monitoring visit per year per center, along with a closing visit. During these visits, the monitors ensured the doctor's comprehension and compliance with the protocol, confirmed the inclusion of patients, verified the accuracy of data recorded in the case report form against source data, checked the Site Master File (SMF) for proper maintenance, and validated the reporting of adverse events to the Pfizer pharmacovigilance department.

Key indicators of proper conduct of this study (number of active centres, number of patients included, number of follow-ups performed, etc.) were generated using the study database. This database enabled the creation of study progress reports allowing for the generation of reminders to centres.

9.10.3. Quality and accuracy of data

The participating doctor were responsible for collection of reports of all clinical data, of safety data and laboratory data entered in the eCRF and/or other forms of data collection (source documents), and ensured that they were accurate, authentic, attributable to the patient, complete, consistent, readable, contemporaneous, and available if needed.

To enable controls and/or audits by the regulatory authorities or by Pfizer, the participating doctor accepted to keep registries including the identity of all participating patients (sufficient information to review the dossiers (e.g. eCRF and hospital medical dossiers). Original signed informed consent forms, copies of serious adverse event reports, source documents, and medical results influencing treatment decisions were to be retained by the participating doctor.

9.11. Protection of human subjects

Subject information and consent

Written informed consent (reference Appendix 6) was obtained prior to the subject entering the study (before initiation of study protocol-specified procedures) by study personnel; the nature, purpose, and duration of the study was explained to each subject. Each subject was informed that he/she could withdraw from the study at any time and for any reason. Each subject was given sufficient time to consider the implications of the study before deciding whether to participate. Subjects who chose to participate signed an informed consent document.

Independent Ethics Committee (IEC)/Institutional Review Board (IRB)

In compliance with law 78-17 of 6 January 1978 relating to data processing, computer files and freedoms, as modified by law 2004-801 of 6 August 2004 relating to protection of physical persons with regard to processing of personal data, this protocol has been submitted in a request for an opinion from the Consultative Committee on Data Processing in the Area of Research in the Field of Health (CCTIRS). Upon receipt of a favorable opinion from this committee, the computer file used to

write the present study has been the subject of a request for authorization form the National Committee for Data Processing and Freedoms (CNIL). This computer file can be used only after receipt of authorization from the CNIL.

Since this involves the potential competence of the Consultative Committee on Data Processing in the Area of Research in the Field of Health (CCTIRS) which has been eliminated on 5 May 2017, date of a decision concerning creation of the Expert Committee on Research, Studies and Evaluations in the Field of Health (CEREES) in application of French law no. 2016-41 of modernization of the health system of 26 January 2016, and of the application decision of the so-called Jardé law no. 2016-1537 of 16 November 2016, the departments of the ministry of research are no longer competent for analysis of corrections made to research projects.

This trial was an observational study that did not alter the regular medical management of individuals entering the study. It did not pose any harm to the physical or psychological integrity of participants, and no specific follow-up visits were required for those entering the study. All procedures and product usage adhered to standard practices, with no unusual or additional diagnostic or monitoring measures. Given these conditions, the study did not fall within the scope of application of law of program no. 2006-450 of 18 April 2006 for research nor law no. 2004-806 of 9 August 2004 article 88 chapter II article L1121-1 and therefore the project was not subject to submission to the National Agency for Medicines and Health Products Safety (ANSM), nor to a Committee for Protection for Persons (CPP) (ethics committee).

Regulation no. 2016-800 of 16 June 2016 relating to research involving a human person stipulates in its article 8 that research regularly reported or authorized at date of entry in force of the application decision (application decision of the so-called Jardé law no. 2016-1537 of 16 November 2016) continues in force during five years in compliance with legislation which was initially applicable to them.

In this regard, for an opinion which has been issued prior to 16 November 2017, the Ethics Committee was not competent for substantial changes on this project.

Ethical conduct of the study

The study was conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and followed generally accepted research practices described in:

- Recommendations on Good Pharmacoepidemiologic Practice (GPP) published by International Society for Pharmacoepidemiology (ISPE), https://www.pharmacoepi.org/resources/guidelines_08027.cfm
- Recommendations on Good Epidemiological Practice (GEP) published by the International Epidemiological Association (IEA), http://ieaweb.org/2010/04/good-epidemiological-practice-gep/
- Good practice of research on results on results published by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), http://www.ispor.org/workpaper/practices_index.asp
- Recommendations on Good Practice for studies on health data under real life conditions concerning a treatment and/or comparative efficacy: recommendations of the joint working group ISPOR-ISPE on concrete evidence in decision making in the area of healthcare https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5639372/
- International ethical recommendations for epidemiological research published by the Council for International Organizations of Medical Sciences (CIOMS) http://ieaweb.org/wp-content/uploads/2012/06/cioms.pdf
- European Medicines Agency (EMA) European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology
- The ENCePP Code of Conduct for scientific independence and transparency in conduct of studies of pharmacoepidemiology and pharmacovigilance http://www.encepp.eu/code_of_conduct/documents/ENCePPCodeofConduct_Rev3.pdf

- Guide of methodological standards in pharmacoepidemiology, guidelines of the Food and Drug Administration (FDA) for industry: Good Practice of pharmacovigilance and of pharmacoepidemiologic evaluation (Good Pharmacovigilance and Pharmacoepidemiologic Assessment), https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm071696.pdf

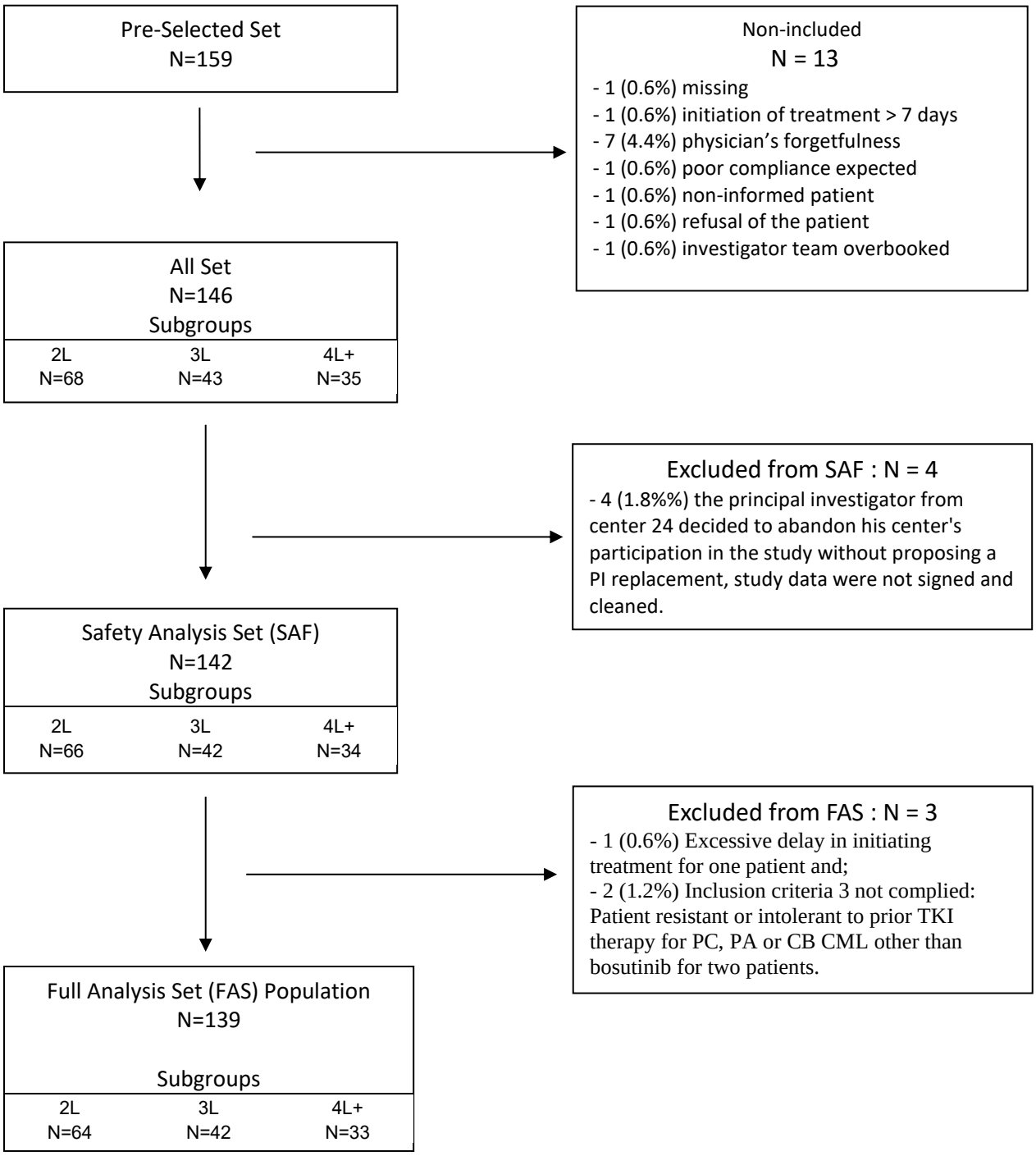
- FDA guidelines for industry and FDA staff: Good Practice of conduct and reporting of pharmacoepidemiologic studies of safety using all electronic medical data http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM243537.pdf

- Guidelines for industry: Measures evolution recorded by the patient: Use in development of medical products to support labelling of the label. http://www.fda.gov/downloads/Drugs/Guidances/UCM193282.pdf

10. RESULTS

10.1. Participants

Figure 2: Flow-chart



From October 15, 2015 to December 19,2019, among the 159 patients pre-selected (see A**ppendix 7.12**) 146 patients were included in 23 centers (Table 7).

Among the total set of patients 142 were included in the safety population, while 4 patients were excluded from the SAF population (Table 5). Reason for exclusion was that the principal investigator from center 24 decided to abandon his center's participation in the study without proposing a PI replacement, study data were not signed and cleaned.

Three patients from the SAF population were excluded from the FAS population which finally included 139 patients (Table5). Reasons for exclusion were:

- Excessive delay in initiating treatment for one patient and;
- Inclusion criteria 3 not complied: Patient resistant or intolerant to prior TKI therapy for PC, PA or CB CML other than bosutinib for two patients.

Overall, 7 patients were then excluded from the study for major protocol deviations, see **Appendix 7.2** for a full listing of deviations and **Appendix 7.3** for subject excluded.

In the FAS population, 19 patients (13.6%) were prematurely withdrawn from the study. Main reason for premature withdrawal was death (7 patients, 5%), 2 patients (1.4%) were prematurely withdrawn due to loss of follow-up and 10 patients (7.2%) were prematurely withdrawn due to other reasons (details about patient withdrawal is presented in **Appendix 7.1**).

Patient distribution according to the previous lines of treatment 2L; 3L and 4L+ is summarized in Figure 2 and Table 5

Table 5: Population - All Subjects

Variables		2L (N=68)	3L (N=43)	4L+ (N=35)	Total (N=146)
All set	Yes	68 (100%)	43 (100%)	35 (100%)	146 (100%)
Safety Analysis Set (SAF)	No	2 (2.9%)	1 (2.3%)	1 (2.9%)	4 (2.7%)
	Yes	66 (97.1%)	42 (97.7%)	34 (97.1%)	142 (97.3%)
Exclusion of SAF	Center 24	2 (100%)	1 (100%)	1 (100%)	4 (100%)
Full Analysis Set (FAS)	No	4 (5.9%)	1 (2.3%)	2 (5.7%)	7 (4.8%)
	Yes	64 (94.1%)	42 (97.7%)	33 (94.3%)	139 (95.2%)
Exclusion of FAS	Center 24	2 (50%)	1 (100%)	1 (50%)	4 (57.1%)
	Excessive delay in initiating treatment	1 (25%)	0 (0%)	0 (0%)	1 (14.3%)
	Inclusion criteria 3 not complied: Patient resistant or intolerant to prior TKI therapy for PC, PA or CB CML other than bosutinib	1 (25%)	0 (0%)	1 (50%)	2 (28.6%)

Appendix 7.1 Population - All Subject

10.2. Descriptive data

10.2.1. Demographic and Baseline Characteristics

Baseline characteristics of patients included and not included but screened are summarized in Table 6.

A total of 159 patients were pre-selected, however, 13 were not included in the study. Reasons for non-inclusion are detailed in Table 6, main reason was physician's forgetfulness (7 patients). Overall, 146 patients were included in a total of 23 centres, as presented in Table 7. We observed a higher proportion of patients included in the CH of Versailles (16.4%) and the CH Annecy (15.1%), then the CHU of Limoges (8.2%) and CHU of Brest and CHRU of Montpellier (6.8% each). This heterogeneity in inclusion could have influenced the representativeness of the population included.

Regarding baseline characteristics, patients included were aged 61.9 ± 13.0 years and mainly men (57.5%), no major differences were observed regarding baseline characteristics of patients non-included.

Table 6: Subject Characteristics for Included and Non-Included Patients

Variables		Inclusion (N=146)	Non-inclusion (N=13)	Total (N=159)
Age (years)	N	146	11	157
	Mean ± SD	61.9 ± 13.0	63.9 ± 12.6	62.0 ± 13.0
	Median	65.0	69.0	65.0
	Q1 ; Q3	53.0 ; 71.0	51.0 ; 73.0	53.0 ; 71.0
	Min. ; Max.	23 ; 88	42 ; 80	23 ; 88
	Missing	0	2	2
Sex	Female	62 (42.5%)	4 (30.8%)	66 (41.5%)
	Male	84 (57.5%)	9 (69.2%)	93 (58.5%)
Reason for non-inclusion	Missing	146	1	147

Variables		Inclusion (N=146)	Non-inclusion (N=13)	Total (N=159)
	Poor compliance for follow-up and treatment	0 (0%)	1 (8.3%)	1 (8.3%)
	Initiation delay > 7 Days	0 (0%)	1 (8.3%)	1 (8.3%)
	Physician's forgetfulness	0 (0%)	7 (55.2%)	7 (55.2%)
	Patient uninformed (unreachable by phone)	0 (0%)	1 (8.3%)	1 (8.3%)
	Refusal of the patient	0 (0%)	1 (8.3%)	1 (8.3%)
	Work overload	0 (0%)	1 (8.3%)	1 (8.3%)

Table 15.5.1 Subject Characteristics for Included and Non-Included Patients - All Subjects

Table 7: Representativeness of the Participating Centres - All Subjects

Variable(s)		Total (N=146)
Center	AP-HM	2 (1.4%)
	APHP	4 (2.7%)
	CENTRE DE RADIOTHERAPIE - STRASBOURG	6 (4.1%)
	CH ANNNECY	22 (15.1%)
	CH BOURG EN BRESSE	2 (1.4%)
	CH CHALON	4 (2.7%)
	CH CHAMBERY	8 (5.5%)
	CH LIBOURNE	2 (1.4%)
	CH MEAUX	1 (0.7%)
	CH ORLEANS	1 (0.7%)
	CH PERIGUEUX	3 (2.1%)
	CH SAINT BRIEUC	3 (2.1%)
	CH VALENCE	1 (0.7%)
	CH VERSAILLES	24 (16.4%)
	CHRU GRENOBLE	7 (4.8%)
	CHRU LILLE	6 (4.1%)
	CHRU MONTPELLIER	10 (6.8%)
	CHU ANGERS	1 (0.7%)
	CHU BREST	10 (6.8%)
	CHU DE NANCY	7 (4.8%)
	CHU LIMOGES	12 (8.2%)
	CLCC INSTITUT BERGONIE	7 (4.8%)
	MEDIPOLE SAVOIE	3 (2.1%)

Table 15.5.2 Representativeness of the Participating Centres - All Subjects

Considering baseline characteristics of patients in the FAS population according to the line of previous treatment (Table 8), patients were aged 62.0 ± 13.6 years in the 2L group, 62.0 ± 11.1 years in the 3L group and 61.8 ± 15.0 years in the 4L+ group. Overall, men were more represented in the 2L group and 3L group, with a proportion of 56.1% in the total FAS population, nevertheless, in the 4L+ group female represented 51.5%. The mean BMI (kg/m²) was similar in all groups, 28.98 ± 6.41 in the 2L group, 27.99 ± 5.40 in the 3L group and 26.01 ± 4.59 in the 4L+ group. Finally, the ECOG scores were similar between groups, with 64 (57.1%) patients in total having a score of 0 and 48 (42.9%) patients having a score ≥ 1.

Table 8: Demographic and Baseline Characteristics - FAS (n=139)

Variables		2L (N=64)	3L (N=42)	4L+ (N=33)	Total (N=139)
Age (years)	N	64	42	33	139
	Mean ± SD	62.0 ± 13.6	62.0 ± 11.1	61.8 ± 15.0	62.0 ± 13.2
	Median	65.0	65.5	66.0	65.0
	Q1 ; Q3	52.5 ; 73.0	57.0 ; 70.0	52.0 ; 71.0	53.0 ; 71.0
	Min. ; Max.	31 ; 85	34 ; 78	23 ; 88	23 ; 88
	Missing	0	0	0	0
Sex	Female	26 (40.6%)	18 (42.9%)	17 (51.5%)	61 (43.9%)
	Male	38 (59.4%)	24 (57.1%)	16 (48.5%)	78 (56.1%)
Weight (kg)	N	59	34	25	118
	Mean ± SD	84.91 ± 18.65	79.94 ± 18.03	71.61 ± 14.77	80.66 ± 18.32
	Median	83.00	81.50	72.50	81.00
	Q1 ; Q3	68.00 ; 100.00	66.00 ; 92.00	59.00 ; 86.00	64.60 ; 92.00
	Min. ; Max.	52.1 ; 118	50 ; 122	38 ; 95	38 ; 122
	Missing	5	8	8	21
Height (cm)	N	63	40	31	134
	Mean ± SD	170.26 ± 8.91	168.24 ± 8.05	166.13 ± 8.47	168.70 ± 8.66
	Median	171.00	168.50	168.00	170.00
	Q1 ; Q3	164.00 ; 177.00	162.00 ; 175.00	157.00 ; 172.00	162.00 ; 175.00

Variables		2L (N=64)	3L (N=42)	4L+ (N=33)	Total (N=139)
	Min. ; Max.	150 ; 190	150 ; 183	150 ; 180	150 ; 190
	Missing	1	2	2	5
BMI (kg/m²)	N	58	34	24	116
	Mean ± SD	28.977 ± 6.407	27.996 ± 5.403	26.011 ± 4.592	28.076 ± 5.852
	Median	27.640	27.750	27.005	27.635
	Q1 ; Q3	24.220 ; 35.010	24.820 ; 32.390	23.170 ; 28.900	24.000 ; 32.020
	Min. ; Max.	19.15 ; 43.87	17.93 ; 40.3	15.42 ; 32.11	15.42 ; 43.87
	Missing	6	8	9	23
ECOG score	Missing	5	10	12	27
	0	34 (57.6%)	17 (53.1%)	13 (61.9%)	64 (57.1%)
	>=1	25 (42.4%)	15 (46.9%)	8 (38.1%)	48 (42.9%)

Table 15.1.1 Demographic and Baseline Characteristics - FAS (n=139)

Regarding baseline characteristics in subject with complete or incomplete follow-up (Table 9), there was no observable difference in term of age and BMI. Nevertheless, there was a greater proportion of women in patients with incomplete follow-up compared to complete follow-up (63.2% vs 40.8%), and the proportion of patients ECOG ≥ 1 was higher in the group which had an incomplete follow-up (71.4% vs 38.8%).

Table 9: Baseline Characteristics btw Subjects with Complete and Incomplete Follow-up - FAS (n=139)

Variables		Complete follow-up (N=120)	Incomplete follow-up (N=19)	Total (N=139)
Age (years)	N	120	19	139
	Mean ± SD	61.6 ± 12.9	64.6 ± 14.8	62.0 ± 13.2
	Median	65.0	68.0	65.0
	Q1 ; Q3	52.5 ; 71.0	54.0 ; 74.0	53.0 ; 71.0
	Min. ; Max.	23 ; 80	35 ; 88	23 ; 88
	Missing	0	0	0
Sex	Female	49 (40.8%)	12 (63.2%)	61 (43.9%)
	Male	71 (59.2%)	7 (36.8%)	78 (56.1%)
Weight (kg)	N	102	16	118
	Mean ± SD	81.23 ± 18.17	77.04 ± 19.46	80.66 ± 18.32
	Median	82.00	73.00	81.00
	Q1 ; Q3	66.00 ; 92.00	60.00 ; 89.35	64.60 ; 92.00
	Min. ; Max.	38 ; 122	50 ; 111	38 ; 122
	Missing	18	3	21
Height (cm)	N	117	17	134
	Mean ± SD	169.01 ± 8.36	166.56 ± 10.52	168.70 ± 8.66

Variables		Complete follow-up (N=120)	Incomplete follow-up (N=19)	Total (N=139)
	Median	170.00	164.00	170.00
	Q1 ; Q3	162.00 ; 176.00	159.00 ; 174.00	162.00 ; 175.00
	Min. ; Max.	150 ; 190	150 ; 190	150 ; 190
	Missing	3	2	5
BMI (kg/m2)	N	101	15	116
	Mean ± SD	28.098 ± 5.745	27.927 ± 6.748	28.076 ± 5.852
	Median	27.590	27.850	27.635
	Q1 ; Q3	24.240 ; 32.110	23.120 ; 31.220	24.000 ; 32.020
	Min. ; Max.	15.42 ; 43.87	19.15 ; 41.78	15.42 ; 43.87
	Missing	19	4	23
ECOG score	Missing	22	5	27
	0	60 (61.2%)	4 (28.6%)	64 (57.1%)
	1	30 (30.6%)	8 (57.1%)	38 (33.9%)
	2	6 (6.1%)	2 (14.3%)	8 (7.1%)
	3	2 (2%)	0 (0%)	2 (1.8%)

Table 15.5.3 Baseline Characteristics btw Subjects with Complete and Incomplete Follow-up - FAS (n=139)

10.2.2. Medical History

10.2.2.1. Initial diagnostic of CML

Regarding initial diagnosis of CML, mean time between initial diagnosis and initiation of bosutinib was 3.19 ± 4.24 years in the 2L groups, 7.37 ± 6.40 years in the 3L group and 9.82 ± 6.44 years in the 4L+ group, and all patients were diagnosed with a chronic phase, except one patient in the 2L group diagnosed in accelerated phase.

Bone marrow karyotype was analysed in 88.5% of the total population, and among these patients 89.4% had at (9,22) rearrangement.

Additionally, molecular analyses by qRT-PCR revealed that most patients had an expression of the ABL 81.2%, followed by 13.7% having a BCR expression.

Details about bone marrow karyotype, cytogenetic and mutations reported are summarized in Table 10.

Table 10: Medical History : initial diagnostic of CML and antecedent of transplant - FAS (n=139)

Variables		2L (N=64)	3L (N=42)	4L+ (N=33)	Total (N=139)
Time between initial diagnosis and initiation of bosutinib treatment (years)	N	64	42	33	139
	Mean ± SD	3.19 ± 4.24	7.37 ± 6.40	9.82 ± 6.44	6.03 ± 6.14
	Median	1.55	5.65	8.40	3.90
	Q1 ; Q3	0.90 ; 4.00	2.90 ; 8.60	5.00 ; 14.30	1.40 ; 8.50
	Min. ; Max.	0.2 ; 19.7	0.4 ; 29.2	0.7 ; 24.4	0.2 ; 29.2
	Missing	0	0	0	0
Phase of CML on diagnosis	Chronic	63 (98.4%)	42 (100%)	33 (100%)	138 (99.3%)
	Accelerated	1 (1.6%)	0 (0%)	0 (0%)	1 (0.7%)
Bone marrow karyotype	No	2 (3.1%)	2 (4.8%)	3 (9.1%)	7 (5%)
	Yes	61 (95.3%)	39 (92.9%)	23 (69.7%)	123 (88.5%)
	Unknown	1 (1.6%)	1 (2.4%)	7 (21.2%)	9 (6.5%)
If bone marrow karyotype, is rearrangement t(9,22) present?	Missing	16	12	10	38
	No	2 (4.4%)	1 (3.7%)	0 (0%)	3 (3.5%)
	Yes	39 (86.7%)	26 (96.3%)	11 (84.6%)	76 (89.4%)
	Unknown	4 (8.9%)	0 (0%)	2 (15.4%)	6 (7.1%)

Variables		2L (N=64)	3L (N=42)	4L+ (N=33)	Total (N=139)
Cytogenic analyses by FISH	No	42 (65.6%)	28 (66.7%)	16 (48.5%)	86 (61.9%)
	Yes	16 (25%)	13 (31%)	9 (27.3%)	38 (27.3%)
	Unknown	6 (9.4%)	1 (2.4%)	8 (24.2%)	15 (10.8%)
If cytogenic analyses by FISH, sample source	Missing	3	1	1	5
	Bone marrow	8 (61.5%)	10 (83.3%)	6 (75%)	24 (72.7%)
	Peripheral blood	5 (38.5%)	2 (16.7%)	2 (25%)	9 (27.3%)
Percentage of positive nuclei	N	23	11	12	46
	Mean ± SD	87.1 ± 24.0	92.5 ± 13.2	92.2 ± 15.0	89.7 ± 19.5
	Median	97.0	99.0	100.0	99.5
	Q1 ; Q3	85.0 ; 100.0	90.0 ; 100.0	88.0 ; 100.0	90.0 ; 100.0
	Min. ; Max.	9 ; 100	60 ; 100	50 ; 100	9 ; 100
	Missing	41	31	21	93
Molecular analyses by qRT-PCR	No	4 (6.3%)	4 (9.5%)	5 (15.2%)	13 (9.4%)
	Yes	58 (90.6%)	37 (88.1%)	22 (66.7%)	117 (84.2%)
	Unknown	2 (3.1%)	1 (2.4%)	6 (18.2%)	9 (6.5%)
If molecular analyses by qRT-PCR, control gene	ABL	49 (84.5%)	27 (73%)	19 (86.4%)	95 (81.2%)
	BCR	5 (8.6%)	9 (24.3%)	2 (9.1%)	16 (13.7%)

Variables		2L (N=64)	3L (N=42)	4L+ (N=33)	Total (N=139)
	BCR ABL/ABL	1 (1.7%)	0 (0%)	0 (0%)	1 (0.9%)
	BCR-ABL/ABL	1 (1.7%)	0 (0%)	0 (0%)	1 (0.9%)
	BCR/ABL	1 (1.7%)	0 (0%)	0 (0%)	1 (0.9%)
	INCONNU	1 (1.7%)	1 (2.7%)	1 (4.5%)	3 (2.6%)
If molecular analyses by qRT-PCR, BCR-ABL transcript (%)	N	55	35	17	107
	Mean ± SD	88.31797 ± 77.74909	80.65285 ± 65.87927	131.44000 ± 158.08006	92.66185 ± 92.42367
	Median	68.44000	68.57800	81.32000	68.50000
	Q1 ; Q3	39.40000 ; 106.00000	33.83400 ; 106.15000	36.00000 ; 146.00000	37.72000 ; 106.24000
	Min. ; Max.	1.3992 ; 340	2.6 ; 309	1.28 ; 597.7	1.28 ; 597.7
	Missing	1	1	3	5
SOKAL score	Missing	3	2	8	13
	Low	31 (50.8%)	15 (37.5%)	14 (56%)	60 (47.6%)
	Intermediate	19 (31.1%)	18 (45%)	7 (28%)	44 (34.9%)
	High	11 (18%)	7 (17.5%)	4 (16%)	22 (17.5%)
Progression of the phase of CML since the initial diagnosis	No	64 (100%)	41 (97.6%)	30 (90.9%)	135 (97.1%)
	Yes	0 (0%)	1 (2.4%)	3 (9.1%)	4 (2.9%)

Variables		2L (N=64)	3L (N=42)	4L+ (N=33)	Total (N=139)
If progression of the phase of CML since the initial diagnosis	Accelerated phase		1 (100%)	2 (66.7%)	3 (75%)
	Blast-phase		0 (0%)	1 (33.3%)	1 (25%)
History of transplant	No	64 (100%)	40 (95.2%)	30 (90.9%)	134 (96.4%)
	Yes	0 (0%)	2 (4.8%)	3 (9.1%)	5 (3.6%)
Time between transplant and initiation of bosutinib treatment (years)	N		2	3	5
	Mean ± SD		18.60 ± 2.69	20.43 ± 0.06	19.70 ± 1.68
	Median		18.60	20.40	20.40
	Q1 ; Q3		16.70 ; 20.50	20.40 ; 20.50	20.40 ; 20.50
	Min. ; Max.		16.7 ; 20.5	20.4 ; 20.5	16.7 ; 20.5
	Missing		0	0	0
Type	Autologue		2 (100%)	3 (100%)	5 (100%)
Source	Bone marrow		1 (50%)	0 (0%)	1 (20%)
	Peripheral blood		1 (50%)	3 (100%)	4 (80%)
Mutation analysis of the BCR-ABL gene performed since diagnosis of CML	No	43 (67.2%)	22 (52.4%)	13 (39.4%)	78 (56.1%)

Variables		2L (N=64)	3L (N=42)	4L+ (N=33)	Total (N=139)
	Yes	21 (32.8%)	20 (47.6%)	20 (60.6%)	61 (43.9%)
Mutation(s) identified	Missing	0	0	2	2
	No	20 (95.2%)	17 (85%)	12 (66.7%)	49 (83.1%)
	Yes	1 (4.8%)	3 (15%)	6 (33.3%)	10 (16.9%)
Mutation(s) identified: specify	E286K	0 (0%)	0 (0%)	1 (16.7%)	1 (10%)
	E292V	0 (0%)	0 (0%)	1 (16.7%)	1 (10%)
	E459G	0 (0%)	0 (0%)	1 (16.7%)	1 (10%)
	F2591	0 (0%)	1 (33.3%)	0 (0%)	1 (10%)
	INSERTION 35NT INTRON 8	0 (0%)	0 (0%)	1 (16.7%)	1 (10%)
	K294R ET F317L	0 (0%)	0 (0%)	1 (16.7%)	1 (10%)
	L354P,L248L,V260V	0 (0%)	1 (33.3%)	0 (0%)	1 (10%)
	PRESENCE DE MUTATION P.C475FS*11	1 (100%)	0 (0%)	0 (0%)	1 (10%)
	T315I	0 (0%)	0 (0%)	1 (16.7%)	1 (10%)
	Y253F	0 (0%)	1 (33.3%)	0 (0%)	1 (10%)
Concomitant medication	No	2 (3.1%)	0 (0%)	0 (0%)	2 (1.4%)
	Yes	62 (96.9%)	42 (100%)	33 (100%)	137 (98.6%)
Number of concomitant medications	N	64	42	33	139

Variables		2L (N=64)	3L (N=42)	4L+ (N=33)	Total (N=139)
	Mean ± SD	12.6 ± 10.5	11.4 ± 8.4	14.9 ± 14.2	12.8 ± 10.9
	Median	10.5	8.0	11.0	9.0
	Q1 ; Q3	5.0 ; 16.0	5.0 ; 17.0	6.0 ; 18.0	5.0 ; 18.0
	Min. ; Max.	0 ; 51	1 ; 34	2 ; 75	0 ; 75
	Missing	0	0	0	0
Antecedent or comorbidities	No	1 (1.6%)	1 (2.4%)	0 (0%)	2 (1.4%)
	Yes	63 (98.4%)	41 (97.6%)	33 (100%)	137 (98.6%)
Number of antecedent or comorbidities	N	64	42	33	139
	Mean ± SD	9.9 ± 7.2	9.1 ± 5.0	8.9 ± 5.3	9.4 ± 6.1
	Median	8.0	9.0	9.0	8.0
	Q1 ; Q3	5.0 ; 14.0	6.0 ; 12.0	5.0 ; 13.0	5.0 ; 13.0
	Min. ; Max.	0 ; 31	0 ; 19	1 ; 21	0 ; 31
	Missing	0	0	0	0

Table 15.1.2a Medical History : initial diagnostic of LMC and antecedent of transplant - FAS (n=139)

10.2.2.2. Previous TKI therapies

The description of previous treatment with TKI revealed that 64 (46%) patients had one previous line, 42 (30.2%) had two previous lines, 22 (15.8%) had 3 previous lines, 8 (5.8%) had 4 previous lines, while only 2(1.4%) and one (0.7%) patients had 5 and 6 previous lines respectively.

Most patients were previously treated with imatinib (46.8%) and dasatinib (33.1%) compared to nilotimib (18.7%) and ponatinib (1.4%).

History of best hematological, cytogenetic and molecular responses to previous treatment according to the line of treatment is summarized in Table 11. The predominant consideration for change of treatment until the 4th line was intolerance which was reported in 67 (49.6%) patients for the first line, 54 (73.0%) patients after 2nd line, 22 (66.7%) patients after 3rd line and 10 (90.9%) patients after the 4th line.

Details are presented in table 11 below.

Table 11: Medical History : previous TKI therapies - FAS (n=139)

Variables		2L (N=64)	3L (N=42)	4L+ (N=33)	Total (N=139)
Number of previous lines of treatment	1	64 (100%)	0 (0%)	0 (0%)	64 (46%)
	2	0 (0%)	42 (100%)	0 (0%)	42 (30.2%)
	3	0 (0%)	0 (0%)	22 (66.7%)	22 (15.8%)
	4	0 (0%)	0 (0%)	8 (24.2%)	8 (5.8%)
	5	0 (0%)	0 (0%)	2 (6.1%)	2 (1.4%)
	6	0 (0%)	0 (0%)	1 (3%)	1 (0.7%)
Last therapy	Imatinib	50 (78.1%)	6 (14.3%)	9 (27.3%)	65 (46.8%)
	Dasatinib	7 (10.9%)	26 (61.9%)	13 (39.4%)	46 (33.1%)
	Nilotinib	7 (10.9%)	10 (23.8%)	9 (27.3%)	26 (18.7%)
	Ponatinib	0 (0%)	0 (0%)	2 (6.1%)	2 (1.4%)
Best hematological response in last line	Missing	0	1	0	1
	Complete	59 (92.2%)	41 (100%)	32 (97%)	132 (95.7%)
	Partial	2 (3.1%)	0 (0%)	0 (0%)	2 (1.4%)
	No response	2 (3.1%)	0 (0%)	1 (3%)	3 (2.2%)
	Unknown / Not evaluated	1 (1.6%)	0 (0%)	0 (0%)	1 (0.7%)
Best cytogenetic response in last line	Missing	6	4	1	11

Variables		2L (N=64)	3L (N=42)	4L+ (N=33)	Total (N=139)
	Complete	44 (75.9%)	34 (89.5%)	23 (71.9%)	101 (78.9%)
	Partial	7 (12.1%)	2 (5.3%)	1 (3.1%)	10 (7.8%)
	Minor	1 (1.7%)	0 (0%)	1 (3.1%)	2 (1.6%)
	No response	0 (0%)	0 (0%)	1 (3.1%)	1 (0.8%)
	Unknown / Not evaluated	6 (10.3%)	2 (5.3%)	6 (18.8%)	14 (10.9%)
Best molecular response in last line	Missing	10	3	1	14
	Major: MR3	12 (22.2%)	9 (23.1%)	8 (25%)	29 (23.2%)
	MR4	5 (9.3%)	8 (20.5%)	4 (12.5%)	17 (13.6%)
	MR4.5	4 (7.4%)	5 (12.8%)	4 (12.5%)	13 (10.4%)
	MR5	9 (16.7%)	13 (33.3%)	8 (25%)	30 (24%)
	No response	20 (37%)	4 (10.3%)	6 (18.8%)	30 (24%)
	Unknown / Not evaluated	4 (7.4%)	0 (0%)	2 (6.3%)	6 (4.8%)
Reason for change of line in last line	Lack of response	2 (3.1%)	2 (4.8%)	1 (3%)	5 (3.6%)
	Loss of response	10 (15.6%)	4 (9.5%)	3 (9.1%)	17 (12.2%)
	Suboptimum response	14 (21.9%)	5 (11.9%)	3 (9.1%)	22 (15.8%)
	Intolerance	34 (53.1%)	31 (73.8%)	25 (75.8%)	90 (64.7%)
	Other, specify	4 (6.3%)	0 (0%)	1 (3%)	5 (3.6%)
Therapy in 1st line	Missing	0	0	4	4
	Imatinib	50 (78.1%)	31 (73.8%)	24 (82.8%)	105 (77.8%)

Variables		2L (N=64)	3L (N=42)	4L+ (N=33)	Total (N=139)
	Dasatinib	7 (10.9%)	2 (4.8%)	3 (10.3%)	12 (8.9%)
	Nilotinib	7 (10.9%)	9 (21.4%)	1 (3.4%)	17 (12.6%)
	Ponatinib	0 (0%)	0 (0%)	1 (3.4%)	1 (0.7%)
Best hematological response in 1st line	Missing	0	3	4	7
	Complete	59 (92.2%)	39 (100%)	26 (89.7%)	124 (93.9%)
	Partial	2 (3.1%)	0 (0%)	0 (0%)	2 (1.5%)
	No response	2 (3.1%)	0 (0%)	0 (0%)	2 (1.5%)
	Unknown / Not evaluated	1 (1.6%)	0 (0%)	3 (10.3%)	4 (3%)
Best cytogenetic response in 1st line	Missing	6	5	6	17
	Complete	44 (75.9%)	28 (75.7%)	17 (63%)	89 (73%)
	Partial	7 (12.1%)	3 (8.1%)	4 (14.8%)	14 (11.5%)
	Major	0 (0%)	0 (0%)	1 (3.7%)	1 (0.8%)
	Minor	1 (1.7%)	1 (2.7%)	1 (3.7%)	3 (2.5%)
	No response	0 (0%)	2 (5.4%)	0 (0%)	2 (1.6%)
	Unknown / Not evaluated	6 (10.3%)	3 (8.1%)	4 (14.8%)	13 (10.7%)
Best molecular response in 1st line	Missing	10	9	11	30
	Major: MR3	12 (22.2%)	6 (18.2%)	7 (31.8%)	25 (22.9%)
	MR4	5 (9.3%)	4 (12.1%)	1 (4.5%)	10 (9.2%)
	MR4.5	4 (7.4%)	1 (3%)	0 (0%)	5 (4.6%)

Variables		2L (N=64)	3L (N=42)	4L+ (N=33)	Total (N=139)
	MR5	9 (16.7%)	6 (18.2%)	3 (13.6%)	18 (16.5%)
	No response	20 (37%)	16 (48.5%)	7 (31.8%)	43 (39.4%)
	Unknown / Not evaluated	4 (7.4%)	0 (0%)	4 (18.2%)	8 (7.3%)
Reason for change of line in 1st line	Missing	0	0	4	4
	Lack of response	2 (3.1%)	2 (4.8%)	2 (6.9%)	6 (4.4%)
	Loss of response	10 (15.6%)	2 (4.8%)	6 (20.7%)	18 (13.3%)
	Suboptimum response	14 (21.9%)	15 (35.7%)	7 (24.1%)	36 (26.7%)
	Disease progression (change of phase)	0 (0%)	1 (2.4%)	0 (0%)	1 (0.7%)
	Intolerance	33 (51.6%)	21 (50%)	13 (44.8%)	67 (49.6%)
	Other, specify	5 (7.8%)	1 (2.4%)	1 (3.4%)	7 (5.2%)
Therapy in 2nd line	Missing		0	1	1
	Imatinib		6 (14.3%)	6 (18.8%)	12 (16.2%)
	Dasatinib		27 (64.3%)	12 (37.5%)	39 (52.7%)
	Nilotinib		9 (21.4%)	14 (43.8%)	23 (31.1%)
Best hematological response in 2nd line	Missing		1	1	2
	Complete		41 (100%)	32 (100%)	73 (100%)
Best cytogenetic response in 2nd line	Missing		4	3	7
	Complete		34 (89.5%)	24 (80%)	58 (85.3%)

Variables		2L (N=64)	3L (N=42)	4L+ (N=33)	Total (N=139)
	Partial		2 (5.3%)	2 (6.7%)	4 (5.9%)
	Minor		0 (0%)	2 (6.7%)	2 (2.9%)
	Unknown / Not evaluated		2 (5.3%)	2 (6.7%)	4 (5.9%)
Best molecular response in 2nd line	Missing		3	5	8
	Major: MR3		10 (25.6%)	10 (35.7%)	20 (29.9%)
	MR4		8 (20.5%)	2 (7.1%)	10 (14.9%)
	MR4.5		5 (12.8%)	4 (14.3%)	9 (13.4%)
	MR5		13 (33.3%)	6 (21.4%)	19 (28.4%)
	No response		3 (7.7%)	4 (14.3%)	7 (10.4%)
	Unknown / Not evaluated		0 (0%)	2 (7.1%)	2 (3%)
Reason for change of line in 2nd line	Missing		0	1	1
	Lack of response		2 (4.8%)	0 (0%)	2 (2.7%)
	Loss of response		4 (9.5%)	4 (12.5%)	8 (10.8%)
	Suboptimum response		4 (9.5%)	3 (9.4%)	7 (9.5%)
	Intolerance		32 (76.2%)	22 (68.8%)	54 (73%)
	Other, specify		0 (0%)	3 (9.4%)	3 (4.1%)
Therapy in 3rd line	Imatinib			10 (30.3%)	10 (30.3%)
	Dasatinib			14 (42.4%)	14 (42.4%)
	Nilotinib			8 (24.2%)	8 (24.2%)

Variables		2L (N=64)	3L (N=42)	4L+ (N=33)	Total (N=139)
	Ponatinib			1 (3%)	1 (3%)
Best hematological response in 3rd line	Missing			1	1
	Complete			30 (93.8%)	30 (93.8%)
	Partial			1 (3.1%)	1 (3.1%)
	No response			1 (3.1%)	1 (3.1%)
Best cytogenetic response in 3rd line	Missing			2	2
	Complete			23 (74.2%)	23 (74.2%)
	Partial			1 (3.2%)	1 (3.2%)
	No response			3 (9.7%)	3 (9.7%)
	Unknown / Not evaluated			4 (12.9%)	4 (12.9%)
Best molecular response in 3rd line	Missing			2	2
	Major: MR3			7 (22.6%)	7 (22.6%)
	MR4			3 (9.7%)	3 (9.7%)
	MR4.5			4 (12.9%)	4 (12.9%)
	MR5			8 (25.8%)	8 (25.8%)
	No response			7 (22.6%)	7 (22.6%)
	Unknown / Not evaluated			2 (6.5%)	2 (6.5%)
Reason for change of line in 3rd line	Lack of response			3 (9.1%)	3 (9.1%)

Variables		2L (N=64)	3L (N=42)	4L+ (N=33)	Total (N=139)
	Loss of response			5 (15.2%)	5 (15.2%)
	Suboptimum response			3 (9.1%)	3 (9.1%)
	Intolerance			22 (66.7%)	22 (66.7%)
Therapy in 4st line	Imatinib			1 (9.1%)	1 (9.1%)
	Dasatinib			4 (36.4%)	4 (36.4%)
	Nilotinib			4 (36.4%)	4 (36.4%)
	Ponatinib			2 (18.2%)	2 (18.2%)
Best hematological response in 4st line	Complete			10 (90.9%)	10 (90.9%)
	No response			1 (9.1%)	1 (9.1%)
Best cytogenetic response in 4st line	Missing			1	1
	Complete			7 (70%)	7 (70%)
	Unknown / Not evaluated			3 (30%)	3 (30%)
Best molecular response in 4st line	Major: MR3			5 (45.5%)	5 (45.5%)
	MR4			2 (18.2%)	2 (18.2%)
	MR5			1 (9.1%)	1 (9.1%)
	No response			2 (18.2%)	2 (18.2%)
	Unknown / Not evaluated			1 (9.1%)	1 (9.1%)

Variables		2L (N=64)	3L (N=42)	4L+ (N=33)	Total (N=139)
Reason for change of line in 4st line	Intolerance			10 (90.9%)	10 (90.9%)
	Other, specify			1 (9.1%)	1 (9.1%)
Therapy in 5st line	Imatinib			3 (100%)	3 (100%)
Best hematological response in 5st line	Complete			2 (66.7%)	2 (66.7%)
	No response			1 (33.3%)	1 (33.3%)
Best cytogenetic response in 5st line	Missing			1	1
	No response			1 (50%)	1 (50%)
	Unknown / Not evaluated			1 (50%)	1 (50%)
Best molecular response in 5st line	No response			2 (66.7%)	2 (66.7%)
	Unknown / Not evaluated			1 (33.3%)	1 (33.3%)
Reason for change of line in 5st line	Lack of response			1 (33.3%)	1 (33.3%)
	Intolerance			1 (33.3%)	1 (33.3%)
	Other, specify			1 (33.3%)	1 (33.3%)
Therapy in 6st line	Ponatinib			1 (100%)	1 (100%)
Best hematological response in 6st line	Complete			1 (100%)	1 (100%)

Variables		2L (N=64)	3L (N=42)	4L+ (N=33)	Total (N=139)
Best cytogenetic response in 6st line	Minor			1 (100%)	1 (100%)
Best molecular response in 6st line	No response			1 (100%)	1 (100%)
Reason for change of line in 6st line	Loss of response			1 (100%)	1 (100%)

Table 15.1.2b Medical History : previous TKI therapies - FAS (n=139)

10.2.2.3. Antecedent and comorbidities

Overall, concomitant medication was reported in 98.6% of patients who takes on average 12.8 ± 10.9 medications (see **Appendix 7.5** for concomitant drug treatment for the SAF population details) and was associated with a mean of 9.4 ± 6.1 antecedent or comorbidities. Vascular disorders, metabolism and nutrition disorder as well as musculoskeletal and connective tissue disorders were the prevailing antecedent and comorbidities (> 50%) see **Table 12** for more details.

Table 12: Medical History : antecedent and comorbidities - FAS (n=139)

SOC Name and PT Name		Total N=139 n	n(%) patients
ALL		**1312**	**137 (98.6%)**
Vascular disorders	**ALL**	**133**	**89 (64%)**
	Hypertension	76	75 (54%)
	Peripheral arterial occlusive disease	24	24 (17.3%)
	Arteriosclerosis	6	6 (4.3%)
	Peripheral venous disease	5	5 (3.6%)
	Phlebitis	5	5 (3.6%)
	Aortic aneurysm	3	3 (2.2%)
	Infarction	2	2 (1.4%)
	Raynaud's phenomenon	2	2 (1.4%)

SOC Name and PT Name		Total N=139 n	Total N=139 n(%) patients
	Angiodysplasia	1	1 (0.7%)
	Aortic arteriosclerosis	1	1 (0.7%)
	Arteritis	1	1 (0.7%)
	Deep vein thrombosis	1	1 (0.7%)
	Extremity necrosis	1	1 (0.7%)
	Hot flush	1	1 (0.7%)
	Hypotension	1	1 (0.7%)
	Intermittent claudication	1	1 (0.7%)
	Pallor	1	1 (0.7%)
	Varicose vein	1	1 (0.7%)
Metabolism and nutrition disorders	**ALL**	**123**	**80 (57.6%)**
	Diabetes mellitus	31	31 (22.3%)
	Dyslipidaemia	26	26 (18.7%)
	Hypercholesterolaemia	23	23 (16.5%)
	Obesity	13	13 (9.4%)
	Gout	7	7 (5%)
	Overweight	5	5 (3.6%)
	Decreased appetite	4	4 (2.9%)
	Hyperkalaemia	4	4 (2.9%)
	Hyperuricaemia	3	3 (2.2%)
	Iron deficiency	3	3 (2.2%)

SOC Name and PT Name		Total N=139 n	Total N=139 n(%) patients
	Dehydration	1	1 (0.7%)
	Diabetes mellitus inadequate control	1	1 (0.7%)
	Fluid retention	1	1 (0.7%)
	Type 2 diabetes mellitus	1	1 (0.7%)
Musculoskeletal and connective tissue disorders	**ALL**	**118**	**74 (53.2%)**
	Osteoarthritis	20	20 (14.4%)
	Back pain	15	14 (10.1%)
	Intervertebral disc protrusion	12	12 (8.6%)
	Arthralgia	9	8 (5.8%)
	Muscle spasms	9	9 (6.5%)
	Myalgia	6	6 (4.3%)
	Osteoporosis	5	5 (3.6%)
	Pain in extremity	5	4 (2.9%)
	Musculoskeletal pain	3	3 (2.2%)
	Rotator cuff syndrome	3	3 (2.2%)
	Spinal osteoarthritis	3	3 (2.2%)
	Intervertebral disc degeneration	2	2 (1.4%)
	Intervertebral disc disorder	2	2 (1.4%)
	Lumbar spinal stenosis	2	2 (1.4%)
	Osteitis	2	2 (1.4%)
	Osteopenia	2	2 (1.4%)

SOC Name and PT Name		Total N=139 n	n(%) patients
	Polymyalgia rheumatica	2	2 (1.4%)
	Tendon disorder	2	2 (1.4%)
	Tendonitis	2	2 (1.4%)
	Bone pain	1	1 (0.7%)
	Chondrocalcinosis	1	1 (0.7%)
	Dupuytren's contracture	1	1 (0.7%)
	Fibromyalgia	1	1 (0.7%)
	Foot deformity	1	1 (0.7%)
	Joint lock	1	1 (0.7%)
	Muscle necrosis	1	1 (0.7%)
	Polyarthritis	1	1 (0.7%)
	Rheumatic disorder	1	1 (0.7%)
	Scoliosis	1	1 (0.7%)
	Synovial cyst	1	1 (0.7%)
	Vertebral column mass	1	1 (0.7%)
Surgical and medical procedures	**ALL**	**113**	**65 (46.8%)**
	Appendicectomy	13	13 (9.4%)
	Cholecystectomy	10	10 (7.2%)
	Hip arthroplasty	9	8 (5.8%)
	Hysterectomy	9	9 (6.5%)
	Carpal tunnel decompression	5	5 (3.6%)

SOC Name and PT Name		Total N=139	
		n	n(%) patients
	Cataract operation	5	5 (3.6%)
	Thyroidectomy	5	5 (3.6%)
	Amygdalotomy	4	4 (2.9%)
	Knee arthroplasty	4	4 (2.9%)
	Angioplasty	3	3 (2.2%)
	Caesarean section	3	3 (2.2%)
	Incisional hernia repair	3	3 (2.2%)
	Phlebectomy	3	3 (2.2%)
	Carotid endarterectomy	2	2 (1.4%)
	Cervical conisation	2	2 (1.4%)
	Haemorrhoid operation	2	2 (1.4%)
	Hernia repair	2	2 (1.4%)
	Large intestinal polypectomy	2	2 (1.4%)
	Peripheral artery bypass	2	2 (1.4%)
	Prostatectomy	2	2 (1.4%)
	Abdominal wall operation	1	1 (0.7%)
	Adenoidectomy	1	1 (0.7%)
	Breast cyst excision	1	1 (0.7%)
	Coronary angioplasty	1	1 (0.7%)
	Coronary artery bypass	1	1 (0.7%)
	Female sterilisation	1	1 (0.7%)

SOC Name and PT Name		Total N=139	
		n	n(%) patients
	Finger amputation	1	1 (0.7%)
	Foot operation	1	1 (0.7%)
	Hysterosalpingo-oophorectomy	1	1 (0.7%)
	Leg amputation	1	1 (0.7%)
	Lipoma excision	1	1 (0.7%)
	Meniscus removal	1	1 (0.7%)
	Mitral valve repair	1	1 (0.7%)
	Peripheral artery angioplasty	1	1 (0.7%)
	Rotator cuff repair	1	1 (0.7%)
	Shoulder arthroplasty	1	1 (0.7%)
	Sigmoidectomy	1	1 (0.7%)
	Spinal fusion surgery	1	1 (0.7%)
	Spinal operation	1	1 (0.7%)
	Strabismus correction	1	1 (0.7%)
	Urinary incontinence surgery	1	1 (0.7%)
	Varicose vein operation	1	1 (0.7%)
	Vascular graft	1	1 (0.7%)
Respiratory, thoracic and mediastinal disorders	**ALL**	**96**	**61 (43.9%)**
	Pleural effusion	21	21 (15.1%)
	Sleep apnoea syndrome	12	12 (8.6%)
	Dyspnoea	10	10 (7.2%)

SOC Name and PT Name		Total N=139 n	Total N=139 n(%) patients
	Asthma	7	6 (4.3%)
	Chronic obstructive pulmonary disease	7	7 (5%)
	Pulmonary embolism	6	6 (4.3%)
	Dyspnoea exertional	5	5 (3.6%)
	Pulmonary hypertension	4	4 (2.9%)
	Rhinitis allergic	4	4 (2.9%)
	Cough	2	2 (1.4%)
	Obstructive airways disorder	2	2 (1.4%)
	Pulmonary mass	2	2 (1.4%)
	Acute pulmonary oedema	1	1 (0.7%)
	Bronchial obstruction	1	1 (0.7%)
	Bronchiectasis	1	1 (0.7%)
	Bronchitis chronic	1	1 (0.7%)
	Emphysema	1	1 (0.7%)
	Interstitial lung disease	1	1 (0.7%)
	Lung disorder	1	1 (0.7%)
	Oropharyngeal discomfort	1	1 (0.7%)
	Pharyngeal oedema	1	1 (0.7%)
	Pulmonary arterial hypertension	1	1 (0.7%)
	Pulmonary sarcoidosis	1	1 (0.7%)
	Respiratory failure	1	1 (0.7%)

SOC Name and PT Name		Total N=139 n	Total N=139 n(%) patients
	Snoring	1	1 (0.7%)
	Widal syndrome	1	1 (0.7%)
Gastrointestinal disorders	**ALL**	**95**	**64 (46%)**
	Gastrooesophageal reflux disease	14	14 (10.1%)
	Inguinal hernia	9	9 (6.5%)
	Diarrhoea	8	8 (5.8%)
	Abdominal pain upper	5	5 (3.6%)
	Chronic gastritis	4	4 (2.9%)
	Constipation	4	4 (2.9%)
	Abdominal pain	3	3 (2.2%)
	Gastritis	3	3 (2.2%)
	Gastrointestinal disorder	3	3 (2.2%)
	Haemorrhoids	3	3 (2.2%)
	Hiatus hernia	3	3 (2.2%)
	Nausea	3	3 (2.2%)
	Barrett's oesophagus	2	2 (1.4%)
	Gastric ulcer	2	2 (1.4%)
	Intestinal polyp	2	2 (1.4%)
	Oesophagitis	2	2 (1.4%)
	Pancreatitis acute	2	2 (1.4%)
	Salivary gland calculus	2	2 (1.4%)

SOC Name and PT Name		Total N=139 n	n(%) patients
	Vomiting	2	2 (1.4%)
	Abdominal hernia	1	1 (0.7%)
	Aphthous stomatitis	1	1 (0.7%)
	Colitis	1	1 (0.7%)
	Colonic fistula	1	1 (0.7%)
	Diverticulum	1	1 (0.7%)
	Diverticulum intestinal	1	1 (0.7%)
	Dyspepsia	1	1 (0.7%)
	Dysphagia	1	1 (0.7%)
	Functional gastrointestinal disorder	1	1 (0.7%)
	Gastrointestinal haemorrhage	1	1 (0.7%)
	Gingival recession	1	1 (0.7%)
	Haematochezia	1	1 (0.7%)
	Intestinal ulcer	1	1 (0.7%)
	Large intestine polyp	1	1 (0.7%)
	Oesophageal achalasia	1	1 (0.7%)
	Pancreatitis	1	1 (0.7%)
	Pancreatitis chronic	1	1 (0.7%)
	Tooth impacted	1	1 (0.7%)
	Umbilical hernia	1	1 (0.7%)
Nervous system disorders	**ALL**	**75**	**47 (33.8%)**

SOC Name and PT Name		Total N=139	
		n	n(%) patients
	Sciatica	9	6 (4.3%)
	Thrombotic stroke	9	9 (6.5%)
	Carotid arteriosclerosis	4	4 (2.9%)
	Cerebrovascular accident	4	4 (2.9%)
	Dizziness	4	4 (2.9%)
	Migraine	4	4 (2.9%)
	Epilepsy	3	3 (2.2%)
	Paraesthesia	3	3 (2.2%)
	Carotid artery stenosis	2	2 (1.4%)
	Carpal tunnel syndrome	2	2 (1.4%)
	Cervicobrachial syndrome	2	2 (1.4%)
	Headache	2	2 (1.4%)
	Neuropathy peripheral	2	2 (1.4%)
	Tremor	2	2 (1.4%)
	Ageusia	1	1 (0.7%)
	Axonal neuropathy	1	1 (0.7%)
	Balance disorder	1	1 (0.7%)
	Cognitive disorder	1	1 (0.7%)
	Complex regional pain syndrome	1	1 (0.7%)
	Convulsion in childhood	1	1 (0.7%)
	Cubital tunnel syndrome	1	1 (0.7%)

SOC Name and PT Name		Total N=139 n	Total N=139 n(%) patients
	Diabetic neuropathy	1	1 (0.7%)
	Disturbance in attention	1	1 (0.7%)
	Dysgeusia	1	1 (0.7%)
	Guillain-Barre syndrome	1	1 (0.7%)
	Language disorder	1	1 (0.7%)
	Memory impairment	1	1 (0.7%)
	Migraine with aura	1	1 (0.7%)
	Occipital neuralgia	1	1 (0.7%)
	Parkinson's disease	1	1 (0.7%)
	Peripheral sensory neuropathy	1	1 (0.7%)
	Petit mal epilepsy	1	1 (0.7%)
	Quadriplegia	1	1 (0.7%)
	Radicular pain	1	1 (0.7%)
	Seizure	1	1 (0.7%)
	Status epilepticus	1	1 (0.7%)
	Tension headache	1	1 (0.7%)
Cardiac disorders	**ALL**	**60**	**42 (30.2%)**
	Atrial fibrillation	9	9 (6.5%)
	Cardiac failure	8	5 (3.6%)
	Myocardial ischaemia	6	6 (4.3%)
	Coronary artery disease	5	5 (3.6%)

SOC Name and PT Name		Total N=139	
		n	n(%) patients
	Angina pectoris	3	3 (2.2%)
	Myocardial infarction	3	3 (2.2%)
	Pericardial effusion	3	3 (2.2%)
	Pericarditis	3	3 (2.2%)
	Tachycardia	3	3 (2.2%)
	Acute coronary syndrome	1	1 (0.7%)
	Arrhythmia	1	1 (0.7%)
	Arrhythmia supraventricular	1	1 (0.7%)
	Atrial flutter	1	1 (0.7%)
	Atrial tachycardia	1	1 (0.7%)
	Bundle branch block left	1	1 (0.7%)
	Cardiac disorder	1	1 (0.7%)
	Cardiac hypertrophy	1	1 (0.7%)
	Congestive cardiomyopathy	1	1 (0.7%)
	Coronary artery insufficiency	1	1 (0.7%)
	Coronary artery stenosis	1	1 (0.7%)
	Extrasystoles	1	1 (0.7%)
	Left ventricular failure	1	1 (0.7%)
	Mitral valve incompetence	1	1 (0.7%)
	Pleuropericarditis	1	1 (0.7%)
	Supraventricular extrasystoles	1	1 (0.7%)

SOC Name and PT Name		Total N=139 n	Total N=139 n(%) patients
	Wolff-Parkinson-White syndrome	1	1 (0.7%)
Infections and infestations	**ALL**	**54**	**42 (30.2%)**
	Hepatitis B	5	5 (3.6%)
	Urinary tract infection	4	4 (2.9%)
	Appendicitis	2	2 (1.4%)
	Bronchitis	2	2 (1.4%)
	Diverticulitis	2	2 (1.4%)
	Hepatitis C	2	2 (1.4%)
	Herpes zoster	2	2 (1.4%)
	Peritonitis	2	2 (1.4%)
	Skin infection	2	2 (1.4%)
	Tuberculosis	2	2 (1.4%)
	Vestibular neuronitis	2	2 (1.4%)
	Arthritis infective	1	1 (0.7%)
	Chronic sinusitis	1	1 (0.7%)
	Cystitis	1	1 (0.7%)
	Cytomegalovirus infection	1	1 (0.7%)
	Encephalitis viral	1	1 (0.7%)
	Folliculitis	1	1 (0.7%)
	Fungal infection	1	1 (0.7%)
	Helicobacter gastritis	1	1 (0.7%)

SOC Name and PT Name		Total N=139 n	Total N=139 n(%) patients
	Infection	1	1 (0.7%)
	Legionella infection	1	1 (0.7%)
	Meningitis	1	1 (0.7%)
	Myelitis	1	1 (0.7%)
	Necrotising ulcerative gingivostomatitis	1	1 (0.7%)
	Orchitis	1	1 (0.7%)
	Pilonidal cyst	1	1 (0.7%)
	Pneumocystis jirovecii pneumonia	1	1 (0.7%)
	Pneumonia pneumococcal	1	1 (0.7%)
	Prostatitis Escherichia coli	1	1 (0.7%)
	Pseudomembranous colitis	1	1 (0.7%)
	Pulmonary tuberculosis	1	1 (0.7%)
	Pyelonephritis	1	1 (0.7%)
	Sepsis	1	1 (0.7%)
	Sialoadenitis	1	1 (0.7%)
	Sinusitis	1	1 (0.7%)
	Staphylococcal infection	1	1 (0.7%)
	Tooth abscess	1	1 (0.7%)
	Vaginal infection	1	1 (0.7%)
Renal and urinary disorders	**ALL**	**54**	**43 (30.9%)**
	Renal disorder	19	18 (12.9%)

SOC Name and PT Name		Total N=139	
		n	n(%) patients
	Renal colic	9	9 (6.5%)
	Renal failure	7	7 (5%)
	Chronic kidney disease	4	4 (2.9%)
	Nephrolithiasis	3	3 (2.2%)
	Renal cyst	2	2 (1.4%)
	Urinary incontinence	2	2 (1.4%)
	Urinary tract disorder	2	2 (1.4%)
	Calculus urinary	1	1 (0.7%)
	Nocturia	1	1 (0.7%)
	Polyuria	1	1 (0.7%)
	Renal artery stenosis	1	1 (0.7%)
	Urinary bladder polyp	1	1 (0.7%)
	Urogenital fistula	1	1 (0.7%)
General disorders and administration site conditions	**ALL**	**48**	**36 (25.9%)**
	Fatigue	15	15 (10.8%)
	Oedema	10	9 (6.5%)
	Asthenia	7	7 (5%)
	Drug intolerance	6	3 (2.2%)
	Gait disturbance	2	2 (1.4%)
	Pain	2	2 (1.4%)
	Generalised oedema	1	1 (0.7%)

SOC Name and PT Name		Total N=139	
		n	n(%) patients
	Hernia	1	1 (0.7%)
	Ill-defined disorder	1	1 (0.7%)
	Oedema peripheral	1	1 (0.7%)
	Polyp	1	1 (0.7%)
	Strangulated hernia	1	1 (0.7%)
Immune system disorders	**ALL**	**45**	**31 (22.3%)**
	Drug hypersensitivity	28	22 (15.8%)
	Iodine allergy	4	4 (2.9%)
	Seasonal allergy	4	4 (2.9%)
	Allergy to plants	3	3 (2.2%)
	Allergy to animal	2	2 (1.4%)
	Contrast media allergy	1	1 (0.7%)
	Hypogammaglobulinaemia	1	1 (0.7%)
	Multiple allergies	1	1 (0.7%)
	Rubber sensitivity	1	1 (0.7%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**ALL**	**43**	**33 (23.7%)**
	Bladder cancer	3	3 (2.2%)
	Prostate cancer	3	3 (2.2%)
	Thyroid neoplasm	3	3 (2.2%)
	Breast cancer	2	2 (1.4%)
	Lipoma	2	2 (1.4%)

SOC Name and PT Name		Total N=139	
		n	n(%) patients
	Malignant melanoma	2	2 (1.4%)
	Meningioma	2	2 (1.4%)
	Prostatic adenoma	2	2 (1.4%)
	Squamous cell carcinoma	2	2 (1.4%)
	Uterine leiomyoma	2	2 (1.4%)
	Adenocarcinoma pancreas	1	1 (0.7%)
	Adrenal adenoma	1	1 (0.7%)
	Basal cell carcinoma	1	1 (0.7%)
	Carcinoid tumour	1	1 (0.7%)
	Chronic lymphocytic leukaemia	1	1 (0.7%)
	Colon adenoma	1	1 (0.7%)
	Colon cancer	1	1 (0.7%)
	Fibroadenoma of breast	1	1 (0.7%)
	Fibroma	1	1 (0.7%)
	Haemangioma	1	1 (0.7%)
	Hepatic cancer	1	1 (0.7%)
	Hodgkin's disease	1	1 (0.7%)
	Medullary thyroid cancer	1	1 (0.7%)
	Metastases to liver	1	1 (0.7%)
	Metastatic bronchial carcinoma	1	1 (0.7%)
	Papillary thyroid cancer	1	1 (0.7%)

SOC Name and PT Name		Total N=139	
		n	n(%) patients
	Rectal adenocarcinoma	1	1 (0.7%)
	Rectal cancer	1	1 (0.7%)
	Skin papilloma	1	1 (0.7%)
	Thyroid cancer	1	1 (0.7%)
Injury, poisoning and procedural complications	**ALL**	**41**	**29 (20.9%)**
	Joint dislocation	3	3 (2.2%)
	Lumbar vertebral fracture	3	3 (2.2%)
	Tendon rupture	3	3 (2.2%)
	Clavicle fracture	2	2 (1.4%)
	Epicondylitis	2	2 (1.4%)
	Lower limb fracture	2	2 (1.4%)
	Tibia fracture	2	2 (1.4%)
	Upper limb fracture	2	2 (1.4%)
	Wrist fracture	2	2 (1.4%)
	Ankle fracture	1	1 (0.7%)
	Arteriovenous fistula occlusion	1	1 (0.7%)
	Eschar	1	1 (0.7%)
	Femur fracture	1	1 (0.7%)
	Foot fracture	1	1 (0.7%)
	Humerus fracture	1	1 (0.7%)
	Ligament rupture	1	1 (0.7%)

SOC Name and PT Name		Total N=139	
		n	n(%) patients
	Ligament sprain	1	1 (0.7%)
	Limb traumatic amputation	1	1 (0.7%)
	Multiple fractures	1	1 (0.7%)
	Muscle rupture	1	1 (0.7%)
	Patella fracture	1	1 (0.7%)
	Post-traumatic pain	1	1 (0.7%)
	Procedural pain	1	1 (0.7%)
	Spinal compression fracture	1	1 (0.7%)
	Spinal fracture	1	1 (0.7%)
	Splinter	1	1 (0.7%)
	Tooth avulsion	1	1 (0.7%)
	Toxicity to various agents	1	1 (0.7%)
	Ulnar nerve injury	1	1 (0.7%)
Skin and subcutaneous tissue disorders	**ALL**	**37**	**31 (22.3%)**
	Dry skin	5	5 (3.6%)
	Pruritus	5	5 (3.6%)
	Eczema	3	3 (2.2%)
	Skin ulcer	3	2 (1.4%)
	Alopecia	2	2 (1.4%)
	Psoriasis	2	2 (1.4%)
	Rash	2	2 (1.4%)

SOC Name and PT Name		Total N=139	
		n	n(%) patients
	Angioedema	1	1 (0.7%)
	Dermal cyst	1	1 (0.7%)
	Dermatitis	1	1 (0.7%)
	Dermatitis acneiform	1	1 (0.7%)
	Dermatitis bullous	1	1 (0.7%)
	Diffuse alopecia	1	1 (0.7%)
	Ecchymosis	1	1 (0.7%)
	Eczema infantile	1	1 (0.7%)
	Hyperhidrosis	1	1 (0.7%)
	Night sweats	1	1 (0.7%)
	Pemphigoid	1	1 (0.7%)
	Skin oedema	1	1 (0.7%)
	Skin striae	1	1 (0.7%)
	Stasis dermatitis	1	1 (0.7%)
	Vitiligo	1	1 (0.7%)
Psychiatric disorders	**ALL**	**35**	**28 (20.1%)**
	Depression	11	11 (7.9%)
	Anxiety	5	5 (3.6%)
	Alcoholism	4	4 (2.9%)
	Insomnia	4	4 (2.9%)
	Sleep disorder	3	3 (2.2%)

SOC Name and PT Name		Total N=139	
		n	n(%) patients
	Affective disorder	2	2 (1.4%)
	Depressed mood	2	2 (1.4%)
	Bipolar disorder	1	1 (0.7%)
	Bruxism	1	1 (0.7%)
	Polydipsia psychogenic	1	1 (0.7%)
	Poor quality sleep	1	1 (0.7%)
Endocrine disorders	**ALL**	**33**	**29 (20.9%)**
	Hypothyroidism	18	18 (12.9%)
	Goitre	5	5 (3.6%)
	Hyperthyroidism	2	2 (1.4%)
	Hypogonadism	2	2 (1.4%)
	Hypopituitarism	2	2 (1.4%)
	Autoimmune thyroiditis	1	1 (0.7%)
	Cushingoid	1	1 (0.7%)
	Hypercorticisme	1	1 (0.7%)
	Inappropriate antidiuretic hormone secretion	1	1 (0.7%)
Eye disorders	**ALL**	**29**	**21 (15.1%)**
	Cataract	4	4 (2.9%)
	Diabetic retinopathy	4	3 (2.2%)
	Blindness unilateral	2	2 (1.4%)
	Eye disorder	2	2 (1.4%)

SOC Name and PT Name		Total N=139 n	n(%) patients
	Eyelid oedema	2	2 (1.4%)
	Glaucoma	2	2 (1.4%)
	Age-related macular degeneration	1	1 (0.7%)
	Conjunctivitis allergic	1	1 (0.7%)
	Eye movement disorder	1	1 (0.7%)
	Eyelid retraction	1	1 (0.7%)
	Keratitis	1	1 (0.7%)
	Myopia	1	1 (0.7%)
	Periorbital oedema	1	1 (0.7%)
	Retinal detachment	1	1 (0.7%)
	Retinal haemorrhage	1	1 (0.7%)
	Retinal tear	1	1 (0.7%)
	Retinal vein occlusion	1	1 (0.7%)
	Retinopathy	1	1 (0.7%)
	Visual acuity reduced	1	1 (0.7%)
Reproductive system and breast disorders	**ALL**	**21**	**20 (14.4%)**
	Benign prostatic hyperplasia	7	7 (5%)
	Endometriosis	4	4 (2.9%)
	Erectile dysfunction	4	4 (2.9%)
	Breast pain	1	1 (0.7%)
	Genital haemorrhage	1	1 (0.7%)

SOC Name and PT Name		Total N=139 n	Total N=139 n(%) patients
	Testicular torsion	1	1 (0.7%)
	Uterine polyp	1	1 (0.7%)
	Varicocele	1	1 (0.7%)
	Varicose veins pelvic	1	1 (0.7%)
Blood and lymphatic system disorders	**ALL**	**17**	**16 (11.5%)**
	Anaemia	5	5 (3.6%)
	Iron deficiency anaemia	3	3 (2.2%)
	Lymphadenitis	2	2 (1.4%)
	Splenomegaly	2	2 (1.4%)
	Eosinophilia	1	1 (0.7%)
	Immune thrombopenic purpura	1	1 (0.7%)
	Neutropenia	1	1 (0.7%)
	Splenic infarction	1	1 (0.7%)
	Thrombocytopenia	1	1 (0.7%)
Hepatobiliary disorders	**ALL**	**17**	**15 (10.8%)**
	Cholestasis	3	2 (1.4%)
	Liver disorder	3	3 (2.2%)
	Cholelithiasis	2	2 (1.4%)
	Hepatocellular injury	2	2 (1.4%)
	Cholangitis	1	1 (0.7%)
	Cholecystitis	1	1 (0.7%)

SOC Name and PT Name		Total N=139	
		n	n(%) patients
	Cirrhosis alcoholic	1	1 (0.7%)
	Gallbladder polyp	1	1 (0.7%)
	Hepatic function abnormal	1	1 (0.7%)
	Hepatic steatosis	1	1 (0.7%)
	Hyperbilirubinaemia	1	1 (0.7%)
Congenital, familial and genetic disorders	**ALL**	**8**	**6 (4.3%)**
	Coarctation of the aorta	1	1 (0.7%)
	Congenital gastric anomaly	1	1 (0.7%)
	Dolichocolon	1	1 (0.7%)
	Factor IX deficiency	1	1 (0.7%)
	Heart disease congenital	1	1 (0.7%)
	Hypospadias	1	1 (0.7%)
	Phimosis	1	1 (0.7%)
	Von Willebrand's disease	1	1 (0.7%)
Investigations	**ALL**	**5**	**5 (3.6%)**
	Weight increased	3	3 (2.2%)
	Blood creatinine increased	1	1 (0.7%)
	Cardiac murmur	1	1 (0.7%)
Ear and labyrinth disorders	**ALL**	**4**	**4 (2.9%)**
	Deafness unilateral	1	1 (0.7%)
	Ear pain	1	1 (0.7%)

SOC Name and PT Name		Total N=139	
		n	n(%) patients
	Presbyacusis	1	1 (0.7%)
	Tinnitus	1	1 (0.7%)
Pregnancy, puerperium and perinatal conditions	**ALL**	**4**	**4 (2.9%)**
	Abortion spontaneous	1	1 (0.7%)
	Ectopic pregnancy	1	1 (0.7%)
	Pregnancy	1	1 (0.7%)
	Retroplacental haematoma	1	1 (0.7%)
Social circumstances	**ALL**	**4**	**4 (2.9%)**
	Tobacco user	2	2 (1.4%)
	Contraindication to medical treatment	1	1 (0.7%)
	Menopause	1	1 (0.7%)

Table 15.1.2c Medical History : antecedent and comorbidities - FAS (n=139)

10.3. Outcome data

The efficacy outcomes were described for the 139 patients from the FAS population overall, and according to the line of treatment.

The safety outcomes were described for the 142 patients from the safety population overall, and according to the line of treatment.

10.4. Main results

10.4.1. Safety primary analysis

10.4.1.1. AE related to bosutinib

Regarding safety analysis, a total of 141 patients among the 142 patients of the SAF population experienced at least one AE. In more details, 65 (98.5%) patients in the 2L group, and all the patients from the 3L group and 4L+ group. All AEs are summarized in Adverse events / adverse reactions section of this report and full listing for measure taken to prevent AE are presented in **Appendix 7.7**.

Overall, a total of 466 AEs related to bosutinib were recorded in 125 (88%) patients. Regarding the distribution by subgroups, 56 (84.8%) patients in the 2L group, 37 (88.1%) patients in the 3L group and 32 (94.1%) patients in the 4L+ group had at least one AE related to the treatment with bosutinib (Table 13).

The SOC for which most AEs were documented were gastrointestinal disorders, observed in 68.3% of the population, in 46 (69.7%) patients in the 2L group, 30 (71.4%) patients in the 3L group and 21 (61.8%) patients in the 4L+ group; and general disorders and administration site conditions (23.2%), observed in 15 (22.7%) patients in the 2L group, 9 (21.4%) patients in the 3L group and 9 (26.5%) patients in the 4L+ group.

Among the 466 drug-related AEs reported, 398 of them were grade 1-2, 67 were grade 3-4 and one patient had a grade 5 AE.

Considering the more frequent (≥ 10%) grade 1-2 drug-related, the SOC for which the more drug-related AEs were recorded were gastrointestinal disorders observed in 45 (68.2%) patients in the 2L group, 29 (69%) patients in the 3L group and 20 (58.8%) patients in the 4L+ group. General disorders and administration site conditions were also frequent drug-related AEs, observed in 15 (22.7%) patients in the 2L group, 8 (19%) patients in the 3L group and 9 (26.5%) patients in the 4L+ group (Table 14). Additionally, more than 10% of patients reported drug-related AEs belonging to the SOC Skin and subcutaneous tissue disorders (12.7%), Respiratory, thoracic and mediastinal disorders (12.7%) Musculoskeletal and connective tissue disorders (12%) and Nervous system disorders (10.6%).

Regarding bosutinib-related AEs of interest it appears that most frequent were diarrhea (50.7%) and nausea (14.1%), asthenia and fatigue were reported (9.2% and 4.9% respectively) and we also observed several pleural effusions (6.3%) and dyspnea (7.0%).

Considering most frequent (≥ 5%) grade 3-4 drug-related AEs, the SOC for which the more AEs were recorded were hepatobiliary disorders (9.9%), reported in 8 (12.1%) patients in the 2L group, 3 (7.1%) patients in the 3L group and 3 (8.8%) patients in the 4L+ group; and gastrointestinal disorders (7%), reported in 3 (4.5%) patients in the 2L group, 5 (11.9%) patients in the 3L group and 2 (5.9%) patients in the 4L+ group. (Table 15).

Finally, only one patient presented a drug-related pneumonia grade 5 (Table 16). This patient was a men aged 68 years from group 3L. at the end of the study the patient was not recovered, while he started bosutinib the 30-01-2019, he died on the 27-06-2021 due to pneumonia which occurred the 18-06-2021.

Table 13: Adverse Events by System Organ Class and Preferred Term (Treatment Related and all grade) - SAF (n=142)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n event	of n (%) of patients	n event	of n (%) of patients	n event	of n (%) of patients	n event	of n (%) of patients
ALL		**214**	**56 (84.8%)**	**135**	**37 (88.1%)**	**117**	**32 (94.1%)**	**466**	**125 (88%)**
Gastrointestinal disorders	**ALL**	**96**	**46 (69.7%)**	**55**	**30 (71.4%)**	**46**	**21 (61.8%)**	**197**	**97 (68.3%)**
	Diarrhoea	55	37 (56.1%)	26	22 (52.4%)	21	17 (50%)	102	76 (53.5%)
	Nausea	6	6 (9.1%)	10	9 (21.4%)	5	5 (14.7%)	21	20 (14.1%)
	Abdominal pain	8	7 (10.6%)	3	3 (7.1%)	5	5 (14.7%)	16	15 (10.6%)
	Abdominal pain upper	7	7 (10.6%)	4	4 (9.5%)	1	1 (2.9%)	12	12 (8.5%)
	Vomiting	5	5 (7.6%)	4	3 (7.1%)	3	3 (8.8%)	12	11 (7.7%)
	Constipation	2	2 (3%)	1	1 (2.4%)	3	2 (5.9%)	6	5 (3.5%)
	Abdominal distension	1	1 (1.5%)	1	1 (2.4%)	2	1 (2.9%)	4	3 (2.1%)
	Gastrointestinal disorder	2	2 (3%)	1	1 (2.4%)	1	1 (2.9%)	4	4 (2.8%)
	Flatulence	1	1 (1.5%)	1	1 (2.4%)	1	1 (2.9%)	3	3 (2.1%)
	Gastrooesophageal reflux disease	1	1 (1.5%)	-	-	2	2 (5.9%)	3	3 (2.1%)
	Dyspepsia	2	2 (3%)	-	-	-	-	2	2 (1.4%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n event	of n of patients (%)	n event	of n of patients (%)	n event	of n of patients (%)	n event	of n of patients (%)
	Aphthous stomatitis	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Dry mouth	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Eosinophilic colitis	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Eructation	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Faeces soft	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Functional gastrointestinal disorder	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Gingival bleeding	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Haemorrhoids	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Intestinal obstruction	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Melaena	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Pancreatitis acute	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Reflux gastritis	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
General disorders and administration site conditions	**ALL**	**21**	**15 (22.7%)**	**11**	**9 (21.4%)**	**16**	**9 (26.5%)**	**48**	**33 (23.2%)**
	Asthenia	8	7 (10.6%)	3	3 (7.1%)	7	4 (11.8%)	18	14 (9.9%)
	Fatigue	3	3 (4.5%)	2	2 (4.8%)	2	2 (5.9%)	7	7 (4.9%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n event	of n (%) patients	n event	of n (%) patients	n event	of n (%) patients	n event	of n (%) patients
	Drug ineffective	3	3 (4.5%)	1	1 (2.4%)	1	1 (2.9%)	5	5 (3.5%)
	Reduced drug effect	-	-	1	1 (2.4%)	2	1 (2.9%)	3	2 (1.4%)
	Chills	1	1 (1.5%)	-	-	1	1 (2.9%)	2	2 (1.4%)
	Oedema peripheral	1	1 (1.5%)	-	-	1	1 (2.9%)	2	2 (1.4%)
	Therapeutic response decreased	-	-	1	1 (2.4%)	1	1 (2.9%)	2	2 (1.4%)
	Chest pain	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Gait disturbance	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	General physical health deterioration	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Generalised oedema	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Hyperthermia	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Inflammation	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Pain	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Pyrexia	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Treatment noncompliance	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n event	of n of patients (%)	n event	of n of patients (%)	n event	of n of patients (%)	n event	of n of patients (%)
Respiratory, thoracic and mediastinal disorders	**ALL**	**14**	**10 (15.2%)**	**6**	**5 (11.9%)**	**8**	**5 (14.7%)**	**28**	**20 (14.1%)**
	Pleural effusion	8	5 (7.6%)	3	3 (7.1%)	4	4 (11.8%)	15	12 (8.5%)
	Dyspnoea	4	4 (6.1%)	3	3 (7.1%)	3	3 (8.8%)	10	10 (7%)
	Cough	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Dyspnoea exertional	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Lung disorder	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
Hepatobiliary disorders	**ALL**	**14**	**13 (19.7%)**	**7**	**6 (14.3%)**	**5**	**5 (14.7%)**	**26**	**24 (16.9%)**
	Hepatocellular injury	12	12 (18.2%)	7	6 (14.3%)	3	3 (8.8%)	22	21 (14.8%)
	Hepatitis	1	1 (1.5%)	-	-	1	1 (2.9%)	2	2 (1.4%)
	Hepatic pain	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Jaundice cholestatic	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
Investigations	**ALL**	**10**	**5 (7.6%)**	**12**	**9 (21.4%)**	**4**	**3 (8.8%)**	**26**	**17 (12%)**
	Alanine aminotransferase increased	3	2 (3%)	2	2 (4.8%)	1	1 (2.9%)	6	5 (3.5%)

SOC AND PT		2L N=66 n event	of n (%) patients	3L N=42 n event	of n (%) patients	4L+ N=34 n event	of n (%) patients	Total N=142 n event	of n (%) patients
	Aspartate aminotransferase increased	2	1 (1.5%)	2	2 (4.8%)	1	1 (2.9%)	5	4 (2.8%)
	Weight decreased	1	1 (1.5%)	3	3 (7.1%)	-	-	4	4 (2.8%)
	Lipase increased	-	-	2	2 (4.8%)	1	1 (2.9%)	3	3 (2.1%)
	Blood creatinine increased	1	1 (1.5%)	1	1 (2.4%)	-	-	2	2 (1.4%)
	Blood urea increased	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Gamma-glutamyltransferase increased	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Intestinal transit time increased	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Liver function test abnormal	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Transaminases increased	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Troponin increased	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
Skin and subcutaneous tissue disorders	**ALL**	**13**	**10 (15.2%)**	**8**	**5 (11.9%)**	**5**	**3 (8.8%)**	**26**	**18 (12.7%)**
	Rash	3	2 (3%)	4	3 (7.1%)	-	-	7	5 (3.5%)
	Pruritus	2	2 (3%)	1	1 (2.4%)	3	3 (8.8%)	6	6 (4.2%)
	Dry skin	3	3 (4.5%)	-	-	-	-	3	3 (2.1%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n event	of n (%) patients	n event	of n (%) patients	n event	of n (%) patients	n event	of n (%) patients
	Erythema	1	1 (1.5%)	1	1 (2.4%)	-	-	2	2 (1.4%)
	Eczema	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Nail pigmentation	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Psoriasis	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Rash maculo-papular	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Scab	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Skin lesion	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Skin odour abnormal	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Urticaria	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
Musculoskeletal and connective tissue disorders	**ALL**	**12**	**9 (13.6%)**	**7**	**6 (14.3%)**	**4**	**3 (8.8%)**	**23**	**18 (12.7%)**
	Arthralgia	5	4 (6.1%)	2	2 (4.8%)	2	2 (5.9%)	9	8 (5.6%)
	Myalgia	2	2 (3%)	2	1 (2.4%)	1	1 (2.9%)	5	4 (2.8%)
	Muscle spasms	-	-	3	3 (7.1%)	1	1 (2.9%)	4	4 (2.8%)
	Musculoskeletal pain	3	3 (4.5%)	-	-	-	-	3	3 (2.1%)
	Neck pain	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Tendon pain	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n event	of n of patients (%)	n event	of n of patients (%)	n event	of n of patients (%)	n event	of n of patients (%)
Nervous system disorders	**ALL**	**8**	**6 (9.1%)**	**8**	**7 (16.7%)**	**5**	**4 (11.8%)**	**21**	**17 (12%)**
	Headache	4	4 (6.1%)	3	3 (7.1%)	3	3 (8.8%)	10	10 (7%)
	Dizziness	1	1 (1.5%)	2	2 (4.8%)	1	1 (2.9%)	4	4 (2.8%)
	Head discomfort	-	-	2	1 (2.4%)	-	-	2	1 (0.7%)
	Axonal neuropathy	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Disturbance in attention	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Dysgeusia	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Hypersomnia	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Hypoaesthesia	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
Metabolism and nutrition disorders	**ALL**	**6**	**6 (9.1%)**	**5**	**5 (11.9%)**	**3**	**3 (8.8%)**	**14**	**14 (9.9%)**
	Decreased appetite	3	3 (4.5%)	4	4 (9.5%)	-	-	7	7 (4.9%)
	Hypertriglyceridaemia	1	1 (1.5%)	-	-	1	1 (2.9%)	2	2 (1.4%)
	Dyslipidaemia	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Fluid retention	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Hypokalaemia	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n event	of n of patients (%)	n event	of n of patients (%)	n event	of n of patients (%)	n event	of n of patients (%)
	Hyponatraemia	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Malnutrition	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
Cardiac disorders	**ALL**	**3**	**3 (4.5%)**	**5**	**3 (7.1%)**	**5**	**3 (8.8%)**	**13**	**9 (6.3%)**
	Cardiac failure	2	2 (3%)	-	-	2	2 (5.9%)	4	4 (2.8%)
	Pericarditis	-	-	4	3 (7.1%)	-	-	4	3 (2.1%)
	Pericardial effusion	-	-	1	1 (2.4%)	1	1 (2.9%)	2	2 (1.4%)
	Atrial fibrillation	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Palpitations	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Tachyarrhythmia	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
Renal and urinary disorders	**ALL**	**5**	**5 (7.6%)**	**2**	**2 (4.8%)**	**2**	**2 (5.9%)**	**9**	**9 (6.3%)**
	Renal failure	5	5 (7.6%)	-	-	1	1 (2.9%)	6	6 (4.2%)
	Acute kidney injury	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Nocturia	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Pollakiuria	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n event	of n of patients (%)	n event	of n of patients (%)	n event	of n of patients (%)	n event	of n of patients (%)
Blood and lymphatic system disorders	**ALL**	**2**	**2 (3%)**	**1**	**1 (2.4%)**	**5**	**4 (11.8%)**	**8**	**7 (4.9%)**
	Anaemia	1	1 (1.5%)	1	1 (2.4%)	3	2 (5.9%)	5	4 (2.8%)
	Thrombocytopenia	1	1 (1.5%)	-	-	1	1 (2.9%)	2	2 (1.4%)
	Lymphopenia	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
Vascular disorders	**ALL**	**3**	**3 (4.5%)**	**3**	**3 (7.1%)**	**2**	**2 (5.9%)**	**8**	**8 (5.6%)**
	Hypertension	1	1 (1.5%)	2	2 (4.8%)	1	1 (2.9%)	4	4 (2.8%)
	Arteriosclerosis	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Hypertensive crisis	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Hypotension	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Pallor	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
Infections and infestations	**ALL**	**1**	**1 (1.5%)**	**2**	**2 (4.8%)**	**3**	**2 (5.9%)**	**6**	**5 (3.5%)**
	Erysipelas	-	-	-	-	2	1 (2.9%)	2	1 (0.7%)
	Pneumonia	-	-	1	1 (2.4%)	1	1 (2.9%)	2	2 (1.4%)
	Gastrointestinal infection	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Herpes zoster	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n event	of n of patients (%)	n event	of n of patients (%)	n event	of n of patients (%)	n event	of n of patients (%)
Injury, poisoning and procedural complications	**ALL**	**2**	**1 (1.5%)**	**-**	**-**	**2**	**2 (5.9%)**	**4**	**3 (2.1%)**
	Omissions of a medication dose	2	1 (1.5%)	-	-	1	1 (2.9%)	3	2 (1.4%)
	Scratch	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
Psychiatric disorders	**ALL**	**2**	**2 (3%)**	**2**	**2 (4.8%)**	**-**	**-**	**4**	**4 (2.8%)**
	Affective disorder	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Depression	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Insomnia	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Libido decreased	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
Ear and labyrinth disorders	**ALL**	**1**	**1 (1.5%)**	**1**	**1 (2.4%)**	**-**	**-**	**2**	**2 (1.4%)**
	Tinnitus	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Vertigo	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
Eye disorders	**ALL**	**1**	**1 (1.5%)**	**-**	**-**	**-**	**-**	**1**	**1 (0.7%)**

SOC AND PT		2L N=66 n event	of n (%)	of patients	3L N=42 n event	of n (%)	of patients	4L+ N=34 n event	of n (%)	of patients	Total N=142 n event	of n (%)	of patients
	Eyelid oedema	1	1 (1.5%)		-	-		-	-		1	1 (0.7%)	
Immune system disorders	**ALL**	**-**	**-**		**-**	**-**		**1**	**1 (2.9%)**		**1**	**1 (0.7%)**	
	Hypersensitivity	-	-		-	-		1	1 (2.9%)		1	1 (0.7%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**ALL**	**-**	**-**		**-**	**-**		**1**	**1 (2.9%)**		**1**	**1 (0.7%)**	
	Neoplasm progression	-	-		-	-		1	1 (2.9%)		1	1 (0.7%)	

Table 15.3.7a Adverse Events by System Organ Class and Preferred Term (Treatment Related and all grade) - SAF (n=142)

Table 14: Adverse Events by System Organ Class and Preferred Term (Treatment Related and grade 1-2) - SAF (n=142)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n event	of n (%) of patients	n event	of n (%) of patients	n event	of n (%) of patients	n event	of n (%) of patients
ALL		**189**	**52 (78.8%)**	**116**	**37 (88.1%)**	**93**	**31 (91.2%)**	**398**	**120 (84.5%)**
Gastrointestinal disorders	**ALL**	**93**	**45 (68.2%)**	**49**	**29 (69%)**	**44**	**20 (58.8%)**	**186**	**94 (66.2%)**
	Diarrhoea	53	35 (53%)	24	21 (50%)	19	16 (47.1%)	96	72 (50.7%)
	Nausea	6	6 (9.1%)	10	9 (21.4%)	5	5 (14.7%)	21	20 (14.1%)
	Abdominal pain	7	6 (9.1%)	2	2 (4.8%)	5	5 (14.7%)	14	13 (9.2%)
	Abdominal pain upper	7	7 (10.6%)	4	4 (9.5%)	1	1 (2.9%)	12	12 (8.5%)
	Vomiting	5	5 (7.6%)	3	2 (4.8%)	3	3 (8.8%)	11	10 (7%)
	Constipation	2	2 (3%)	1	1 (2.4%)	3	2 (5.9%)	6	5 (3.5%)
	Abdominal distension	1	1 (1.5%)	1	1 (2.4%)	2	1 (2.9%)	4	3 (2.1%)
	Gastrointestinal disorder	2	2 (3%)	1	1 (2.4%)	1	1 (2.9%)	4	4 (2.8%)
	Flatulence	1	1 (1.5%)	1	1 (2.4%)	1	1 (2.9%)	3	3 (2.1%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n event	of n of patients (%)	n event	of n of patients (%)	n event	of n of patients (%)	n event	of n of patients (%)
	Gastrooesophageal reflux disease	1	1 (1.5%)	-	-	2	2 (5.9%)	3	3 (2.1%)
	Dyspepsia	2	2 (3%)	-	-	-	-	2	2 (1.4%)
	Aphthous stomatitis	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Dry mouth	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Eosinophilic colitis	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Eructation	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Faeces soft	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Functional gastrointestinal disorder	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Gingival bleeding	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Haemorrhoids	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Melaena	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Reflux gastritis	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
General disorders and administration site conditions	**ALL**	**20**	**15 (22.7%)**	**10**	**8 (19%)**	**14**	**9 (26.5%)**	**44**	**32 (22.5%)**
	Asthenia	7	6 (9.1%)	3	3 (7.1%)	6	4 (11.8%)	16	13 (9.2%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n event	of n of patients (%)	n event	of n of patients (%)	n event	of n of patients (%)	n event	of n of patients (%)
	Fatigue	3	3 (4.5%)	2	2 (4.8%)	2	2 (5.9%)	7	7 (4.9%)
	Drug ineffective	3	3 (4.5%)	1	1 (2.4%)	1	1 (2.9%)	5	5 (3.5%)
	Chills	1	1 (1.5%)	-	-	1	1 (2.9%)	2	2 (1.4%)
	Oedema peripheral	1	1 (1.5%)	-	-	1	1 (2.9%)	2	2 (1.4%)
	Reduced drug effect	-	-	1	1 (2.4%)	1	1 (2.9%)	2	2 (1.4%)
	Therapeutic response decreased	-	-	1	1 (2.4%)	1	1 (2.9%)	2	2 (1.4%)
	Chest pain	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Gait disturbance	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	General physical health deterioration	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Generalised oedema	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Hyperthermia	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Inflammation	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Pyrexia	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Treatment noncompliance	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
Skin and subcutaneous tissue disorders	**ALL**	**13**	**10 (15.2%)**	**8**	**5 (11.9%)**	**5**	**3 (8.8%)**	**26**	**18 (12.7%)**

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n event	of n of patients (%)	n event	of n of patients (%)	n event	of n of patients (%)	n event	of n of patients (%)
	Rash	3	2 (3%)	4	3 (7.1%)	-	-	7	5 (3.5%)
	Pruritus	2	2 (3%)	1	1 (2.4%)	3	3 (8.8%)	6	6 (4.2%)
	Dry skin	3	3 (4.5%)	-	-	-	-	3	3 (2.1%)
	Erythema	1	1 (1.5%)	1	1 (2.4%)	-	-	2	2 (1.4%)
	Eczema	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Nail pigmentation	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Psoriasis	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Rash maculo-papular	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Scab	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Skin lesion	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Skin odour abnormal	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Urticaria	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
Respiratory, thoracic and mediastinal disorders	**ALL**	**14**	**10 (15.2%)**	**5**	**5 (11.9%)**	**5**	**3 (8.8%)**	**24**	**18 (12.7%)**
	Pleural effusion	8	5 (7.6%)	2	2 (4.8%)	2	2 (5.9%)	12	9 (6.3%)
	Dyspnoea	4	4 (6.1%)	3	3 (7.1%)	3	3 (8.8%)	10	10 (7%)
	Cough	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n event	of n of patients (%)	n event	of n of patients (%)	n event	of n of patients (%)	n event	of n of patients (%)
	Dyspnoea exertional	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
Musculoskeletal and connective tissue disorders	**ALL**	**10**	**8 (12.1%)**	**7**	**6 (14.3%)**	**4**	**3 (8.8%)**	**21**	**17 (12%)**
	Arthralgia	5	4 (6.1%)	2	2 (4.8%)	2	2 (5.9%)	9	8 (5.6%)
	Myalgia	2	2 (3%)	2	1 (2.4%)	1	1 (2.9%)	5	4 (2.8%)
	Muscle spasms	-	-	3	3 (7.1%)	1	1 (2.9%)	4	4 (2.8%)
	Musculoskeletal pain	2	2 (3%)	-	-	-	-	2	2 (1.4%)
	Tendon pain	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
Nervous system disorders	**ALL**	**7**	**5 (7.6%)**	**7**	**6 (14.3%)**	**5**	**4 (11.8%)**	**19**	**15 (10.6%)**
	Headache	3	3 (4.5%)	3	3 (7.1%)	3	3 (8.8%)	9	9 (6.3%)
	Dizziness	1	1 (1.5%)	2	2 (4.8%)	1	1 (2.9%)	4	4 (2.8%)
	Head discomfort	-	-	2	1 (2.4%)	-	-	2	1 (0.7%)
	Disturbance in attention	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Dysgeusia	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Hypersomnia	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Hypoaesthesia	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)

SOC AND PT		2L N=66 n event	2L N=66 of n (%)	3L N=42 n event	3L N=42 of n (%)	4L+ N=34 n event	4L+ N=34 of n (%)	Total N=142 n event	Total N=142 of n (%)
Investigations	**ALL**	**7**	**5 (7.6%)**	**8**	**7 (16.7%)**	**1**	**1 (2.9%)**	**16**	**13 (9.2%)**
	Weight decreased	1	1 (1.5%)	3	3 (7.1%)	-	-	4	4 (2.8%)
	Alanine aminotransferase increased	2	2 (3%)	-	-	-	-	2	2 (1.4%)
	Blood creatinine increased	1	1 (1.5%)	1	1 (2.4%)	-	-	2	2 (1.4%)
	Lipase increased	-	-	2	2 (4.8%)	-	-	2	2 (1.4%)
	Aspartate aminotransferase increased	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Blood urea increased	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Gamma-glutamyltransferase increased	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Intestinal transit time increased	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Liver function test abnormal	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Troponin increased	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
Hepatobiliary disorders	**ALL**	**6**	**6 (9.1%)**	**4**	**4 (9.5%)**	**2**	**2 (5.9%)**	**12**	**12 (8.5%)**

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n event	of n of patients (%)	n event	of n of patients (%)	n event	of n of patients (%)	n event	of n of patients (%)
	Hepatocellular injury	5	5 (7.6%)	4	4 (9.5%)	1	1 (2.9%)	10	10 (7%)
	Hepatic pain	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Jaundice cholestatic	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
Metabolism and nutrition disorders	**ALL**	**4**	**4 (6.1%)**	**5**	**5 (11.9%)**	**2**	**2 (5.9%)**	**11**	**11 (7.7%)**
	Decreased appetite	2	2 (3%)	4	4 (9.5%)	-	-	6	6 (4.2%)
	Hypertriglyceridaemia	1	1 (1.5%)	-	-	1	1 (2.9%)	2	2 (1.4%)
	Dyslipidaemia	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Fluid retention	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Hypokalaemia	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
Renal and urinary disorders	**ALL**	**3**	**3 (4.5%)**	**2**	**2 (4.8%)**	**2**	**2 (5.9%)**	**7**	**7 (4.9%)**
	Renal failure	3	3 (4.5%)	-	-	1	1 (2.9%)	4	4 (2.8%)
	Acute kidney injury	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Nocturia	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Pollakiuria	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n event	of n of patients (%)	n event	of n of patients (%)	n event	of n of patients (%)	n event	of n of patients (%)
Vascular disorders	**ALL**	**3**	**3 (4.5%)**	**3**	**3 (7.1%)**	**1**	**1 (2.9%)**	**7**	**7 (4.9%)**
	Hypertension	1	1 (1.5%)	2	2 (4.8%)	1	1 (2.9%)	4	4 (2.8%)
	Arteriosclerosis	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Hypotension	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Pallor	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
Cardiac disorders	**ALL**	**1**	**1 (1.5%)**	**4**	**3 (7.1%)**	**1**	**1 (2.9%)**	**6**	**5 (3.5%)**
	Pericarditis	-	-	3	3 (7.1%)	-	-	3	3 (2.1%)
	Pericardial effusion	-	-	1	1 (2.4%)	1	1 (2.9%)	2	2 (1.4%)
	Palpitations	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
Injury, poisoning and procedural complications	**ALL**	**2**	**1 (1.5%)**	**-**	**-**	**2**	**2 (5.9%)**	**4**	**3 (2.1%)**
	Omissions of a medication dose	2	1 (1.5%)	-	-	1	1 (2.9%)	3	2 (1.4%)
	Scratch	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
Psychiatric disorders	**ALL**	**2**	**2 (3%)**	**2**	**2 (4.8%)**	**-**	**-**	**4**	**4 (2.8%)**

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n event	of n of patients (%)	n event	of n of patients (%)	n event	of n of patients (%)	n event	of n of patients (%)
	Affective disorder	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Depression	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Insomnia	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Libido decreased	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
Blood and lymphatic system disorders	**ALL**	**1**	**1 (1.5%)**	**1**	**1 (2.4%)**	**1**	**1 (2.9%)**	**3**	**3 (2.1%)**
	Anaemia	1	1 (1.5%)	1	1 (2.4%)	-	-	2	2 (1.4%)
	Lymphopenia	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
Infections and infestations	**ALL**	**1**	**1 (1.5%)**	**-**	**-**	**2**	**1 (2.9%)**	**3**	**2 (1.4%)**
	Erysipelas	-	-	-	-	2	1 (2.9%)	2	1 (0.7%)
	Herpes zoster	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
Ear and labyrinth disorders	**ALL**	**1**	**1 (1.5%)**	**1**	**1 (2.4%)**	**-**	**-**	**2**	**2 (1.4%)**
	Tinnitus	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Vertigo	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n event	of n of patients (%)	n event	of n of patients (%)	n event	of n of patients (%)	n event	of n of patients (%)
Eye disorders	**ALL**	**1**	**1 (1.5%)**	**-**	**-**	**-**	**-**	**1**	**1 (0.7%)**
	Eyelid oedema	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
Immune system disorders	**ALL**	**-**	**-**	**-**	**-**	**1**	**1 (2.9%)**	**1**	**1 (0.7%)**
	Hypersensitivity	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**ALL**	**-**	**-**	**-**	**-**	**1**	**1 (2.9%)**	**1**	**1 (0.7%)**
	Neoplasm progression	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)

Table 15.3.7b Adverse Events by System Organ Class and Preferred Term (Treatment Related and grade 1-2) - SAF (n=142)

Table 15: Adverse Events by System Organ Class and Preferred Term (Treatment Related and grade 3-4) - SAF (n=142)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
ALL		**25**	**16 (24.2%)**	**18**	**14 (33.3%)**	**24**	**15 (44.1%)**	**67**	**45 (31.7%)**
Hepatobiliary disorders	**ALL**	**8**	**8 (12.1%)**	**3**	**3 (7.1%)**	**3**	**3 (8.8%)**	**14**	**14 (9.9%)**
	Hepatocellular injury	7	7 (10.6%)	3	3 (7.1%)	2	2 (5.9%)	12	12 (8.5%)
	Hepatitis	1	1 (1.5%)	-	-	1	1 (2.9%)	2	2 (1.4%)
Gastrointestinal disorders	**ALL**	**3**	**3 (4.5%)**	**6**	**5 (11.9%)**	**2**	**2 (5.9%)**	**11**	**10 (7%)**
	Diarrhoea	2	2 (3%)	2	2 (4.8%)	2	2 (5.9%)	6	6 (4.2%)
	Abdominal pain	1	1 (1.5%)	1	1 (2.4%)	-	-	2	2 (1.4%)
	Intestinal obstruction	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Pancreatitis acute	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Vomiting	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
Investigations	**ALL**	**3**	**1 (1.5%)**	**4**	**2 (4.8%)**	**3**	**3 (8.8%)**	**10**	**6 (4.2%)**

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
	Alanine aminotransferase increased	1	1 (1.5%)	2	2 (4.8%)	1	1 (2.9%)	4	4 (2.8%)
	Aspartate aminotransferase increased	2	1 (1.5%)	2	2 (4.8%)	-	-	4	3 (2.1%)
	Lipase increased	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Transaminases increased	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
Cardiac disorders	**ALL**	**2**	**2 (3%)**	**1**	**1 (2.4%)**	**4**	**2 (5.9%)**	**7**	**5 (3.5%)**
	Cardiac failure	2	2 (3%)	-	-	2	2 (5.9%)	4	4 (2.8%)
	Atrial fibrillation	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Pericarditis	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Tachyarrhythmia	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
Blood and lymphatic system disorders	**ALL**	**1**	**1 (1.5%)**	**-**	**-**	**4**	**3 (8.8%)**	**5**	**4 (2.8%)**
	Anaemia	-	-	-	-	3	2 (5.9%)	3	2 (1.4%)
	Thrombocytopenia	1	1 (1.5%)	-	-	1	1 (2.9%)	2	2 (1.4%)
General disorders and administration site conditions	**ALL**	**1**	**1 (1.5%)**	**1**	**1 (2.4%)**	**2**	**2 (5.9%)**	**4**	**4 (2.8%)**

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
	Asthenia	1	1 (1.5%)	-	-	1	1 (2.9%)	2	2 (1.4%)
	Pain	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Reduced drug effect	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
Respiratory, thoracic and mediastinal disorders	**ALL**	**-**	**-**	**1**	**1 (2.4%)**	**3**	**3 (8.8%)**	**4**	**4 (2.8%)**
	Pleural effusion	-	-	1	1 (2.4%)	2	2 (5.9%)	3	3 (2.1%)
	Lung disorder	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
Metabolism and nutrition disorders	**ALL**	**2**	**2 (3%)**	**-**	**-**	**1**	**1 (2.9%)**	**3**	**3 (2.1%)**
	Decreased appetite	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Hyponatraemia	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Malnutrition	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
Infections and infestations	**ALL**	**-**	**-**	**1**	**1 (2.4%)**	**1**	**1 (2.9%)**	**2**	**2 (1.4%)**
	Gastrointestinal infection	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Pneumonia	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
Musculoskeletal and connective tissue disorders	**ALL**	**2**	**1 (1.5%)**	**-**	**-**	**-**	**-**	**2**	**1 (0.7%)**
	Musculoskeletal pain	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Neck pain	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
Nervous system disorders	**ALL**	**1**	**1 (1.5%)**	**1**	**1 (2.4%)**	**-**	**-**	**2**	**2 (1.4%)**
	Axonal neuropathy	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Headache	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
Renal and urinary disorders	**ALL**	**2**	**2 (3%)**	**-**	**-**	**-**	**-**	**2**	**2 (1.4%)**
	Renal failure	2	2 (3%)	-	-	-	-	2	2 (1.4%)
Vascular disorders	**ALL**	**-**	**-**	**-**	**-**	**1**	**1 (2.9%)**	**1**	**1 (0.7%)**
	Hypertensive crisis	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)

Table 15.3.7c Adverse Events by System Organ Class and Preferred Term (Treatment Related and grade 3-4) - SAF (n=142)

Table 16: Adverse Events by System Organ Class and Preferred Term (Treatment Related and grade 5 or missing) - SAF (n=142)

Patient No.	Date of initiation of bosutinib treatment	SOC name	PT name	CTCAE grade	Date of event occurrence	Is the event serious?	Status	Date of recovery	Is it reasonably possible that the event may be related to the study medication?	Is it reasonably possible that the event may be related to a concomitant drug?	If yes, specify the concomitant drug	Name of the drug (1)	Action taken (1)	Name of the drug (2)	Action taken (2)
16-08	30/01/2019	Infections and infestations	Pneumonia	Grade 5	18/06/2021	Yes	Subject not recovered		Yes	No			No dose modification		.

Listing 15.3.7d Adverse Events by System Organ Class and Preferred Term (Treatment Related and grade 5 or missing) - SAF (n=142)

10.4.1.2. Discontinuation due to AE

Among the total SAF population, 63 (44.4%) patients permanently discontinued bosutinib, among who 46 (32.4%) due to AE. Indeed 39 (27.5%) permanently discontinued due to bosutinib-related AE define as intolerance. 3 (2.1%) due to suboptimum response of bosutinib, 1 (0.7%) due to lack of efficacy of bosutinib and 3 (2.1%) for other reasons. (Table 17). According to the safety narrative plan all detailed reports of AE leading to treatment discontinuation are provided in **APPENDIX 8.**

The design of the eCRF did not enable to differentiate when an AE led to a temporary discontinuation or a permanent discontinuation. Accordingly, it has been necessary to perform a medical review and cross-checked between patient who discontinued due to intolerance and patients with AEs leading to discontinuation in order to identify the AEs leading to permanent discontinuation of bosutinib.

Few patients needed a more careful review regarding the AE which led to the permanent discontinuation of bosutinib.

Accordingly, it is important to note that patient 08-02 discontinued due to intolerance according to the investigator on the 26-12-2017, regarding AEs ongoing at that date, 2 AEs were related to a discontinuation vomiting and hepatic pain reported on the NK-12-2017 both. Nevertheless, during medical review it appears that hepatocellular injury occurred the 13-09-2017 inducing a temporary discontinuation. Regarding the fact that the resolution date of hepatocellular injury was after the permanent discontinuation and that vomiting and hepatic pain seems related to this AE, hepatocellular injury was considered as an AE leading to permanent discontinuation.

Regarding patient 09-10, the investigator reported a permanent discontinuation due to intolerance on the 05-06-2018, two AEs considered related to bosutinib and leading to a discontinuation by the investigator, vomiting and diarrhea reported the 04-06-2018 and the 09-02-2018 respectively and after the cross-check done by the medical team the bronchitis reported the 19-05-2018 but not considered related to bosutinib by the investigator was also considered related to permanent discontinuation. Indeed, the treatment was not start again after bronchitis, the influence of bronchitis could not then be minimized on the decision to discontinue bosutinib.

Regarding patient 11-12, he stopped bosutinib the 27-09-2018, due to a resection syndrome of the rectum occurring the 12-09-2018, which was not related to bosutinib according to the investigator. However, considering the investigator decision to report intolerance in the eCRF and considering the date of discontinuation and occurrence of the AE, it was considered after the medical review to include this patient in the population with permanent discontinuation due to intolerance. For patient 16-10, the investigator reported a permanent discontinuation due to intolerance, however, no AE related could be found in the eCRF. This discrepancy has not been highlighted during monitoring or the data review. Nonetheless, regarding the investigator decision we considered this patient in the population of patient who permanently discontinued due to intolerance but no AE related could be described in the relevant table.

Moreover, 3 permanently discontinued due to other reasons not related to bosutinib. Regarding the details of these patients, patient 16-03 discontinued due to multivisceral decompensation and patient 23-02 due to an adenocarcinoma. Considering patient 09-21, a non-programmed pregnancy was reported the 03-06-2021 leading to a temporary discontinuation, then bosutinib was restart in February 2022, leading to the occurrence of diarrhea the 22-02-2022 which was reported as treatment-related by the investigator. Finaly, this patient had a depression in April 2022 which was not related to bosutinib and discontinued bosutinib in April 2022. During the medical review, it has been decided that the non-programmed pregnancy was the most relevant AE which would have induced discontinuation of bosutinib. Therefore, it has been assumed that it was the patient choice to discontinued most probably due to an AE which was not related to bosutinib, the pregnancy.

Therefore, considering all AEs leading to discontinuation, the most frequent were diarrhea observed in 11 (7.7%), pleural effusion reported in 7 (4.9%) patients and hepatocellular injury reported in 7 (4.9%) patients.

The listing of AE leading to permanent discontinuation is summarized in Table 18.

Table 17: Discontinuations Due to Adverse Events related to bosutinib- SAF (n=142)

Variables		2L (N=66)	3L (N=42)	4L+ (N=34)	Total (N=142)
n% of patients with permanent discontinuation of Bosutinib	No	36 (54.5%)	21 (50%)	22 (64.7%)	79 (55.6%)
	Yes	30 (45.5%)	21 (50%)	12 (35.3%)	63 (44.4%)
n% of patients with at least one AE leading to permanent discontinuation of Bosutinib	No	44 (66.7%)	28 (66.7%)	24 (70.6%)	96 (67.6%)
	Yes	22 (33.3%)	14 (33.3%)	10 (29.4%)	46 (32.4%)
n% of patients with permanent discontinuation of Bosutinib due to intolerance	No	47 (71.2%)	29 (69%)	27 (79.4%)	103 (72.5%)
	Yes	19 (28.8%)	13 (31%)	7 (20.6%)	39 (27.5%)
n% of patients with permanent discontinuation of Bosutinib due to suboptimum response	No	66 (100%)	41 (97.6%)	32 (94.1%)	139 (97.9%)
	Yes	0 (0%)	1 (2.4%)	2 (5.9%)	3 (2.1%)
n% of patients with permanent discontinuation of Bosutinib due to lack of efficacy	No	65 (98.5%)	42 (100%)	34 (100%)	141 (99.3%)
	Yes	1 (1.5%)	0 (0%)	0 (0%)	1 (0.7%)
n% of patients with permanent discontinuation of Bosutinib due to other reason	No	64 (97%)	42 (100%)	33 (97.1%)	139 (97.9%)
	Yes	2 (3%)	0 (0%)	1 (2.9%)	3 (2.1%)

Note: On table 15.4.2a we can find 15 patients with suboptimal responses, 2 disease progressions (accelerated phase, blast crisis), 1 loss of response, 4 patient choice. As we can see into present table (from AE declared in eCRF form): 3 patients with suboptimal responses, 1 lack of efficacy (disease progression), 3 other reason (pregnancy, adenocarcinoma, multimineral failure)

Table 15.3.1 Discontinuations Due to Adverse Events - SAF (n=142)

Table 18: Adverse Events leading to permanent discontinuation by System Organ Class and Preferred Term - SAF (n=142)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
ALL		**40**	**22 (33.3%)**	**20**	**14 (33.3%)**	**17**	**9 (26.5%)**	**77**	**45 (31.7%)**
Gastrointestinal disorders	**ALL**	**9**	**7 (10.6%)**	**3**	**2 (4.8%)**	**4**	**3 (8.8%)**	**16**	**12 (8.5%)**
	Diarrhoea	6	6 (9.1%)	2	2 (4.8%)	3	3 (8.8%)	11	11 (7.7%)
	Vomiting	2	2 (3%)	1	1 (2.4%)	-	-	3	3 (2.1%)
	Abdominal pain	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Nausea	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
General disorders and administration site conditions	**ALL**	**6**	**5 (7.6%)**	**2**	**2 (4.8%)**	**3**	**3 (8.8%)**	**11**	**10 (7%)**
	Drug ineffective	1	1 (1.5%)	-	-	1	1 (2.9%)	2	2 (1.4%)
	Fatigue	2	2 (3%)	-	-	-	-	2	2 (1.4%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
	General physical health deterioration	2	2 (3%)	-	-	-	-	2	2 (1.4%)
	Reduced drug effect	-	-	1	1 (2.4%)	1	1 (2.9%)	2	2 (1.4%)
	Chills	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Multiviceral failure	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Pain	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
Investigations	**ALL**	**4**	**1 (1.5%)**	**4**	**2 (4.8%)**	**2**	**1 (2.9%)**	**10**	**4 (2.8%)**
	Alanine aminotransferase increased	1	1 (1.5%)	2	2 (4.8%)	1	1 (2.9%)	4	4 (2.8%)
	Aspartate aminotransferase increased	1	1 (1.5%)	2	2 (4.8%)	1	1 (2.9%)	4	4 (2.8%)
	Blood creatinine increased	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Gamma-glutamyltransferase increased	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
Respiratory, thoracic and mediastinal disorders	**ALL**	**4**	**4 (6.1%)**	**3**	**3 (7.1%)**	**3**	**3 (8.8%)**	**10**	**10 (7%)**
	Pleural effusion	2	2 (3%)	3	3 (7.1%)	2	2 (5.9%)	7	7 (4.9%)
	Dyspnoea	2	2 (3%)	-	-	-	-	2	2 (1.4%)
	Lung disorder	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
Hepatobiliary disorders	**ALL**	**6**	**5 (7.6%)**	**2**	**2 (4.8%)**	**1**	**1 (2.9%)**	**9**	**8 (5.6%)**
	Hepatocellular injury	4	4 (6.1%)	2	2 (4.8%)	1	1 (2.9%)	7	7 (4.9%)
	Hepatic pain	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Hepatitis	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
Cardiac disorders	**ALL**	**1**	**1 (1.5%)**	**1**	**1 (2.4%)**	**3**	**1 (2.9%)**	**5**	**3 (2.1%)**
	Cardiac failure	1	1 (1.5%)	-	-	1	1 (2.9%)	2	2 (1.4%)
	Atrial fibrillation	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Pericarditis	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Tachyarrhythmia	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
Nervous system disorders	**ALL**	**1**	**1 (1.5%)**	**3**	**3 (7.1%)**	**-**	**-**	**4**	**4 (2.8%)**
	Headache	-	-	2	2 (4.8%)	-	-	2	2 (1.4%)
	Axonal neuropathy	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Dysgeusia	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
Renal and urinary disorders	**ALL**	**2**	**2 (3%)**	**1**	**1 (2.4%)**	**-**	**-**	**3**	**3 (2.1%)**
	Renal failure	2	2 (3%)	-	-	-	-	2	2 (1.4%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
	Acute kidney injury	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
Injury, poisoning and procedural complications	**ALL**	**2**	**2 (3%)**	**-**	**-**	**-**	**-**	**2**	**2 (1.4%)**
	Maternal exposure during pregnancy	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Post procedural complication	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
Metabolism and nutrition disorders	**ALL**	**2**	**2 (3%)**	**-**	**-**	**-**	**-**	**2**	**2 (1.4%)**
	Decreased appetite	2	2 (3%)	-	-	-	-	2	2 (1.4%)
Musculoskeletal and connective tissue disorders	**ALL**	**2**	**2 (3%)**	**-**	**-**	**-**	**-**	**2**	**2 (1.4%)**
	Arthralgia	2	2 (3%)	-	-	-	-	2	2 (1.4%)
Immune system disorders	**ALL**	**-**	**-**	**-**	**-**	**1**	**1 (2.9%)**	**1**	**1 (0.7%)**
	Hypersensitivity	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
Infections and infestations	**ALL**	**1**	**1 (1.5%)**	**-**	**-**	**-**	**-**	**1**	**1 (0.7%)**
	Bronchitis	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
Skin and subcutaneous tissue disorders	**ALL**	**-**	**-**	**1**	**1 (2.4%)**	**-**	**-**	**1**	**1 (0.7%)**
	Rash maculo-papular	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)

Table 15.3.8a Adverse Events leading to permanent discontinuation by System Organ Class and Preferred Term - SAF (n=142)

Note: Subject 16-10 is considered to have an AE leading to permanent discontinuation according to the PI, but is not included in this table as he had no AE reported.

10.4.1.3. Discontinuation due to AE related to treatment

Considering AE related to bosutinib and leading to permanent discontinuation because of intolerance, most frequent were diarrhea observed in 11 (7.7%) patients, pleural effusion in 7 (4.9%) patients and hepatocellular injury observed in 7 (4.9%) patients (Table 19).

Overall, 3 patients exhibited AE related to bosutinib which led to permanent discontinuation due to suboptimum response according to the investigator, 2 patients with reduced drug effect and one with drug ineffective (Table 20). One patient had an AE leading to permanent discontinuation due to lack of efficacy (Table 21).

Finaly, 3 patients reported AEs leading to permanent discontinuation of bosutinib due to other reasons, multiviceral failure, general physical health deterioration, pregnancy, and lung disorder (Table 22).

Table 19: Adverse Events leading to permanent discontinuation due to intolerance by System Organ Class and Preferred Term - SAF (n=142)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
ALL		**37**	**19 (28.8%)**	**19**	**13 (31%)**	**13**	**6 (17.6%)**	**69**	**38 (26.8%)**
Gastrointestinal disorders	**ALL**	**9**	**7 (10.6%)**	**3**	**2 (4.8%)**	**4**	**3 (8.8%)**	**16**	**12 (8.5%)**
	Diarrhoea	6	6 (9.1%)	2	2 (4.8%)	3	3 (8.8%)	11	11 (7.7%)
	Vomiting	2	2 (3%)	1	1 (2.4%)	-	-	3	3 (2.1%)
	Abdominal pain	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Nausea	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
Investigations	**ALL**	**4**	**1 (1.5%)**	**4**	**2 (4.8%)**	**2**	**1 (2.9%)**	**10**	**4 (2.8%)**
	Alanine aminotransferase increased	1	1 (1.5%)	2	2 (4.8%)	1	1 (2.9%)	4	4 (2.8%)
	Aspartate aminotransferase increased	1	1 (1.5%)	2	2 (4.8%)	1	1 (2.9%)	4	4 (2.8%)
	Blood creatinine increased	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Gamma-glutamyltransferase increased	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
Hepatobiliary disorders	**ALL**	**6**	**5 (7.6%)**	**2**	**2 (4.8%)**	**1**	**1 (2.9%)**	**9**	**8 (5.6%)**
	Hepatocellular injury	4	4 (6.1%)	2	2 (4.8%)	1	1 (2.9%)	7	7 (4.9%)
	Hepatic pain	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Hepatitis	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
Respiratory, thoracic and mediastinal disorders	**ALL**	**4**	**4 (6.1%)**	**3**	**3 (7.1%)**	**2**	**2 (5.9%)**	**9**	**9 (6.3%)**
	Pleural effusion	2	2 (3%)	3	3 (7.1%)	2	2 (5.9%)	7	7 (4.9%)
	Dyspnoea	2	2 (3%)	-	-	-	-	2	2 (1.4%)
Cardiac disorders	**ALL**	**1**	**1 (1.5%)**	**1**	**1 (2.4%)**	**3**	**1 (2.9%)**	**5**	**3 (2.1%)**
	Cardiac failure	1	1 (1.5%)	-	-	1	1 (2.9%)	2	2 (1.4%)
	Atrial fibrillation	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Pericarditis	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Tachyarrhythmia	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
General disorders and administration site conditions	**ALL**	**4**	**3 (4.5%)**	**1**	**1 (2.4%)**	**-**	**-**	**5**	**4 (2.8%)**
	Fatigue	2	2 (3%)	-	-	-	-	2	2 (1.4%)
	Chills	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
	General physical health deterioration	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Pain	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
Nervous system disorders	**ALL**	**1**	**1 (1.5%)**	**3**	**3 (7.1%)**	**-**	**-**	**4**	**4 (2.8%)**
	Headache	-	-	2	2 (4.8%)	-	-	2	2 (1.4%)
	Axonal neuropathy	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Dysgeusia	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
Renal and urinary disorders	**ALL**	**2**	**2 (3%)**	**1**	**1 (2.4%)**	**-**	**-**	**3**	**3 (2.1%)**
	Renal failure	2	2 (3%)	-	-	-	-	2	2 (1.4%)
	Acute kidney injury	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
Metabolism and nutrition disorders	**ALL**	**2**	**2 (3%)**	**-**	**-**	**-**	**-**	**2**	**2 (1.4%)**
	Decreased appetite	2	2 (3%)	-	-	-	-	2	2 (1.4%)
Musculoskeletal and connective tissue disorders	**ALL**	**2**	**2 (3%)**	**-**	**-**	**-**	**-**	**2**	**2 (1.4%)**
	Arthralgia	2	2 (3%)	-	-	-	-	2	2 (1.4%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
Immune system disorders	**ALL**	**-**	**-**	**-**	**-**	**1**	**1 (2.9%)**	**1**	**1 (0.7%)**
	Hypersensitivity	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
Infections and infestations	**ALL**	**1**	**1 (1.5%)**	**-**	**-**	**-**	**-**	**1**	**1 (0.7%)**
	Bronchitis	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
Injury, poisoning and procedural complications	**ALL**	**1**	**1 (1.5%)**	**-**	**-**	**-**	**-**	**1**	**1 (0.7%)**
	Post procedural complication	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
Skin and subcutaneous tissue disorders	**ALL**	**-**	**-**	**1**	**1 (2.4%)**	**-**	**-**	**1**	**1 (0.7%)**
	Rash maculo-papular	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)

Table 15.3.8b Bosutinib-related Adverse Events leading to permanent discontinuation by System Organ Class and Preferred Term - SAF (n=142)

Table 20: Adverse Events leading to permanent discontinuation of Bosutinib due to suboptimum response by System Organ Class and Preferred Term - SAF (n=142)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
ALL		**0**	**0 (0%)**	**1**	**1 (2.4%)**	**2**	**2 (5.9%)**	**3**	**3 (2.1%)**
General disorders and administration site conditions	**ALL**	**-**	**-**	**1**	**1 (2.4%)**	**2**	**2 (5.9%)**	**3**	**3 (2.1%)**
	Reduced drug effect	-	-	1	1 (2.4%)	1	1 (2.9%)	2	2 (1.4%)
	Drug ineffective	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)

Table 21: Adverse Events leading to permanent discontinuation of Bosutinib due to lack of efficacy by System Organ Class and Preferred Term - SAF (n=142)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
ALL		**1**	**1 (1.5%)**	**0**	**0 (0%)**	**0**	**0 (0%)**	**1**	**1 (0.7%)**
General disorders and administration site conditions	**ALL**	**1**	**1 (1.5%)**	**-**	**-**	**-**	**-**	**1**	**1 (0.7%)**
	Drug ineffective	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)

Table 22: Adverse Events leading to permanent discontinuation of Bosutinib due to other reason by System Organ Class and Preferred Term - SAF (n=142)

SOC AND PT	2L N=66		3L N=42		4L+ N=34		Total N=142	
	n	n(%)	n	n(%)	n	n(%)	n	n(%)
ALL	**2**	**2 (3%)**	**0**	**0 (0%)**	**2**	**1 (2.9%)**	**4**	**3 (2.1%)**

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
General disorders and administration site conditions	**ALL**	**1**	**1 (1.5%)**	**-**	**-**	**1**	**1 (2.9%)**	**2**	**2 (1.4%)**
	General physical health deterioration	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Multiviceral failure	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
Injury, poisoning and procedural complications	**ALL**	**1**	**1 (1.5%)**	**-**	**-**	**-**	**-**	**1**	**1 (0.7%)**
	Maternal exposure during pregnancy	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
Respiratory, thoracic and mediastinal disorders	**ALL**	**-**	**-**	**-**	**-**	**1**	**1 (2.9%)**	**1**	**1 (0.7%)**
	Lung disorder	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)

10.4.2. Secondary analysis: Effectiveness

All effectiveness analyses have been performed in the FAS.

10.4.2.1. Response to bosutinib

10.4.2.1.1. Hematological response over 3 years

10.4.2.1.1.1. Hematological response

Most patients (127/139 (91.4%)) had complete hematological response, while one (0.7%) patient had a partial response (Table 23).

Table 23: Hematological responses to Bosutinib - FAS (n=139)

Variables		2L (N=64)	3L (N=42)	4L+ (N=33)	Total (N=139)
Hematological evaluation	Not done	8 (12.5%)	1 (2.4%)	2 (6.1%)	11 (7.9%)
	Done	56 (87.5%)	41 (97.6%)	31 (93.9%)	128 (92.1%)
Hematological partial response	No	64 (100%)	42 (100%)	32 (97%)	138 (99.3%)
	Yes	0 (0%)	0 (0%)	1 (3%)	1 (0.7%)
Hematological complete response (CHR)	No	8 (12.5%)	1 (2.4%)	3 (9.1%)	12 (8.6%)
	Yes	56 (87.5%)	41 (97.6%)	30 (90.9%)	127 (91.4%)
Cumulative hematological response	No	8 (12.5%)	1 (2.4%)	2 (6.1%)	11 (7.9%)
	Yes	56 (87.5%)	41 (97.6%)	31 (93.9%)	128 (92.1%)

Table 15.2.1a Cumulative hematological responses to Bosutinib - FAS (n=139) and additional table Table 1 Evaluati- FAS (n=139)

Considering hematological response according to bosutinib's dose, it has been observed that among the 16 patients who received a dose ≤ 200 mg/day, 14 (87.5%) patients had hematological complete response and 2 patients no response.

For patients who received a dose comprised between 200 and 300 mg/day, 46 (92%) had a complete response, one had partial response whereas 3 had no response.

For patients who received a dose comprised between 300 and 400 mg/day, 30 (90.9%) patients had a complete response while 3 had no response.

For patients who received a dose comprised above 400 mg/day, 27 (93.1%) had a complete response whereas 2 had no response.

The bosutinib dose was missing for 11 patients (see **Appendix 7.11**), among who 10 (90.9%) had a complete response and 1 (9.1%) no response.

Therefore, among the 139 patients 128 (92.1%) had a cumulative response, 127 (91.4%) patients had a complete response and one (0.7%) patient had a partial response while 11 (7.9%) patients did not present cumulative hematological response (

Table 24).

Table 24: Hematological responses to Bosutinib according to mean dose received during the follow up - FAS (n=139)

Variables		<=200 (N=16)	]200-300] (N=50)	]300-400] (N=33)	>400 (N=29)	Missing dose (N=11)	Total (N=139)
Hematological partial response	No	16 (100%)	49 (98%)	33 (100%)	29 (100%)	11 (100%)	138 (99.3%)
	Yes	0 (0%)	1 (2%)	0 (0%)	0 (0%)	0 (0%)	1 (0.7%)
Hematological complete response (CHR)	No	2 (12.5%)	4 (8%)	3 (9.1%)	2 (6.9%)	1 (9.1%)	12 (8.6%)
	Yes	14 (87.5%)	46 (92%)	30 (90.9%)	27 (93.1%)	10 (90.9%)	127 (91.4%)
Cumulative hematological response	No	2 (12.5%)	3 (6%)	3 (9.1%)	2 (6.9%)	1 (9.1%)	11 (7.9%)
	Yes	14 (87.5%)	47 (94%)	30 (90.9%)	27 (93.1%)	10 (90.9%)	128 (92.1%)

Table 15.2.1b Cumulative hematological responses to Bosutinib according to the mean dose received during the follow-up - FAS (n=139)

10.4.2.1.1.2. Time to response to bosutinib

The time to response corresponds to the duration between date of initiation of bosutinib and the first date of response.

Among 128 patients having a hematological response, the median time to response was 0.24 [0.23-0.25] year (Table 25).

At one year all evaluable patients for hematological response achieved a response.

The time-to-hematological response was less than 1 year, therefore, estimates of CI95% could not be evaluated at 1, 2 and 3 years.

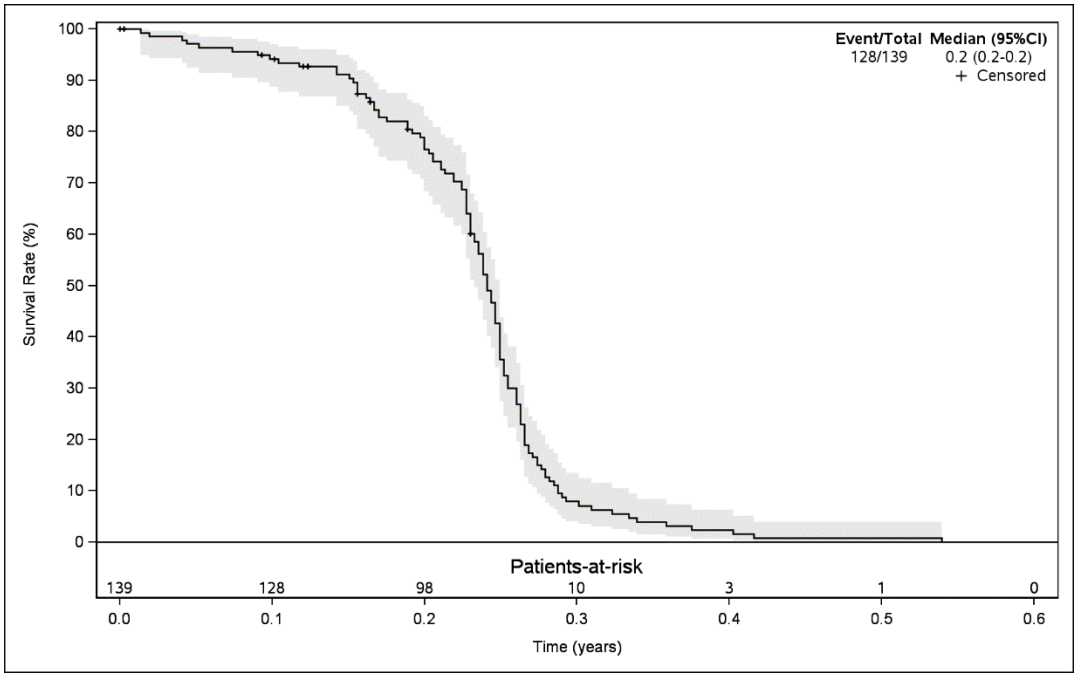
Table 25: Time-to-hematological Response - FAS (n=139)

Variables		2L (N=64)	3L (N=42)	4L+ (N=33)	Total (N=139)
Event hematological (time to response)	No	8 (12.5%)	1 (2.4%)	2 (6.1%)	11 (7.9%)
	Yes	56 (87.5%)	41 (97.6%)	31 (93.9%)	128 (92.1%)
Event/censoring hematological (time to response)	Permanent discontinuation of bosutinib	8 (12.5%)	1 (2.4%)	2 (6.1%)	11 (7.9%)
	Response to bosutinib (all types)	56 (87.5%)	41 (97.6%)	31 (93.9%)	128 (92.1%)

Timepoint	Real time	Survival	[CI95%]	Failure	Erreur type de survie	Number Failed	Number Left	Estimate
1 year	0.54	0.00		1.00	.	128	0	
2 years	0.54	0.00		1.00	.	128	0	
3 years	0.54	0.00		1.00	.	128	0	
Median [CI95%]	.				.	.	.	0.24 [0.23-0.25]

Table 15.2.2a Time-to-hematological Response - FAS (n=139)

Figure 3: Time-to-hematological Response - FAS (n=139)



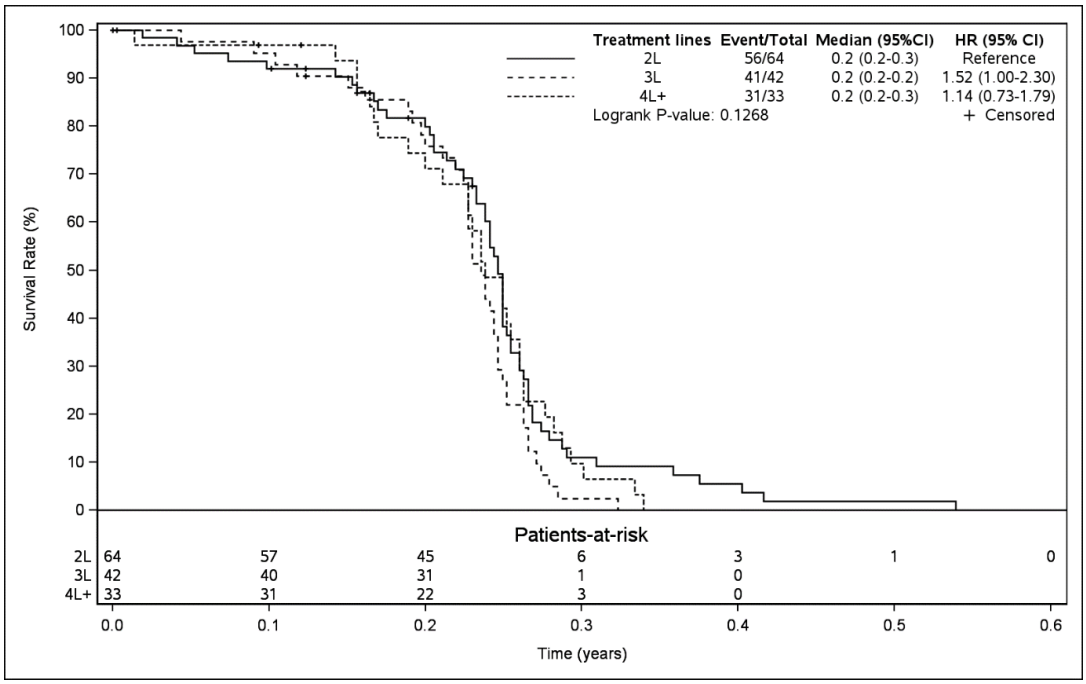


Figure 15.2.2a Time-to-hematological Response - FAS (n=139)

10.4.2.1.1.3. Duration of hematological Response

Considering duration of hematological response (HR) (Table 26), among the 128 patients having hematological response, 10 presented an event of duration response. Indeed, 118 patients were censored, for they were alive at the end of follow-up or lost to follow-up.

At 1 year, 95% of patient still retained a HR. As of the data cutoff, 92% of the evaluable patients who achieved a HR still retained their response, with a median duration of HR not reached (Figure 4).

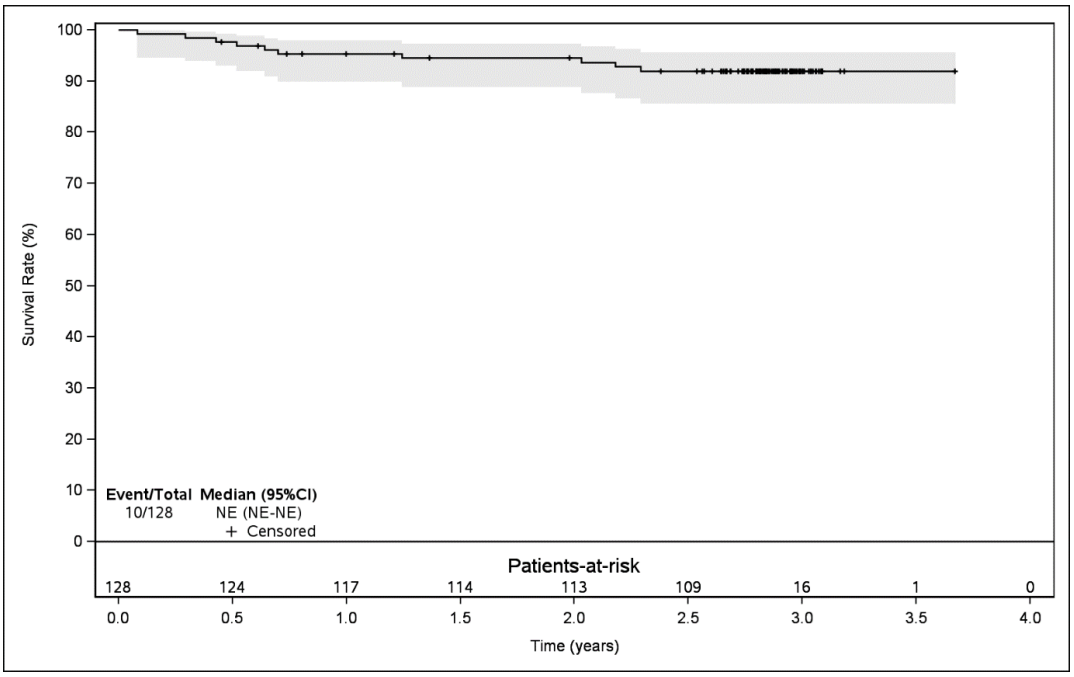
Table 26: Duration of hematological Response - FAS (n=139)

Variables		2L (N=64)	3L (N=42)	4L+ (N=33)	Total (N=139)
Cumulative hematological response	No	8 (12.5%)	1 (2.4%)	2 (6.1%)	11 (7.9%)
	Yes	56 (87.5%)	41 (97.6%)	31 (93.9%)	128 (92.1%)
Event hematological (duration of response)	No	52 (92.9%)	39 (95.1%)	27 (87.1%)	118 (92.2%)
	Yes	4 (7.1%)	2 (4.9%)	4 (12.9%)	10 (7.8%)
Event/censoring hematological (duration of response)	Alive at end of follow-up or lost to follow-up	52 (92.9%)	39 (95.1%)	27 (87.1%)	118 (92.2%)
	Death while responding	0 (0%)	1 (2.4%)	2 (6.5%)	3 (2.3%)
	Disease progression	4 (7.1%)	0 (0%)	1 (3.2%)	5 (3.9%)
	Loss of response	0 (0%)	1 (2.4%)	1 (3.2%)	2 (1.6%)

Timepoint	Real time	Survival	[CI95%]	Failure	Erreur type de survie	Number Failed	Number Left	Estimate
1 year	0.7	0.95	[0.9-0.98]	0.05	0.0188	6	117	
2 years	1.24	0.94	[0.89-0.97]	0.06	0.0204	7	113	
3 years	2.29	0.92	[0.86-0.96]	0.08	0.0244	10	16	
Median [CI95%]	.				.	.	.	Not evaluable

Table 15.2.3a Duration of hematological Response - FAS (n=139)

Figure 4: Duration of hematological Response - FAS (n=139)



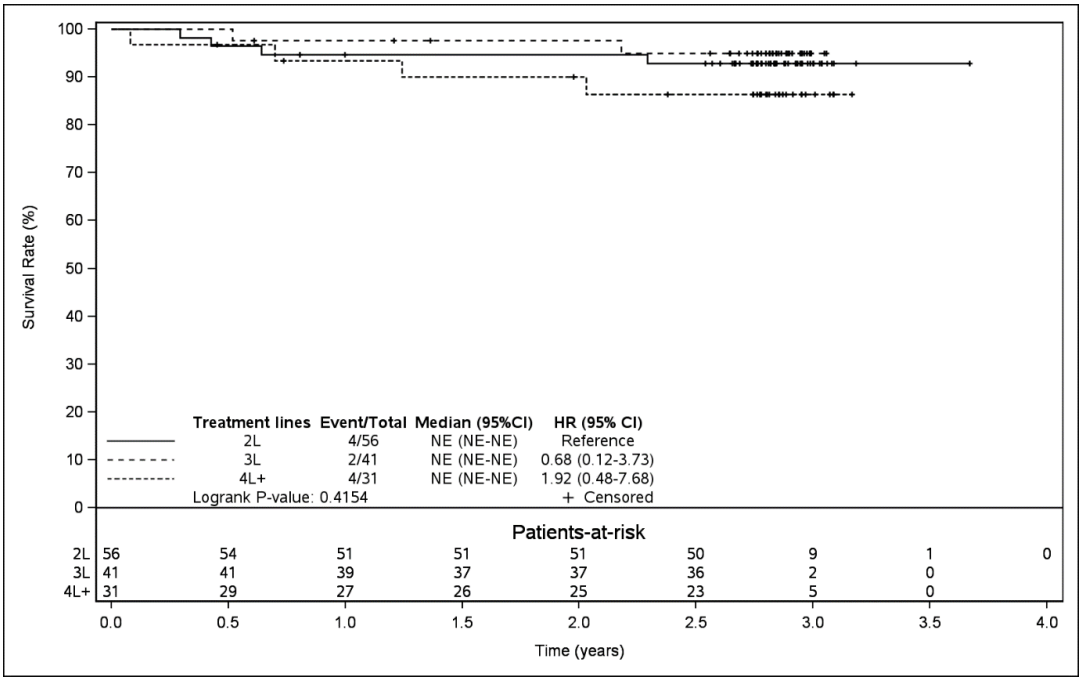


Figure 15.2.3a Duration of hematological Response - FAS (n=139)

10.4.2.1.1.4. Prognostic Factors for hematological Response

The univariable analysis identified 5 predictive factors for hematological response which were significantly associated at the 10% level; sex (male vs female) (p-value=0.0435); Baseline LDH (UI/L) levels (p-value=0.0463); Baseline lipase (UI/L) levels (p-value=0.0430); Baseline basophils (g/L) levels (p-value=0.0926) (Table 27).

Table 27: Prognostic Factors for hematological Response - Univariable analysis - FAS (n=139)

Variable	Comparison	Pvalue (ML)	OR [95%CI] (ML)	Number of observations used (%)
Age (years)		0.2581	0.97 [0.91-1.02]	139 (100%)
Sex	**Male vs Female**	**0.0435**	**3.77 [1.04-17.84]**	**139 (100%)**
Weight (kg)		0.5614	1.01 [0.98-1.05]	118 (84.9%)
Height (cm)		0.1330	1.06 [0.98-1.14]	134 (96.4%)
BMI (kg/m²)		0.8202	0.99 [0.89-1.10]	116 (83.5%)
ECOG score		0.1948		112 (80.6%)
ECOG score	1 vs 0	.	0.26 [0.05-1.06]	
ECOG score	2-3 vs 0	.	0.44 [0.05-9.48]	
BCR-ABL mutations		0.9435		139 (100%)
BCR-ABL mutations	BCR vs ABL	.	1.38 [0.23-26.52]	
BCR-ABL mutations	Oth vs ABL	.	1.20 [0.28-8.24]	
SOKAL score		0.9381		126 (90.6%)

Variable	Comparison	Pvalue (ML)	OR [95%CI] (ML)	Number of observations used (%)
SOKAL score	High vs Low	.	0.91 [0.18-6.70]	
SOKAL score	Intermediate vs Low	.	1.24 [0.29-6.33]	
Time between initial diagnosis and initiation of bosutinib treatment (years)		0.7577	1.02 [0.92-1.15]	139 (100%)
Bone marrow karyotype	Yes vs No/Unknown	0.7871	0.75 [0.04-4.37]	139 (100%)
Rearrangement t(9,22) present	Yes vs No/Unknown	0.2152	0.00 [NE-2.81]	139 (100%)
Concomitant medication	Yes vs No	0.1111	12.70 [0.48-337.71]	139 (100%)
Number of concomitant medication		0.8600	1.00 [0.95-1.06]	139 (100%)
Antecedent or comorbidities	Yes vs No	0.1111	12.70 [0.48-337.71]	139 (100%)
Number of antecedent or comorbidities		0.7539	0.98 [0.90-1.09]	139 (100%)
Treatment line		0.2033		139 (100%)
Treatment line	3L vs 2L	.	5.86 [1.02-110.81]	
Treatment line	4L+ vs 2L	.	2.21 [0.52-15.28]	
Last therapy		0.6989		139 (100%)
Last therapy	Dasatinib vs Imatinib	.	2.66 [0.61-18.40]	
Last therapy	Nilotinib vs Imatinib	.	1.45 [0.32-10.19]	
Last therapy	Ponatinib vs Imatinib	.	Not evaluable	
Hematological response in last line	Response vs No response/Unknown	0.3812	3.10 [0.15-23.62]	139 (100%)
Cytogenetic response in last line	Response vs No response/Unknown	0.4680	1.71 [0.35-6.44]	139 (100%)
Molecular response in last line	Response vs No response/Unknown	0.9775	1.02 [0.26-3.56]	139 (100%)

Variable	Comparison	Pvalue (ML)	OR [95%CI] (ML)	Number of observations used (%)
Reason for change of line in last line		0.9363		139 (100%)
Reason for change of line in last line	Intolerance vs Lack of response	.	0.00 [NE-4.66]	
Reason for change of line in last line	Loss of response vs Lack of response	.	0.00 [NE-20.93]	
Reason for change of line in last line	Other, specify vs Lack of response	.	1.00 [NE]	
Reason for change of line in last line	Suboptimum response vs Lack of response	.	0.00 [NE-27.31]	
Baseline: ALAT (UI/L)		0.5906	1.01 [0.97-1.08]	101 (72.7%)
Baseline: ASAT (UI/L)		0.5410	1.02 [0.96-1.12]	102 (73.4%)
Baseline: Total bilirubin (µmol/L)		0.8404	0.99 [0.87-1.17]	84 (60.4%)
Baseline: Conjugated bilirubin (µmol/L)		0.4223	0.83 [0.52-1.36]	20 (14.4%)
Baseline: LDH (UI/L)		**0.0463**	**1.01 [1.00-1.03]**	**50 (36%)**
Baseline: Albumin (g/L)		0.7915	0.96 [0.77-1.39]	25 (18%)
Baseline: Amylase (UI/L)		0.7770	0.99 [0.91-1.08]	8 (5.8%)
Baseline: Lipase (UI/L)		**0.0430**	**0.98 [0.96-1.00]**	**27 (19.4%)**
Baseline: Serum creatinine (µmol/L)		0.6300	1.01 [0.98-1.03]	103 (74.1%)
Baseline: Blood glucose (fasting) (mmol/L)		0.1705	4.60 [0.71-348.58]	18 (12.9%)
Baseline: Blood glucose (non-fasting) (mmol/L)		0.9336	1.01 [0.84-1.77]	31 (22.3%)
Baseline: Magnesium (mmol/L)		0.1651	0.00 [0.00-153.65]	18 (12.9%)
Baseline: Calcium (mmol/L)		0.8719	0.62 [0.00-228.59]	59 (42.4%)
Baseline: Blood urea (mmol/L)		0.8176	0.98 [0.82-1.24]	81 (58.3%)

Variable	Comparison	Pvalue (ML)	OR [95%CI] (ML)	Number of observations used (%)
Baseline: Uric acid (µmol/L)		0.8944	1.00 [0.99-1.01]	42 (30.2%)
Baseline: Hemoglobin (g/dL)		0.9067	1.02 [0.73-1.32]	116 (83.5%)
Baseline: Hematocrit (%)		0.5309	1.04 [0.91-1.17]	115 (82.7%)
Baseline: Leukocytes (g/L)		0.8837	1.00 [0.96-1.09]	113 (81.3%)
Baseline: Platelets (g/L)		0.2335	1.00 [1.00-1.01]	111 (79.9%)
Baseline: Blasts (peripheral blood) (%)		0.2475	Not evaluable	41 (29.5%)
Baseline: Basophils (g/L)		**0.0926**	**4.15 [0.89-110.85]**	**116 (83.5%)**
Baseline: Eosinophils (g/L)		0.1600	1.48 [0.93-4.19]	116 (83.5%)
Baseline: Neutrophils (g/L)		0.8024	1.00 [0.98-1.03]	116 (83.5%)
Baseline: Monocytes (g/L)		0.9348	1.01 [0.87-1.24]	115 (82.7%)
Baseline: Lymphocytes (g/L)		0.2389	1.04 [0.98-1.15]	116 (83.5%)

Table 15.2.4a Prognostic Factors for hematological Response - Univariable analysis - FAS (n=139)

Only variables with more than 50% available data were included in the multivariate model, therefore only sex and baseline basophils level were included. None of these two factors were significantly associated with hematological response (Table 28).

Table 28: Prognostic Factors for hematological Response - Multivariable analysis - FAS (n=139)

Step	Effect deleted	Pvalue (Wald)
1	Baseline: Basophils (g/L)	0.2204
2	Sex	0.0811

Table 15.2.4b Prognostic Factors for hematological Response - Multivariable analysis - FAS (n=139)

10.4.2.1.2. Cytogenetic response over 3 years

Overall, 18 (12.9%) patients had cytogenetic response, 8 (12.5%) patients had a major response in the 2L group, 6 (14.3%) patients in the 3L group and 2 (6.1%) patients in the 4L+ group. Only 1 (1.6%) patient in the 2L group and 1 (2.4%) in the 3L group had a minor response. However, we observed that only 21 (15.1%) patients were tested for cytogenetic response. Therefore, it is not relevant to evaluate time to response and duration of response based on the responding patients considering the low percentage of patients tested. Nevertheless, we could observe that among the 21 patients tested, 18 (85.7%) had a cytogenetic response.

Table 29: Cytogenetic responses to Bosutinib - FAS (n=139)

Variables		2L (N=64)	3L (N=42)	4L+ (N=33)	Total (N=139)
Cytogenetic evaluation	Not done	52 (81.3%)	35 (83.3%)	31 (93.9%)	118 (84.9%)
	Done	12 (18.8%)	7 (16.7%)	2 (6.1%)	21 (15.1%)
Minor cumulative cytogenetic response (mCyR)	No	63 (98.4%)	41 (97.6%)	33 (100%)	137 (98.6%)
	Yes	1 (1.6%)	1 (2.4%)	0 (0%)	2 (1.4%)
Complete cumulative cytogenetic response (CCyR)	No	57 (89.1%)	37 (88.1%)	32 (97%)	126 (90.6%)
	Yes	7 (10.9%)	5 (11.9%)	1 (3%)	13 (9.4%)
Major cumulative cytogenetic response (MCyR)	No	56 (87.5%)	36 (85.7%)	31 (93.9%)	123 (88.5%)
	Yes	8 (12.5%)	6 (14.3%)	2 (6.1%)	16 (11.5%)
Cumulative cytogenetic response (CyR)	No	55 (85.9%)	35 (83.3%)	31 (93.9%)	121 (87.1%)
	Yes	9 (14.1%)	7 (16.7%)	2 (6.1%)	18 (12.9%)

Table 15.2.1c Cumulative cytogenetic responses to Bosutinib - FAS (n=139)

10.4.2.1.3. Molecular response over 3 years

10.4.2.1.3.1. Major molecular response

Most patients (98/139 (70.5%)) had at major molecular response. Among these patients, 21 (15.1%) had a major molecular response (MMR), 14 (10.1%) had a MR4 response, 22 (15.8%) had a MR4.5, 41 (29.5%) had a MR5 response (Table 30).

Considering molecular response by subgroups, in the 2L group, 9 (14.1%) patients had a major molecular response (MMR), 10 (15.6%) had a MR4 response, 5 (7.8%) had a MR4.5, 19 (29.7%) had a MR5 response.

Regarding the 3L group, 8 (19%) patients had a major molecular response (MMR), none had a MR4 response, 11 (26.2%) had a MR4.5, 12 (28.6%) had a MR5 response.

In the 4L+ group 4 (12.1%) patients had a major molecular response (MMR), 4 (12.1%) had a MR4 response, 6 (18.2%) had a MR4.5 and 10 (30.3%) had a MR5 response.

Table 30: Molecular responses to Bosutinib - FAS (n=139)

Variables		2L (N=64)	3L (N=42)	4L+ (N=33)	Total (N=139)
Molecular evaluation	Not done	10 (15.6%)	1 (2.4%)	3 (9.1%)	14 (10.1%)
	Done	54 (84.4%)	41 (97.6%)	30 (90.9%)	125 (89.9%)
Major molecular response (MMR)	No	55 (85.9%)	34 (81%)	29 (87.9%)	118 (84.9%)
	Yes	9 (14.1%)	8 (19%)	4 (12.1%)	21 (15.1%)
Molecular response (MR4)	No	54 (84.4%)	42 (100%)	29 (87.9%)	125 (89.9%)
	Yes	10 (15.6%)	0 (0%)	4 (12.1%)	14 (10.1%)
Molecular response (MR4.5)	No	59 (92.2%)	31 (73.8%)	27 (81.8%)	117 (84.2%)
	Yes	5 (7.8%)	11 (26.2%)	6 (18.2%)	22 (15.8%)

Molecular response (MR5)	No	45 (70.3%)	30 (71.4%)	23 (69.7%)	98 (70.5%)
	Yes	19 (29.7%)	12 (28.6%)	10 (30.3%)	41 (29.5%)
Cumulative molecular response	No	21 (32.8%)	11 (26.2%)	9 (27.3%)	41 (29.5%)
- MMR	Yes	43 (67.2%)	31 (73.8%)	24 (72.7%)	98 (70.5%)
- MR4	Yes	34 (53,1%)	23 (54.8%)	20 (60.6%)	77 (55.4%)
- MR4.5	Yes	24 (37.5%)	23 (54.8%)	16 (48.5%)	63 (45.3%)

Table 15.2.1e Cumulative molecular responses to Bosutinib - FAS (n=139) and additional table Table 1 Evaluations - FAS (n=139)

Considering molecular response according to bosutinib's dose, it has been observed that among the 16 patients who received a dose ≤ 200 mg/day, 9 (56.3%) patients had a major molecular response (MMR, MR4, MR4.5 or MR5).

For patients who received a dose comprised between 200 and 300 mg/day, 37 (74%) patients had major molecular response (MMR, MR4, MR4.5 or MR5).

For patients who received a dose comprised between 300 and 400 mg/day, 23 (69.7%) patients had major molecular response (MMR, MR4, MR4.5 or MR5).

For patients who received a dose comprised above 400 mg/day, 20 (69%) patients had major molecular response (MMR, MR4, MR4.5 or MR5).

The bosutinib dose was missing for 11 patients, among who 9 (81.8%) patients had major molecular response (MMR, MR4, MR4.5 or MR5).

Details are presented in Table 31.

Table 31: Molecular responses to Bosutinib according to mean dose received during the follow up - FAS (n=139)

Variables		<=200 (N=16)	]200-300] (N=50)	]300-400] (N=33)	>400 (N=29)	Missing dose (N=11)	Total (N=139)
Major molecular response (MMR)	No	14 (87.5%)	43 (86%)	29 (87.9%)	27 (93.1%)	5 (45.5%)	118 (84.9%)
	Yes	2 (12.5%)	7 (14%)	4 (12.1%)	2 (6.9%)	6 (54.5%)	21 (15.1%)
Molecular response (MR4)	No	15 (93.8%)	47 (94%)	29 (87.9%)	23 (79.3%)	11 (100%)	125 (89.9%)
	Yes	1 (6.3%)	3 (6%)	4 (12.1%)	6 (20.7%)	0 (0%)	14 (10.1%)
Molecular response (CMR)	No	14 (87.5%)	42 (84%)	24 (72.7%)	28 (96.6%)	9 (81.8%)	117 (84.2%)
	Yes	2 (12.5%)	8 (16%)	9 (27.3%)	1 (3.4%)	2 (18.2%)	22 (15.8%)
Molecular response (MR5)	No	12 (75%)	31 (62%)	27 (81.8%)	18 (62.1%)	10 (90.9%)	98 (70.5%)
	Yes	4 (25%)	19 (38%)	6 (18.2%)	11 (37.9%)	1 (9.1%)	41 (29.5%)
Cumulative molecular response	No	7 (43.8%)	13 (26%)	10 (30.3%)	9 (31%)	2 (18.2%)	41 (29.5%)
	Yes	9 (56.3%)	37 (74%)	23 (69.7%)	20 (69%)	9 (81.8%)	98 (70.5%)

Table 15.2.1f Cumulative molecular responses to Bosutinib according to the mean dose received during the follow-up - FAS (n=139)

10.4.2.1.3.2. Time to molecular response to bosutinib

Among the 139 patients, 98 presented a molecular response, while 2 died before the response, 3 were lost to follow-up and 36 permanently discontinued bosutinib before having a molecular response.

At 1 year, 81% of patients reached a molecular response, at 2 year and 3 years there were 86% of patients who reached a molecular response (Figure 5).

The median time to response was 0.28 [0.25-0.45] year and was similar between subgroups (Table 32).

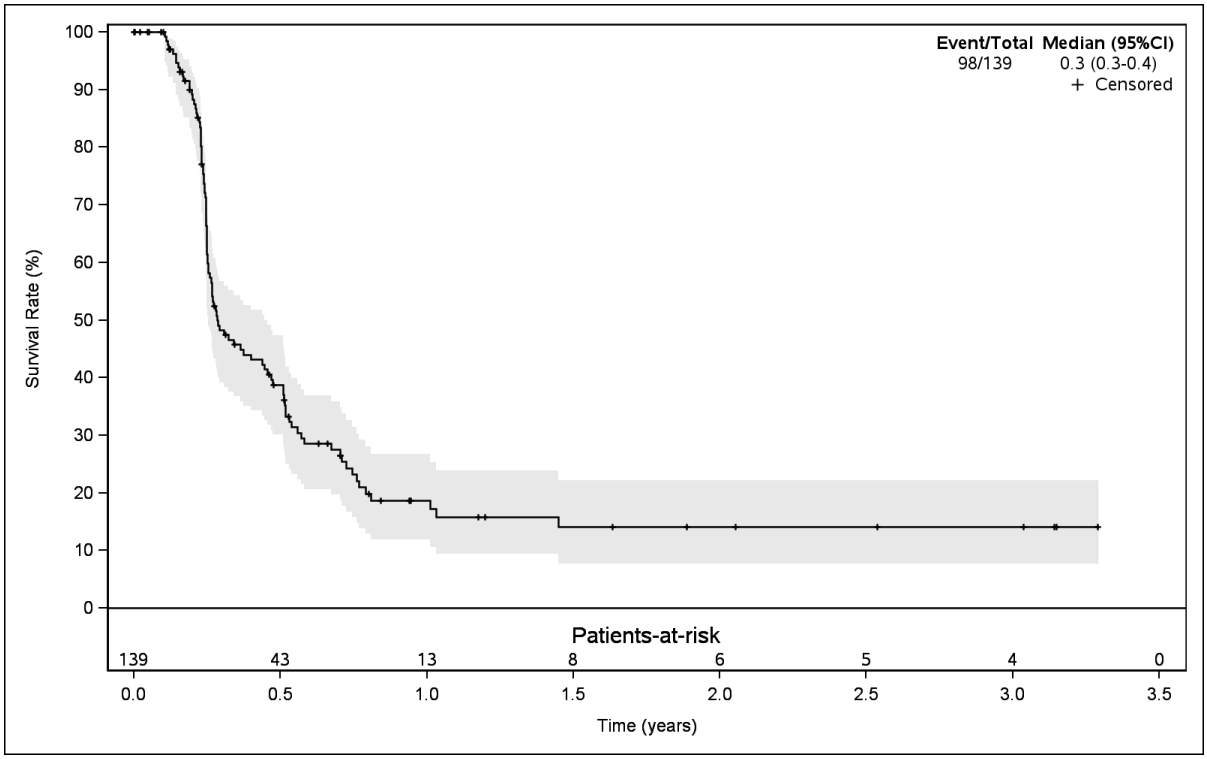
Table 32: Time-to-molecular Response - FAS (n=139)

Variables		2L (N=64)	3L (N=42)	4L+ (N=33)	Total (N=139)
Event molecular (time to response)	No	21 (32.8%)	11 (26.2%)	9 (27.3%)	41 (29.5%)
	Yes	43 (67.2%)	31 (73.8%)	24 (72.7%)	98 (70.5%)
Event/censoring molecular (time to response)	Death during bosutinib	0 (0%)	0 (0%)	2 (6.1%)	2 (1.4%)
	Lost to follow-up	1 (1.6%)	1 (2.4%)	1 (3%)	3 (2.2%)
	Permanent discontinuation of bosutinib	20 (31.3%)	10 (23.8%)	6 (18.2%)	36 (25.9%)
	Response to bosutinib (all types)	43 (67.2%)	31 (73.8%)	24 (72.7%)	98 (70.5%)

Timepoint	Real time	Survival	[CI95%]	Failure	Erreur type de survie	Number Failed	Number Left	Estimate
1 year	0.81	0.19	[0.12-0.27]	0.81	0.0384	95	13	
2 years	1.45	0.14	[0.08-0.22]	0.86	0.0372	98	6	
3 years	1.45	0.14	[0.08-0.22]	0.86	0.0372	98	4	
Median [CI95%]	.				.	.	.	0.28 [0.25-0.45]

Figure 15.2.2c Time-to-molecular Response - FAS (n=139)

Figure 5: Time-to-molecular Response - FAS (n=139)



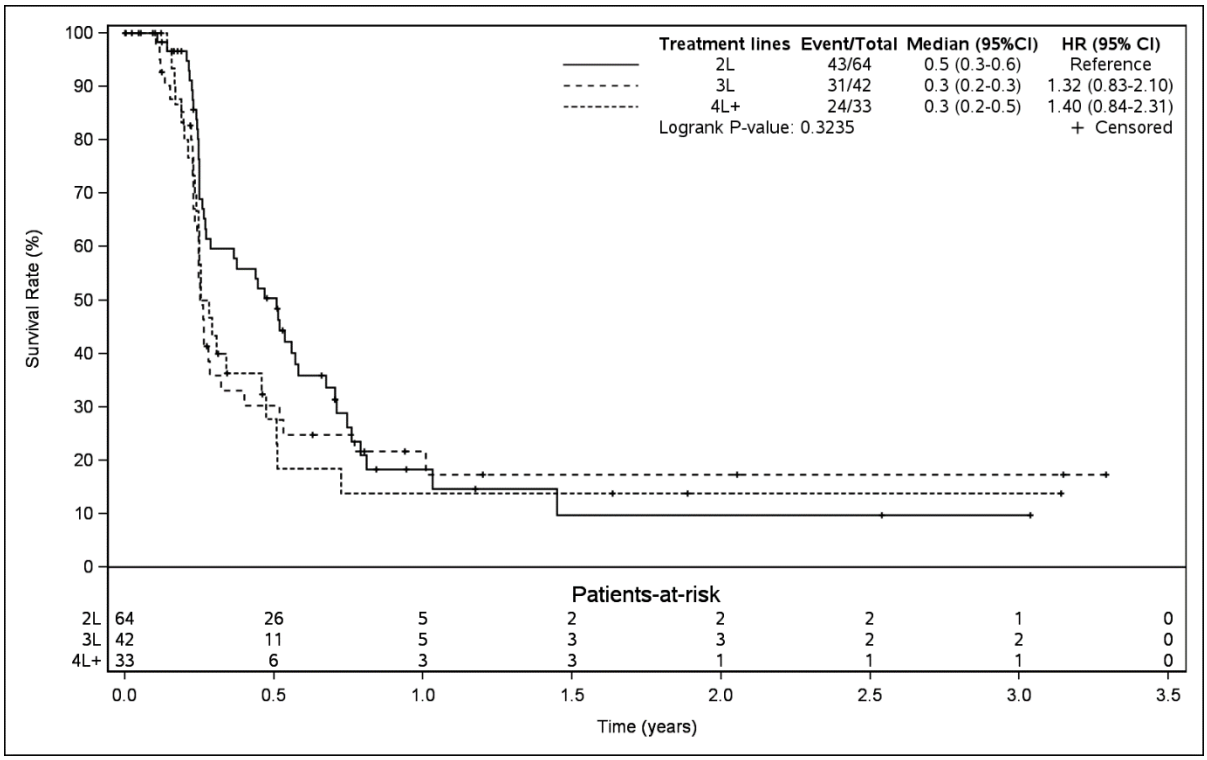


Figure 15.2.2c Time-to-molecular Response - FAS (n=139)

10.4.2.1.3.3. Duration of molecular Response

Considering duration of molecular response, among the 98 patients having molecular response, 18 presented an event of duration response. Indeed, 80 patients were censored, for they were alive at the end of follow-up or lost to follow-up.

The median duration not reached at the end of the study (Table 33).

Overall, 89% of patients were still responding after 1 year since the start of molecular response, this percentage only decreased to 83% after 2 years and 81% at 3 years.

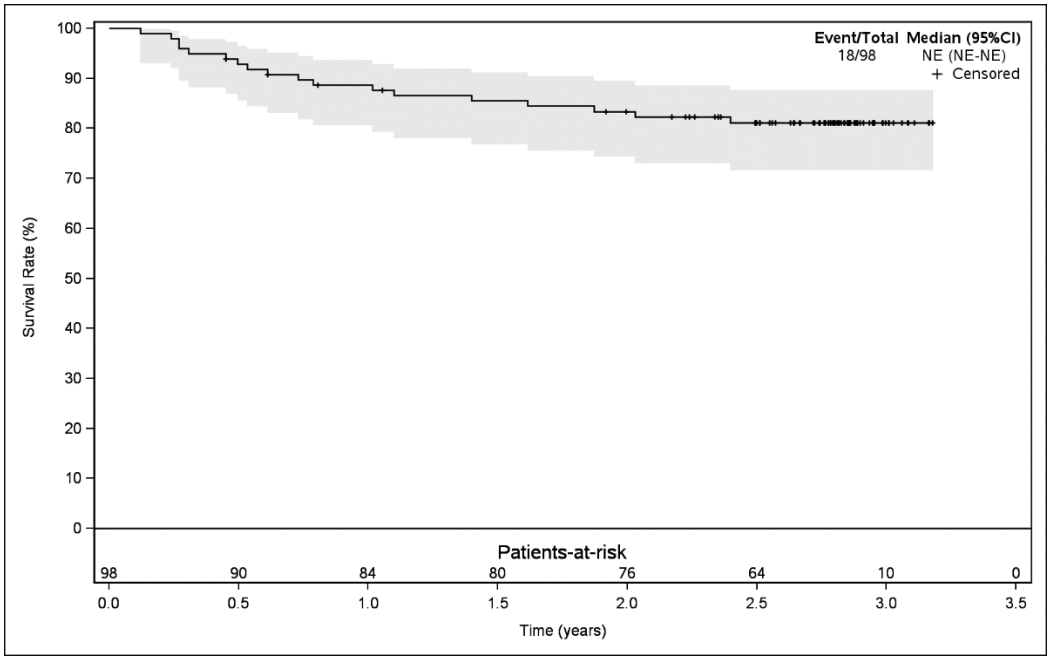
Table 33: Duration of molecular Response - FAS (n=139)

Variables		2L (N=64)	3L (N=42)	4L+ (N=33)	Total (N=139)
Cumulative molecular response	No	21 (32.8%)	11 (26.2%)	9 (27.3%)	41 (29.5%)
	Yes	43 (67.2%)	31 (73.8%)	24 (72.7%)	98 (70.5%)
Event molecular (duration of response)	No	32 (74.4%)	27 (87.1%)	21 (87.5%)	80 (81.6%)
	Yes	11 (25.6%)	4 (12.9%)	3 (12.5%)	18 (18.4%)
Event/censoring molecular (duration of response)	Alive at end of follow-up or lost to follow-up	32 (74.4%)	27 (87.1%)	21 (87.5%)	80 (81.6%)
	Death while responding	0 (0%)	0 (0%)	1 (4.2%)	1 (1%)
	Loss of response	11 (25.6%)	4 (12.9%)	2 (8.3%)	17 (17.3%)

Timepoint	Real time	Survival	[CI95%]	Failure	Erreur type de survie	Number Failed	Number Left	Estimate
1 year	0.79	0.89	[0.81-0.94]	0.11	0.0321	11	84	
2 years	1.87	0.83	[0.74-0.89]	0.17	0.0380	16	76	
3 years	2.4	0.81	[0.72-0.88]	0.19	0.0403	18	10	
Median [CI95%]	.				.	.	.	Not evaluable

Figure 15.2.3c Duration of molecular Response - FAS (n=139)

Figure 6: Duration of molecular Response - FAS (n=139)



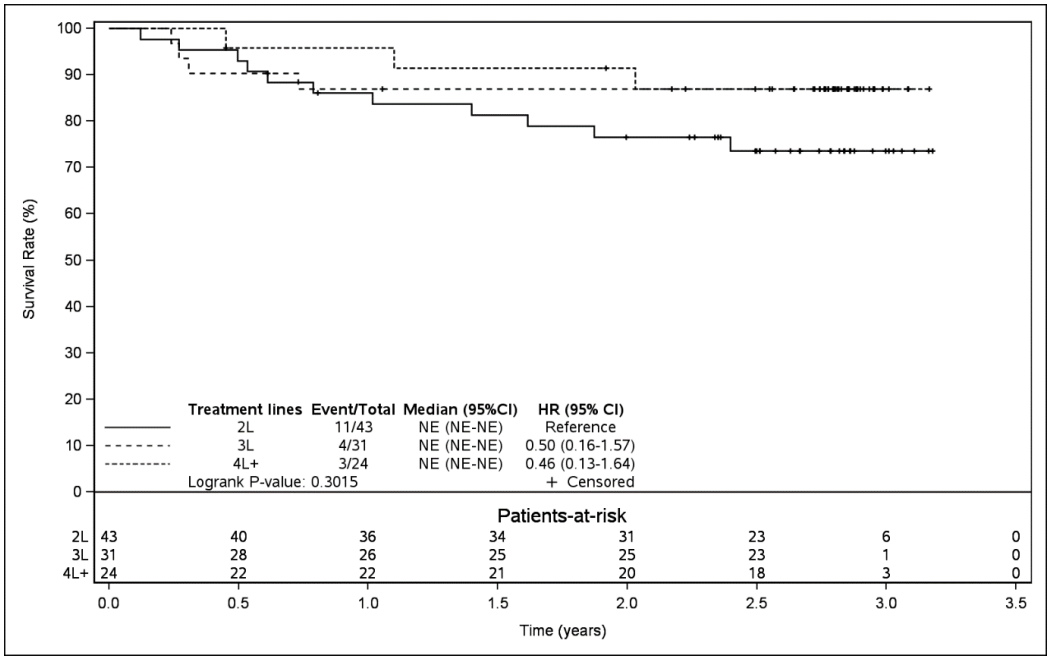


Figure 15.2.3c Duration of molecular Response - FAS (n=139)

10.4.2.1.3.4. Prognostic Factors for molecular Response

The univariable analysis identified 10 predictive factors for cytogenetic response which were significantly associated at the 10% level; sex (p-value=0.0246), ECOG score (p-value=0.0705); concomitant medication (p-value=0.0260), antecedent or comorbidities (p-value=0.0260), Hematological response in last line (p-value=0. 0.0004); Cytogenetic response in last line (p-value=0.0450); Molecular response in last line (p-value=0.0004); Baseline: Total bilirubin (µmol/L) (p-value=0.0658); Baseline: Albumin (g/L) (p-value=0.0477); Baseline: Blood glucose (fasting) (mmol/L) (p-value=0.0586); Baseline: Leukocytes (g/L) (<.0001); Baseline: Platelets (g/L) (p-value=0.0285); Baseline: Blasts (peripheral blood) (%) (p-value=0.0251); Baseline: Basophils (g/L) (p-value=0.0536)

Table 34: Prognostic Factors for molecular Response - Univariable analysis - FAS (n=139)

Variable	Comparison	Pvalue (ML)	OR [95%CI] (ML)	Number of observations used (%)
Age (years)		0.2797	0.98 [0.96-1.01]	139 (100%)
Sex	**Male vs Female**	**0.0246**	**2.33 [1.11-4.96]**	**139 (100%)**
Weight (kg)		0.1463	1.02 [0.99-1.04]	118 (84.9%)
Height (cm)		0.1672	1.03 [0.99-1.08]	134 (96.4%)
BMI (kg/m²)		0.3743	1.03 [0.96-1.11]	116 (83.5%)
ECOG score		**0.0705**		**112 (80.6%)**
ECOG score	1 vs 0	.	0.43 [0.18-1.03]	
ECOG score	2-3 vs 0	.	0.28 [0.07-1.13]	
BCR-ABL mutations		0.4810		139 (100%)
BCR-ABL mutations	BCR vs ABL	.	0.60 [0.20-1.90]	
BCR-ABL mutations	Oth vs ABL	.	0.64 [0.26-1.62]	
SOKAL score		0.6736		126 (90.6%)
SOKAL score	High vs Low	.	0.64 [0.23-1.85]	
SOKAL score	Intermediate vs Low	.	0.97 [0.40-2.36]	
Time between initial diagnosis and initiation of bosutinib treatment (years)		0.2555	1.04 [0.98-1.11]	139 (100%)
Bone marrow karyotype	Yes vs No/Unknown	0.6707	0.77 [0.21-2.39]	139 (100%)
Rearrangement t(9,22) present	Yes vs No/Unknown	0.1732	0.28 [0.01-1.61]	139 (100%)
Concomitant medication	**Yes vs No**	**0.0260**	**Not evaluable**	**139 (100%)**

Variable	Comparison	Pvalue (ML)	OR [95%CI] (ML)	Number of observations used (%)
Number of concomitant medication		0.3218	0.98 [0.95-1.02]	139 (100%)
Antecedent or comorbidities	**Yes vs No**	**0.0260**	**Not evaluable**	**139 (100%)**
Number of antecedent or comorbidities		0.4320	0.98 [0.92-1.04]	139 (100%)
Treatment line		0.7277		139 (100%)
Treatment line	3L vs 2L	.	1.38 [0.59-3.34]	
Treatment line	4L+ vs 2L	.	1.30 [0.52-3.40]	
Last therapy		0.1417		139 (100%)
Last therapy	Dasatinib vs Imatinib	.	2.57 [1.09-6.48]	
Last therapy	Nilotinib vs Imatinib	.	2.08 [0.77-6.33]	
Last therapy	Ponatinib vs Imatinib	.	0.63 [0.02-16.27]	
Hematological response in last line	**Response vs No response/Unknown**	**0.0004**	**Not evaluable**	**139 (100%)**
Cytogenetic response in last line	**Response vs No response/Unknown**	**0.0450**	**2.48 [1.02-6.00]**	**139 (100%)**
Molecular response in last line	**Response vs No response/Unknown**	**0.0004**	**3.91 [1.83-8.55]**	**139 (100%)**
Reason for change of line in last line		0.1505		139 (100%)
Reason for change of line in last line	Intolerance vs Lack of response	.	12.36 [1.72-248.66]	
Reason for change of line in last line	Loss of response vs Lack of response	.	9.60 [1.09-215.33]	
Reason for change of line in last line	Other, specify vs Lack of response	.	16.00 [1.00-702.29]	
Reason for change of line in last line	Suboptimum response vs Lack of response	.	5.78 [0.71-123.45]	
Baseline: ALAT (UI/L)		0.1567	1.02 [0.99-1.07]	101 (72.7%)

Variable	Comparison	Pvalue (ML)	OR [95%CI] (ML)	Number of observations used (%)
Baseline: ASAT (UI/L)		0.1757	1.03 [0.99-1.09]	102 (73.4%)
Baseline: Total bilirubin (µmol/L)		**0.0658**	**1.09 [0.99-1.23]**	**84 (60.4%)**
Baseline: Conjugated bilirubin (µmol/L)		0.6676	1.09 [0.75-1.69]	20 (14.4%)
Baseline: LDH (UI/L)		0.7768	1.00 [1.00-1.00]	50 (36%)
Baseline: Albumin (g/L)		**0.0477**	**1.35 [1.00-2.06]**	**25 (18%)**
Baseline: Amylase (UI/L)		0.2407	1.05 [0.97-1.17]	8 (5.8%)
Baseline: Lipase (UI/L)		0.2515	0.99 [0.97-1.01]	27 (19.4%)
Baseline: Serum creatinine (µmol/L)		0.3680	1.01 [0.99-1.02]	103 (74.1%)
Baseline: Blood glucose (fasting) (mmol/L)		**0.0586**	**3.22 [0.97-42.17]**	**18 (12.9%)**
Baseline: Blood glucose (non-fasting) (mmol/L)		0.8670	1.01 [0.89-1.22]	31 (22.3%)
Baseline: Magnesium (mmol/L)		0.2973	0.00 [0.00-466.64]	18 (12.9%)
Baseline: Calcium (mmol/L)		0.1932	14.18 [0.27-1092.94]	59 (42.4%)
Baseline: Blood urea (mmol/L)		0.6392	0.97 [0.85-1.11]	81 (58.3%)
Baseline: Uric acid (µmol/L)		0.4697	1.00 [0.99-1.00]	42 (30.2%)
Baseline: Hemoglobin (g/dL)		0.5078	1.07 [0.88-1.29]	116 (83.5%)
Baseline: Hematocrit (%)		0.3182	1.04 [0.96-1.14]	115 (82.7%)
Baseline: Leukocytes (g/L)		**<.0001**	**0.89 [0.80-0.96]**	**113 (81.3%)**
Baseline: Platelets (g/L)		**0.0285**	**1.00 [0.99-1.00]**	**111 (79.9%)**
Baseline: Blasts (peripheral blood) (%)		**0.0251**	**0.19 [0.00-0.87]**	**41 (29.5%)**

Variable	Comparison	Pvalue (ML)	OR [95%CI] (ML)	Number of observations used (%)
Baseline: Basophils (g/L)		**0.0536**	**0.70 [0.44-1.01]**	**116 (83.5%)**
Baseline: Eosinophils (g/L)		0.2620	1.11 [0.94-1.47]	116 (83.5%)
Baseline: Neutrophils (g/L)		0.1939	0.99 [0.97-1.01]	116 (83.5%)
Baseline: Monocytes (g/L)		0.6654	1.03 [0.92-1.16]	115 (82.7%)
Baseline: Lymphocytes (g/L)		0.7439	1.01 [0.98-1.04]	116 (83.5%)

Table 15.2.4f Prognostic Factors for molecular Response - Univariable analysis - FAS (n=139)

Only variables with more than 50% available data and factors with at least a 5% level significance were included in the multivariate model. The results revealed no factor significantly associated with molecular response.

Table 35: Prognostic Factors for molecular Response - Multivariable analysis - FAS (n=139)

Step	Effect deleted	Pvalue (Wald)
1	Hematological response in last line	0.9910
2	Sex	0.9829
3	Baseline: Total bilirubin (µmol/L)	0.7589
4	Baseline: Basophils (g/L)	0.5569
5	Cytogenetic response in last line	0.5097
6	ECOG score	0.3709
7	Baseline: Platelets (g/L)	0.3690
8	Baseline: Leukocytes (g/L)	0.0951

Table 15.2.4g Prognostic Factors for molecular Response - Multivariable analysis - FAS (n=139)

10.4.2.2. Time-to-Treatment Failure

Among the 142 patients of the SAF population, 63 presented a discontinuation of bosutinib considered as treatment failure.

At 1 year, 28% of patients presented a treatment failure, at 2 year and 3 years there were 38% and 44% patients respectively, which had a treatment failure (Table 36).

The median time to treatment failure was 3.29 [2.53-NE] years. Regarding time to treatment failure in each subgroup, it appears that median time was only reached for the 3L group at 3.3 [1.4-NE] years (Figure 7).

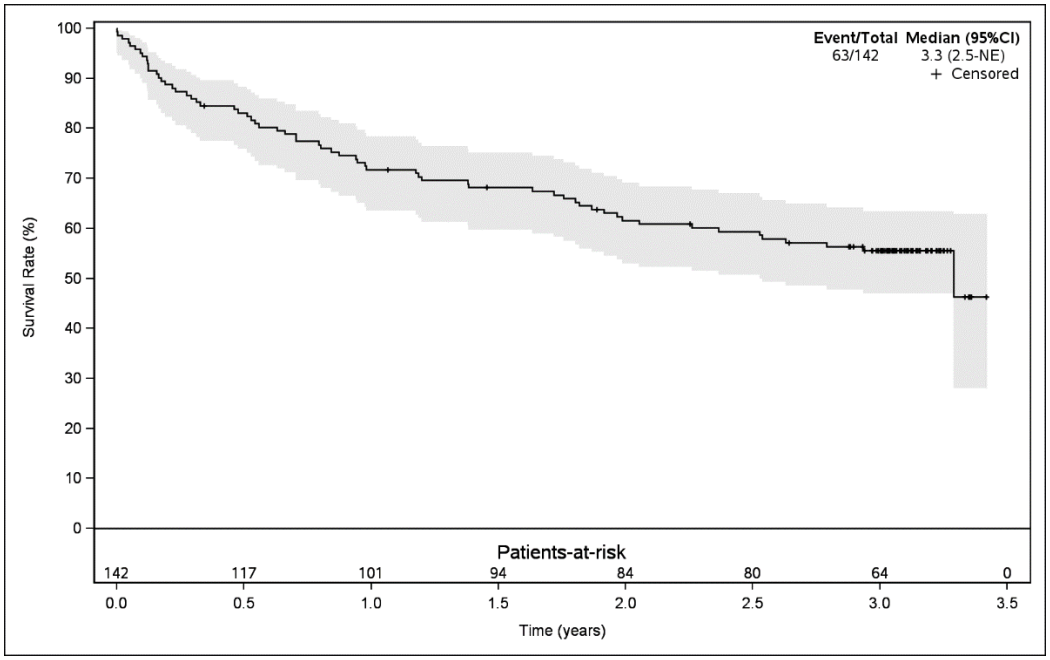
Table 36: Time-to-Treatment Failure - SAF (n=142)

Variables		2L (N=66)	3L (N=42)	4L+ (N=34)	Total (N=142)
Event Time to treatment failure (TTF)	No	36 (54.5%)	21 (50%)	22 (64.7%)	79 (55.6%)
	Yes	30 (45.5%)	21 (50%)	12 (35.3%)	63 (44.4%)
Event/censoring Time to treatment failure (TTF)	Alive and treated with bosutinib	36 (54.5%)	21 (50%)	20 (58.8%)	77 (54.2%)
	Death during bosutinib	0 (0%)	0 (0%)	2 (5.9%)	2 (1.4%)
	Permanent Bosutinib discontinuation (all causes)	30 (45.5%)	21 (50%)	12 (35.3%)	63 (44.4%)

Timepoint	Real time	Survival	[CI95%]	Failure	Erreur type de survie	Number Failed	Number Left	Estimate
1 year	0.98	0.72	[0.64-0.78]	0.28	0.0379	40	101	
2 years	1.99	0.62	[0.53-0.69]	0.38	0.0411	54	84	
3 years	2.93	0.56	[0.47-0.63]	0.44	0.0422	62	64	
Median [CI95%]	.				.	.	.	3.29 [2.53-Not evaluable]

Table 15.3.2a Time-to-Treatment Failure - SAF (n=142)

Figure 7: Time-to-Treatment Failure - SAF (n=142)



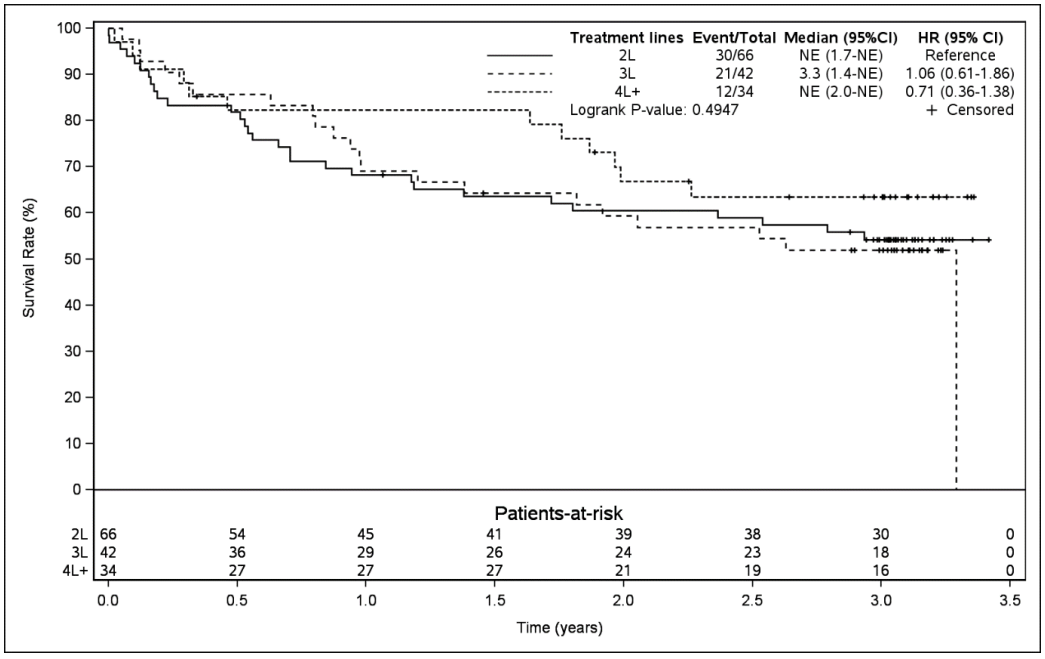


Figure 15.3.2a Time-to-Treatment Failure - SAF (n=142)

10.4.2.3. Progression of CML

Among the FAS population, 5 (3.6%) patients had a progression disease during the study: one patient from the 2L group progressed from AP to AP, 2 progressed from CP to AP and 1 from CP to BP and one patient from 4L+ group progressed from CP to AP.

Table 37: Changes in Disease Phase - FAS (n=139)

Variables		2L (N=64)	3L (N=42)	4L+ (N=33)	Total (N=139)
Progression of CML	No	60 (93.8%)	42 (100%)	32 (97%)	134 (96.4%)
	Yes	4 (6.3%)	0 (0%)	1 (3%)	5 (3.6%)
Progression of CML (description)	AP to AP	1 (25%)		0 (0%)	1 (20%)
	CP to AP	2 (50%)		1 (100%)	3 (60%)
	CP to BP	1 (25%)		0 (0%)	1 (20%)

Table 15.2.5 Changes in Disease Phase - FAS (n=139)

10.4.2.4. Progression free survival

The analyze of Progression Free Survival on the total FAS population revealed that 10 patients had a PFS Event, either death after permanent discontinuation treatment, death during treatment or disease progression. At 1 and 2 years, 96% and 95% of patients respectively were progression free. The median time of PFS was not reached at the cut-off date (Table 38).

Table 38: Progression Free Survival - FAS (n=139)

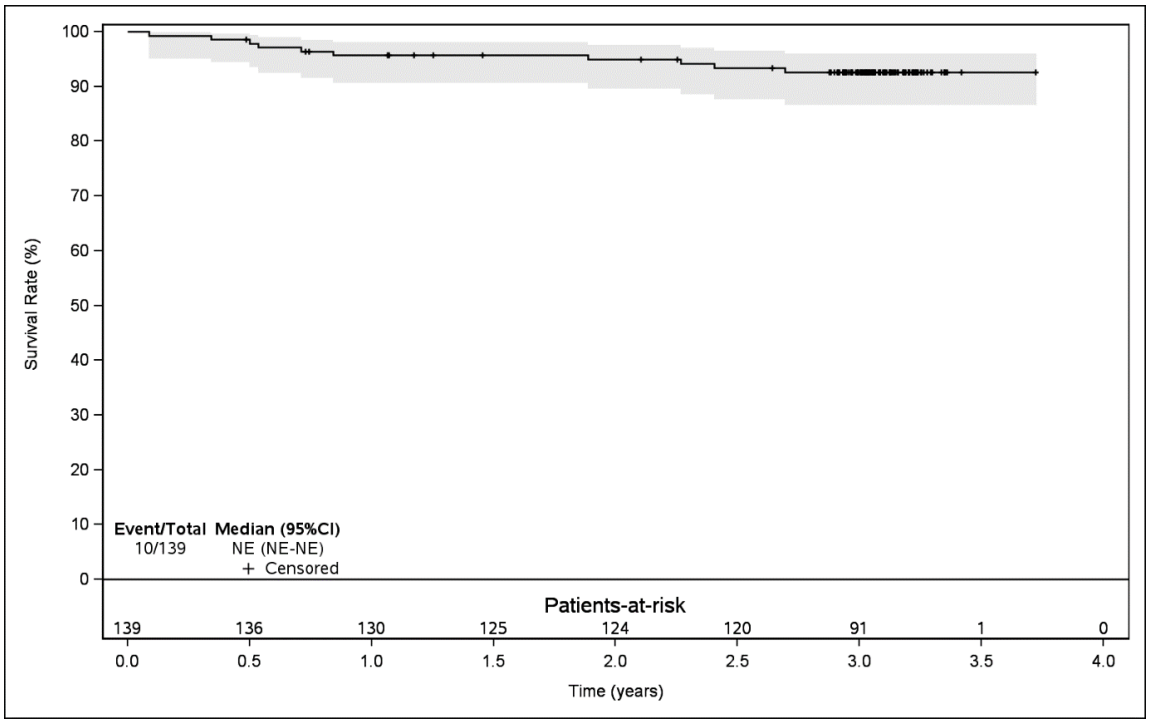
Variables		2L (N=64)	3L (N=42)	4L+ (N=33)	Total (N=139)
Event Progression Free Survival (PFS)	No	59 (92.2%)	41 (97.6%)	29 (87.9%)	129 (92.8%)
	Yes	5 (7.8%)	1 (2.4%)	4 (12.1%)	10 (7.2%)
Event/censoring Progression Free Survival (PFS)	Alive at end of follow-up or lost to follow-up	59 (92.2%)	41 (97.6%)	29 (87.9%)	129 (92.8%)
	Death after permanent discontinuation treatment	1 (1.6%)	1 (2.4%)	1 (3%)	3 (2.2%)
	Death during bosutinib	0 (0%)	0 (0%)	2 (6.1%)	2 (1.4%)
	Disease progression after permanent discontinuation treatment	0 (0%)	0 (0%)	1 (3%)	1 (0.7%)
	Disease progression during bosutinib	4 (6.3%)	0 (0%)	0 (0%)	4 (2.9%)

Timepoint	Real time	Survival	[CI95%]	Failure	Erreur type de survie	Number Failed	Number Left	Estimate
1 year	0.84	0.96	[0.91-0.98]	0.04	0.0174	6	130	

Variables								2L (N=64)	3L (N=42)	4L+ (N=33)	Total (N=139)
2 years	1.89	0.95	[0.9-0.98]	0.05	0.0188	7	124				
3 years	2.69	0.93	[0.87-0.96]	0.07	0.0227	10	91				
Median [CI95%]	.				.	.	.	Not evaluable			

Table 15.2.6a Progression Free Survival - FAS (n=139)

Figure 8: Progression Free Survival - FAS (n=139)



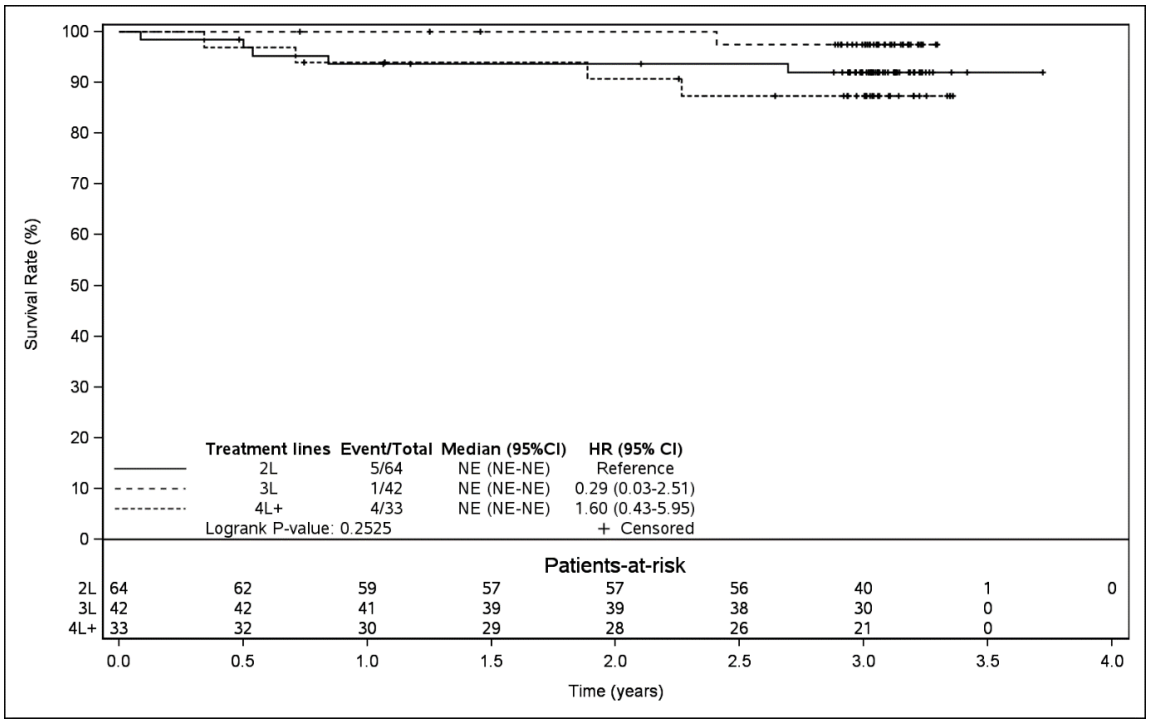


Figure 15.2.6a Progression Free Survival - FAS (n=139)

10.4.2.5. Overall survival

The analysis of overall survival (OS) on the total FAS population revealed that 7 patients had an OS event, either death after permanent discontinuation treatment or death during treatment.

At 1 and 2 years, 98% and 96% of patients respectively, were alive. At 3 years 95% of patients were still alive.

The median overall survival not reached at the cut-off date (Table 39).

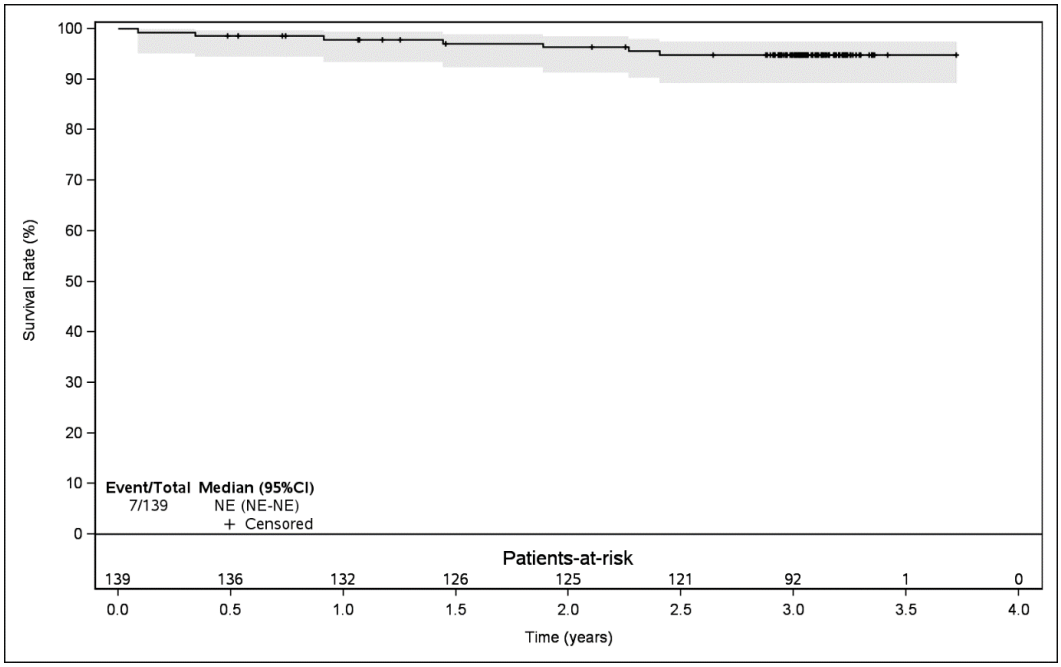
Table 39: Overall Survival - FAS (n=139)

Variables		2L (N=64)	3L (N=42)	4L+ (N=33)	Total (N=139)
Event Overall Survival (OS)	No	62 (96.9%)	41 (97.6%)	29 (87.9%)	132 (95%)
	Yes	2 (3.1%)	1 (2.4%)	4 (12.1%)	7 (5%)
Event/censoring Overall Survival (OS)	Alive at end of follow-up or lost to follow-up	62 (96.9%)	41 (97.6%)	29 (87.9%)	132 (95%)
	Death after permanent discontinuation treatment	2 (3.1%)	1 (2.4%)	2 (6.1%)	5 (3.6%)
	Death during bosutinib	0 (0%)	0 (0%)	2 (6.1%)	2 (1.4%)

Timepoint	Real time	Survival	[CI95%]	Failure	Erreur type de survie	Number Failed	Number Left	Estimate
1 year	0.91	0.98	[0.93-0.99]	0.02	0.0124	3	132	
2 years	1.89	0.96	[0.91-0.98]	0.04	0.0163	5	125	
3 years	2.41	0.95	[0.89-0.97]	0.05	0.0194	7	92	
Median [CI95%]	.				.	.	.	Not evaluable

Table 15.2.7a Overall Survival - FAS (n=139)

Figure 9: Overall Survival - FAS (n=139)



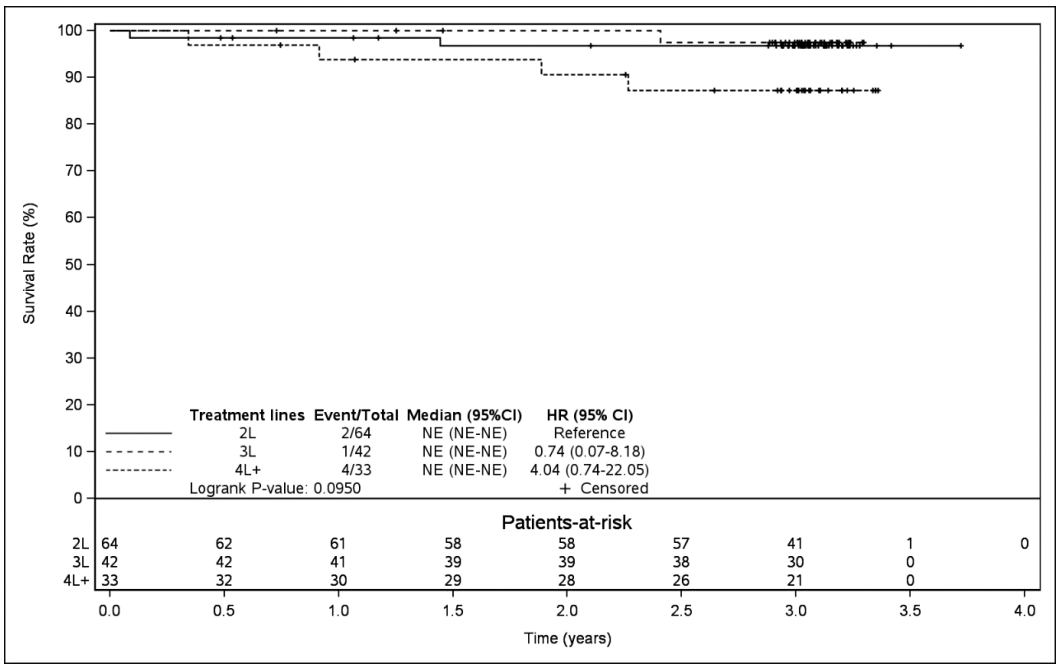


Figure 15.2.7a Overall Survival - FAS (n=139)

10.4.3. Secondary analysis: Safety

10.4.3.1. Treatment modalities for Bosutinib

The initial median dosage prescribed for patients in the 2L group was 200 [100; 200] (mg/day), for the 3L group it was 200 [100 , 300] (mg/day), and for the 4L+ group, it was 200 [100 , 300] (mg/day). Thus, across the entire population, the median dosage was 200 [100 , 300] (mg/day). However, the median dosage during treatment was higher, with patients in the 2L group receiving 326.20 [282.80 ; 440.40] (mg/day), those in the 3L group receiving 306.20 [270.60 ; 391.40] (mg/day), and those in the 4L+ group receiving 264.00 [201.20 ; 303.20] (mg/day). Consequently, the overall median dosage during treatment was 300.00 [252.00 ; 396.80] (mg/day). Regarding dose intensity, median dose appears to be higher in the 2L group, 207.40 [105.10 ; 311.80] %, compared to 3L group and 4L+ group with a mean dose intensity at 148.60 [100.00 ; 245.80] % and 151.60 [100.00 ; 199.20] %, respectively. Relative dose intensity was 65.24 [56.56 ; 88.08] % in the 2L group, 61.240 [54.12 ; 78.28] % in the 3L group and 52.80 [40.24 ; 60.64] % in the 4L+ group.

A majority of patients underwent dose modifications during the study, with 76.1% requiring an increase and 50% requiring a reduction. Specifically, a dose increase was observed in 52 (78.8%) patients in the 2L group, 33 (78.6%) in the 3L group, and 23 (67.6%) in the 4L+ group (see more details in Table 40 and Table 42). Conversely, a dose reduction was noted in 30 (45.5%) patients in the 2L group, 22 (52.4%) in the 3L group, and 19 (55.9%) in the 4L+ group (see more details in Table 40 and Table 41).

Temporary discontinuation of treatment was necessary for 43.7% of patients, lasting an average of 29.4 ± 35.3 days. Although the mean duration was similar across groups, ranging from 26.8 ± 30.3 days in the 3L group to 33.1 ± 44.4 days in the 4L+ group, the median time varied, with durations of 18 [1 ; 123] days in the 2L group, 16 [1 ; 97] days in the 3L group, and 7 [1 ; 160] days in the 4L+ group, indicating differences in treatment discontinuation patterns according to the treatment line.

Moreover, permanent discontinuation was recorded for 63 (44.4%) patients, with 30 (45.5%) in the 2L group, 21 (50%) in the 3L group, and 12 (35.3%) in the 4L+ group. The primary reasons for

permanent discontinuation were intolerance (61.9%) and suboptimal response (23.8%), while discontinuation due to disease progression or death were reported for only 2 patients each.

The cumulative duration of treatment slightly increased according to the number of previous treatment line, with an average duration of 2.92 [0.50 ; 3.06] years in the 2L group, 2.63 [0.87 ; 3.10] years in the 3L group, and 2.85 [1.87 ; 3.10]years in the 4L+ group.

Treatment modalities for bosutinib are summarized in Table 40.

Table 40: Treatment Modalities for Bosutinib - SAF (n=142)

Variables		2L (N=66)	3L (N=42)	4L+ (N=34)	Total (N=142)
Dosage prescribed at time of initiation (mg/day)	N	66	42	34	142
	Mean ± SD	192.4 ± 120.7	223.8 ± 110.0	200.0 ± 104.4	203.5 ± 113.9
	Median	200.0	200.0	200.0	200.0
	Q1 ; Q3	100.0 ; 200.0	100.0 ; 300.0	100.0 ; 300.0	100.0 ; 300.0
	Min. ; Max.	100 ; 500	100 ; 500	100 ; 500	100 ; 500
	Missing	0	0	0	0
Average dose during the treatment (mg/day)	N	59	39	33	131
	Mean ± SD	345.97 ± 106.43	323.18 ± 89.43	268.03 ± 98.49	319.55 ± 103.80
	Median	326.20	306.20	264.00	300.00
	Q1 ; Q3	282.80 ; 440.40	270.60 ; 391.40	201.20 ; 303.20	252.00 ; 396.80
	Min. ; Max.	59.6 ; 500	168.8 ; 500	57 ; 496.8	57 ; 500
	Missing	7	3	1	11
Patients with dose increase	No	14 (21.2%)	9 (21.4%)	11 (32.4%)	34 (23.9%)
	Yes	52 (78.8%)	33 (78.6%)	23 (67.6%)	108 (76.1%)

Variables		2L (N=66)	3L (N=42)	4L+ (N=34)	Total (N=142)
Patients with dose reduction	No	36 (54.5%)	20 (47.6%)	15 (44.1%)	71 (50%)
	Yes	30 (45.5%)	22 (52.4%)	19 (55.9%)	71 (50%)
Dose intensity (%)	N	59	39	33	131
	Mean ± SD	230.465 ± 122.176	175.344 ± 91.076	160.665 ± 77.454	196.472 ± 107.447
	Median	207.400	148.600	151.600	163.400
	Q1 ; Q3	105.100 ; 311.800	100.000 ; 245.800	100.000 ; 199.200	100.000 ; 265.000
	Min. ; Max.	59.6 ; 488.6	55.7 ; 450.8	57 ; 392.4	55.7 ; 488.6
	Missing	7	3	1	11
Relative dose intensity (%)	N	59	39	33	131
	Mean ± SD	69.193 ± 21.285	64.637 ± 17.887	53.606 ± 19.698	63.910 ± 20.759
	Median	65.240	61.240	52.800	60.000
	Q1 ; Q3	56.560 ; 88.080	54.120 ; 78.280	40.240 ; 60.640	50.400 ; 79.360
	Min. ; Max.	11.92 ; 100	33.76 ; 100	11.4 ; 99.36	11.4 ; 100
	Missing	7	3	1	11
Temporary discontinuation of treatment	No	36 (54.5%)	28 (66.7%)	16 (47.1%)	80 (56.3%)
	Yes	30 (45.5%)	14 (33.3%)	18 (52.9%)	62 (43.7%)

Variables		2L (N=66)	3L (N=42)	4L+ (N=34)	Total (N=142)
Duration of temporary discontinuations (days)	N	25	12	17	54
	Mean ± SD	28.1 ± 31.6	26.8 ± 30.3	33.1 ± 44.4	29.4 ± 35.3
	Median	18.0	16.0	7.0	16.0
	Q1 ; Q3	5.0 ; 30.0	8.5 ; 30.0	4.0 ; 36.0	5.0 ; 36.0
	Min. ; Max.	1 ; 123	1 ; 97	1 ; 160	1 ; 160
	Missing	5	2	1	8
Cumulative duration of treatment (years)	N	61	40	33	134
	Mean ± SD	1.978 ± 1.308	2.059 ± 1.175	2.257 ± 1.102	2.071 ± 1.217
	Median	2.920	2.630	2.850	2.810
	Q1 ; Q3	0.500 ; 3.060	0.870 ; 3.105	1.870 ; 3.100	0.790 ; 3.080
	Min. ; Max.	0 ; 3.42	0.04 ; 3.29	0.02 ; 3.35	0 ; 3.42
	Missing	5	2	1	8
Permanent discontinuation	No	36 (54.5%)	21 (50%)	22 (64.7%)	79 (55.6%)
	Yes	30 (45.5%)	21 (50%)	12 (35.3%)	63 (44.4%)
Reason for permanent discontinuation	Death (ADENOCARCINOME PEU DIFFERENCIE POLYMETASTATIQUE)	1 (3.3%)	0 (0%)	0 (0%)	1 (1.6%)
	Death (DEFAILLANCE MULTIVISCERALE)	0 (0%)	0 (0%)	1 (8.3%)	1 (1.6%)
	Disease progression (Accelerated phase)	1 (3.3%)	0 (0%)	0 (0%)	1 (1.6%)
	Disease progression (Blast crisis)	1 (3.3%)	0 (0%)	0 (0%)	1 (1.6%)

Variables		2L (N=66)	3L (N=42)	4L+ (N=34)	Total (N=142)
	Intolerance	19 (63.3%)	13 (61.9%)	7 (58.3%)	39 (61.9%)
	Loss of response	1 (3.3%)	0 (0%)	0 (0%)	1 (1.6%)
	Patient's choice	2 (6.7%)	1 (4.8%)	1 (8.3%)	4 (6.3%)
	Suboptimum response	5 (16.7%)	7 (33.3%)	3 (25%)	15 (23.8%)

Table 15.4.2a Treatment Modalities for Bosutinib - SAF (n=142)

10.4.3.2. Reasons for dose modifications

In this section "N=XX" mentioned in the column of each subgroup and total, correspond to the number of events, not to the population effective.

10.4.3.2.1. Reasons for dose reduction

As mentioned previously, a dose reduction was reported in 30 (45.5%) patients from 2L group, 22 (52.4%) patients in the 3L group and 19 (55.9%) patients in the 4L+ group.

Main reason for dose reduction was AE which was related to 90 (80.4%) dose reduction in total, 37 (77.1%) in the 2L group, 30 (88.2%) in the 3L group and 23 (76.7%) in the 4L+ group. Reasons for reduction are details in Table 41.

Table 41: Reasons for dose reduction - SAF (n=142)

Variables		2L (N=48)	3L (N=34)	4L+ (N=30)	Total (N=112)
Reasons for dose reduction	AGGRAVATION OF CHRONIC RENAL INSUFFICIENCY	1 (2.1%)	0 (0%)	0 (0%)	1 (0.9%)
	WEIGHT LOSS	0 (0%)	0 (0%)	1 (3.3%)	1 (0.9%)
	AFTER STOPPING, PATIENT RESUMED AT 300 MG DUE TO RESPONSE	1 (2.1%)	0 (0%)	0 (0%)	1 (0.9%)
	GOOD RESPONSE	1 (2.1%)	1 (2.9%)	0 (0%)	2 (1.8%)
	INVESTIGATOR'S CHOICE	1 (2.1%)	1 (2.9%)	0 (0%)	2 (1.8%)
	PATIENT'S CHOICE	2 (4.2%)	0 (0%)	0 (0%)	2 (1.8%)

Variables		2L (N=48)	3L (N=34)	4L+ (N=30)	Total (N=112)
	COMMON DECISION OF HEMATOLOGIST AND PNEUMOLOGIST TO ASSESS THE FOLLOW-UP OF PLEURAL EFFUSIONS	0 (0%)	1 (2.9%)	0 (0%)	1 (0.9%)
	AE	37 (77.1%)	30 (88.2%)	23 (76.7%)	90 (80.4%)
	IN AGREEMENT WITH NEPHROLOGIST	1 (2.1%)	0 (0%)	0 (0%)	1 (0.9%)
	DUE TO TRAMADOL	1 (2.1%)	0 (0%)	0 (0%)	1 (0.9%)
	THE PATIENT SOMETIMES TAKES 200MG	0 (0%)	0 (0%)	1 (3.3%)	1 (0.9%)
	NOT PRECISED	0 (0%)	1 (2.9%)	0 (0%)	1 (0.9%)
	PATIENT STATES TAKING 100MG /DAY	0 (0%)	0 (0%)	1 (3.3%)	1 (0.9%)
	RESUMPTION AFTER TEMPORARY STOP DUE TO PLEURAL EFFUSION	1 (2.1%)	0 (0%)	0 (0%)	1 (0.9%)
	RESUMPTION AFTER AE	1 (2.1%)	0 (0%)	0 (0%)	1 (0.9%)
	RESUMPTION AFTER PREGNANCY	0 (0%)	0 (0%)	1 (3.3%)	1 (0.9%)
	RESUMPTION OF BOSUTINIB	0 (0%)	0 (0%)	2(5.6%)	2 (1.8%)
	RM5 LESIONS	0 (0%)	0 (0%)	1 (3.3%)	1 (0.9%)
	SUPPLY SHORTAGE	1 (2.1%)	0 (0%)	0 (0%)	1 (0.9%)

Table 15.4.2b Reasons for dose reduction - SAF (n=142); when it was possible, similar reason were grouped: patient's choice and investigator's choice compared to source table. See **Appendix 7.13** for source table .

10.4.3.2.2. Reasons for dose increase

Indeed, a dose increase was reported in 52 (78.8%) patients from 2L group, 33 (78.6%) patients in the 3L group and23 (67.6%) patients in the 4L+ group.

Main reasons for dose increase were dose adaptation/optimization for 187(66,55%) cases and investigator's decision 46 (16,37%).

Table 42: Reasons for dose increase - SAF (n=142)

Variables		2L (N=143)		3L (N=82)		4L+ (N=56)		Total (N=281)	
Reasons for dose increase	ADAPTATION	2	1,40%	0	0,00%	0	0,00%	2	0,71%
	DOSE ADAPTATION / DOSE OPTIMISATION	112	78,32%	43	52,44%	32	57,14%	187	66,55%
	PROGRESSIVE IMPROVEMENT OF LIVER FUNCTION	0	0,00%	1	1,22%	0	0,00%	1	0,36%
	PREVENTIV DISCONTINUATION FOR TRAVEL	0	0,00%	0	0,00%	2	3,57%	2	0,71%
	DOSE INCREASE	0	0,00%	0	0,00%	1	1,79%	1	0,36%
	DOSE INCREASE AFTER DISCONTINUATION	4	2,80%	2	2,44%	2	3,57%	8	2,85%
	INCREASE ACCORDING TO RCP	5	3,50%	2	2,44%	2	3,57%	9	3,20%
	INVESTIGATOR S DECISION	15	10,49%	24	29,27%	7	12,50%	46	16,37%
	DISAPPEARANCE OF DIARRHEA	1	0,70%	0	0,00%	0	0,00%	1	0,36%
	AE	1	0,70%	2	2,44%	1	1,79%	4	1,42%
	DISEASE PROGRESSION	1	0,70%	0	0,00%	0	0,00%	1	0,36%
	GOOD TOLERANCE	1	0,70%	0	0,00%	0	0,00%	1	0,36%

THE PATIENT SHOULD INCREASE TO 300 MG AFTER 15 DAYS OF TREATMENT	0	0,00%	1	1,22%	0	0,00%	1	0,36%
TOO HIGH RESIDUAL DISEASE	0	0,00%	1	1,22%	0	0,00%	1	0,36%
NOT SPECIFIED	0	0,00%	1	1,22%	0	0,00%	1	0,36%
NEW DOSE AFTER INITIATION	0	0,00%	0	0,00%	1	1,79%	1	0,36%
TREATMENT INITIATION	0	0,00%	0	0,00%	2	3,57%	2	0,71%
LOSS OF RESPONSE	1	0,70%	3	3,66%	6	10,71%	10	3,56%
RESOLUTION AE	0	0,00%	1	1,22%	0	0,00%	1	0,36%
STABLE MOLECULAR RESPONSE	0	0,00%	1	1,22%	0	0,00%	1	0,36%

Table 15.4.2c Reasons for dose increase - SAF (n=142): In order to analyze the results, groupings were made for reasons for dose increase. Thus, the following reasons are grouped under the term "dose adaptation/ dose optimization": dose adaptation, planned increase, gradual increase, good tolerance, non-optimal dose, planned dose escalation, suboptimal response, Bosutinib step optimization, medical prescription, planned per protocol, protocol to achieve effective dose, increase for better efficacy, and dose escalation scheme. The following reasons are grouped under the term “dose increase after discontinuation”: resumption and dose increase after discontinuation. See **Appendix 7.13** for source table in French.

10.4.3.2.3. Reasons for temporary discontinuation of treatment

The main reason for temporary discontinuation was AE (76.5%), indeed, in the 2L group 47 (72.3%) temporary discontinuation were due to an AE, 30 (85.7%) in the 3L group and 24 (75%) patients in the 4L+ group had a temporary discontinuation related to AE. Main reasons for temporary discontinuation were AEs 101 (76.5%), found in equivalent proportions across the groups of treatment line. Other reasons included patient's choice (8.3%) equally found in subgroups and poor compliance (6.8%) mostly in the 2L group (Table 43).

Table 43: Reasons for temporary discontinuation of treatment - SAF (n=142)

Variables		2L (N=65)	3L (N=35)	4L+ (N=32)	Total (N=132)
Reasons for temporary discontinuation	PATIENT'S CHOICE	4 (6.1%)	2 (5.7%)	5 (15.6%)	11 (8.3%)
	ADVERSE EVENT	47 (72.3%)	30 (85.7%)	24 (75%)	101 (76.5%)
	COLOSCOPY	1 (1.5%)	0 (0%)	0 (0%)	1 (0.8%)
	MOVING	0 (0%)	0 (0%)	1 (3.1%)	1 (0.8%)
	DESIR OF PREGNANCY	0 (0%)	0 (0%)	1 (3.1%)	1 (0.8%)
	FIBROMYALGIA KNOWN BEFORE TREATMENT	1 (1.5%)	0 (0%)	0 (0%)	1 (0.8%)
	UNKNOWN	0 (0%)	2 (5.7%)	0 (0%)	2 (1.5%)
	POOR COMPLAINCE	8 (12.3%)	0 (0%)	1 (3.1%)	9 (6.8%)
	INVESTIGATOR S DECISION PRECONISER PAR INVESTIGATEUR POUR EFFECTUER LA VACCINATION COVID	1 (1.5%)	1 (2.9%)	0 (0%)	2 (1.5%)

SOTCKOUT	2 (3.0%)	0 (0%)	0 (0%)	2 (1.6%)
UNKNOWN	1 (1.5%)	0 (0%)	0 (0%)	1 (0.8%)

Table 15.4.2d Reasons for temporary discontinuation of treatment - SAF (n=142): In order to analyze the results, groupings were made for reasons for reasons for temporary discontinuation of treattment. Thus, the following reasons are grouped under the term "Patient’s choice": stop by the patient due to a blistering skin lesion on the finger, stop by the patient for the holidays, patient's decision for her comfort on the day of the hospital consultation, patient’s decision. The following reasons are grouped under the term “poor compliance”: patient forgetfulness, forgot and poor compliance. See **Appendix 7.13** for source table in French.

10.4.3.3. Duration of Treatment

10.4.3.3.1. Duration of Treatment (all causes)

Considering duration of treatment, among the 142 patients, 62 had a temporary discontinuation (all causes). Indeed, 76 patients were censored, for they were alive and treated with bosutinib and 4 died and never had a temporary discontinuation.

Overall, 34% of patients needed a temporary discontinuation during the first year of treatment, then at 3 years of treatment 45% of patients had a temporary discontinuation, at the cutoff date the duration of treatment did not reach the median (Table 44).

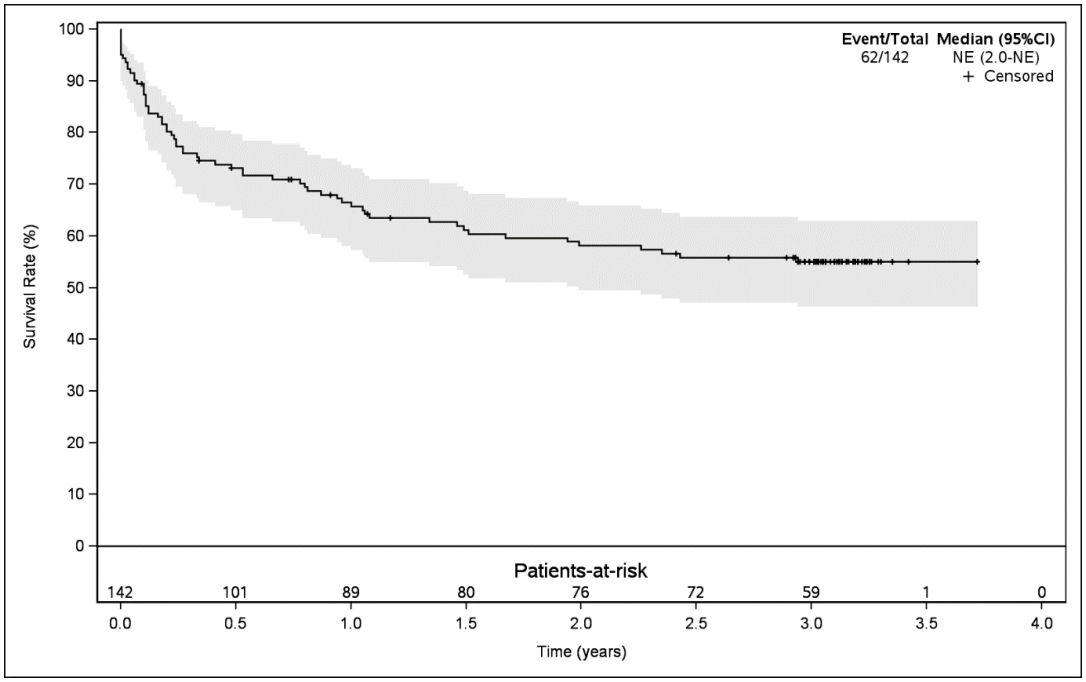
Table 44: Duration of Treatment (all causes) - SAF (n=142)

Variables		2L (N=66)	3L (N=42)	4L+ (N=34)	Total (N=142)
Event Duration of Treatment (all causes)	No	36 (54.5%)	28 (66.7%)	16 (47.1%)	80 (56.3%)
	Yes	30 (45.5%)	14 (33.3%)	18 (52.9%)	62 (43.7%)
Event/censoring Duration of Treatment (all causes)	Alive and treated with bosutinib	35 (53%)	27 (64.3%)	14 (41.2%)	76 (53.5%)
	Bosutinib temporary discontinuation (all causes)	30 (45.5%)	14 (33.3%)	18 (52.9%)	62 (43.7%)
	Death during bosutinib	1 (1.5%)	1 (2.4%)	2 (5.9%)	4 (2.8%)

Timepoint	Real time	Survival	[CI95%]	Failure	Erreur type de survie	Number Failed	Number Left	Estimate
1 year	1	0.66	[0.57-0.73]	0.34	0.0402	48	88	
2 years	1.99	0.58	[0.49-0.66]	0.42	0.0421	58	76	
3 years	2.94	0.55	[0.46-0.63]	0.45	0.0427	62	59	
Median [CI95%]	.				.	.	.	Not evaluable

Table 15.4.3a Duration of Treatment (all causes) - SAF (n=142)

Figure 10: Duration of Treatment (all causes) - SAF (n=142)



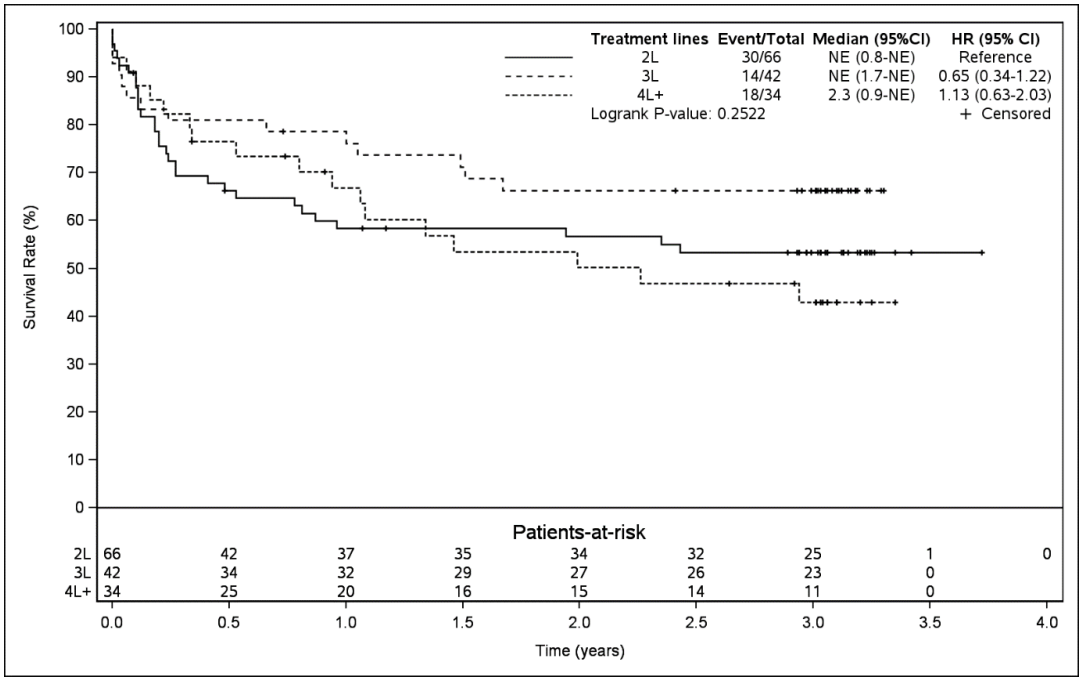


Figure 15.4.3a Duration of Treatment (all causes) - SAF (n=142)

10.4.3.3.2. Duration of Treatment (AE causes)

Considering duration of treatment, among the 142 patients, 56 had a temporary discontinuation (AE causes). Indeed, 82 patients were censored, for they were alive and treated with bosutinib without having a temporary discontinuation due to AE and 4 died and never had a temporary discontinuation.

It has been observed that 71% of patients did not have a temporary discontinuation after 1 year of treatment, then 63% after 2 years and 59% at 3 years.

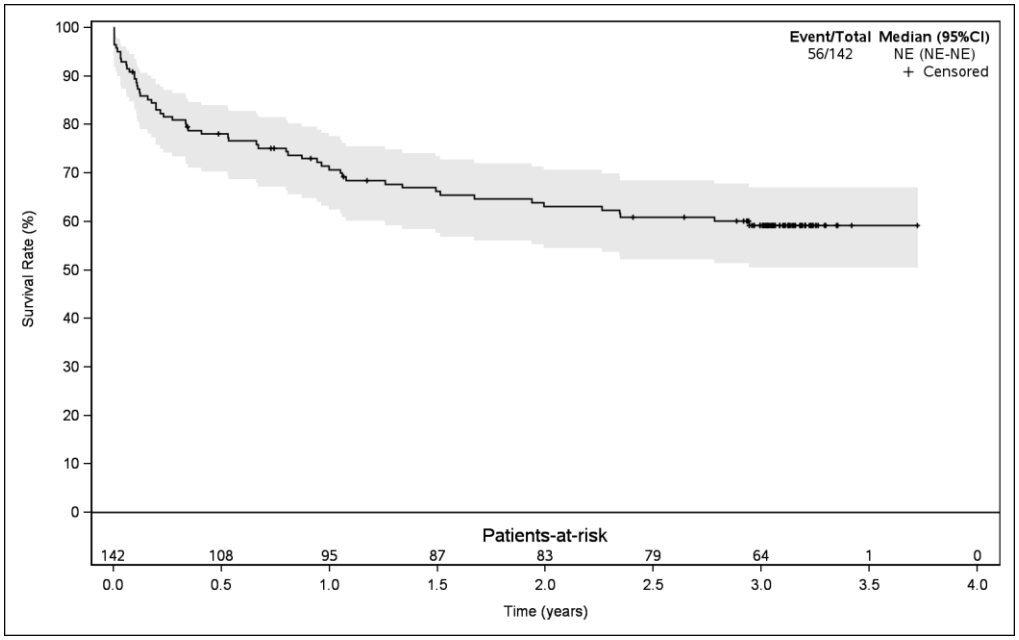
Table 45: Duration of Treatment (AE causes) - SAF (n=142)

Variables		2L (N=66)	3L (N=42)	4L+ (N=34)	Total (N=142)
Event Duration of Treatment (AE causes)	No	40 (60.6%)	28 (66.7%)	18 (52.9%)	86 (60.6%)
	Yes	26 (39.4%)	14 (33.3%)	16 (47.1%)	56 (39.4%)
Event/censoring Duration of Treatment (AE causes)	Alive and treated with bosutinib	39 (59.1%)	27 (64.3%)	16 (47.1%)	82 (57.7%)
	Bosutinib temporary discontinuation (AE causes)	26 (39.4%)	14 (33.3%)	16 (47.1%)	56 (39.4%)
	Death during bosutinib	1 (1.5%)	1 (2.4%)	2 (5.9%)	4 (2.8%)

Timepoint	Real time	Survival	[CI95%]	Failure	Erreur type de survie	Number Failed	Number Left	Estimate
1 year	1	0.71	[0.62-0.78]	0.29	0.0385	41	95	
2 years	1.99	0.63	[0.55-0.71]	0.37	0.0412	51	83	
3 years	2.94	0.59	[0.51-0.67]	0.41	0.0422	56	64	
Median [CI95%]	.				.	.	.	Not evaluable

Table 15.4.3b Duration of Treatment (AE causes) - SAF (n=142)

Figure 11: Duration of Treatment (AE causes) - SAF (n=142)



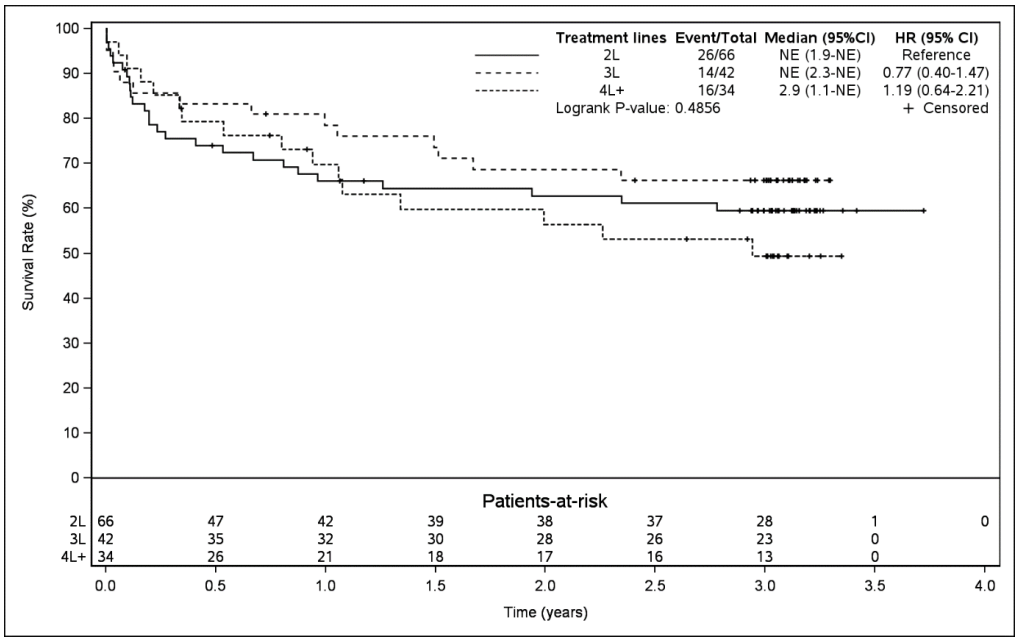


Figure 15.4.3b Duration of Treatment (AE causes) - SAF (n=142)

10.4.3.3.3. Duration of Treatment (other causes)

Considering duration of treatment, among the 142 patients, 17 had a temporary discontinuation due to other causes than AE. Indeed, 119 patients were censored, for they were alive and treated with bosutinib without having a temporary discontinuation due to another cause and 6 died and never had a temporary discontinuation due to another cause.

It has been observed that 92% of patients did not have a temporary discontinuation after 1 year of treatment, then 90% after 2 years and 87% at 3 years (Figure 12).

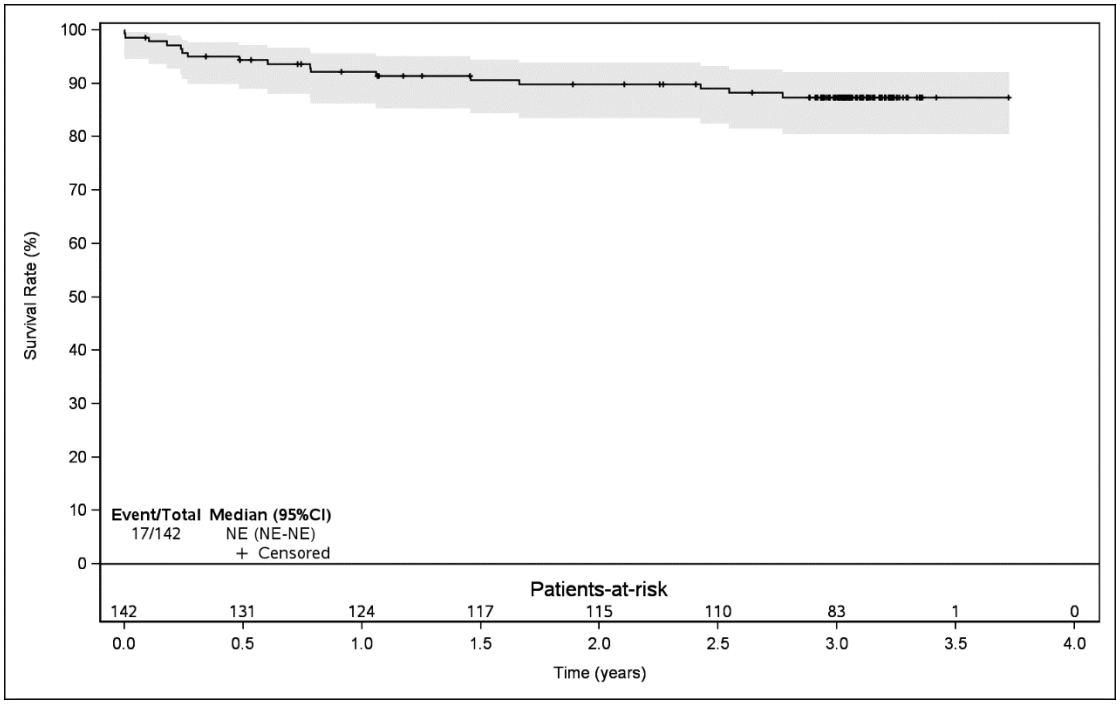
Table 46: Duration of Treatment (other causes) - SAF (n=142)

Variables		2L (N=66)	3L (N=42)	4L+ (N=34)	Total (N=142)
Event Duration of Treatment (other causes)	No	56 (84.8%)	39 (92.9%)	30 (88.2%)	125 (88%)
	Yes	10 (15.2%)	3 (7.1%)	4 (11.8%)	17 (12%)
Event/censoring Duration of Treatment (other causes)	Alive and treated with bosutinib	55 (83.3%)	38 (90.5%)	26 (76.5%)	119 (83.8%)
	Bosutinib temporary discontinuation (other causes)	10 (15.2%)	3 (7.1%)	4 (11.8%)	17 (12%)
	Death during bosutinib	1 (1.5%)	1 (2.4%)	4 (11.8%)	6 (4.2%)

Timepoint	Real time	Survival	[CI95%]	Failure	Erreur type de survie	Number Failed	Number Left	Estimate
1 year	0.79	0.92	[0.86-0.96]	0.08	0.0228	11	124	
2 years	1.66	0.90	[0.83-0.94]	0.10	0.0258	14	115	
3 years	2.77	0.87	[0.8-0.92]	0.13	0.0287	17	83	
Median [CI95%]	.				.	.	.	Not evaluable

Table 15.4.3c Duration of Treatment (other causes) - SAF (n=142)

Figure 12: Duration of Treatment (other causes) - SAF (n=142)



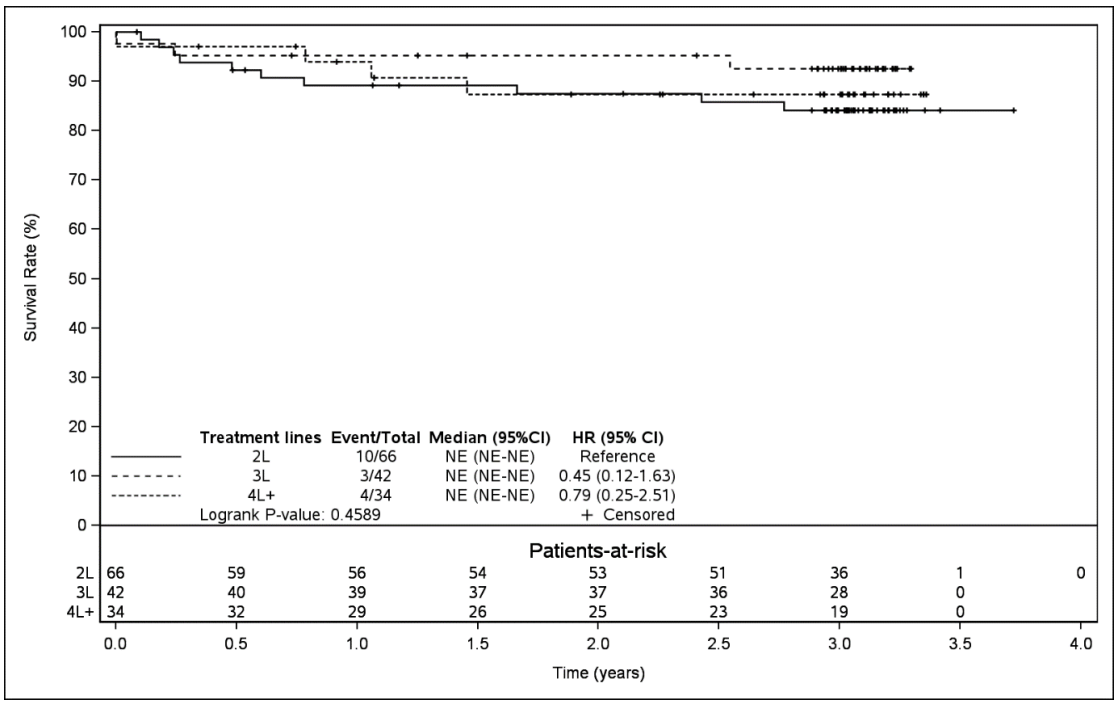


Figure 15.4.3c Duration of Treatment (other causes) - SAF (n=142)

10.4.3.4. Adherence to treatment: Morisky total scores

Treatment adherence was assessed using the Morisky score during each follow-up visit, revealing that the majority of patients treated with bosutinib demonstrated high adherence to treatment. This ranged from 54.9% of patient with high adherence at 3 months to 58.6% at 36 months, with a maximum of 78.1% at 15 months. However, data for 51 patients were missing at the 3-month mark, increasing to 113 missing data points at 36 months.

Regarding adherence according to group, scores were similar with the vast majority of patients presenting high adherence or average adherence.

The mean score for the entire population at 3 months was 0.753 ± 1.248, with no significant differences observed throughout the study, maintaining a mean score of 0.621 ± 1.123 at 36 months.

Regarding scores in the 2L group, it ranged from 0.843 ± 1.341 at 3 months to 0.529 ± 1.355 at 36 months, with a minimum of 0.182 ± 0.501 at 18 months and a maximum of 1.036 ± 1.982 at 27 months, without a linear tendency from visit to visit.

Regarding scores in the 3L group, it ranged from 0.870 ± 1.447 at 3 months to 0.643 ± 0.734 at 36 months, with a minimum of 0.107 ± 0.289 at 24 months and a maximum of 1.389 ± 2.315 at 33 months, without a linear tendency from visit to visit.

Regarding scores in the 4L+ group, it ranged from 0.417 ± 0.599 at 3 months to 0.900 ± 0.742 at 36 months, with a minimum of 0.167 ± 0.514 at 15 months and a maximum of 0.905 ± 1.147 at 12 months, without a linear tendency from visit to visit.

Detailed Morisky scores are presented in Table 47 as mean score by visit as well as for absolute changes from baseline to each follow-up visit.

Table 47: Morisky total scores and absolute change - SAF (n=142)

Variables		2L (N=66)	3L (N=42)	4L+ (N=34)	Total (N=142)
Month 3	N	43	27	21	91
	Mean ± SD	0.843 ± 1.341	0.870 ± 1.447	0.417 ± 0.599	0.753 ± 1.248
	Median	0.000	0.000	0.000	0.000
	Q1 ; Q3	0.000 ; 1.500	0.000 ; 1.000	0.000 ; 1.000	0.000 ; 1.000
	Min. ; Max.	0 ; 6	0 ; 7	0 ; 2	0 ; 7
	Missing	23	15	13	51
Month 6	N	43	21	18	82
	Mean ± SD	0.698 ± 1.483	0.643 ± 0.960	0.639 ± 0.850	0.671 ± 1.233
	Median	0.000	0.000	0.000	0.000
	Q1 ; Q3	0.000 ; 1.000	0.000 ; 1.000	0.000 ; 1.250	0.000 ; 1.000
	Min. ; Max.	0 ; 7	0 ; 3	0 ; 2	0 ; 7
	Missing	23	21	16	60
Month 9	N	35	26	16	77
	Mean ± SD	1.000 ± 1.762	0.365 ± 0.920	0.594 ± 0.632	0.701 ± 1.352
	Median	0.000	0.000	0.625	0.000
	Q1 ; Q3	0.000 ; 1.500	0.000 ; 0.000	0.000 ; 1.000	0.000 ; 1.000
	Min. ; Max.	0 ; 7	0 ; 3.25	0 ; 2	0 ; 7
	Missing	31	16	18	65
Month 12	N	28	21	15	64
	Mean ± SD	0.911 ± 1.919	0.905 ± 1.147	0.767 ± 1.821	0.875 ± 1.654
	Median	0.000	0.000	0.000	0.000
	Q1 ; Q3	0.000 ; 0.625	0.000 ; 2.000	0.000 ; 1.000	0.000 ; 1.500
	Min. ; Max.	0 ; 7	0 ; 3.5	0 ; 7	0 ; 7
	Missing	38	21	19	78

Variables		2L (N=66)	3L (N=42)	4L+ (N=34)	Total (N=142)
Month 15	N	27	19	18	64
	Mean ± SD	0.380 ± 0.902	0.553 ± 0.892	0.167 ± 0.514	0.371 ± 0.810
	Median	0.000	0.000	0.000	0.000
	Q1 ; Q3	0.000 ; 0.000	0.000 ; 1.000	0.000 ; 0.000	0.000 ; 0.000
	Min. ; Max.	0 ; 4	0 ; 2.25	0 ; 2	0 ; 4
	Missing	39	23	16	78
Month 18	N	22	21	12	55
	Mean ± SD	0.182 ± 0.501	0.571 ± 0.891	0.583 ± 1.443	0.418 ± 0.924
	Median	0.000	0.000	0.000	0.000
	Q1 ; Q3	0.000 ; 0.000	0.000 ; 1.000	0.000 ; 0.500	0.000 ; 0.000
	Min. ; Max.	0 ; 2	0 ; 2.25	0 ; 5	0 ; 5
	Missing	44	21	22	87
Month 21	N	24	14	16	54
	Mean ± SD	0.531 ± 1.415	0.446 ± 0.695	0.313 ± 0.793	0.444 ± 1.083
	Median	0.000	0.000	0.000	0.000
	Q1 ; Q3	0.000 ; 0.000	0.000 ; 1.000	0.000 ; 0.000	0.000 ; 0.000
	Min. ; Max.	0 ; 5.25	0 ; 2.25	0 ; 3	0 ; 5.25
	Missing	42	28	18	88
Month 24	N	25	14	14	53
	Mean ± SD	0.470 ± 0.873	0.107 ± 0.289	0.571 ± 0.958	0.401 ± 0.797
	Median	0.000	0.000	0.000	0.000
	Q1 ; Q3	0.000 ; 1.000	0.000 ; 0.000	0.000 ; 1.000	0.000 ; 0.500
	Min. ; Max.	0 ; 3	0 ; 1	0 ; 3	0 ; 3
	Missing	41	28	20	89
Month 27	N	21	9	7	37
	Mean ± SD	1.036 ± 1.982	0.333 ± 0.500	0.500 ± 0.764	0.764 ± 1.561
	Median	0.000	0.000	0.000	0.000

Variables		2L (N=66)	3L (N=42)	4L+ (N=34)	Total (N=142)
	Q1 ; Q3	0.000 ; 1.000	0.000 ; 1.000	0.000 ; 1.000	0.000 ; 1.000
	Min. ; Max.	0 ; 7	0 ; 1	0 ; 2	0 ; 7
	Missing	45	33	27	105
Month 30	N	23	11	7	41
	Mean ± SD	0.728 ± 1.496	0.591 ± 0.970	0.357 ± 0.476	0.628 ± 1.233
	Median	0.000	0.000	0.000	0.000
	Q1 ; Q3	0.000 ; 1.000	0.000 ; 1.000	0.000 ; 1.000	0.000 ; 1.000
	Min. ; Max.	0 ; 7	0 ; 3	0 ; 1	0 ; 7
	Missing	43	31	27	101
Month 33	N	17	9	9	35
	Mean ± SD	0.912 ± 2.054	0.361 ± 0.782	1.389 ± 2.315	0.893 ± 1.879
	Median	0.000	0.000	0.500	0.000
	Q1 ; Q3	0.000 ; 1.000	0.000 ; 0.000	0.000 ; 1.000	0.000 ; 1.000
	Min. ; Max.	0 ; 6.75	0 ; 2.25	0 ; 7	0 ; 7
	Missing	49	33	25	107
Month 36	N	17	7	5	29
	Mean ± SD	0.529 ± 1.355	0.643 ± 0.734	0.900 ± 0.742	0.621 ± 1.123
	Median	0.000	0.250	1.000	0.000
	Q1 ; Q3	0.000 ; 0.000	0.000 ; 1.000	0.500 ; 1.000	0.000 ; 1.000
	Min. ; Max.	0 ; 4.75	0 ; 2	0 ; 2	0 ; 4.75
	Missing	49	35	29	113
Absolute change from M3 to M6	N	37	17	15	69
	Mean ± SD	-0.176 ± 1.605	0.118 ± 0.702	0.117 ± 0.920	-0.040 ± 1.295
	Median	0.000	0.000	0.000	0.000
	Q1 ; Q3	-0.500 ; 0.000	0.000 ; 0.500	-0.250 ; 0.000	-0.250 ; 0.000
	Min. ; Max.	-3.5 ; 7	-1 ; 1.5	-1 ; 2	-3.5 ; 7
	Missing	29	25	19	73

Variables		2L (N=66)	3L (N=42)	4L+ (N=34)	Total (N=142)
Absolute change from M3 to M9	N	30	18	14	62
	Mean ± SD	0.492 ± 1.687	-0.028 ± 0.555	0.089 ± 0.585	0.250 ± 1.253
	Median	0.000	0.000	0.000	0.000
	Q1 ; Q3	0.000 ; 0.500	0.000 ; 0.000	0.000 ; 0.000	0.000 ; 0.500
	Min. ; Max.	-2 ; 6	-1 ; 1	-1 ; 1	-2 ; 6
	Missing	36	24	20	80
Absolute change from M3 to M12	N	22	15	13	50
	Mean ± SD	0.011 ± 2.094	0.317 ± 0.879	0.288 ± 1.755	0.175 ± 1.696
	Median	0.000	0.000	0.000	0.000
	Q1 ; Q3	-0.500 ; 0.250	0.000 ; 1.000	0.000 ; 0.000	-0.250 ; 0.250
	Min. ; Max.	-4.5 ; 7	-1 ; 2	-1 ; 6	-4.5 ; 7
	Missing	44	27	21	92
Absolute change from M3 to M15	N	22	14	14	50
	Mean ± SD	-0.500 ± 1.689	0.107 ± 0.561	-0.321 ± 0.608	-0.280 ± 1.212
	Median	0.000	0.000	0.000	0.000
	Q1 ; Q3	-1.000 ; 0.000	0.000 ; 0.000	-0.500 ; 0.000	-0.250 ; 0.000
	Min. ; Max.	-5 ; 4	-1 ; 1.5	-2 ; 0	-5 ; 4
	Missing	44	28	20	92
Absolute change from M3 to M18	N	17	14	11	42
	Mean ± SD	-0.397 ± 1.293	0.143 ± 0.738	0.273 ± 1.421	-0.042 ± 1.187
	Median	0.000	0.000	0.000	0.000
	Q1 ; Q3	-0.250 ; 0.000	0.000 ; 0.000	0.000 ; 0.000	0.000 ; 0.000
	Min. ; Max.	-4.5 ; 1	-1 ; 1.5	-2 ; 4	-4.5 ; 4
	Missing	49	28	23	100
Absolute change from M3 to M21	N	19	11	13	43
	Mean ± SD	0.000 ± 0.862	-0.227 ± 0.410	-0.115 ± 0.870	-0.093 ± 0.764

Variables		2L (N=66)	3L (N=42)	4L+ (N=34)	Total (N=142)
	Median	0.000	0.000	0.000	0.000
	Q1 ; Q3	0.000 ; 0.000	-0.500 ; 0.000	0.000 ; 0.000	0.000 ; 0.000
	Min. ; Max.	-2 ; 3	-1 ; 0	-2 ; 2	-2 ; 3
	Missing	47	31	21	99
Absolute change from M3 to M24	N	21	9	12	42
	Mean ± SD	-0.131 ± 1.305	-0.333 ± 0.500	0.250 ± 0.892	-0.065 ± 1.068
	Median	0.000	0.000	0.000	0.000
	Q1 ; Q3	-0.250 ; 0.000	-1.000 ; 0.000	0.000 ; 0.750	-0.250 ; 0.000
	Min. ; Max.	-3.5 ; 3	-1 ; 0	-1 ; 2	-3.5 ; 3
	Missing	45	33	22	100
Absolute change from M3 to M27	N	17	7	7	31
	Mean ± SD	0.794 ± 2.047	-0.464 ± 1.326	0.500 ± 0.764	0.444 ± 1.722
	Median	0.000	0.000	0.000	0.000
	Q1 ; Q3	0.000 ; 1.000	-2.000 ; 1.000	0.000 ; 1.000	0.000 ; 1.000
	Min. ; Max.	-2 ; 6.5	-2.25 ; 1	0 ; 2	-2.25 ; 6.5
	Missing	49	35	27	111
Absolute change from M3 to M30	N	18	9	5	32
	Mean ± SD	0.306 ± 1.932	-0.139 ± 0.574	-0.100 ± 1.140	0.117 ± 1.532
	Median	0.000	0.000	0.000	0.000
	Q1 ; Q3	0.000 ; 1.000	-0.500 ; 0.000	0.000 ; 0.500	-0.125 ; 0.500
	Min. ; Max.	-3.5 ; 6.5	-1 ; 1	-2 ; 1	-3.5 ; 6.5
	Missing	48	33	29	110
Absolute change from M3 to M33	N	14	8	7	29
	Mean ± SD	0.071 ± 1.310	-0.344 ± 1.060	1.214 ± 2.157	0.233 ± 1.557
	Median	0.000	0.000	0.500	0.000
	Q1 ; Q3	-0.250 ; 0.000	-1.125 ; 0.000	0.000 ; 1.000	0.000 ; 0.500
	Min. ; Max.	-2 ; 3.5	-2 ; 1.5	0 ; 6	-2 ; 6

Variables		2L (N=66)	3L (N=42)	4L+ (N=34)	Total (N=142)
	Missing	52	34	27	113
Absolute change from M3 to M36	N	15	6	4	25
	Mean ± SD	0.067 ± 1.197	-0.208 ± 0.485	0.625 ± 1.250	0.090 ± 1.073
	Median	0.000	-0.125	0.750	0.000
	Q1 ; Q3	-0.250 ; 0.000	-0.500 ; 0.250	-0.250 ; 1.500	-0.250 ; 0.250
	Min. ; Max.	-2 ; 3	-1 ; 0.25	-1 ; 2	-2 ; 3
	Missing	51	36	30	117
Month 3	Missing	23	15	13	51
	High adherence	23 (53.5%)	14 (51.9%)	13 (61.9%)	50 (54.9%)
	Average adherence	15 (34.9%)	11 (40.7%)	8 (38.1%)	34 (37.4%)
	Low adherence	5 (11.6%)	2 (7.4%)	0 (0%)	7 (7.7%)
Month 6	Missing	23	21	16	60
	High adherence	26 (60.5%)	13 (61.9%)	10 (55.6%)	49 (59.8%)
	Average adherence	14 (32.6%)	5 (23.8%)	8 (44.4%)	27 (32.9%)
	Low adherence	3 (7%)	3 (14.3%)	0 (0%)	6 (7.3%)
Month 9	Missing	31	16	18	65
	High adherence	21 (60%)	22 (84.6%)	7 (43.8%)	50 (64.9%)
	Average adherence	10 (28.6%)	1 (3.8%)	9 (56.3%)	20 (26%)
	Low adherence	4 (11.4%)	3 (11.5%)	0 (0%)	7 (9.1%)
Month 12	Missing	38	21	19	78
	High adherence	20 (71.4%)	12 (57.1%)	10 (66.7%)	42 (65.6%)
	Average adherence	3 (10.7%)	7 (33.3%)	4 (26.7%)	14 (21.9%)
	Low adherence	5 (17.9%)	2 (9.5%)	1 (6.7%)	8 (12.5%)
Month 15	Missing	39	23	16	78
	High adherence	21 (77.8%)	13 (68.4%)	16 (88.9%)	50 (78.1%)

Variables		2L (N=66)	3L (N=42)	4L+ (N=34)	Total (N=142)
	Average adherence	4 (14.8%)	4 (21.1%)	2 (11.1%)	10 (15.6%)
	Low adherence	2 (7.4%)	2 (10.5%)	0 (0%)	4 (6.3%)
Month 18	Missing	44	21	22	87
	High adherence	19 (86.4%)	14 (66.7%)	9 (75%)	42 (76.4%)
	Average adherence	3 (13.6%)	4 (19%)	2 (16.7%)	9 (16.4%)
	Low adherence	0 (0%)	3 (14.3%)	1 (8.3%)	4 (7.3%)
Month 21	Missing	42	28	18	88
	High adherence	20 (83.3%)	9 (64.3%)	13 (81.3%)	42 (77.8%)
	Average adherence	2 (8.3%)	4 (28.6%)	2 (12.5%)	8 (14.8%)
	Low adherence	2 (8.3%)	1 (7.1%)	1 (6.3%)	4 (7.4%)
Month 24	Missing	41	28	20	89
	High adherence	18 (72%)	12 (85.7%)	9 (64.3%)	39 (73.6%)
	Average adherence	5 (20%)	2 (14.3%)	4 (28.6%)	11 (20.8%)
	Low adherence	2 (8%)	0 (0%)	1 (7.1%)	3 (5.7%)
Month 27	Missing	45	33	27	105
	High adherence	15 (71.4%)	6 (66.7%)	4 (57.1%)	25 (67.6%)
	Average adherence	2 (9.5%)	3 (33.3%)	3 (42.9%)	8 (21.6%)
	Low adherence	4 (19%)	0 (0%)	0 (0%)	4 (10.8%)
Month 30	Missing	43	31	27	101
	High adherence	14 (60.9%)	7 (63.6%)	4 (57.1%)	25 (61%)
	Average adherence	8 (34.8%)	3 (27.3%)	3 (42.9%)	14 (34.1%)
	Low adherence	1 (4.3%)	1 (9.1%)	0 (0%)	2 (4.9%)
Month 33	Missing	49	33	25	107
	High adherence	12 (70.6%)	7 (77.8%)	4 (44.4%)	23 (65.7%)
	Average adherence	3 (17.6%)	1 (11.1%)	3 (33.3%)	7 (20%)

Variables		2L (N=66)	3L (N=42)	4L+ (N=34)	Total (N=142)
	Low adherence	2 (11.8%)	1 (11.1%)	2 (22.2%)	5 (14.3%)
Month 36	Missing	49	35	29	113
	High adherence	14 (82.4%)	2 (28.6%)	1 (20%)	17 (58.6%)
	Average adherence	1 (5.9%)	5 (71.4%)	4 (80%)	10 (34.5%)
	Low adherence	2 (11.8%)	0 (0%)	0 (0%)	2 (6.9%)

Table 15.3.3 Morisky total scores and absolute change - SAF (n=142)

10.4.3.5. Cross intolerance

Among the SAF population, 19 patients had a permanent discontinuation due to an AE related to previous TKI treatment (Table 49) and 20 a discontinuation due to a bosutinib-related AE.

AEs leading to treatment discontinuation of previous TKI (imatinib, dasatinib, nilotinib) and bosutinib are presented in Table 49 and Table 50, respectively. When comparing these two listings, it appears that 7 patients have a cross intolerance between bosutinib and a previous TKI treatment (Table 48).

Indeed, patients 01-04, 15-05, 33-08 and 38-01 developed a pleural effusion with dasatinib therapy and similarly developed a bosutinib-related pleural effusion leading to discontinuation. Drug related pleural effusion was also observed for imatinib for patient 38-01. For patient 13-06 renal and cardiac failure occurred with Imatinib and a cardiac failure related to Bosutinib was also observed. The patient 15-05 developed a dypsnea with Dasatinib therapy and a pleural effusion with Bosutinib leading to discontinuation. Moreover, the patient 15-02 developed diarrhea with imatinib and bosutinib leading to discontinuation, and the patient 16-05 experienced arthralgia/myalgia with nilotinib, then lower back pain with imatinib, and finally pain with bosutinib, which was leading to discontinuation.

Table 48: Cross Intolerance – SAF (n=142)

Cross intolerance			Listing 15.3.8c	Listing 15.3.8d	Validation of the cross intolerance
Patient No.	Line	Therapy	Previous AE (grade) by lines of patients with discontinuation with Bosutinib	TRAEs leading Bosutinib discontinuation (PT Name)	
01-04	1	Nilotinib	Diabetes (k)		
	2	Dasatinib	Pleural effusion (2)/renal function degradation (2)	Pleural effusion	Yes
01-06	1	Imatinib	Hand-foot syndrome (3)/mucositis - dysgeusia (3)		
	2	Dasatinib	Increased lipase (4)		
03-02	2	Dasatinib	Myalgia (2)/depressive syndrome (2)	Hypersensitivity	No
	4	Nilotinib	Pericardial effusion (3)		
08-02	1	Imatinib	Oedema (3)		
08-04	1	Imatinib	Cutaneous toxicities (3)		
09-10	1	Imatinib	Cutaneous lesions with hemorrhagic blisters (2)		
09-21	1	Nilotinib	Hypercholesterolemia (2)	-	-
10-02	1	Nilotinib	Headache (1)		
11-12	1	Imatinib	Cramps (1)		
11-21	2	Dasatinib	Pleural effusion (1)		
12-02	1	Imatinib	Aggravation dilated non-ischemic cardiomyopathy (3)		

Cross intolerance | Listing 15.3.8c | Listing 15.3.8d | **Validation of the cross intolerance**

Patient No.	Line	Therapy	Previous AE (grade) by lines of patients with discontinuation with Bosutinib	**TRAEs leading Bosutinib discontinuation (PT Name)**	
12-03	1	Nilotinib	High blood pressure (2)/diabetes (2)		
	2	Imatinib	Fatigue (2)/oedema (2)/dizziness (2)/obesity (2)		
12-04	1	Nilotinib	Peripheral obliterative arteriopathy (2)		
13-03	1	Imatinib	Bilateral medullary necrosis of both ankles (2)		
	2	Dasatinib	Pleural effusion (3)/ cardiac decompensation (3)		
13-06	1	Imatinib	Edema (2)/renal failure (2)/ heart failure (2)	Cardiac failure	Yes
15-02	1	Imatinib	Diarrhea (2)	Diarrhea	Yes
15-05	1	Dasatinib	Dyspnea (2)	Pleural effusion	Yes
15-06	1	Nilotinib	Cutaneous (1)		
	2	Dasatinib	Pleural effusion (1)		
15-07	2	Dasatinib	Pulmonary arterial hypertension (1)	Pleural effusion	No
15-08	2	Dasatinib	Pulmonary arterial hypertension (3)	Pleural effusion	No
16-01	2	Nilotinib	Abdominal pains (1)/fatigue (1)/tremors (2)/sweating (1)		
16-03	1	Imatinib	Anemia (2)/neutropenia (3)		
	2	Dasatinib	Renal failure (3)/cardiac failure (2)	Multiviceral failure	No
	4	Dasatinib	Cardiac failure exacerbation (2)/renal failure exacerbation (2)		
16-04	1	Dasatinib	Fatigue (1)		

Cross intolerance | Listing 15.3.8c | Listing 15.3.8d | **Validation of the cross intolerance**

Patient No.	Line	Therapy	Previous AE (grade) by lines of patients with discontinuation with Bosutinib	**TRAEs leading Bosutinib discontinuation (PT Name)**	
16-05	1	Nilotinib	Arthralgia (1)/Myalgia (1)		
	2	Imatinib	Lower back pains (3)	Pain	Yes
23-02	1	Imatinib	Oedema (3)	-	
33-01	1	Imatinib	Digestive (2)		
	2	Dasatinib	Anemia (2)/thrombocytopenia (2)/leucopenia (1)		
33-02	1	Imatinib	Oedema (1)		
33-03	2	Nilotinib	Pericardial effusion (3)		
	3	Dasatinib	Oedema (2)/ B-type natriuretic peptide neutrophile augmentation (1)/ENDOCRINE (1)		
33-06	1	Imatinib	Diarrhea (1)/immunoallergic pneumopathy (3)		
33-08	2	Nilotinib	Peripheral obliterative arteriopathy (3)		
	3	Dasatinib	Pleural effusion (2)	Pleural effusion	Yes
38-01	2	Dasatinib	Pleural effusion (4)/pericardial effusion (4)	Pleural effusion	Yes
	3	Imatinib	Pleural effusion (3)		
42-02	1	Nilotinib	Pulmonary arterial hypertension (3)/dyslipidemia (2)		
	2	Dasatinib	Oedema (2)		
43-01	1	Imatinib	Cough on chronic obstructive pulmonary disease (3)		
	2	Nilotinib	High blood pressure (2)		

Cross intolerance

Listing 15.3.8c

Listing 15.3.8d

Validation of the cross intolerance

Patient No.	Line	Therapy	Previous AE (grade) by lines of patients with discontinuation with Bosutinib	**TRAEs leading Bosutinib discontinuation (PT Name)**	
47-03	1	Imatinib	Edema (2)/skin reaction (2)	aminotransferase increased	No
	2	Dasatinib	Alopecia (1)		
48-01	1	Nilotinib	Nausea (3)/itching and skin eruption (3)/Scalp pain (2)		
	2	Imatinib	Pneumopathy (3)		
49-01	1	Imatinib	Oedema (3)		

Table 49: Cross Intolerance by System Organ Class - SAF (n=142)

Patient no.	Line	Therapy	AE (grade) for intolerance
01-04	1	Nilotinib	Diabetes (k)
	2	Dasatinib	Pleural effusion (2)/renal function degradation (2)
01-06	1	Imatinib	Hand-foot syndrome (3)/mucositis - dysgeusia (3)
	2	Dasatinib	Increased lipase (4)
03-02	2	Dasatinib	Myalgia (2)/depressive syndrome (2)
	4	Nilotinib	Pericardial effusion (3)
08-04	1	Imatinib	Cutaneous toxicities (3)
09-10	1	Imatinib	Cutaneous lesions with hemorrhagic blisters (2)
09-21	1	Nilotinib	Hypercholesterolemia (2)
10-02	1	Nilotinib	Headache (1)
11-12	1	Imatinib	Cramps (1)
13-03	1	Imatinib	Bilateral medullary necrosis of both ankles (2)
	2	Dasatinib	Pleural effusion (3)/ cardiac decompensation (3)
13-06	1	Imatinib	Edema (2)/renal failure (2)/ heart failure (2)
15-05	1	Dasatinib	Dyspnea (2)
15-06	1	Nilotinib	Cutaneous (1)
	2	Dasatinib	Pleural effusion (1)
16-01	2	Nilotinib	Abdominal pains (1)/fatigue (1)/tremors (2)/sweating (1)
16-03	1	Imatinib	Anemia (2)/neutropenia (3)
	2	Dasatinib	Renal failure (3)/cardiac failure (2)
	4	Dasatinib	Cardiac failure exacerbation (2)/renal failure exacerbation (2)
23-02	1	Imatinib	Edema (3)
33-01	1	Imatinib	Digestive (2)
	2	Dasatinib	Anemia (2)/thrombocytopenia (2)/leucopenia (1)
33-02	1	Imatinib	Edema (1)
38-01	2	Dasatinib	Pleural effusion (4)/pericardial effusion (4)
	3	Imatinib	Pleural effusion (3)

Patient no.	Line	Therapy	AE (grade) for intolerance
47-03	1	Imatinib	Edema (2)/skin reaction (2)
	2	Dasatinib	Alopecia (1)

Listing 15.3.8c Cross Intolerance by System Organ Class: Patients who permanently discontinued bosutinib because of an AE which had resulted in discontinuation of a previous treatment (imatinib, dasatinib, nilotinib) - SAF (n=142)

Table 50: Cross Intolerance by System Organ Class: Patients who permanently discontinued bosutinib because of an AE - SAF (n=142)

Patient No.	Date of initiation bosutinib treatment	SOC name	PT name	CTCAE grade	Date of occurrence	Is the event serious?	Status	Date of recovery	Is it reasonably possible that the event may be related to the study medication?	Is it reasonably possible that the event may be related to a concomitant drug?	If yes, specify the concomitant drug	Name of the drug (1)	Action taken (1)	Name of the drug (2)	Action taken (2)
01-04	07/03/2018	Respiratory, thoracic and mediastinal disorders	Pleural effusion	Grade 3	02/07/2018	Yes	Recovery	23/08/2018	Yes	No		BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.
01-06	16/01/2019	Hepatobiliary disorders	Hepatocellular injury	Grade 3	02/03/2019	No	Recovery	23/03/2019	Yes	No		BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.
03-02	09/12/2019	Immune system disorders	Hypersensitivity	Grade 2	NK/04/2020	No	Recovery	NK/05/2020	Yes	No		BOSUTINIB	Withdrawal (temporary or permanent, or deferred administration)		.
08-04	13/10/2018	Hepatobiliary disorders	Hepatocellular injury	Grade 4	08/12/2018	Yes	Recovery	04/02/2019	Yes	No		BOSUTINIB	Withdrawal (temporary or permanent, or deferred administration)		.

Patient No.	Date of initiation of bosutinib treatment	SOC name	PT name	CTCAE grade	Date of occurrence	Is the event serious?	Status	Date of recovery	Is it reasonably possible that the event may be related to the study medication?	Is it reasonably possible that the event may be related to a concomitant drug?	If yes, specify the concomitant drug	Name of the drug (1)	Action taken (1)	Name of the drug (2)	Action taken (2)
09-04	10/10/2016	Skin and subcutaneous tissue disorders	Rash maculo-papular	Grade 2	15/01/2017	No	Recovery	26/01/2017	Yes	Yes	VALSARTAN	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)	VALSARTAN	No dose modification
		Hepatobiliary disorders	Hepatocellular injury	Grade 2	15/01/2017	No	Recovery	10/03/2017	Yes	Yes	VALSARTAN	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)	VALSARTAN	No dose modification
		Nervous system disorders	Headache	Grade 2	15/01/2017	No	Recovery	26/01/2017	Yes	No		BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.
09-10	21/09/2017	Gastrointestinal disorders	Vomiting	Grade 2	04/06/2018	No	Recovery	05/06/2018	Yes	No		BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.

Patient No.	Date of initiation of bosutinib treatment	SOC name	PT name	CTCAE grade	Date of occurrence	Is the event serious?	Status	Date of recovery	Is it reasonably possible that the event may be related to the study medication?	Is it reasonably possible that the event may be related to a concomitant drug?	If yes, specify the concomitant drug	Name of the drug (1)	Action taken (1)	Name of the drug (2)	Action taken (2)
09-19	23/05/2019	General disorders and administration site conditions	Drug ineffective	Grade 1	26/03/2020	No	Subject not recovered		Yes	No		BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.
09-21	19/11/2019	Psychiatric disorders	Depression	Grade 2	ND/04/2022	No	Subject not recovered		No	No		BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.
10-02	20/04/2016	Gastrointestinal disorders	Diarrhoea	Grade 2	20/04/2016	No	Recovery	26/04/2016	Yes	No			Withdrawal (temporary or permanent, or deferred administration)		.
10-04	07/11/2019	Hepatobiliary disorders	Hepatitis	Grade 3	02/12/2019	No	Recovery	13/01/2020	Yes	No			Withdrawal (temporary or permanent, or deferred administration)		.

Patient No.	Date of initiation of bosutinib treatment	SOC name	PT name	CTCAE grade	Date of occurrence	Is the event serious?	Status	Date of recovery	Is it reasonably possible that the event may be related to the study medication?	Is it reasonably possible that the event may be related to a concomitant drug?	If yes, specify the concomitant drug	Name of the drug (1)	Action taken (1)	Name of the drug (2)	Action taken (2)
11-03	18/04/2016	General disorders and administration site conditions	Reduced drug effect	Grade 1	30/06/2017	No	Unknown		Yes	No		BOSUTINIB	Withdrawal (temporary or permanent, or deferred administration)		.
11-12	07/03/2018	Injury, poisoning and procedural complications	Post procedural complication	Grade 3	12/09/2018	Yes	Subject not recovered		No	No		BOSUTINIB	Withdrawal (temporary or permanent, or deferred administration)		.
11-22	10/11/2019	Respiratory, thoracic and mediastinal disorders	Pleural effusion	Grade 2	15/01/2021	No	Recovery	04/02/2021	Yes	No		BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.
13-03	12/12/2016	Renal and urinary disorders	Acute kidney injury	Grade 2	23/02/2017	No	Recovery	17/03/2017	Yes	No		BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.

Patient No.	Date of initiation of bosutinib treatment	SOC name	PT name	CTCAE grade	Date of occurrence	Is the event serious?	Status	Date of recovery	Is it reasonably possible that the event may be related to the study medication?	Is it reasonably possible that the event may be related to a concomitant drug?	If yes, specify the concomitant drug	Name of the drug (1)	Action taken (1)	Name of the drug (2)	Action taken (2)
13-06	12/04/2018	Renal and urinary disorders	Renal failure	Grade 3	20/06/2018	Yes	Recovery	03/07/2018	Yes	No		BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.
		Cardiac disorders	Cardiac failure	Grade 3	20/06/2018	Yes	Recovery	03/07/2018	Yes	No		BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.
15-05	14/05/2018	Respiratory, thoracic and mediastinal disorders	Pleural effusion	Grade 1	08/04/2021	No	Recovery in progress		Yes	No		BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.
15-06	14/01/2019	Cardiac disorders	Pericarditis	Grade 1	29/11/2019	Yes	Recovery	13/01/2020	Yes	No		BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.

Patient No.	Date of initiation of bosutinib treatment	SOC name	PT name	CTCAE grade	Date of occurrence	Is the event serious?	Status	Date of recovery	Is it reasonably possible that the event may be related to the study medication?	Is it reasonably possible that the event may be related to a concomitant drug?	If yes, specify the concomitant drug	Name of the drug (1)	Action taken (1)	Name of the drug (2)	Action taken (2)
16-01	21/03/2016	General disorders and administration site conditions	Reduced drug effect	Grade 3	09/03/2018	No	Recovery	11/05/2018	Yes	No			Withdrawal (temporary or permanent, or deferred administration)		.
16-03	24/07/2016	General disorders and administration site conditions	Multiviceral failure	Grade 5	30/10/2018	Yes	Subject not recovered		No	No		BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.
23-02	01/10/2016	General disorders and administration site conditions	General physical health deterioration	Grade 5	20/10/2016	Yes	Subject not recovered		No	No		BOSULIF	Withdrawal (temporary or permanent, or deferred administration)	PREVISCAN	Withdrawal (temporary or permanent, or deferred administration)
33-01	04/10/2016	General disorders and administration site conditions	Drug ineffective	Grade 1	24/05/2018	No	Recovery in progress		Yes	No		BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.

Patient No.	Date of initiation of bosutinib treatment	SOC name	PT name	CTCAE grade	Date of occurrence	Is the event serious?	Status	Date of recovery	Is it reasonably possible that the event may be related to the study medication?	Is it reasonably possible that the event may be related to a concomitant drug?	If yes, specify the concomitant drug	Name of the drug (1)	Action taken (1)	Name of the drug (2)	Action taken (2)
33-02	02/05/2017	Musculoskeletal and connective tissue disorders	Arthralgia	Grade 2	12/05/2017	No	Recovery	UK/05/2017	Yes	No			Withdrawal (temporary or permanent, or deferred administration)		.
		Renal and urinary disorders	Renal failure	Grade 1	10/05/2017	Yes	Recovery	21/06/2017	Yes	No			Withdrawal (temporary or permanent, or deferred administration)		.
		General disorders and administration site conditions	Fatigue	Grade 2	12/05/2017	No	Recovery	UK/05/2017	Yes	No			Withdrawal (temporary or permanent, or deferred administration)		.
		Gastrointestinal disorders	Diarrhoea	Grade 2	12/05/2017	No	Recovery	UK/05/2017	Yes	No			Withdrawal (temporary or permanent, or deferred administration)		.

Patient No.	Date of initiation of bosutinib treatment	SOC name	PT name	CTCAE grade	Date of occurrence	Is the event serious?	Status	Date of recovery	Is it reasonably possible that the event may be related to the study medication?	Is it reasonably possible that the event may be related to a concomitant drug?	If yes, specify the concomitant drug	Name of the drug (1)	Action taken (1)	Name of the drug (2)	Action taken (2)
		Respiratory, thoracic and mediastinal disorders	Dyspnoea	Grade 2	12/05/2017	No	Recovery	UK/05/2017	Yes	No			Withdrawal (temporary or permanent, or deferred administration)		.
38-01	14/09/2017	Cardiac disorders	Cardiac failure	Grade 3	17/06/2019	Yes	Recovery	24/06/2019	Yes	No		BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.
		Cardiac disorders	Tachyarrhythmia	Grade 3	17/06/2019	Yes	Recovery	24/06/2019	Yes	No		BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.
		Respiratory, thoracic and mediastinal disorders	Pleural effusion	Grade 3	17/06/2019	Yes	Recovery	31/03/2020	Yes	No		BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.

Patient No.	Date of initiation bosutinib treatment	SOC name	PT name	CTCAE grade	Date of occurrence	Is the event serious?	Status	Date of recovery	Is it reasonably possible that the event may be related to the study medication?	Is it reasonably possible that the event may be related to a concomitant drug?	If yes, specify the concomitant drug	Name of the drug (1)	Action taken (1)	Name of the drug (2)	Action taken (2)
		Cardiac disorders	Atrial fibrillation	Grade 3	17/06/2019	Yes	Recovery	24/06/2019	Yes	No		BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.
47-03	18/03/2019	Investigations	Aspartate aminotransferase increased	Grade 4	29/04/2019	Yes	Recovery	03/06/2019	Yes	No		BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.
		Investigations	Alanine aminotransferase increased	Grade 3	30/04/2019	Yes	Recovery	03/06/2019	Yes	No		BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.

Listing 15.3.8d Cross Intolerance by System Organ Class: Patients who permanently discontinued bosutinib because of an AE - SAF (n=142)

10.4.3.6. Biological and Hematological Parameters

Biological parameters such as ALAT, ASAT, total and conjugated bilirubin, LDH, albumin, amylase, lipase, creatinine, blood glucose (fasting and non-fasting), magnesium, calcium, urea, uric acid have been collected all along the study. Moreover, hematological parameters such as hemoglobin, hematocrit, leukocytes, platelets, Blasts, basophils, neutrophils, eosinophils, monocytes, and lymphocytes have been recorded at every visit study from baseline to 36 months.

Considering the sparsity of biological and hematological data that have been collected in this study, the longitudinal analysis initially planned in the protocol have not been conducted. A summary table with only descriptive statistics have only been provided at each time point. Detailed tables are provided in **Appendix 7.8**.

10.5. Other analyses

10.5.1. Quality of life

The quality of life (QoL) of the patient was assessed with the FACT-leu version 4, a specific questionnaire on Leukemia for Functional Assessment of Cancer Therapy. The questionnaire includes 44 items organized in 5 subscale domains:

- Physical Well-Being or PWB): sum score ranges from 0 to 28,
- Social/Family Well-Being or SWB sum score ranges from 0 to 28.
- Emotional Well-Being or EWB sum score ranges from 0 to 24,
- Functional Well-Being or FWB sum score ranges from 0 to 28.
- Leukemia Subscale or LeuS sum score ranges from 0 to 68.

Higher score meaning a better quality of life.

Then the following scores have been derived where the higher the score, the better the QoL:

- FACT-Leukemia Trial Outcome Index (TOI) as the sum of PWB, FWB and LeuS range from 0 to 124.
- FACT-G total score as the sum of PWB, SWB, EWB and FWB range from 0 to 108.
- FACT-Leukemia total score as the sum of PWB, SWB, EWB, FWB and LeuS range from 0 to 176.

It is noteworthy that whereas at baseline most patients responded to the questionnaire, 57 patients in the 2L group, 38 in the 3L group and 30 in the 4L+ group, this number decreased over follow-up time, to reach 28 patients in the 2L group, 13 in the 3L group and only 8 in the 4L+ group at 36 months.

10.5.1.1. Physical Well-Being

The analysis of physical well-being showed a slight clinical score decrease over the time of the study. While the overall score was 8.40 ± 5.96 at baseline, it was 5.93 ± 4.99 at 36 months of follow-up (Table 51).

At baseline the score was similar between groups, 8.45 ± 5.99 in the 2L groups, 7.46 ± 6.10 in the 3L group and 9.49 ± 5.74in the 4L+ group. Compared to baseline, the score at 36 months of follow-up was 6.25 ± 5.12 in the 2L group, 6.69 ± 5.51 in the 3L group and 3.56 ± 3.11 in the 4L+ group. Overall, patient from the SAF population reported low physical well-being score.

Table 51: Physical Well-Being - FAS (n=139)

Variables		2L (N=64)	3L (N=42)	4L+ (N=33)	Total (N=139)
Baseline	N	57	38	30	125
	Mean ± SD	8.445 ± 5.985	7.456 ± 6.096	9.492 ± 5.742	8.396 ± 5.961
	Median	8.170	7.000	9.500	8.750
	Q1 ; Q3	3.000 ; 14.000	1.000 ; 12.000	6.000 ; 13.000	3.000 ; 13.000
	Min. ; Max.	0 ; 21	0 ; 20	0 ; 24	0 ; 24
	Missing	7	4	3	14
Month 3	N	45	32	25	102
	Mean ± SD	6.437 ± 5.244	6.120 ± 5.151	7.528 ± 5.552	6.605 ± 5.267
	Median	5.000	5.500	7.000	6.000
	Q1 ; Q3	2.000 ; 9.000	1.585 ; 10.000	3.000 ; 11.200	2.000 ; 10.000
	Min. ; Max.	0 ; 23	0 ; 18	0 ; 19	0 ; 23
	Missing	19	10	8	37
Month 6	N	46	24	20	90
	Mean ± SD	6.572 ± 6.150	5.854 ± 6.068	8.634 ± 5.525	6.839 ± 6.015
	Median	4.000	4.000	9.085	5.000
	Q1 ; Q3	2.000 ; 9.000	0.000 ; 10.500	5.000 ; 12.335	2.000 ; 11.000
	Min. ; Max.	0 ; 25	0 ; 19	0 ; 18	0 ; 25
	Missing	18	18	13	49

Variables		2L (N=64)	3L (N=42)	4L+ (N=33)	Total (N=139)
Month 12	N	34	28	17	79
	Mean ± SD	6.392 ± 6.226	7.375 ± 6.331	7.612 ± 5.616	7.003 ± 6.086
	Median	5.000	7.000	7.000	6.000
	Q1 ; Q3	2.000 ; 9.000	2.000 ; 10.000	3.000 ; 11.000	2.000 ; 10.000
	Min. ; Max.	0 ; 23.33	0 ; 24	0 ; 21	0 ; 24
	Missing	30	14	16	60
Month 18	N	26	18	18	62
	Mean ± SD	5.628 ± 5.248	6.491 ± 4.370	6.621 ± 5.569	6.167 ± 5.047
	Median	4.000	6.000	5.000	5.000
	Q1 ; Q3	2.000 ; 8.000	2.000 ; 10.000	2.000 ; 12.000	2.000 ; 10.000
	Min. ; Max.	0 ; 22.17	0 ; 13	0 ; 15.17	0 ; 22.17
	Missing	38	24	15	77
Month 24	N	29	16	16	61
	Mean ± SD	5.190 ± 5.096	5.375 ± 4.334	6.229 ± 4.812	5.511 ± 4.774
	Median	3.000	4.000	6.500	4.000
	Q1 ; Q3	1.000 ; 8.000	3.000 ; 6.500	2.000 ; 10.000	1.000 ; 8.000
	Min. ; Max.	0 ; 19	0 ; 15	0 ; 15	0 ; 19
	Missing	35	26	17	78
Month 36	N	28	13	8	49
	Mean ± SD	6.25 ± 5.12	6.69 ± 5.51	3.56 ± 3.11	5.93 ± 4.99
	Median	5.00	5.00	2.75	5.00
	Q1 ; Q3	2.00 ; 10.00	2.00 ; 9.00	1.00 ; 6.50	2.00 ; 9.00
	Min. ; Max.	0 ; 19	0 ; 16	0 ; 8	0 ; 19
	Missing	36	29	25	90

Table 15.5.4a FACT-leu - Physical Well-Being - FAS (n=139)

10.5.1.2. Social/Familial Well-Being

No clinical changes in social/familial well-being score were observed, the overall score was 20.37 ± 5.99 at baseline, it was 20.79 ± 5.24 at 36 months of follow-up (Table 52).

At baseline the score was similar between groups, 21.53 ± 5.26 in the 2L groups, 18.04 ± 7.15 in the 3L group and 21.11 ± 4.93 in the 4L+ group. Compared to baseline, the score at 36 months of follow-up was 21.57 ± 4.50 in the 2L group, 18.96 ± 7.40 in the 3L group and 21.04 ± 2.81 in the 4L+ group. Score collection at 3 months, 6 months, 16 months, 18 months and 24 months did not reveal important clinical changes.

Considering 28 as the maximum score for social well-being, it appears that overall, patient felt well socially.

Table 52: Social/Familial Well-Being - FAS (n=139)

Variables		2L (N=64)	3L (N=42)	4L+ (N=33)	Total (N=139)
Baseline	N	57	38	30	125
	Mean ± SD	21.526 ± 5.261	18.041 ± 7.150	21.114 ± 4.928	20.368 ± 5.987
	Median	22.000	19.000	21.500	21.000
	Q1 ; Q3	18.670 ; 26.000	13.000 ; 23.000	17.500 ; 25.670	17.000 ; 25.000
	Min. ; Max.	0 ; 28	0 ; 28	10.5 ; 28	0 ; 28
	Missing	7	4	3	14
Month 3	N	45	32	25	102
	Mean ± SD	21.538 ± 5.806	19.002 ± 6.963	18.947 ± 6.166	20.107 ± 6.343
	Median	22.000	20.500	20.000	21.000
	Q1 ; Q3	19.000 ; 26.830	16.000 ; 24.500	17.000 ; 23.000	18.000 ; 25.000
	Min. ; Max.	3.5 ; 28	0 ; 28	0 ; 26	0 ; 28
	Missing	19	10	8	37

Variables		2L (N=64)	3L (N=42)	4L+ (N=33)	Total (N=139)
Month 6	N	46	24	20	90
	Mean ± SD	23.250 ± 4.320	19.596 ± 5.923	20.067 ± 6.311	21.568 ± 5.479
	Median	23.565	21.000	20.500	22.085
	Q1 ; Q3	21.000 ; 27.000	15.085 ; 23.665	17.750 ; 25.000	19.830 ; 25.670
	Min. ; Max.	11 ; 28	2 ; 27	0 ; 28	0 ; 28
	Missing	18	18	13	49
Month 12	N	33	28	17	78
	Mean ± SD	21.990 ± 5.167	20.579 ± 3.516	21.821 ± 3.951	21.447 ± 4.371
	Median	22.000	21.000	21.000	21.000
	Q1 ; Q3	19.000 ; 26.830	18.335 ; 22.750	20.000 ; 24.000	19.000 ; 24.000
	Min. ; Max.	10 ; 28	13 ; 28	12 ; 28	10 ; 28
	Missing	31	14	16	61
Month 18	N	26	18	18	62
	Mean ± SD	19.545 ± 7.706	20.152 ± 6.297	20.296 ± 4.064	19.939 ± 6.333
	Median	21.500	20.500	20.500	21.000
	Q1 ; Q3	16.330 ; 25.000	15.000 ; 26.000	17.000 ; 22.000	16.000 ; 25.000
	Min. ; Max.	0 ; 28	7 ; 28	14 ; 26.83	0 ; 28
	Missing	38	24	15	77
Month 24	N	29	16	16	61
	Mean ± SD	20.211 ± 7.104	19.855 ± 6.808	21.052 ± 5.628	20.338 ± 6.577
	Median	21.000	19.915	21.500	21.000
	Q1 ; Q3	19.000 ; 24.500	15.865 ; 26.135	19.600 ; 25.085	18.000 ; 25.000
	Min. ; Max.	0 ; 28	5.25 ; 28	7 ; 28	0 ; 28
	Missing	35	26	17	78

Variables		2L (N=64)	3L (N=42)	4L+ (N=33)	Total (N=139)
Month 36	N	28	13	8	49
	Mean ± SD	21.568 ± 4.498	18.962 ± 7.395	21.043 ± 2.809	20.791 ± 5.241
	Median	22.000	19.000	21.000	21.000
	Q1 ; Q3	17.750 ; 26.250	15.000 ; 25.000	18.835 ; 23.000	17.500 ; 25.000
	Min. ; Max.	14 ; 28	3 ; 28	17 ; 25.67	3 ; 28
	Missing	36	29	25	90

Table 15.5.4b FACT-leu - Social/Familial Well-Being - FAS (n=139)

10.5.1.3. Emotional Well-Being

No clinical changes in emotional well-being score were observed, the overall score was 8.26 ± 4.40 at baseline, it was 7.60 ± 4.40 at 36 months of follow-up (Table 53).

At baseline the score was similar between groups, 7.76 ± 4.19 in the 2L groups, 8.67 ± 4.94 in the 3L group and 8.70 ± 4.11 in the 4L+ group. Compared to baseline, the score at 36 months of follow-up was 6.8 ± 3.9 in the 2L group, 9.0 ± 4.2 in the 3L group and 8.0 ± 6.0 in the 4L+ group. Score collection at 3 months, 6 months, 16 months, 18 months, and 24 months did not reveal important clinical changes.

Considering 24 as the maximum score for emotional well-being, it appears that overall, patients were not in a well emotional state.

Table 53: Emotional Well-Being - FAS (n=139)

Variables	2L (N=64)	3L (N=42)	4L+ (N=33)	Total (N=139)

Variables		2L (N=64)	3L (N=42)	4L+ (N=33)	Total (N=139)
Baseline	N	57	38	30	125
	Mean ± SD	7.76 ± 4.19	8.67 ± 4.94	8.70 ± 4.11	8.26 ± 4.40
	Median	7.00	8.50	8.50	8.00
	Q1 ; Q3	5.00 ; 10.00	5.00 ; 13.00	5.00 ; 11.00	5.00 ; 11.00
	Min. ; Max.	0 ; 22	0 ; 19	3 ; 20	0 ; 22
	Missing	7	4	3	14
Month 3	N	45	32	25	102
	Mean ± SD	7.08 ± 3.62	7.19 ± 4.00	7.38 ± 3.78	7.19 ± 3.75
	Median	6.00	7.00	7.00	7.00
	Q1 ; Q3	4.00 ; 9.00	4.50 ; 10.00	5.00 ; 9.00	4.00 ; 10.00
	Min. ; Max.	2 ; 17	0 ; 17	2 ; 18	0 ; 18
	Missing	19	10	8	37
Month 6	N	46	23	20	89
	Mean ± SD	6.8 ± 4.6	6.7 ± 3.6	7.9 ± 4.3	7.0 ± 4.3
	Median	6.0	5.0	6.0	6.0
	Q1 ; Q3	4.0 ; 10.0	4.0 ; 10.0	5.5 ; 11.0	4.0 ; 10.0
	Min. ; Max.	0 ; 24	0 ; 14	1 ; 18	0 ; 24
	Missing	18	19	13	50
Month 12	N	34	28	17	79
	Mean ± SD	7.65 ± 4.20	6.60 ± 3.81	6.06 ± 2.14	6.93 ± 3.72
	Median	6.00	5.00	5.00	6.00
	Q1 ; Q3	5.00 ; 9.00	4.00 ; 9.80	5.00 ; 7.00	4.00 ; 9.00
	Min. ; Max.	2 ; 20	0 ; 14	4 ; 11	0 ; 20
	Missing	30	14	16	60
Month 18	N	26	18	18	62

Variables		2L (N=64)	3L (N=42)	4L+ (N=33)	Total (N=139)
	Mean ± SD	7.1 ± 4.0	6.9 ± 4.0	6.1 ± 3.2	6.8 ± 3.7
	Median	6.0	6.0	5.0	6.0
	Q1 ; Q3	4.0 ; 10.0	4.0 ; 8.0	4.0 ; 7.0	4.0 ; 8.0
	Min. ; Max.	2 ; 16	1 ; 16	1 ; 14	1 ; 16
	Missing	38	24	15	77
Month 24	N	29	16	16	61
	Mean ± SD	7.1 ± 4.2	6.0 ± 3.4	8.9 ± 3.8	7.3 ± 4.0
	Median	7.0	5.5	8.5	7.0
	Q1 ; Q3	4.0 ; 11.0	4.0 ; 7.0	6.0 ; 12.0	4.0 ; 9.0
	Min. ; Max.	0 ; 15	1 ; 16	4 ; 18	0 ; 18
	Missing	35	26	17	78
Month 36	N	28	13	8	49
	Mean ± SD	6.8 ± 3.9	9.0 ± 4.2	8.0 ± 6.0	7.6 ± 4.4
	Median	6.0	8.0	6.5	6.0
	Q1 ; Q3	4.5 ; 8.5	6.0 ; 12.0	4.0 ; 8.5	5.0 ; 10.0
	Min. ; Max.	0 ; 15	4 ; 17	4 ; 22	0 ; 22
	Missing	36	29	25	90

Table 15.5.4c FACT-leu - Emotional Well-Being - FAS (n=139)

10.5.1.4. Functional Well-Being

No clinical changes in functional well-being score were observed, the overall score was 16.84 ± 6.51 at baseline, it was 18.07 ± 5.15 at 36 months of follow-up (Table 54).

At baseline the score was similar between groups, 17.94 ± 6.89 in the 2L groups, 15.86 ± 6.52 in the 3L group and 16.00 ± 5.55 in the 4L+ group. Compared to baseline, the score at 36 months of follow-up was 17.94 ± 4.81 in the 2L group, 18.89 ± 5.87 in the 3L group and 17.15 ± 5.56 in the 4L+ group. Score collection at 3 months, 6 months, 16 months, 18 months, and 24 months did not reveal important clinical changes.

Considering 28 as the maximum score for functional well-being, it appears that overall, patients were functionally well.

Table 54: Functional Well-Being - FAS (n=139)

Variables		2L (N=64)	3L (N=42)	4L+ (N=33)	Total (N=139)
Baseline	N	57	38	30	125
	Mean ± SD	17.936 ± 6.891	15.858 ± 6.517	16.000 ± 5.552	16.840 ± 6.507
	Median	18.000	15.700	16.500	18.000
	Q1 ; Q3	14.000 ; 22.000	13.000 ; 21.000	13.000 ; 20.000	13.000 ; 21.000
	Min. ; Max.	1 ; 28	0 ; 28	4 ; 28	0 ; 28
	Missing	7	4	3	14
Month 3	N	45	31	25	101
	Mean ± SD	18.244 ± 6.932	16.747 ± 6.260	15.880 ± 6.014	17.200 ± 6.525
	Median	19.000	18.000	16.000	18.000
	Q1 ; Q3	15.000 ; 23.000	13.000 ; 21.000	12.000 ; 20.000	13.000 ; 21.000
	Min. ; Max.	1 ; 28	0 ; 27	3.5 ; 28	0 ; 28

Variables		2L (N=64)	3L (N=42)	4L+ (N=33)	Total (N=139)
	Missing	19	11	8	38
Month 6	N	46	24	20	90
	Mean ± SD	19.467 ± 6.556	17.236 ± 4.759	15.420 ± 5.673	17.973 ± 6.101
	Median	20.000	15.500	15.000	18.000
	Q1 ; Q3	14.000 ; 25.000	14.000 ; 21.000	12.000 ; 18.000	14.000 ; 23.000
	Min. ; Max.	5 ; 28	9 ; 27	1.4 ; 28	1.4 ; 28
	Missing	18	18	13	49
Month 12	N	34	28	17	79
	Mean ± SD	19.101 ± 7.131	17.047 ± 4.494	18.225 ± 5.693	18.185 ± 5.998
	Median	19.000	16.665	19.000	18.000
	Q1 ; Q3	16.000 ; 26.000	14.500 ; 20.000	12.000 ; 21.000	14.000 ; 21.000
	Min. ; Max.	5 ; 28	7 ; 28	11 ; 28	5 ; 28
	Missing	30	14	16	60
Month 18	N	26	18	18	62
	Mean ± SD	17.936 ± 6.420	18.556 ± 3.944	17.893 ± 4.489	18.103 ± 5.189
	Median	19.000	18.500	17.500	18.670
	Q1 ; Q3	12.000 ; 22.000	16.000 ; 20.000	14.000 ; 22.000	15.000 ; 22.000
	Min. ; Max.	4 ; 28	12 ; 26	11 ; 27	4 ; 28
	Missing	38	24	15	77
Month 24	N	29	16	16	61
	Mean ± SD	17.690 ± 5.708	17.563 ± 4.098	16.677 ± 6.263	17.391 ± 5.422
	Median	18.000	17.000	14.000	18.000
	Q1 ; Q3	16.000 ; 21.000	15.000 ; 21.000	12.500 ; 19.915	14.000 ; 21.000
	Min. ; Max.	4 ; 27	10 ; 24	9 ; 28	4 ; 28
	Missing	35	26	17	78

Variables		2L (N=64)	3L (N=42)	4L+ (N=33)	Total (N=139)
Month 36	N	27	13	8	48
	Mean ± SD	17.944 ± 4.811	18.892 ± 5.872	17.150 ± 5.562	18.069 ± 5.153
	Median	19.000	18.000	15.000	18.000
	Q1 ; Q3	15.000 ; 21.000	15.000 ; 25.000	12.800 ; 20.500	14.500 ; 21.000
	Min. ; Max.	4 ; 25	11 ; 28	12.6 ; 28	4 ; 28
	Missing	37	29	25	91

Table 15.5.4d FACT-leu - Functional Well-Being - FAS (n=139)

10.5.1.5. Leukemia subscale

Regarding leukemia subscale, no clinical changes were observed, the overall score was 46.56 ± 11.52 at baseline and was 50.63 ± 10.57 at 36 months of follow-up (Table 55).

At baseline the score was similar between groups, 46.72 ± 12.86 in the 2L groups, 46.45 ± 11.01 in the 3L group and 46.39 ± 9.65 in the 4L+ group. Compared to baseline, the score at 36 months of follow-up was 50.81 ± 11.18 in the 2L group, 48.62 ± 11.06 in the 3L group and 53.300± 7.75 in the 4L+ group. Score collection at 3 months, 6 months, 16 months, 18 months, and 24 months did not reveal important clinical changes.

Table 55: Leukemia subscale - FAS (n=139)

Variables		2L (N=64)	3L (N=42)	4L+ (N=33)	Total (N=139)
Baseline	N	57	38	30	125
	Mean ± SD	46.717 ± 12.856	46.447 ± 11.012	46.389 ± 9.645	46.556 ± 11.515
	Median	48.000	47.500	47.905	48.000
	Q1 ; Q3	41.000 ; 55.000	37.000 ; 54.000	42.000 ; 51.000	40.000 ; 55.000

Variables		2L (N=64)	3L (N=42)	4L+ (N=33)	Total (N=139)
	Min. ; Max.	14 ; 66	28 ; 68	19 ; 63	14 ; 68
	Missing	7	4	3	14
Month 3	N	45	31	25	101
	Mean ± SD	51.458 ± 9.837	50.455 ± 11.895	50.237 ± 8.787	50.848 ± 10.192
	Median	54.000	54.000	50.000	53.000
	Q1 ; Q3	46.000 ; 60.000	44.000 ; 60.000	44.630 ; 57.000	44.630 ; 59.000
	Min. ; Max.	24.44 ; 67	26 ; 67	35 ; 66	24.44 ; 67
	Missing	19	11	8	38
Month 6	N	46	24	20	90
	Mean ± SD	52.450 ± 11.321	54.271 ± 9.217	48.462 ± 6.444	52.049 ± 9.996
	Median	56.500	56.000	48.500	53.000
	Q1 ; Q3	47.000 ; 60.000	48.000 ; 61.500	44.035 ; 51.000	47.000 ; 60.000
	Min. ; Max.	20.19 ; 68	34 ; 68	38 ; 64.81	20.19 ; 68
	Missing	18	18	13	49
Month 12	N	34	28	17	79
	Mean ± SD	51.846 ± 10.938	49.933 ± 10.689	52.041 ± 7.577	51.210 ± 10.142
	Median	52.565	47.500	52.000	51.000
	Q1 ; Q3	44.000 ; 61.000	43.780 ; 60.000	48.000 ; 58.000	44.000 ; 60.000
	Min. ; Max.	24.73 ; 67	26.56 ; 66	38 ; 64	24.73 ; 67
	Missing	30	14	16	60
Month 18	N	26	18	18	62
	Mean ± SD	52.397 ± 10.709	52.646 ± 7.467	52.868 ± 6.543	52.606 ± 8.632
	Median	53.565	52.500	51.500	53.065
	Q1 ; Q3	46.000 ; 60.000	46.750 ; 60.000	49.000 ; 58.000	47.000 ; 59.000
	Min. ; Max.	19 ; 67	41 ; 63	38 ; 64	19 ; 67

Variables		2L (N=64)	3L (N=42)	4L+ (N=33)	Total (N=139)
	Missing	38	24	15	77
Month 24	N	29	16	16	61
	Mean ± SD	51.315 ± 8.410	53.918 ± 9.290	49.646 ± 9.219	51.560 ± 8.850
	Median	53.000	55.500	51.635	54.000
	Q1 ; Q3	44.000 ; 58.000	48.000 ; 60.500	45.315 ; 56.000	46.000 ; 58.000
	Min. ; Max.	36 ; 64	28.69 ; 66	24.44 ; 60	24.44 ; 66
	Missing	35	26	17	78
Month 36	N	27	13	8	48
	Mean ± SD	50.806 ± 11.178	48.615 ± 11.064	53.300 ± 7.748	50.628 ± 10.568
	Median	52.000	49.000	55.200	51.500
	Q1 ; Q3	46.000 ; 60.000	44.000 ; 56.000	48.000 ; 58.000	45.500 ; 59.000
	Min. ; Max.	21.25 ; 66	29 ; 64	40 ; 64	21.25 ; 66
	Missing	37	29	25	91

Table 15.5.4e FACT-leu - Leukemia subscale - FAS (n=139)

10.5.1.6. FACT-Leukemia Trial Outcome Index

Regarding FACT-Leukemia Trial Outcome Index, no clinical change was observed, the overall score was 71.79 ± 11.96 at baseline and was 73.22 ± 14.84 at 36 months of follow-up (Table 56).

At baseline the score was similar between groups, 73.10 ± 13.23 in the 2L groups, 69.76 ± 11.88 in the 3L group and 71.88 ± 9.18 in the 4L+ group. Compared to baseline, the score at 36 months of follow-up was 72.55 ± 17.42 in the 2L group, 74.20 ± 11.93 in the 3L group and 74.01 ± 9.63 in the 4L+ group. Score collection at 3 months, 6 months, 16 months, 18 months, and 24 months did not reveal significant clinical change.

Table 56: FACT-Leukemia Trial Outcome Index - FAS (n=139)

Variables		2L (N=64)	3L (N=42)	4L+ (N=33)	Total (N=139)
Baseline	N	57	38	30	125
	Mean ± SD	73.098 ± 13.234	69.761 ± 11.876	71.881 ± 9.183	71.791 ± 11.956
	Median	74.000	69.585	72.000	73.000
	Q1 ; Q3	62.200 ; 82.000	60.000 ; 77.250	65.000 ; 77.000	63.000 ; 80.560
	Min. ; Max.	41 ; 96	45 ; 96	54 ; 91	41 ; 96
	Missing	7	4	3	14
Month 3	N	45	32	25	102
	Mean ± SD	76.140 ± 11.540	71.223 ± 17.160	73.645 ± 9.950	73.986 ± 13.283
	Median	78.940	75.000	73.000	75.500
	Q1 ; Q3	68.000 ; 84.000	64.000 ; 82.585	65.500 ; 81.000	67.000 ; 84.000
	Min. ; Max.	48.44 ; 97	2 ; 94	56 ; 91	2 ; 97
	Missing	19	10	8	37
Month 6	N	46	24	20	90
	Mean ± SD	78.490 ± 11.992	77.361 ± 8.478	72.516 ± 8.639	76.861 ± 10.626
	Median	80.000	76.000	70.500	78.500
	Q1 ; Q3	71.000 ; 88.000	73.000 ; 82.780	66.370 ; 80.500	70.000 ; 85.000
	Min. ; Max.	46.19 ; 97	60 ; 94	56.93 ; 86.81	46.19 ; 97
	Missing	18	18	13	49
Month 12	N	34	28	17	79
	Mean ± SD	77.338 ± 12.181	74.355 ± 9.063	77.878 ± 8.566	76.397 ± 10.422
	Median	79.565	73.000	78.000	78.000
	Q1 ; Q3	68.000 ; 86.000	67.335 ; 82.500	72.130 ; 82.000	68.000 ; 83.000
	Min. ; Max.	50 ; 96	57.56 ; 93	64 ; 94	50 ; 96
	Missing	30	14	16	60

Variables		2L (N=64)	3L (N=42)	4L+ (N=33)	Total (N=139)
Month 18	N	26	18	18	62
	Mean ± SD	75.962 ± 12.383	77.692 ± 7.286	77.382 ± 9.583	76.876 ± 10.191
	Median	77.565	75.940	77.000	77.000
	Q1 ; Q3	69.670 ; 84.000	73.000 ; 84.000	71.000 ; 86.000	71.000 ; 84.000
	Min. ; Max.	47.17 ; 95	65.75 ; 90	62.63 ; 95.57	47.17 ; 95.57
	Missing	38	24	15	77
Month 24	N	29	16	16	61
	Mean ± SD	74.194 ± 9.439	76.856 ± 8.977	72.553 ± 10.616	74.462 ± 9.614
	Median	75.000	77.000	72.135	75.000
	Q1 ; Q3	70.000 ; 81.000	71.000 ; 83.000	65.815 ; 81.000	70.000 ; 81.000
	Min. ; Max.	49 ; 88	55.69 ; 90	47.44 ; 88	47.44 ; 90
	Missing	35	26	17	78
Month 36	N	28	13	8	49
	Mean ± SD	72.545 ± 17.415	74.200 ± 11.931	74.013 ± 9.633	73.223 ± 14.844
	Median	77.000	72.000	72.450	74.000
	Q1 ; Q3	69.125 ; 81.835	67.000 ; 83.000	67.600 ; 82.500	67.750 ; 82.000
	Min. ; Max.	2 ; 91	54 ; 92	60 ; 87	2 ; 92
	Missing	36	29	25	90

Table 15.5.4f FACT-leu - FACT-Leukemia Trial Outcome Index - FAS (n=139)

10.5.1.7. FACT-Leukemia Trial Outcome Index absolute change from baseline

Regarding FACT-Leukemia Trial Outcome Index absolute change from baseline in the 2L group, it varied from 1.94 ± 6.99 at 3 months to 0.36 ± 9.35 at 36 months, with a maximum of 3.44 ± 9.71 at 12 months compared to baseline.

Regarding FACT-Leukemia Trial Outcome Index absolute change from baseline in the 3L group, it varied from 1.44 ± 14.19 at 3 months compared to baseline, to 2.81 ± 7.77 at 36 months compared to baseline, with a maximum of 7.25 ± 10.72 at 18 months compared to baseline.

Regarding FACT-Leukemia Trial Outcome Index absolute change from baseline in the 4L+ group, it varied from 0.36 ± 8.69 at 3 months compared to baseline, to -1.11 ± 9.17 at 36 months compared to baseline, with a maximum of 4.37 ± 8.50 at 18 months compared to baseline.

The maximum absolute positive change from baseline was 6.92 ± 9.67 in the 2L group, 8.81 ± 9.78 in the 3L group and 6.75 ± 6.58 in the 4L+ group.

Therefore, the maximum absolute positive change from baseline was similar between group. Overall, in the FAS population the maximum absolute change was 7.51 ± 9.09.

Table 57: FACT-Leukemia Trial Outcome Index - FAS (n=139)

Variables		2L (N=64)	3L (N=42)	4L+ (N=33)	Total (N=139)
Absolute change from baseline to M3	N	42	31	23	96
	Mean ± SD	1.935 ± 6.986	1.440 ± 14.185	0.360 ± 8.689	1.398 ± 10.123
	Median	2.000	3.000	1.000	2.000
	Q1 ; Q3	-2.000 ; 7.440	-3.000 ; 10.000	-9.000 ; 9.000	-3.250 ; 8.570
	Min. ; Max.	-15 ; 17	-61 ; 21	-13.24 ; 15	-61 ; 21
	Missing	22	11	10	43
Absolute change from baseline to M6	N	41	24	18	83
	Mean ± SD	2.566 ± 8.783	7.216 ± 9.977	-0.429 ± 8.890	3.261 ± 9.473
	Median	1.830	6.500	-1.000	3.000
	Q1 ; Q3	-3.000 ; 6.000	0.000 ; 12.250	-7.500 ; 7.000	-3.000 ; 9.000
	Min. ; Max.	-12.5 ; 32.66	-9 ; 40	-13.75 ; 17	-13.75 ; 40
	Missing	23	18	15	56
Absolute change from baseline to M12	N	30	26	16	72
	Mean ± SD	3.436 ± 9.708	3.984 ± 10.849	3.813 ± 4.637	3.718 ± 9.195
	Median	1.595	3.500	4.000	3.000
	Q1 ; Q3	-2.000 ; 7.060	-4.000 ; 10.000	0.080 ; 7.500	-2.000 ; 8.500

Variables		2L (N=64)	3L (N=42)	4L+ (N=33)	Total (N=139)
	Min. ; Max.	-13 ; 34.83	-23 ; 29	-4.6 ; 11.63	-23 ; 34.83
	Missing	34	16	17	67
Absolute change from baseline to M18	N	22	16	18	56
	Mean ± SD	3.258 ± 10.643	7.248 ± 10.720	4.366 ± 8.496	4.754 ± 9.983
	Median	2.000	6.500	5.000	4.000
	Q1 ; Q3	-4.330 ; 10.000	2.415 ; 17.500	-1.000 ; 11.500	-2.375 ; 12.085
	Min. ; Max.	-15 ; 22	-12.25 ; 21.83	-14.24 ; 15	-15 ; 22
	Missing	42	26	15	83
Absolute change from baseline to M24	N	26	13	15	54
	Mean ± SD	2.651 ± 12.121	1.999 ± 9.011	0.124 ± 8.576	1.792 ± 10.405
	Median	1.000	4.000	2.330	1.400
	Q1 ; Q3	-4.000 ; 6.000	-7.000 ; 8.000	-5.000 ; 6.000	-5.000 ; 6.830
	Min. ; Max.	-13 ; 38	-12 ; 14	-15 ; 11	-15 ; 38
	Missing	38	29	18	85
Absolute change from baseline to M36	N	26	12	8	46
	Mean ± SD	0.355 ± 9.352	2.812 ± 7.773	-1.113 ± 9.168	0.741 ± 8.847
	Median	0.875	-0.500	-1.000	0.000
	Q1 ; Q3	-5.000 ; 5.000	-3.000 ; 10.335	-6.500 ; 6.050	-4.930 ; 6.000

Variables		2L (N=64)	3L (N=42)	4L+ (N=33)	Total (N=139)
	Min. ; Max.	-19 ; 20.5	-8 ; 15	-17 ; 11	-19 ; 20.5
	Missing	38	30	25	93
Maximum absolute positive change from baseline	N	49	36	24	109
	Mean ± SD	6.915 ± 9.666	8.814 ± 9.784	6.745 ± 6.581	7.505 ± 9.090
	Median	5.000	8.905	6.500	6.000
	Q1 ; Q3	2.000 ; 11.000	1.735 ; 15.500	3.000 ; 11.815	2.000 ; 12.000
	Min. ; Max.	-15 ; 38	-7 ; 40	-10.13 ; 17	-15 ; 40
	Missing	15	6	9	30

Table 15.5.5 FACT-Leukemia Trial Outcome Index - FAS (n=139)

The mixed model with repeated measure showed a significant effect of visit (p value = 0.0020), however, no effect of treatment lines neither interaction treatment line nor visit were observed (Table 58). Indeed, the FACT-Leukemia Trial Outcome Index increased overtime in patients.

Results of the mixed model with repeated measures (estimates) are provided in **Table 59**.

Table 58: FACT-Leukemia Trial Outcome Index: Results of the mixed model with repeated measures (effects) - FAS (n=139)

Effet	ddl	Valeur F	p-value
Effet visit	**55.4**	**4.03**	**0.0020**
Effect treatment lines	116	0.69	0.5016
Interaction: treatment lines * visit	82.7	1.51	0.1368

Table 15.5.6a. FACT-Leukemia Trial Outcome Index: Results of the mixed model with repeated measures (effects) - FAS (n=139)

Table 59: FACT-Leukemia Trial Outcome Index: Results of the mixed model with repeated measures (estimates) - FAS (n=139)

Treatment lines	Visit	Estimation	IC95%	Number of observations used
Overall	Overall			568
Overall	Baseline	71.64	[69.51;73.78]	125
Overall	Month 3	73.18	[70.58;75.78]	102
Overall	Month 6	75.27	[73.18;77.36]	90
Overall	Month 12	76.37	[74.24;78.51]	79
Overall	Month 18	76.21	[73.68;78.73]	62
Overall	Month 24	73.98	[71.62;76.35]	61
Overall	Month 36	74.48	[69.80;79.16]	49

Treatment lines	Visit	Estimation IC95%		Number of observations used
2L	Baseline	73.44	[70.39;76.49]	57
2L	Month 3	76.49	[72.72;80.25]	45
2L	Month 6	77.62	[74.75;80.48]	46
2L	Month 12	77.66	[74.59;80.74]	34
2L	Month 18	76.17	[72.41;79.93]	26
2L	Month 24	74.84	[71.50;78.18]	29
2L	Month 36	74.39	[68.64;80.15]	28
3L	Baseline	69.58	[65.84;73.33]	38
3L	Month 3	71.37	[66.85;75.88]	32
3L	Month 6	76.56	[72.86;80.27]	24
3L	Month 12	74.12	[70.55;77.69]	28
3L	Month 18	75.81	[71.30;80.33]	18
3L	Month 24	75.67	[71.38;79.95]	16
3L	Month 36	76.96	[68.87;85.04]	13
4L+	Baseline	71.90	[67.70;76.11]	30
4L+	Month 3	71.69	[66.55;76.83]	25
4L+	Month 6	71.63	[67.45;75.82]	20
4L+	Month 12	77.34	[72.99;81.69]	17
4L+	Month 18	76.63	[71.84;81.43]	18
4L+	Month 24	71.45	[66.90;76.00]	16
4L+	Month 36	72.09	[62.15;82.03]	8
Overall	Month 3 vs Baseline	1.54	[-0.70;3.77]	96
Overall	Month 6 vs Baseline	3.63	[1.57;5.69]	83
Overall	Month 12 vs Baseline	4.73	[2.67;6.80]	72
Overall	Month 18 vs Baseline	4.56	[2.03;7.10]	56
Overall	Month 24 vs Baseline	2.34	[-0.23;4.92]	54
Overall	Month 36 vs Baseline	2.84	[-1.79;7.47]	46
2L	Month 3 vs Baseline	3.05	[-0.19;6.29]	42
2L	Month 6 vs Baseline	4.18	[1.35;7.00]	41
2L	Month 12 vs Baseline	4.22	[1.23;7.21]	30
2L	Month 18 vs Baseline	2.73	[-1.03;6.49]	22

Treatment lines	Visit	Estimation IC95%		Number of observations used
2L	Month 24 vs Baseline	1.40	[-2.22;5.01]	26
2L	Month 36 vs Baseline	0.95	[-4.73;6.64]	26
3L	Month 3 vs Baseline	1.78	[-2.05;5.62]	31
3L	Month 6 vs Baseline	6.98	[3.35;10.61]	24
3L	Month 12 vs Baseline	4.54	[1.10;7.97]	26
3L	Month 18 vs Baseline	6.23	[1.69;10.77]	16
3L	Month 24 vs Baseline	6.08	[1.45;10.71]	13
3L	Month 36 vs Baseline	7.37	[-0.66;15.40]	12
4L+	Month 3 vs Baseline	-0.22	[-4.66;4.23]	23
4L+	Month 6 vs Baseline	-0.27	[-4.41;3.87]	18
4L+	Month 12 vs Baseline	5.43	[1.23;9.64]	16
4L+	Month 18 vs Baseline	4.73	[-0.09;9.55]	18
4L+	Month 24 vs Baseline	-0.45	[-5.46;4.56]	15
4L+	Month 36 vs Baseline	0.18	[-9.64;10.00]	8

Table 15.5.6b. FACT-Leukemia Trial Outcome Index: Results of the mixed model with repeated measures (estimates) - FAS (n=139)

10.5.1.8. FACT-G Total Score

Regarding FACT-G Total Score, no clinical changes in score were observed, the overall score was 53.86 ± 11.59 at baseline and was 51.97 ± 8.84 at 36 months of follow-up (Table 60).

At baseline the score was similar between groups, 55.66 ± 11.39 in the 2L groups, 50.02 ± 13.24 in the 3L group and 55.31 ± 8.54 in the 4L+ group. Compared to baseline, the score at 36 months of follow-up was 51.87 ± 9.51 in the 2L group, 53.55 ± 8.69 in the 3L group and 49.76 ± 6.92in the 4L+ group. Score collection at 3 months, 6 months, 16 months, 18 months, and 24 months did not reveal important clinical changes.

Table 60: FACT-G Total Score - FAS (n=139)

Variables		2L (N=64)	3L (N=42)	4L+ (N=33)	Total (N=139)
Baseline	N	57	38	30	125
	Mean ± SD	55.664 ± 11.385	50.024 ± 13.242	55.306 ± 8.535	53.864 ± 11.593
	Median	56.500	50.500	56.250	56.000
	Q1 ; Q3	49.170 ; 61.000	45.330 ; 59.000	49.000 ; 60.000	47.670 ; 60.600
	Min. ; Max.	2 ; 83	1 ; 73	38.33 ; 74	1 ; 83
	Missing	7	4	3	14
Month 3	N	45	32	25	102
	Mean ± SD	53.304 ± 9.752	48.540 ± 13.132	49.731 ± 10.077	50.934 ± 11.098

Variables		2L (N=64)	3L (N=42)	4L+ (N=33)	Total (N=139)
	Median	54.000	52.350	49.670	53.000
	Q1 ; Q3	49.030 ; 60.000	44.500 ; 57.500	45.000 ; 57.000	46.000 ; 59.000
	Min. ; Max.	12.5 ; 67	2 ; 61.4	23 ; 66	2 ; 67
	Missing	19	10	8	37
Month 6	N	46	24	20	90
	Mean ± SD	56.116 ± 8.471	49.103 ± 8.984	52.021 ± 12.268	53.336 ± 9.924
	Median	57.000	50.520	50.500	53.585
	Q1 ; Q3	50.830 ; 61.000	45.000 ; 53.750	47.250 ; 59.415	48.000 ; 59.830
	Min. ; Max.	38.83 ; 80	27 ; 65.1	10.57 ; 70	10.57 ; 80
	Missing	18	18	13	49
Month 12	N	34	28	17	79
	Mean ± SD	54.483 ± 7.221	51.601 ± 7.077	53.717 ± 7.422	53.297 ± 7.238
	Median	55.500	51.050	53.330	54.000
	Q1 ; Q3	49.000 ; 60.670	46.250 ; 56.000	49.000 ; 60.830	48.000 ; 59.000
	Min. ; Max.	40.17 ; 66	40 ; 67	41.2 ; 67	40 ; 67
	Missing	30	14	16	60
Month 18	N	26	18	18	62
	Mean ± SD	50.225 ± 11.981	52.142 ± 9.613	50.921 ± 6.697	50.984 ± 9.886

Variables		2L (N=64)	3L (N=42)	4L+ (N=33)	Total (N=139)
	Median	53.420	53.415	49.000	51.585
	Q1 ; Q3	47.330 ; 58.000	47.000 ; 60.000	46.000 ; 54.000	47.000 ; 58.000
	Min. ; Max.	13 ; 65.17	32 ; 65	41 ; 64.57	13 ; 65.17
	Missing	38	24	15	77
Month 24	N	29	16	16	61
	Mean ± SD	50.159 ± 10.686	48.793 ± 7.695	52.896 ± 9.163	50.519 ± 9.563
	Median	51.000	50.415	54.315	51.670
	Q1 ; Q3	45.500 ; 57.500	43.165 ; 54.835	44.800 ; 59.000	45.500 ; 57.500
	Min. ; Max.	13 ; 67.83	32.25 ; 58.6	36 ; 68	13 ; 68
	Missing	35	26	17	78
Month 36	N	28	13	8	49
	Mean ± SD	51.871 ± 9.506	53.546 ± 8.694	49.755 ± 6.917	51.970 ± 8.843
	Median	51.000	54.000	48.135	51.000
	Q1 ; Q3	47.835 ; 57.000	53.000 ; 57.000	45.750 ; 49.500	47.270 ; 57.000
	Min. ; Max.	23 ; 80	34.6 ; 65	45 ; 66.27	23 ; 80
	Missing	36	29	25	90

Table 15.5.4g FACT-leu - FACT-G Total Score - FAS (n=139)

Regarding absolute changes in FACT-G Total score from baseline to follow-up, the mean maximum absolute positive change was 3.09 ± 10.24 in the overall FAS population and 1.99 ± 9.68 in the 2L group, 4.34 ± 11.42 in the 3L group and 3.46 ± 9.67 in the 4L+ group.

Regarding FACT-G Total score from baseline in the 2L group, it varied from -2.01 ± 8.30 at 3 months compared to baseline, to -3.44 ± 6.32 at 36 months, with a maximum of -5.13 ± 10.88 at 24 months compared to baseline.

Regarding FACT-G Total score from baseline in the 3L group, it varied from -0.86 ± 10.87 at 3 months compared to baseline, to 1.41 ± 6.58 at 36 months compared to baseline, with a maximum of -3.86 ± 5.17 at 24 months compared to baseline.

Regarding FACT-G Total score from baseline in the 4L+ group, it varied from -4.82 ± 10.74 at 3 months compared to baseline, to -6.299 ± 10.53 at 36 months compared to baseline.

To note, among the 139 total patients included in the FAS population while 96 were described at baseline, only 46 were described at 36 months (Table 61).

Results of the mixed model with repeated measures (effects) did not highlight any significant effect of visit, treatment or interaction between visit and treatment on the FACT-G Total score (Table 62).

Table 61: FACT-G Total Score Absolute change from baseline - FAS (n=139)

Variables		2L (N=64)	3L (N=42)	4L+ (N=33)	Total (N=139)
Absolute change from baseline to M3	N	42	31	23	96
	Mean ± SD	-2.005 ± 8.303	-0.863 ± 10.867	-4.824 ± 10.739	-2.311 ± 9.798
	Median	-1.750	-1.330	-4.000	-2.000
	Q1 ; Q3	-7.000 ; 3.330	-6.000 ; 3.000	-11.000 ; 0.670	-7.250 ; 3.000
	Min. ; Max.	-27.1 ; 14	-32.17 ; 29.07	-25.13 ; 23.47	-32.17 ; 29.07
	Missing	22	11	10	43
Absolute change from baseline to M6	N	41	24	18	83
	Mean ± SD	-0.709 ± 10.333	-0.634 ± 12.204	-1.743 ± 7.686	-0.912 ± 10.310
	Median	0.000	-2.915	-3.500	-2.000
	Q1 ; Q3	-8.000 ; 5.000	-6.500 ; 3.085	-7.500 ; 1.000	-7.500 ; 4.000
	Min. ; Max.	-30.77 ; 22.83	-23 ; 47.67	-11 ; 18	-30.77 ; 47.67
	Missing	23	18	15	56
Absolute change from baseline to M12	N	30	26	16	72
	Mean ± SD	-3.422 ± 10.344	-0.265 ± 11.996	-3.127 ± 6.330	-2.216 ± 10.248
	Median	-2.215	-2.365	-3.335	-2.550
	Q1 ; Q3	-9.000 ; 3.400	-6.500 ; 0.670	-4.700 ; 1.415	-7.800 ; 2.000

Variables		2L (N=64)	3L (N=42)	4L+ (N=33)	Total (N=139)
	Min. ; Max.	-27.83 ; 14.67	-13.17 ; 47.5	-16 ; 7	-27.83 ; 47.5
	Missing	34	16	17	67
Absolute change from baseline to M18	N	22	16	18	56
	Mean ± SD	-4.782 ± 11.891	2.400 ± 10.122	-3.731 ± 7.087	-2.392 ± 10.345
	Median	-2.715	1.415	-1.700	-1.915
	Q1 ; Q3	-6.000 ; 0.000	-3.170 ; 5.200	-9.600 ; 0.000	-4.995 ; 1.515
	Min. ; Max.	-43 ; 18.17	-13.5 ; 31	-18.5 ; 6.5	-43 ; 31
	Missing	42	26	15	83
Absolute change from baseline to M24	N	26	13	15	54
	Mean ± SD	-5.131 ± 10.876	-3.855 ± 5.168	-3.265 ± 10.951	-4.306 ± 9.706
	Median	-3.500	-4.070	-4.370	-4.035
	Q1 ; Q3	-7.830 ; 0.330	-5.670 ; -2.160	-13.400 ; 2.500	-8.670 ; 0.330
	Min. ; Max.	-37 ; 11.83	-13.42 ; 8.33	-15.5 ; 25.5	-37 ; 25.5
	Missing	38	29	18	85
Absolute change from baseline to M36	N	26	12	8	46
	Mean ± SD	-3.441 ± 6.322	1.409 ± 6.580	-6.286 ± 10.531	-2.670 ± 7.559
	Median	-3.885	4.000	-5.780	-2.585
	Q1 ; Q3	-7.000 ; 0.500	-2.585 ; 5.085	-13.000 ; -0.500	-7.330 ; 4.000

Variables		2L (N=64)	3L (N=42)	4L+ (N=33)	Total (N=139)
	Min. ; Max.	-20 ; 9	-10 ; 10.67	-23 ; 11.27	-23 ; 11.27
	Missing	38	30	25	93
Maximum absolute positive change from baseline	N	49	36	24	109
	Mean ± SD	1.997 ± 9.683	4.338 ± 11.421	3.457 ± 9.668	3.092 ± 10.244
	Median	2.000	2.950	2.000	2.000
	Q1 ; Q3	-2.270 ; 8.030	-3.765 ; 9.000	-2.750 ; 8.500	-2.600 ; 9.000
	Min. ; Max.	-27.1 ; 22.83	-13.17 ; 47.67	-11 ; 25.5	-27.1 ; 47.67
	Missing	15	6	9	30

Table 15.5.7 FACT-G Total Score - FAS (n=139)

Table 62: FACT-G Total Score: Results of the mixed model with repeated measures (effects) - FAS (n=139)

Effet	ddl	Valeur F	p-value
Effet visit	54.1	2.03	0.0779
Effect treatment lines	105	1.61	0.2046
Interaction: treatment lines * visit	81.3	0.98	0.4766

Table 15.5.8a FACT-G Total Score: Results of the mixed model with repeated measures (effects) - FAS (n=139)

Table 63: FACT-G Total Score: Results of the mixed model with repeated measures (estimates) - FAS (n=139)

Treatment lines	Visit	Estimation IC95%		Number of observations used
Overall	Overall			568
Overall	Baseline	53.28	[51.18;55.38]	125
Overall	Month 3	50.46	[48.24;52.68]	102
Overall	Month 6	52.22	[50.06;54.39]	90
Overall	Month 12	52.79	[51.18;54.40]	79
Overall	Month 18	51.92	[49.66;54.18]	62
Overall	Month 24	50.68	[48.22;53.13]	61
Overall	Month 36	51.57	[48.79;54.34]	49
2L	Baseline	54.82	[51.83;57.82]	57
2L	Month 3	52.45	[49.22;55.68]	45
2L	Month 6	55.86	[53.02;58.70]	46
2L	Month 12	53.92	[51.57;56.27]	34
2L	Month 18	51.00	[47.60;54.39]	26
2L	Month 24	50.57	[47.04;54.10]	29
2L	Month 36	52.32	[48.85;55.80]	28

Treatment lines	Visit	Estimation IC95%	Number of observations used
3L	Baseline	50.02 [46.34;53.70]	38
3L	Month 3	48.84 [44.98;52.69]	32
3L	Month 6	49.42 [45.48;53.36]	24
3L	Month 12	51.37 [48.75;53.99]	28
3L	Month 18	52.52 [48.52;56.53]	18
3L	Month 24	47.77 [43.27;52.27]	16
3L	Month 36	50.93 [46.18;55.68]	13
4L+	Baseline	54.98 [50.85;59.12]	30
4L+	Month 3	50.10 [45.73;54.48]	25
4L+	Month 6	51.39 [47.08;55.71]	20
4L+	Month 12	53.08 [49.76;56.40]	17
4L+	Month 18	52.24 [47.94;56.54]	18
4L+	Month 24	53.68 [49.03;58.34]	16
4L+	Month 36	51.45 [45.55;57.34]	8
Overall	Month 3 vs Baseline	-2.82 [-4.94;-0.69]	96
Overall	Month 6 vs Baseline	-1.05 [-3.73;1.62]	83
Overall	Month 12 vs Baseline	-0.49 [-2.78;1.81]	72
Overall	Month 18 vs Baseline	-1.36 [-4.05;1.33]	56
Overall	Month 24 vs Baseline	-2.60 [-5.31;0.10]	54
Overall	Month 36 vs Baseline	-1.71 [-4.16;0.74]	46
2L	Month 3 vs Baseline	-2.38 [-5.47;0.72]	42
2L	Month 6 vs Baseline	1.04 [-2.59;4.67]	41
2L	Month 12 vs Baseline	-0.90 [-4.21;2.40]	30
2L	Month 18 vs Baseline	-3.83 [-7.77;0.11]	22
2L	Month 24 vs Baseline	-4.25 [-8.10;-0.40]	26
2L	Month 36 vs Baseline	-2.50 [-5.45;0.45]	26
3L	Month 3 vs Baseline	-1.19 [-4.82;2.44]	31
3L	Month 6 vs Baseline	-0.60 [-5.38;4.18]	24
3L	Month 12 vs Baseline	1.35 [-2.54;5.23]	26
3L	Month 18 vs Baseline	2.50 [-2.24;7.24]	16
3L	Month 24 vs Baseline	-2.25 [-7.21;2.71]	13

Treatment lines	Visit	Estimation IC95%		Number of observations used
3L	Month 36 vs Baseline	0.91	[-3.27;5.09]	12
4L+	Month 3 vs Baseline	-4.88	[-9.10;-0.67]	23
4L+	Month 6 vs Baseline	-3.59	[-8.91;1.73]	18
4L+	Month 12 vs Baseline	-1.90	[-6.53;2.72]	16
4L+	Month 18 vs Baseline	-2.74	[-7.95;2.46]	18
4L+	Month 24 vs Baseline	-1.30	[-6.45;3.85]	15
4L+	Month 36 vs Baseline	-3.54	[-8.83;1.76]	8

Table 15.5.8b FACT-G Total Score: Results of the mixed model with repeated measures (estimates) - FAS (n=139)

10.5.1.9. FACT-Leukemia Total Score

Regarding FACT-Leukemia Total Score, no clinical changes in FACT-Leukemia Total Score were observed, the overall score was 100.42 ± 14.57 at baseline, it was 101.57 ± 16.59 at 36 months of follow-up (Table 64).

At baseline the score was similar between groups, 102.38 ± 15.20 in the 2L groups 96.47 ± 16.30 in the 3L group and 101.70 ± 9.63 in the 4L+ group. Compared to baseline, the score at 36 months of follow-up was 100.86 ± 18.74 in the 2L group, 102.16 ± 16.11 in the 3L group and 103.06 ± 9.07 in the 4L+ group. Score collection at 3 months, 6 months, 16 months, 18 months, and 24 months did not reveal important clinical changes.

Table 64: FACT-Leukemia Total Score - FAS (n=139)

Variables		2L (N=64)	3L (N=42)	4L+ (N=33)	Total (N=139)
Baseline	N	57	38	30	125
	Mean ± SD	102.381 ± 15.199	96.471 ± 16.302	101.695 ± 9.628	100.420 ± 14.569

Variables		2L (N=64)	3L (N=42)	4L+ (N=33)	Total (N=139)
	Median	104.560	99.765	100.500	102.000
	Q1 ; Q3	92.000 ; 113.170	86.170 ; 110.000	97.000 ; 107.420	90.830 ; 110.670
	Min. ; Max.	61 ; 129	55 ; 124	81.4 ; 127	55 ; 129
	Missing	7	4	3	14
Month 3	N	45	32	25	102
	Mean ± SD	104.762 ± 13.901	97.419 ± 20.984	99.968 ± 9.095	101.283 ± 15.797
	Median	107.000	100.990	101.000	103.515
	Q1 ; Q3	97.000 ; 114.930	90.200 ; 109.585	91.000 ; 106.630	93.000 ; 111.830
	Min. ; Max.	71.33 ; 129	15.5 ; 126	81.87 ; 120	15.5 ; 129
	Missing	19	10	8	37
Month 6	N	46	24	20	90
	Mean ± SD	108.566 ± 12.817	103.374 ± 9.933	100.483 ± 13.254	105.385 ± 12.561
	Median	109.000	105.085	99.250	106.915
	Q1 ; Q3	100.000 ; 117.550	94.470 ; 112.000	96.250 ; 108.915	96.500 ; 112.870
	Min. ; Max.	79.33 ; 140	86 ; 121	57.93 ; 122	57.93 ; 140
	Missing	18	18	13	49
Month 12	N	34	28	17	79
	Mean ± SD	106.329 ± 14.386	101.534 ± 8.639	105.758 ± 7.632	104.506 ± 11.415
	Median	106.500	101.415	105.000	104.600
	Q1 ; Q3	98.730 ; 118.000	95.215 ; 108.500	102.000 ; 109.830	95.600 ; 111.000
	Min. ; Max.	73.31 ; 130	85.56 ; 119	93.2 ; 122	73.31 ; 130
	Missing	30	14	16	60
Month 18	N	26	18	18	62
	Mean ± SD	102.622 ± 15.169	104.788 ± 11.167	103.789 ± 8.917	103.590 ± 12.331
	Median	105.250	104.615	104.000	104.415
	Q1 ; Q3	95.000 ; 110.000	96.000 ; 115.670	98.000 ; 109.000	96.000 ; 112.000
	Min. ; Max.	57 ; 128	85 ; 122	90.63 ; 122.57	57 ; 128

Variables		2L (N=64)	3L (N=42)	4L+ (N=33)	Total (N=139)
	Missing	38	24	15	77
Month 24	N	29	16	16	61
	Mean ± SD	101.474 ± 11.313	102.711 ± 11.284	102.542 ± 11.918	102.079 ± 11.287
	Median	104.000	100.080	101.335	102.670
	Q1 ; Q3	95.000 ; 108.190	95.000 ; 112.800	94.935 ; 110.565	95.000 ; 109.000
	Min. ; Max.	57 ; 116	82.69 ; 119	82.44 ; 128	57 ; 128
	Missing	35	26	17	78
Month 36	N	28	13	8	49
	Mean ± SD	100.863 ± 18.742	102.162 ± 16.113	103.055 ± 9.074	101.565 ± 16.591
	Median	103.335	99.000	103.500	103.000
	Q1 ; Q3	96.000 ; 110.000	90.000 ; 114.000	96.085 ; 109.000	95.000 ; 112.000
	Min. ; Max.	23 ; 123	72 ; 129	90 ; 117.27	23 ; 129
	Missing	36	29	25	90

Table 15.5.4h FACT-leu - FACT-Leukemia Total Score - FAS (n=139)

Regarding FACT-G Total score from baseline in the 2L group, it varied from 1.00 ± 7.99 at 3 months compared to baseline, to -0.54 ± 8.62 at 36 months, with a maximum of 2.37 ± 10.03 at 6 months compared to baseline.

Regarding FACT-G Total score from baseline in the 3L group, it varied from 0.96 ± 16.70 at 3 months compared to baseline, to 3.33 ± 9.76 at 36 months compared to baseline, with a maximum of 8.94 ± 13.15 at 18 months compared to baseline.

Regarding FACT-G Total score from baseline in the 4L+ group, it varied from -3.10 ± 9.50 at 3 months compared to baseline, -2.36 ± 13.67 at 36 months compared to baseline.

Regarding absolute changes in FACT-Leukemia Total Score from baseline to follow-up, the mean maximum absolute positive change was 7.71± 11.15 in the overall population and 6.57 ± 9.77 in the 2L group, 10.07 ± 13.78 in the 3L group and 6.49 ± 9.09 in the 4L+ group. To note, while data were available for 96 patients only data for 46 patients were available at 36 months. (Table 65).

Results of the mixed model with repeated measures (effects) did not highlight any significant effect of visit, treatment or interaction between visit and treatment on the FACT-G Total score (Table 66 and Table 67).

Table 65: FACT-Leukemia Total Score - FAS (n=139)

Variables		2L (N=64)	3L (N=42)	4L+ (N=33)	Total (N=139)
Absolute change from baseline to M3	N	42	31	23	96
	Mean ± SD	1.003 ± 7.989	0.956 ± 16.695	-3.103 ± 9.495	0.004 ± 11.812
	Median	1.655	2.000	-2.830	1.565
	Q1 ; Q3	-4.170 ; 7.000	-3.830 ; 10.000	-9.000 ; 3.500	-5.315 ; 6.685
	Min. ; Max.	-18.6 ; 19	-63.33 ; 29	-18 ; 16.33	-63.33 ; 29
	Missing	22	11	10	43
Absolute change from baseline to M6	N	41	24	18	83
	Mean ± SD	2.374 ± 10.031	6.648 ± 15.523	-0.899 ± 10.922	2.900 ± 12.199
	Median	0.840	7.735	-1.500	1.170
	Q1 ; Q3	-4.310 ; 9.000	-3.635 ; 13.555	-10.750 ; 5.830	-4.560 ; 9.000
	Min. ; Max.	-16.83 ; 32.83	-22 ; 60.67	-16 ; 27	-22 ; 60.67
	Missing	23	18	15	56
Absolute change from baseline to M12	N	30	26	16	72
	Mean ± SD	1.401 ± 10.976	3.432 ± 15.507	1.729 ± 6.306	2.207 ± 11.965
	Median	0.595	2.200	3.100	1.000
	Q1 ; Q3	-6.000 ; 5.000	-5.170 ; 9.170	-3.170 ; 6.000	-5.085 ; 6.600

Variables		2L (N=64)	3L (N=42)	4L+ (N=33)	Total (N=139)
	Min. ; Max.	-17.96 ; 25.23	-23.67 ; 55.5	-10 ; 12.63	-23.67 ; 55.5
	Missing	34	16	17	67
Absolute change from baseline to M18	N	22	16	18	56
	Mean ± SD	0.415 ± 11.906	8.939 ± 13.148	1.478 ± 9.583	3.192 ± 11.971
	Median	0.000	9.940	4.000	4.000
	Q1 ; Q3	-6.000 ; 10.000	0.580 ; 15.535	-0.400 ; 8.500	-4.665 ; 10.600
	Min. ; Max.	-21 ; 21.95	-20.75 ; 33	-18.5 ; 18	-21 ; 33
	Missing	42	26	15	83
Absolute change from baseline to M24	N	26	13	15	54
	Mean ± SD	0.374 ± 7.401	0.275 ± 9.079	-0.329 ± 12.753	0.155 ± 9.357
	Median	-0.250	2.580	1.500	1.515
	Q1 ; Q3	-4.670 ; 6.000	-7.000 ; 8.000	-7.000 ; 6.500	-5.760 ; 6.330
	Min. ; Max.	-12 ; 16.17	-14.67 ; 11.84	-23.17 ; 24.5	-23.17 ; 24.5
	Missing	38	29	18	85
Absolute change from baseline to M36	N	26	12	8	46
	Mean ± SD	-0.539 ± 8.619	3.326 ± 9.757	-2.361 ± 13.668	0.152 ± 9.884
	Median	-0.800	1.250	0.220	0.200
	Q1 ; Q3	-4.830 ; 5.000	-2.500 ; 9.585	-13.800 ; 9.635	-4.830 ; 5.170

Variables		2L (N=64)	3L (N=42)	4L+ (N=33)	Total (N=139)
	Min. ; Max.	-20.5 ; 15.5	-9.93 ; 21.17	-24 ; 13	-24 ; 21.17
	Missing	38	30	25	93
Maximum absolute positive change from baseline	N	49	36	24	109
	Mean ± SD	6.570 ± 9.774	10.070 ± 13.781	6.488 ± 9.085	7.708 ± 11.152
	Median	4.330	8.490	6.750	6.330
	Q1 ; Q3	1.000 ; 14.000	1.545 ; 17.035	3.000 ; 11.665	1.000 ; 14.000
	Min. ; Max.	-18.6 ; 32.83	-16.17 ; 60.67	-15.03 ; 27	-18.6 ; 60.67
	Missing	15	6	9	30

Table 15.5.9 FACT-Leukemia Total Score - FAS (n=139)

Table 66: FACT-Leukemia Total Score: Results of the mixed model with repeated measures (effects) - FAS (n=139)

Effet	ddl	Valeur F	p-value
Effet visit	38.5	2.01	0.0875
Effect treatment lines	113	1.03	0.3609
Interaction: treatment lines * visit	58.6	0.74	0.7080

Table 15.5.10a FACT-Leukemia Total Score: Results of the mixed model with repeated measures (effects) - FAS (n=139)

Table 67: FACT-Leukemia Total Score: Results of the mixed model with repeated measures (estimates) - FAS (n=139)

Treatment lines	Visit	Estimation	IC95%	Number of observations used
Overall	Overall			568
Overall	Baseline	71.64	[69.51;73.78]	125
Overall	Month 3	73.18	[70.58;75.78]	102
Overall	Month 6	75.27	[73.18;77.36]	90
Overall	Month 12	76.37	[74.24;78.51]	79
Overall	Month 18	76.21	[73.68;78.73]	62
Overall	Month 24	73.98	[71.62;76.35]	61
Overall	Month 36	74.48	[69.80;79.16]	49
2L	Baseline	73.44	[70.39;76.49]	57
2L	Month 3	76.49	[72.72;80.25]	45
2L	Month 6	77.62	[74.75;80.48]	46
2L	Month 12	77.66	[74.59;80.74]	34
2L	Month 18	76.17	[72.41;79.93]	26
2L	Month 24	74.84	[71.50;78.18]	29
2L	Month 36	74.39	[68.64;80.15]	28
3L	Baseline	69.58	[65.84;73.33]	38
3L	Month 3	71.37	[66.85;75.88]	32

Treatment lines	Visit	Estimation IC95%		Number of observations used
3L	Month 6	76.56	[72.86;80.27]	24
3L	Month 12	74.12	[70.55;77.69]	28
3L	Month 18	75.81	[71.30;80.33]	18
3L	Month 24	75.67	[71.38;79.95]	16
3L	Month 36	76.96	[68.87;85.04]	13
4L+	Baseline	71.90	[67.70;76.11]	30
4L+	Month 3	71.69	[66.55;76.83]	25
4L+	Month 6	71.63	[67.45;75.82]	20
4L+	Month 12	77.34	[72.99;81.69]	17
4L+	Month 18	76.63	[71.84;81.43]	18
4L+	Month 24	71.45	[66.90;76.00]	16
4L+	Month 36	72.09	[62.15;82.03]	8
Overall	Month 3 vs Baseline	1.54	[-0.70;3.77]	96
Overall	Month 6 vs Baseline	3.63	[1.57;5.69]	83
Overall	Month 12 vs Baseline	4.73	[2.67;6.80]	72
Overall	Month 18 vs Baseline	4.56	[2.03;7.10]	56
Overall	Month 24 vs Baseline	2.34	[-0.23;4.92]	54
Overall	Month 36 vs Baseline	2.84	[-1.79;7.47]	46
2L	Month 3 vs Baseline	3.05	[-0.19;6.29]	42
2L	Month 6 vs Baseline	4.18	[1.35;7.00]	41

Treatment lines	Visit	Estimation IC95%		Number of observations used
2L	Month 12 vs Baseline	4.22	[1.23;7.21]	30
2L	Month 18 vs Baseline	2.73	[-1.03;6.49]	22
2L	Month 24 vs Baseline	1.40	[-2.22;5.01]	26
2L	Month 36 vs Baseline	0.95	[-4.73;6.64]	26
3L	Month 3 vs Baseline	1.78	[-2.05;5.62]	31
3L	Month 6 vs Baseline	6.98	[3.35;10.61]	24
3L	Month 12 vs Baseline	4.54	[1.10;7.97]	26
3L	Month 18 vs Baseline	6.23	[1.69;10.77]	16
3L	Month 24 vs Baseline	6.08	[1.45;10.71]	13
3L	Month 36 vs Baseline	7.37	[-0.66;15.40]	12
4L+	Month 3 vs Baseline	-0.22	[-4.66;4.23]	23
4L+	Month 6 vs Baseline	-0.27	[-4.41;3.87]	18
4L+	Month 12 vs Baseline	5.43	[1.23;9.64]	16
4L+	Month 18 vs Baseline	4.73	[-0.09;9.55]	18
4L+	Month 24 vs Baseline	-0.45	[-5.46;4.56]	15
4L+	Month 36 vs Baseline	0.18	[-9.64;10.00]	8

Table 15.5.10b FACT-Leukemia Total Score: Results of the mixed model with repeated measures (estimates) - FAS (n=139)

10.5.2. Long-Term Follow-up

As mentioned previously, most patients were in chronic phase at study inclusion, except for one patient in accelerated phase in the 2L group and another patient in blast phase in the 4L+ group. Accordingly, for these two patients only descriptive analysis has been performed (see **Appendix 7.9**)

During long term follow-up 5 patients had a CML progression, mostly in the 2L group, in which 4 patients progressed and one in the 4L+ group. One patient from the 2L group progressed from AP to AP, 2 progressed from CP to AP and 1 from CP to BP and one patient from 4L+ group progressed from CP to AP.

Therefore, at the end of the study, 4 (2.9%) patients were in accelerated phase, 2 (1.4%) patients were in blast phase and 133 (95.7%) patients were still in chronic phase.

After discontinuation of bosutinib 52 (37.4%) patients had a next line of treatment, among them 45 (86.5%) had one other line, 6 (11.5%) two other lines and 1 (1.9%) three other lines. Details about next therapy are presented in Table 68.

During long-term follow-up 61 (43.9%) patients permanently discontinued bosutinib, main reasons were intolerance (60.7%) and suboptimum response (24.6%).

At the end of the study 120 (86.3%) patients were still alive, while death occurred in 7 (5%) patients and 12 (8.6%) were lost during follow-up. The mean treatment duration was 22.42 ± 16.12 months with a median at 31.68 [0 ; 44.64] months. A clinical difference was observed considering median duration between 3L group ,36.12 [0 ; 39.6] months and 4L+ group in which the median duration was 17.52 [0 ; 40.2], while median duration was 25.74 [0 ; 44.64] months in the 2L group.

It has been observed that death occurred in 4 (12.1%) patients from the group 4L+, whereas 1 (2.4%) died in the 3L group and 2 (3.1%) in the 2L group.

Cause of death were, related to illness in 2 cases, adenocarcinoma, comorbidities, SAE, respiratory decompensation and multi visceral failure (see Table 69 and **Appendix 7.10**).

Table 68: Long-Term Follow-up - FAS (n=139)

Variables		2L (N=64)	3L (N=42)	4L+ (N=33)	Total (N=139)
CML phase defined at study inclusion	Accelerated phase (AP)	1 (1.6%)	0 (0%)	0 (0%)	1 (0.7%)
	Blast phase (blast crisis) (BP)	0 (0%)	0 (0%)	1 (3%)	1 (0.7%)
	Chronic phase (CP)	63 (98.4%)	42 (100%)	32 (97%)	137 (98.6%)
Progression of CML	No	60 (93.8%)	42 (100%)	32 (97%)	134 (96.4%)
	Yes	4 (6.3%)	0 (0%)	1 (3%)	5 (3.6%)
Progression of CML	AP to AP	1 (25%)		0 (0%)	1 (20%)
	CP to AP	2 (50%)		1 (100%)	3 (60%)
	CP to BP	1 (25%)		0 (0%)	1 (20%)
CML phase defined at end of follow-up	Accelerated phase (AP)	3 (4.7%)	0 (0%)	1 (3%)	4 (2.9%)
	Blast phase (blast crisis) (BP)	1 (1.6%)	0 (0%)	1 (3%)	2 (1.4%)
	Chronic phase (CP)	60 (93.8%)	42 (100%)	31 (93.9%)	133 (95.7%)

Variables		2L (N=64)	3L (N=42)	4L+ (N=33)	Total (N=139)
Next treatment	No	39 (60.9%)	25 (59.5%)	23 (69.7%)	87 (62.6%)
	Yes	25 (39.1%)	17 (40.5%)	10 (30.3%)	52 (37.4%)
Number of next treatment	1	20 (80%)	15 (88.2%)	10 (100%)	45 (86.5%)
	2	4 (16%)	2 (11.8%)	0 (0%)	6 (11.5%)
	5	1 (4%)	0 (0%)	0 (0%)	1 (1.9%)
Therapy in 1st line after bosutinib	ASCIMINIB	0 (0%)	1 (5.9%)	0 (0%)	1 (1.9%)
	BOSULIF (REPRISE)	0 (0%)	0 (0%)	1 (10%)	1 (1.9%)
	DASATINIB	5 (20%)	2 (11.8%)	2 (20%)	9 (17.3%)
	GLIVEC	0 (0%)	1 (5.9%)	0 (0%)	1 (1.9%)
	GLYVEC	1 (4%)	0 (0%)	0 (0%)	1 (1.9%)
	HYDREA	3 (12%)	0 (0%)	1 (10%)	4 (7.7%)
	HYDREA+DEXAMETHASONE	1 (4%)	0 (0%)	0 (0%)	1 (1.9%)
	ICLUSIG	0 (0%)	1 (5.9%)	2 (20%)	3 (5.8%)
	IMATINIB	4 (16%)	3 (17.6%)	0 (0%)	7 (13.5%)
	NILOTINIB	3 (12%)	3 (17.6%)	2 (20%)	8 (15.4%)
	PONATINIB	2 (8%)	3 (17.6%)	1 (10%)	6 (11.5%)

Variables		2L (N=64)	3L (N=42)	4L+ (N=33)	Total (N=139)
	SPRYCEL	3 (12%)	1 (5.9%)	1 (10%)	5 (9.6%)
	SPRYCEL 70MG/JOUR	0 (0%)	1 (5.9%)	0 (0%)	1 (1.9%)
	TASIGNA	3 (12%)	1 (5.9%)	0 (0%)	4 (7.7%)
Therapy in 2nd line after bosutinib	ASCIMINIB	1 (25%)	1 (50%)		2 (33.3%)
	GLIVEC	1 (25%)	0 (0%)		1 (16.7%)
	HYDREA	1 (25%)	0 (0%)		1 (16.7%)
	IMATINIB	0 (0%)	1 (50%)		1 (16.7%)
	PONATINIB+AZACITIDINE	1 (25%)	0 (0%)		1 (16.7%)
Therapy in 3rd line after bosutinib	IMATINIB	1 (100%)			1 (100%)
Therapy in 4st line after bosutinib	DASATINIB +AZACITIDINE	1 (50%)			1 (50%)
	PONATINIB	1 (50%)			1 (50%)
Therapy in 5st line after bosutinib	PONATINIB	1 (100%)			1 (100%)
Permanent discontinuation	No	36 (56.3%)	21 (50%)	21 (63.6%)	78 (56.1%)
	Yes	28 (43.8%)	21 (50%)	12 (36.4%)	61 (43.9%)

Variables		2L (N=64)	3L (N=42)	4L+ (N=33)	Total (N=139)
Reason for permanent discontinuation	Death (Adenocarcinoma POORLY DIFFERENTIATED POLYMETASTATIC)	1 (3.6%)	0 (0%)	0 (0%)	1 (1.6%)
	Death (Multiviscerale failure)	0 (0%)	0 (0%)	1 (8.3%)	1 (1.6%)
	Disease progression (Accelerated phase)	1 (3.6%)	0 (0%)	0 (0%)	1 (1.6%)
	Disease progression (Blast crisis)	1 (3.6%)	0 (0%)	0 (0%)	1 (1.6%)
	Intolerance	17 (60.7%)	13 (61.9%)	7 (58.3%)	37 (60.7%)
	Loss of response	1 (3.6%)	0 (0%)	0 (0%)	1 (1.6%)
	Patient's choice	2 (7.1%)	1 (4.8%)	1 (8.3%)	4 (6.6%)
	Suboptimum response	5 (17.9%)	7 (33.3%)	3 (25%)	15 (24.6%)

Table 15.5.11 Long-Term Follow-up - FAS (n=139)

Table 69: Subject Status at Last News - FAS (n=139)

Variables		2L (N=64)	3L (N=42)	4L+ (N=33)	Total (N=139)
Patient status	Alive at end of study	57 (89.1%)	38 (90.5%)	25 (75.8%)	120 (86.3%)
	Died	2 (3.1%)	1 (2.4%)	4 (12.1%)	7 (5%)
	Lost to follow-up at end of study	5 (7.8%)	3 (7.1%)	4 (12.1%)	12 (8.6%)
Cause of death	Other (ADENOCARCINOMA POLYMETASTATIC)	1 (50%)	0 (0%)	0 (0%)	1 (14.3%)
	Other (SAE)	0 (0%)	0 (0%)	1 (25%)	1 (14.3%)
	Other (COMORBIDITIES)	0 (0%)	0 (0%)	1 (25%)	1 (14.3%)
	Other (RESPIRATORY DECOMPENSATION)	0 (0%)	1 (100%)	0 (0%)	1 (14.3%)
	Other (MULTIORGANE FAILURE)	0 (0%)	0 (0%)	1 (25%)	1 (14.3%)
	Related to the illness	1 (50%)	0 (0%)	1 (25%)	2 (28.6%)
Duration of treatment (months)	N	64	42	33	139
	Mean ± SD	20.805 ± 16.921	26.214 ± 15.317	20.738 ± 15.130	22.424 ± 16.117
	Median	25.740	36.120	17.520	31.680
	Q1 ; Q3	2.400 ; 37.080	12.000 ; 37.440	6.360 ; 36.360	3.240 ; 37.200
	Min. ; Max.	0 ; 44.64	0 ; 39.6	0 ; 40.2	0 ; 44.64
	Missing	0	0	0	0

Table 15.5.12 Subject Status at Last News - FAS (n=139)

10.6. Adverse events / adverse reactions

10.6.1. Adverse event

Overall, a total of 141 patients among the 142 patients of the SAF population experienced at least one AE. In more details, 65 (98.5%) patients in the 2L group, and all the patients from the 3L group and 4L+ group. All AEs are summarized in Table 70 and full listing for measure taken to prevent AE are presented in **Appendix 7.7**.

Among these patients, 86 (60.6%) had at least one SAE, 39 (59.1%) in the 2L group, 28 (66.7%) in the 3L group and 19 (55.9%) in the 4L+ group.

As already presented in Table 17 part of this report, 125 (88%) patients experienced at least one AE related to bosutinib. In more detail, 56 (84.8%) patients in the 2L group, 37 (88.1%) patients in the 3L group and 32 (94.1%) patients in the 4L+ group had at least one AE related to the treatment with bosutinib. AEs related to treatment are summarized in Table 13.

Moreover, 85 (59.9%) patients exhibited AE which led to treatment change, 36 (54.5%) in the 2L group, 24 (57.1%) in the 3L group and 25 (73.5%) in the 4L group.

In total 1376 grade 1-2 AEs were recorded in 140 (98.6%) patients (Table 72). The most experienced AEs were gastrointestinal disorders observed in 113 (79.6%) patients, with diarrhea, nausea, constipation, and abdominal pain mainly. AEs of the general disorders and administration site conditions System Organ class were also reported in more than half of the population (53.5%) with mostly asthenia, fatigue, and peripheral oedema, as well as AEs which belong to the infection and infestations System Organ class (50.7%) such as bronchitis and other infection.

In total 233 grade 3-4 AEs were recorded in 88 (62%) patients. The most experienced grade 3-4 AEs were hepatocellular injury observed in 12 (8.5%) patients, cardiac failure in 8 (5.6%) patients, anemia in 7 (4.9%) patients, pleural effusion in 5 (3.5%) patients, as well as diarrhea observed in 8 (5.6%). Details about grade 3-5 AE are given in Table 73.

Overall, 7 patients reported grade 5 AEs, one patient had sepsis, 3 had a general physical health deterioration, one had an aggravation of his condition, one had a multi visceral failure, and one developed a pneumonia.

Table 70: Adverse Events - SAF (n=142)

Variables		2L (N=66)	3L (N=42)	4L+ (N=34)	Total (N=142)
n% of patients with at least one AEs	No	1 (1.5%)	0 (0%)	0 (0%)	1 (0.7%)
	Yes	65 (98.5%)	42 (100%)	34 (100%)	141 (99.3%)
n% of patients with at least one AEs grade 3-4	No	32 (48.5%)	13 (31%)	9 (26.5%)	54 (38%)
	Yes	34 (51.5%)	29 (69%)	25 (73.5%)	88 (62%)
n% of patients with at least one AEs grade 5	No	64 (97.0%)	41 (97.6%)	30 (88.2%)	135 (95.1%)
	Yes	2 (3.0%)	1 (2.4%)	4 (11.8%)	7 (4.9%)
n% of patients with at least one SAEs	No	27 (40.9%)	14 (33.3%)	15 (44.1%)	56 (39.4%)
	Yes	39 (59.1%)	28 (66.7%)	19 (55.9%)	86 (60.6%)
n% of patients with at least one treatment related AEs	No	10 (15.2%)	5 (11.9%)	2 (5.9%)	17 (12%)
	Yes	56 (84.8%)	37 (88.1%)	32 (94.1%)	125 (88%)
n% of patients with at least one AEs leading to treatment change	No	30 (45.5%)	18 (42.9%)	9 (26.5%)	57 (40.1%)
	Yes	36 (54.5%)	24 (57.1%)	25 (73.5%)	85 (59.9%)
n% of patients with at least one AE leading to permanent discontinuation	No	54 (81.8%)	35 (83.3%)	29 (85.3%)	118 (83.1%)
	Yes	12 (18.2%)	7 (16.7%)	5 (14.7%)	24 (16.9%)

Table 15.3.4 Adverse Events - SAF (n=142) and Table 15.3.5c Adverse Events by System Organ Class and Preferred Term (All Causalities and grade 3-4) - SAF (n=142) and Listing 15.3.5d Adverse Events by System Organ Class and Preferred Term (All Causalities and grade 5 or missing) - SAF (n=142).

Table 71: Adverse Events by System Organ Class and Preferred Term (All Causalities and all grade) - SAF (n=142)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
ALL		**769**	**65 (98.5%)**	**471**	**42 (100%)**	**383**	**34 (100%)**	**1623**	**141 (99.3%)**
Gastrointestinal disorders	**ALL**	**158**	**56 (84.8%)**	**93**	**37 (88.1%)**	**82**	**25 (73.5%)**	**333**	**118 (83.1%)**
	Diarrhoea	62	41 (62.1%)	31	26 (61.9%)	25	19 (55.9%)	118	86 (60.6%)
	Nausea	13	12 (18.2%)	11	10 (23.8%)	8	7 (20.6%)	32	29 (20.4%)
	Constipation	12	10 (15.2%)	5	5 (11.9%)	9	7 (20.6%)	26	22 (15.5%)
	Abdominal pain	9	8 (12.1%)	6	5 (11.9%)	6	5 (14.7%)	21	18 (12.7%)
	Abdominal pain upper	11	10 (15.2%)	6	5 (11.9%)	4	4 (11.8%)	21	19 (13.4%)
	Vomiting	8	7 (10.6%)	5	4 (9.5%)	5	5 (14.7%)	18	16 (11.3%)
	Gastrointestinal disorder	7	6 (9.1%)	1	1 (2.4%)	2	2 (5.9%)	10	9 (6.3%)
	Abdominal distension	2	2 (3%)	2	2 (4.8%)	2	1 (2.9%)	6	5 (3.5%)
	Aphthous stomatitis	2	2 (3%)	2	2 (4.8%)	1	1 (2.9%)	5	5 (3.5%)
	Rectal haemorrhage	1	1 (1.5%)	2	2 (4.8%)	2	2 (5.9%)	5	5 (3.5%)
	Dyspepsia	3	3 (4.5%)	-	-	1	1 (2.9%)	4	4 (2.8%)
	Flatulence	1	1 (1.5%)	1	1 (2.4%)	2	2 (5.9%)	4	4 (2.8%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
	Gastrooesophageal reflux disease	1	1 (1.5%)	1	1 (2.4%)	2	2 (5.9%)	4	4 (2.8%)
	Haemorrhoids	1	1 (1.5%)	1	1 (2.4%)	1	1 (2.9%)	3	3 (2.1%)
	Hiatus hernia	1	1 (1.5%)	-	-	2	2 (5.9%)	3	3 (2.1%)
	Tooth disorder	2	2 (3%)	1	1 (2.4%)	-	-	3	3 (2.1%)
	Abdominal pain lower	2	2 (3%)	-	-	-	-	2	2 (1.4%)
	Dry mouth	-	-	-	-	2	2 (5.9%)	2	2 (1.4%)
	Dysphagia	2	2 (3%)	-	-	-	-	2	2 (1.4%)
	Eructation	-	-	1	1 (2.4%)	1	1 (2.9%)	2	2 (1.4%)
	Functional gastrointestinal disorder	1	1 (1.5%)	1	1 (2.4%)	-	-	2	2 (1.4%)
	Gastric ulcer	-	-	1	1 (2.4%)	1	1 (2.9%)	2	2 (1.4%)
	Inguinal hernia	1	1 (1.5%)	1	1 (2.4%)	-	-	2	2 (1.4%)
	Intestinal obstruction	1	1 (1.5%)	1	1 (2.4%)	-	-	2	2 (1.4%)
	Oesophagitis	-	-	1	1 (2.4%)	1	1 (2.9%)	2	2 (1.4%)
	Reflux gastritis	1	1 (1.5%)	1	1 (2.4%)	-	-	2	2 (1.4%)
	Abdominal discomfort	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Abdominal hernia	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Abdominal rigidity	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
	Aerophagia	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Anal fissure	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Anal fistula	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Anorectal discomfort	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Cheilitis	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Chronic gastritis	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Eosinophilic colitis	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Erosive duodenitis	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Faecaloma	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Faeces soft	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Gastritis	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Gastroduodenal ulcer	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Gastrointestinal angiodysplasia	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Gastrointestinal motility disorder	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Gingival bleeding	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Glossodynia	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Haemorrhoidal haemorrhage	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
	Intestinal polyp	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Melaena	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Mouth haemorrhage	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Oral discomfort	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Oral lichen planus	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Oral mucosa erosion	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Pancreatitis acute	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Rectal polyp	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Salivary hypersecretion	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Toothache	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
General disorders and administration site conditions	**ALL**	**84**	**40 (60.6%)**	**46**	**22 (52.4%)**	**37**	**19 (55.9%)**	**167**	**81 (57%)**
	Asthenia	25	19 (28.8%)	12	10 (23.8%)	7	4 (11.8%)	44	33 (23.2%)
	Chest pain	11	9 (13.6%)	4	4 (9.5%)	2	2 (5.9%)	17	15 (10.6%)
	Fatigue	8	7 (10.6%)	6	5 (11.9%)	3	3 (8.8%)	17	15 (10.6%)
	Oedema peripheral	9	8 (12.1%)	2	2 (4.8%)	6	6 (17.6%)	17	16 (11.3%)
	General physical health deterioration	4	3 (4.5%)	1	1 (2.4%)	4	4 (11.8%)	9	8 (5.6%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
	Pyrexia	-	-	2	2 (4.8%)	5	5 (14.7%)	7	7 (4.9%)
	Drug ineffective	3	3 (4.5%)	2	1 (2.4%)	1	1 (2.9%)	6	5 (3.5%)
	Malaise	2	1 (1.5%)	3	2 (4.8%)	-	-	5	3 (2.1%)
	Therapeutic response decreased	3	2 (3%)	1	1 (2.4%)	1	1 (2.9%)	5	4 (2.8%)
	Oedema	3	3 (4.5%)	1	1 (2.4%)	-	-	4	4 (2.8%)
	Pain	2	2 (3%)	1	1 (2.4%)	1	1 (2.9%)	4	4 (2.8%)
	Chills	2	2 (3%)	-	-	1	1 (2.9%)	3	3 (2.1%)
	Drug intolerance	2	2 (3%)	1	1 (2.4%)	-	-	3	3 (2.1%)
	Influenza like illness	2	2 (3%)	1	1 (2.4%)	-	-	3	3 (2.1%)
	Reduced drug effect	-	-	1	1 (2.4%)	2	1 (2.9%)	3	2 (1.4%)
	Treatment noncompliance	3	2 (3%)	-	-	-	-	3	2 (1.4%)
	Face oedema	1	1 (1.5%)	-	-	1	1 (2.9%)	2	2 (1.4%)
	Gait disturbance	1	1 (1.5%)	1	1 (2.4%)	-	-	2	2 (1.4%)
	Ill-defined disorder	1	1 (1.5%)	1	1 (2.4%)	-	-	2	2 (1.4%)
	Inflammation	-	-	1	1 (2.4%)	1	1 (2.9%)	2	2 (1.4%)
	Chest discomfort	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Condition aggravated	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
	Feeling cold	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Generalised oedema	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Hernia	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Hyperthermia	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Multiviceral failure	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Polyp	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Ulcer	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
Infections and infestations	**ALL**	**75**	**40 (60.6%)**	**37**	**22 (52.4%)**	**39**	**15 (44.1%)**	**151**	**77 (54.2%)**
	Bronchitis	14	12 (18.2%)	1	1 (2.4%)	3	3 (8.8%)	18	16 (11.3%)
	Urinary tract infection	3	2 (3%)	4	4 (9.5%)	6	5 (14.7%)	13	11 (7.7%)
	Corona virus infection	8	8 (12.1%)	1	1 (2.4%)	1	1 (2.9%)	10	10 (7%)
	Nasopharyngitis	6	6 (9.1%)	2	2 (4.8%)	2	2 (5.9%)	10	10 (7%)
	Infection	2	2 (3%)	2	2 (4.8%)	3	2 (5.9%)	7	6 (4.2%)
	Erysipelas	3	3 (4.5%)	-	-	3	1 (2.9%)	6	4 (2.8%)
	Influenza	2	2 (3%)	2	2 (4.8%)	2	2 (5.9%)	6	6 (4.2%)
	Pneumonia	1	1 (1.5%)	2	2 (4.8%)	3	3 (8.8%)	6	6 (4.2%)
	Gastroenteritis	3	3 (4.5%)	1	1 (2.4%)	1	1 (2.9%)	5	5 (3.5%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
	Folliculitis	3	3 (4.5%)	1	1 (2.4%)	-	-	4	4 (2.8%)
	Sepsis	2	2 (3%)	1	1 (2.4%)	1	1 (2.9%)	4	4 (2.8%)
	Cystitis	1	1 (1.5%)	-	-	2	2 (5.9%)	3	3 (2.1%)
	Fungal infection	1	1 (1.5%)	2	2 (4.8%)	-	-	3	3 (2.1%)
	Herpes zoster	2	2 (3%)	1	1 (2.4%)	-	-	3	3 (2.1%)
	Laryngitis	3	3 (4.5%)	-	-	-	-	3	3 (2.1%)
	Abdominal abscess	-	-	2	1 (2.4%)	-	-	2	1 (0.7%)
	Candida infection	-	-	-	-	2	2 (5.9%)	2	2 (1.4%)
	Diverticulitis	-	-	2	2 (4.8%)	-	-	2	2 (1.4%)
	Ear infection	1	1 (1.5%)	-	-	1	1 (2.9%)	2	2 (1.4%)
	Herpes simplex	2	2 (3%)	-	-	-	-	2	2 (1.4%)
	Localised infection	-	-	1	1 (2.4%)	1	1 (2.9%)	2	2 (1.4%)
	Onychomycosis	2	1 (1.5%)	-	-	-	-	2	1 (0.7%)
	Oral fungal infection	1	1 (1.5%)	1	1 (2.4%)	-	-	2	2 (1.4%)
	Pyelonephritis	-	-	1	1 (2.4%)	1	1 (2.9%)	2	2 (1.4%)
	Rhinitis	2	2 (3%)	-	-	-	-	2	2 (1.4%)
	Staphylococcal infection	1	1 (1.5%)	-	-	1	1 (2.9%)	2	2 (1.4%)
	Tooth abscess	1	1 (1.5%)	1	1 (2.4%)	-	-	2	2 (1.4%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
	Upper respiratory tract infection	1	1 (1.5%)	1	1 (2.4%)	-	-	2	2 (1.4%)
	Vulvovaginal mycotic infection	-	-	1	1 (2.4%)	1	1 (2.9%)	2	2 (1.4%)
	Anal abscess	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Bacterial infection	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Conjunctivitis	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Escherichia infection	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Gastrointestinal infection	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Genital infection female	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Gingivitis	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Hepatitis E	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Herpes ophthalmic	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Klebsiella infection	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Orchitis	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Otitis media acute	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Paronychia	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Perineal abscess	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Pharyngitis	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
	Pneumonia aspiration	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Pneumonia fungal	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Sinusitis	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Skin infection	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Tooth infection	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Urinary tract infection bacterial	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Vaginal infection	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
Musculoskeletal and connective tissue disorders	**ALL**	**66**	**37 (56.1%)**	**47**	**22 (52.4%)**	**27**	**16 (47.1%)**	**140**	**75 (52.8%)**
	Arthralgia	13	10 (15.2%)	7	7 (16.7%)	7	6 (17.6%)	27	23 (16.2%)
	Myalgia	8	7 (10.6%)	6	5 (11.9%)	2	2 (5.9%)	16	14 (9.9%)
	Back pain	6	6 (9.1%)	3	3 (7.1%)	4	4 (11.8%)	13	13 (9.2%)
	Muscle spasms	2	2 (3%)	6	5 (11.9%)	4	4 (11.8%)	12	11 (7.7%)
	Osteoarthritis	6	5 (7.6%)	3	2 (4.8%)	2	2 (5.9%)	11	9 (6.3%)
	Musculoskeletal pain	4	3 (4.5%)	3	2 (4.8%)	3	3 (8.8%)	10	8 (5.6%)
	Pain in extremity	4	4 (6.1%)	3	3 (7.1%)	2	2 (5.9%)	9	9 (6.3%)
	Arthritis	3	3 (4.5%)	3	3 (7.1%)	-	-	6	6 (4.2%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
	Neck pain	2	2 (3%)	2	2 (4.8%)	-	-	4	4 (2.8%)
	Chondrocalcinosis	1	1 (1.5%)	2	2 (4.8%)	-	-	3	3 (2.1%)
	Tendonitis	2	2 (3%)	1	1 (2.4%)	-	-	3	3 (2.1%)
	Bone pain	1	1 (1.5%)	1	1 (2.4%)	-	-	2	2 (1.4%)
	Intervertebral disc disorder	2	2 (3%)	-	-	-	-	2	2 (1.4%)
	Intervertebral disc protrusion	2	2 (3%)	-	-	-	-	2	2 (1.4%)
	Musculoskeletal chest pain	-	-	-	-	2	2 (5.9%)	2	2 (1.4%)
	Spinal osteoarthritis	2	2 (3%)	-	-	-	-	2	2 (1.4%)
	Spinal pain	2	1 (1.5%)	-	-	-	-	2	1 (0.7%)
	Tendon pain	1	1 (1.5%)	-	-	1	1 (2.9%)	2	2 (1.4%)
	Back disorder	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Flank pain	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Groin pain	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Intervertebral disc degeneration	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Joint ankylosis	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Joint effusion	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Limb discomfort	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
	Osteoporosis	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Periarthritis	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Rhabdomyolysis	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Rotator cuff syndrome	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Scoliosis	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
Respiratory, thoracic and mediastinal disorders	**ALL**	**61**	**26 (39.4%)**	**37**	**18 (42.9%)**	**25**	**11 (32.4%)**	**123**	**55 (38.7%)**
	Dyspnoea	12	9 (13.6%)	11	10 (23.8%)	6	6 (17.6%)	29	25 (17.6%)
	Pleural effusion	12	8 (12.1%)	4	4 (9.5%)	6	5 (14.7%)	22	17 (12%)
	Dyspnoea exertional	7	5 (7.6%)	2	2 (4.8%)	1	1 (2.9%)	10	8 (5.6%)
	Cough	6	5 (7.6%)	2	2 (4.8%)	1	1 (2.9%)	9	8 (5.6%)
	Sleep apnoea syndrome	4	4 (6.1%)	3	3 (7.1%)	-	-	7	7 (4.9%)
	Chronic obstructive pulmonary disease	2	2 (3%)	2	2 (4.8%)	1	1 (2.9%)	5	5 (3.5%)
	Lung disorder	3	3 (4.5%)	-	-	2	1 (2.9%)	5	4 (2.8%)
	Asthma	4	3 (4.5%)	-	-	-	-	4	3 (2.1%)
	Dysphonia	1	1 (1.5%)	3	3 (7.1%)	-	-	4	4 (2.8%)
	Rhinorrhoea	1	1 (1.5%)	1	1 (2.4%)	1	1 (2.9%)	3	3 (2.1%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
	Epistaxis	1	1 (1.5%)	-	-	1	1 (2.9%)	2	2 (1.4%)
	Oropharyngeal pain	1	1 (1.5%)	-	-	1	1 (2.9%)	2	2 (1.4%)
	Productive cough	1	1 (1.5%)	-	-	1	1 (2.9%)	2	2 (1.4%)
	Pulmonary pain	-	-	2	2 (4.8%)	-	-	2	2 (1.4%)
	Acute pulmonary oedema	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Acute respiratory distress syndrome	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Acute respiratory failure	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Bronchopulmonary disease	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Haemoptysis	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Hypoventilation	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Hypoxia	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Orthopnoea	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Pleural fibrosis	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Pleurisy	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Pulmonary arterial hypertension	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Pulmonary embolism	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Pulmonary hypertension	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
	Rales	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Respiratory distress	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Upper respiratory tract congestion	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Vocal cord polyp	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
Skin and subcutaneous tissue disorders	**ALL**	**56**	**29 (43.9%)**	**24**	**16 (38.1%)**	**25**	**15 (44.1%)**	**105**	**60 (42.3%)**
	Dry skin	11	11 (16.7%)	2	2 (4.8%)	-	-	13	13 (9.2%)
	Pruritus	7	6 (9.1%)	2	2 (4.8%)	4	3 (8.8%)	13	11 (7.7%)
	Rash	5	3 (4.5%)	5	4 (9.5%)	1	1 (2.9%)	11	8 (5.6%)
	Eczema	6	4 (6.1%)	1	1 (2.4%)	1	1 (2.9%)	8	6 (4.2%)
	Skin lesion	1	1 (1.5%)	1	1 (2.4%)	3	3 (8.8%)	5	5 (3.5%)
	Actinic keratosis	2	2 (3%)	1	1 (2.4%)	1	1 (2.9%)	4	4 (2.8%)
	Erythema	1	1 (1.5%)	3	3 (7.1%)	-	-	4	4 (2.8%)
	Rash pruritic	3	3 (4.5%)	1	1 (2.4%)	-	-	4	4 (2.8%)
	Alopecia	1	1 (1.5%)	1	1 (2.4%)	1	1 (2.9%)	3	3 (2.1%)
	Dermatitis bullous	3	2 (3%)	-	-	-	-	3	2 (1.4%)
	Hyperhidrosis	-	-	1	1 (2.4%)	2	2 (5.9%)	3	3 (2.1%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
	Intertrigo	2	2 (3%)	-	-	1	1 (2.9%)	3	3 (2.1%)
	Dermatitis	-	-	1	1 (2.4%)	1	1 (2.9%)	2	2 (1.4%)
	Ecchymosis	1	1 (1.5%)	1	1 (2.4%)	-	-	2	2 (1.4%)
	Night sweats	-	-	-	-	2	2 (5.9%)	2	2 (1.4%)
	Purpura	1	1 (1.5%)	-	-	1	1 (2.9%)	2	2 (1.4%)
	Skin ulcer	-	-	-	-	2	1 (2.9%)	2	1 (0.7%)
	Urticaria	2	2 (3%)	-	-	-	-	2	2 (1.4%)
	Acne	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Angioedema	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Decubitus ulcer	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Dermatitis contact	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Dermatitis exfoliative	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Lichenoid keratosis	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Nail pigmentation	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Onychoclasis	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Pityriasis	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Prurigo	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Psoriasis	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
	Rash maculo-papular	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Rash vesicular	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Scab	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Skin necrosis	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Skin odour abnormal	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Skin reaction	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Stasis dermatitis	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Vascular skin disorder	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
Nervous system disorders	**ALL**	**38**	**23 (34.8%)**	**21**	**13 (31%)**	**18**	**12 (35.3%)**	**77**	**48 (33.8%)**
	Headache	7	7 (10.6%)	6	6 (14.3%)	6	5 (14.7%)	19	18 (12.7%)
	Dizziness	5	5 (7.6%)	3	3 (7.1%)	4	3 (8.8%)	12	11 (7.7%)
	Sciatica	3	3 (4.5%)	2	2 (4.8%)	-	-	5	5 (3.5%)
	Carotid artery stenosis	2	2 (3%)	-	-	2	1 (2.9%)	4	3 (2.1%)
	Tremor	2	2 (3%)	-	-	1	1 (2.9%)	3	3 (2.1%)
	Balance disorder	-	-	1	1 (2.4%)	1	1 (2.9%)	2	2 (1.4%)
	Head discomfort	-	-	2	1 (2.4%)	-	-	2	1 (0.7%)
	Hypoaesthesia	1	1 (1.5%)	-	-	1	1 (2.9%)	2	2 (1.4%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
	Memory impairment	2	2 (3%)	-	-	-	-	2	2 (1.4%)
	Neuropathy peripheral	2	2 (3%)	-	-	-	-	2	2 (1.4%)
	Somnolence	-	-	1	1 (2.4%)	1	1 (2.9%)	2	2 (1.4%)
	Anosmia	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Areflexia	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Axonal neuropathy	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Carotid arteriosclerosis	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Carpal tunnel syndrome	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Cervicobrachial syndrome	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Cognitive disorder	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Coma	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Disturbance in attention	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Dysgeusia	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Hypersomnia	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Migraine	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Nerve compression	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Nervous system disorder	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Neuralgia	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
	Paraesthesia	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Petit mal epilepsy	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Presyncope	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Sensory disturbance	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Transient ischaemic attack	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Trigeminal neuralgia	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Ulnar tunnel syndrome	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
Metabolism and nutrition disorders	**ALL**	**28**	**16 (24.2%)**	**33**	**18 (42.9%)**	**15**	**10 (29.4%)**	**76**	**44 (31%)**
	Decreased appetite	7	5 (7.6%)	6	6 (14.3%)	3	3 (8.8%)	16	14 (9.9%)
	Iron deficiency	2	2 (3%)	3	3 (7.1%)	4	3 (8.8%)	9	8 (5.6%)
	Vitamin D deficiency	3	3 (4.5%)	2	2 (4.8%)	2	2 (5.9%)	7	7 (4.9%)
	Dyslipidaemia	4	4 (6.1%)	1	1 (2.4%)	-	-	5	5 (3.5%)
	Folate deficiency	1	1 (1.5%)	4	4 (9.5%)	-	-	5	5 (3.5%)
	Hypertriglyceridaemia	3	3 (4.5%)	-	-	2	2 (5.9%)	5	5 (3.5%)
	Hypokalaemia	-	-	4	3 (7.1%)	1	1 (2.9%)	5	4 (2.8%)
	Gout	1	1 (1.5%)	2	2 (4.8%)	1	1 (2.9%)	4	4 (2.8%)
	Hyperkalaemia	1	1 (1.5%)	3	3 (7.1%)	-	-	4	4 (2.8%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
	Malnutrition	2	1 (1.5%)	1	1 (2.4%)	1	1 (2.9%)	4	3 (2.1%)
	Diabetes mellitus inadequate control	1	1 (1.5%)	2	2 (4.8%)	-	-	3	3 (2.1%)
	Diabetes mellitus	-	-	2	2 (4.8%)	-	-	2	2 (1.4%)
	Dehydration	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Fluid retention	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Hypercalcaemia	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Hyperphagia	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Hypocalcaemia	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Hyponatraemia	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Type 2 diabetes mellitus	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
Renal and urinary disorders	**ALL**	**30**	**18 (27.3%)**	**11**	**7 (16.7%)**	**12**	**9 (26.5%)**	**53**	**34 (23.9%)**
	Renal failure	8	6 (9.1%)	4	3 (7.1%)	3	2 (5.9%)	15	11 (7.7%)
	Acute kidney injury	5	4 (6.1%)	1	1 (2.4%)	-	-	6	5 (3.5%)
	Chronic kidney disease	4	4 (6.1%)	-	-	1	1 (2.9%)	5	5 (3.5%)
	Pollakiuria	3	3 (4.5%)	-	-	2	2 (5.9%)	5	5 (3.5%)
	Renal artery stenosis	2	2 (3%)	1	1 (2.4%)	-	-	3	3 (2.1%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
	Dysuria	1	1 (1.5%)	1	1 (2.4%)	-	-	2	2 (1.4%)
	Haematuria	1	1 (1.5%)	1	1 (2.4%)	-	-	2	2 (1.4%)
	Nephrolithiasis	1	1 (1.5%)	-	-	1	1 (2.9%)	2	2 (1.4%)
	Renal colic	-	-	-	-	2	2 (5.9%)	2	2 (1.4%)
	Renal cyst	1	1 (1.5%)	1	1 (2.4%)	-	-	2	2 (1.4%)
	Chromaturia	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Micturition urgency	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Nocturia	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Oliguria	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Polyuria	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Prerenal failure	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Renal impairment	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Urinary retention	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Urinary tract disorder	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
Investigations	**ALL**	**13**	**8 (12.1%)**	**29**	**19 (45.2%)**	**9**	**8 (23.5%)**	**51**	**35 (24.6%)**
	Weight decreased	2	2 (3%)	5	5 (11.9%)	-	-	7	7 (4.9%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
	Alanine aminotransferase increased	3	2 (3%)	2	2 (4.8%)	1	1 (2.9%)	6	5 (3.5%)
	Aspartate aminotransferase increased	2	1 (1.5%)	2	2 (4.8%)	1	1 (2.9%)	5	4 (2.8%)
	Blood creatinine increased	2	2 (3%)	2	2 (4.8%)	1	1 (2.9%)	5	5 (3.5%)
	Lipase increased	-	-	2	2 (4.8%)	1	1 (2.9%)	3	3 (2.1%)
	Weight increased	-	-	2	2 (4.8%)	1	1 (2.9%)	3	3 (2.1%)
	Blood thyroid stimulating hormone increased	1	1 (1.5%)	-	-	1	1 (2.9%)	2	2 (1.4%)
	Breath sounds abnormal	-	-	2	2 (4.8%)	-	-	2	2 (1.4%)
	Liver function test abnormal	-	-	2	2 (4.8%)	-	-	2	2 (1.4%)
	Transaminases increased	-	-	1	1 (2.4%)	1	1 (2.9%)	2	2 (1.4%)
	Blood glucose abnormal	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Blood parathyroid hormone increased	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Blood pressure decreased	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Blood thyroid stimulating hormone decreased	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Blood urea increased	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
	Blood uric acid increased	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Cardiac murmur	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Coronavirus test positive	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Electrocardiogram ST segment depression	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Gamma-glutamyltransferase increased	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Intestinal transit time increased	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Pulse absent	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Serum ferritin normal	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Troponin increased	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
Vascular disorders	**ALL**	**21**	**17 (25.8%)**	**15**	**14 (33.3%)**	**15**	**10 (29.4%)**	**51**	**41 (28.9%)**
	Hypertension	6	6 (9.1%)	6	6 (14.3%)	4	4 (11.8%)	16	16 (11.3%)
	Hot flush	4	4 (6.1%)	1	1 (2.4%)	-	-	5	5 (3.5%)
	Hypotension	2	1 (1.5%)	2	2 (4.8%)	-	-	4	3 (2.1%)
	Pallor	2	2 (3%)	2	2 (4.8%)	-	-	4	4 (2.8%)
	Arteriosclerosis	1	1 (1.5%)	1	1 (2.4%)	1	1 (2.9%)	3	3 (2.1%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
	Hypertensive crisis	1	1 (1.5%)	1	1 (2.4%)	1	1 (2.9%)	3	3 (2.1%)
	Phlebitis	1	1 (1.5%)	1	1 (2.4%)	1	1 (2.9%)	3	3 (2.1%)
	Haematoma	-	-	-	-	2	1 (2.9%)	2	1 (0.7%)
	Peripheral artery stenosis	-	-	-	-	2	2 (5.9%)	2	2 (1.4%)
	Varicose vein	1	1 (1.5%)	1	1 (2.4%)	-	-	2	2 (1.4%)
	Arterial disorder	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Arterial occlusive disease	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Arteritis	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Haemorrhage	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Intermittent claudication	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Peripheral arterial occlusive disease	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Subclavian artery stenosis	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
Cardiac disorders	**ALL**	**21**	**11 (16.7%)**	**14**	**8 (19%)**	**14**	**10 (29.4%)**	**49**	**29 (20.4%)**
	Cardiac failure	9	5 (7.6%)	4	2 (4.8%)	4	4 (11.8%)	17	11 (7.7%)
	Atrial fibrillation	4	2 (3%)	1	1 (2.4%)	1	1 (2.9%)	6	4 (2.8%)
	Pericarditis	-	-	4	3 (7.1%)	-	-	4	3 (2.1%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
	Palpitations	2	2 (3%)	1	1 (2.4%)	-	-	3	3 (2.1%)
	Pericardial effusion	1	1 (1.5%)	1	1 (2.4%)	1	1 (2.9%)	3	3 (2.1%)
	Tachycardia	-	-	1	1 (2.4%)	2	2 (5.9%)	3	3 (2.1%)
	Arrhythmia	1	1 (1.5%)	-	-	1	1 (2.9%)	2	2 (1.4%)
	Extrasystoles	-	-	1	1 (2.4%)	1	1 (2.9%)	2	2 (1.4%)
	Angina pectoris	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Arrhythmia supraventricular	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Bradycardia	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Cardiomegaly	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Coronary artery insufficiency	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Coronary artery stenosis	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Left ventricular failure	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Myocardial infarction	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Tachyarrhythmia	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
Hepatobiliary disorders	**ALL**	**23**	**17 (25.8%)**	**13**	**9 (21.4%)**	**8**	**7 (20.6%)**	**44**	**33 (23.2%)**
	Hepatocellular injury	14	13 (19.7%)	7	6 (14.3%)	4	4 (11.8%)	25	23 (16.2%)
	Cholelithiasis	2	2 (3%)	1	1 (2.4%)	-	-	3	3 (2.1%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
	Cholestasis	2	2 (3%)	-	-	-	-	2	2 (1.4%)
	Hepatic steatosis	1	1 (1.5%)	1	1 (2.4%)	-	-	2	2 (1.4%)
	Hepatitis	1	1 (1.5%)	-	-	1	1 (2.9%)	2	2 (1.4%)
	Hepatomegaly	1	1 (1.5%)	1	1 (2.4%)	-	-	2	2 (1.4%)
	Cholecystitis	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Cholecystitis acute	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Cholecystitis chronic	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Cholelithiasis obstructive	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Hepatic fibrosis	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Hepatic pain	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Hepatotoxicity	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Jaundice cholestatic	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
Blood and lymphatic system disorders	**ALL**	**15**	**10 (15.2%)**	**11**	**6 (14.3%)**	**17**	**12 (35.3%)**	**43**	**28 (19.7%)**
	Anaemia	10	9 (13.6%)	5	4 (9.5%)	11	7 (20.6%)	26	20 (14.1%)
	Iron deficiency anaemia	-	-	5	2 (4.8%)	2	2 (5.9%)	7	4 (2.8%)
	Thrombocytopenia	2	2 (3%)	1	1 (2.4%)	1	1 (2.9%)	4	4 (2.8%)
	Pancytopenia	1	1 (1.5%)	-	-	1	1 (2.9%)	2	2 (1.4%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
	Agranulocytosis	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Lymphopenia	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Neutropenia	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Thrombocytosis	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
Injury, poisoning and procedural complications	**ALL**	**17**	**14 (21.2%)**	**6**	**4 (9.5%)**	**13**	**10 (29.4%)**	**36**	**28 (19.7%)**
	Fall	2	2 (3%)	1	1 (2.4%)	1	1 (2.9%)	4	4 (2.8%)
	Limb injury	2	2 (3%)	-	-	2	1 (2.9%)	4	3 (2.1%)
	Omissions of a medication dose	2	1 (1.5%)	-	-	2	2 (5.9%)	4	3 (2.1%)
	Hip fracture	-	-	1	1 (2.4%)	1	1 (2.9%)	2	2 (1.4%)
	Maternal exposure during pregnancy	1	1 (1.5%)	-	-	1	1 (2.9%)	2	2 (1.4%)
	Wound	1	1 (1.5%)	1	1 (2.4%)	-	-	2	2 (1.4%)
	Accident at work	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Animal bite	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Ankle fracture	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Arteriovenous fistula occlusion	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
	Arthropod bite	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Fractured coccyx	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Head injury	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Intentional product misuse	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Overdose	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Post procedural complication	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Procedural pain	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Scratch	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Spinal compression fracture	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Tendon rupture	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Thermal burn	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Tooth fracture	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Toxicity to various agents	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Vascular graft occlusion	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
Psychiatric disorders	**ALL**	**14**	**13 (19.7%)**	**8**	**8 (19%)**	**8**	**7 (20.6%)**	**30**	**28 (19.7%)**
	Depression	4	4 (6.1%)	3	3 (7.1%)	1	1 (2.9%)	8	8 (5.6%)
	Anxiety	3	3 (4.5%)	2	2 (4.8%)	2	2 (5.9%)	7	7 (4.9%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
	Insomnia	3	3 (4.5%)	2	2 (4.8%)	1	1 (2.9%)	6	6 (4.2%)
	Affective disorder	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Depressed mood	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Irritability	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Libido decreased	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Mental disorder	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Morose	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Nervousness	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Paranoia	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Sleep disorder	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
Eye disorders	**ALL**	**15**	**12 (18.2%)**	**6**	**4 (9.5%)**	**3**	**3 (8.8%)**	**24**	**19 (13.4%)**
	Cataract	4	3 (4.5%)	1	1 (2.4%)	-	-	5	4 (2.8%)
	Eyelid oedema	3	3 (4.5%)	1	1 (2.4%)	-	-	4	4 (2.8%)
	Blepharitis	1	1 (1.5%)	1	1 (2.4%)	-	-	2	2 (1.4%)
	Conjunctival haemorrhage	-	-	1	1 (2.4%)	1	1 (2.9%)	2	2 (1.4%)
	Cystoid macular oedema	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Dry eye	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
	Eye swelling	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Eyelid disorder	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Eyelid ptosis	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Lacrimation increased	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Periorbital oedema	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Photopsia	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Retinal haemorrhage	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Retinal vein occlusion	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Uveitis	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
Reproductive system and breast disorders	**ALL**	**7**	**6 (9.1%)**	**8**	**7 (16.7%)**	**2**	**2 (5.9%)**	**17**	**15 (10.6%)**
	Benign prostatic hyperplasia	1	1 (1.5%)	2	2 (4.8%)	-	-	3	3 (2.1%)
	Gynaecomastia	1	1 (1.5%)	2	2 (4.8%)	-	-	3	3 (2.1%)
	Prostatitis	2	2 (3%)	-	-	-	-	2	2 (1.4%)
	Vulvovaginal burning sensation	2	2 (3%)	-	-	-	-	2	2 (1.4%)
	Erectile dysfunction	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Genital burning sensation	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
	Ovarian cyst	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Pelvic discomfort	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Pelvic pain	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Prostatism	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Testicular pain	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**ALL**	**9**	**9 (13.6%)**	**4**	**4 (9.5%)**	**2**	**2 (5.9%)**	**15**	**15 (10.6%)**
	Acrochordon	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Benign pancreatic neoplasm	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Bowen's disease	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Chronic myeloid leukaemia	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Gastrointestinal stromal tumour	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Leiomyoma	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Lipoma	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Melanocytic naevus	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Meningioma	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Monoclonal gammopathy	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
	Neoplasm progression	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Prostate cancer	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Prostatic adenoma	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Seborrhoeic keratosis	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Uterine leiomyoma	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
Endocrine disorders	**ALL**	**3**	**3 (4.5%)**	**5**	**5 (11.9%)**	**3**	**2 (5.9%)**	**11**	**10 (7%)**
	Hypothyroidism	-	-	3	3 (7.1%)	1	1 (2.9%)	4	4 (2.8%)
	Hyperthyroidism	1	1 (1.5%)	-	-	1	1 (2.9%)	2	2 (1.4%)
	Basedow's disease	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Haemorrhagic thyroid cyst	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Hyperparathyroidism	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Hyperparathyroidism secondary	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Thyroid mass	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
Ear and labyrinth disorders	**ALL**	**6**	**5 (7.6%)**	**2**	**2 (4.8%)**	**2**	**2 (5.9%)**	**10**	**9 (6.3%)**
	Vertigo	2	2 (3%)	-	-	1	1 (2.9%)	3	3 (2.1%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
	Hypoacusis	1	1 (1.5%)	1	1 (2.4%)	-	-	2	2 (1.4%)
	Tinnitus	-	-	1	1 (2.4%)	1	1 (2.9%)	2	2 (1.4%)
	Deafness unilateral	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Ear discomfort	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Vestibular disorder	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
Immune system disorders	**ALL**	**4**	**4 (6.1%)**	**-**	**-**	**2**	**2 (5.9%)**	**6**	**6 (4.2%)**
	Hypersensitivity	2	2 (3%)	-	-	2	2 (5.9%)	4	4 (2.8%)
	Anaphylactic shock	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Food allergy	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
Surgical and medical procedures	**ALL**	**1**	**1 (1.5%)**	**-**	**-**	**4**	**3 (8.8%)**	**5**	**4 (2.8%)**
	Foot amputation	-	-	-	-	2	1 (2.9%)	2	1 (0.7%)
	Angioplasty	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Thyroidectomy	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Vasectomy	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
Social circumstances	**ALL**	**2**	**1 (1.5%)**	**1**	**1 (2.4%)**	**-**	**-**	**3**	**2 (1.4%)**

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
	Miscarriage of partner	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Physical disability	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Pregnancy of partner	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
Congenital, familial and genetic disorders	**ALL**	**2**	**2 (3%)**	**-**	**-**	**-**	**-**	**2**	**2 (1.4%)**
	Dilatation intrahepatic duct congenital	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Gene mutation	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
Pregnancy, puerperium and perinatal conditions	**ALL**	**-**	**-**	**-**	**-**	**1**	**1 (2.9%)**	**1**	**1 (0.7%)**
	Complication of pregnancy	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)

Table 15.3.5a Adverse Events by System Organ Class and Preferred Term (All Causalities and all grade) - SAF (n=142)

Table 72: Adverse Events by System Organ Class and Preferred Term (All Causalities and grade 1-2) - SAF (n=142)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
ALL		**663**	**64 (97%)**	**412**	**42 (100%)**	**301**	**34 (100%)**	**1376**	**140 (98.6%)**
Gastrointestinal disorders	**ALL**	**152**	**53 (80.3%)**	**86**	**36 (85.7%)**	**76**	**24 (70.6%)**	**314**	**113 (79.6%)**
	Diarrhoea	58	38 (57.6%)	29	25 (59.5%)	23	18 (52.9%)	110	81 (57%)
	Nausea	13	12 (18.2%)	11	10 (23.8%)	7	6 (17.6%)	31	28 (19.7%)
	Constipation	12	10 (15.2%)	4	4 (9.5%)	9	7 (20.6%)	25	21 (14.8%)
	Abdominal pain upper	11	10 (15.2%)	6	5 (11.9%)	4	4 (11.8%)	21	19 (13.4%)
	Abdominal pain	8	7 (10.6%)	5	4 (9.5%)	6	5 (14.7%)	19	16 (11.3%)
	Vomiting	8	7 (10.6%)	4	3 (7.1%)	3	3 (8.8%)	15	13 (9.2%)
	Gastrointestinal disorder	7	6 (9.1%)	1	1 (2.4%)	2	2 (5.9%)	10	9 (6.3%)
	Abdominal distension	2	2 (3%)	2	2 (4.8%)	2	1 (2.9%)	6	5 (3.5%)
	Aphthous stomatitis	2	2 (3%)	2	2 (4.8%)	1	1 (2.9%)	5	5 (3.5%)
	Dyspepsia	3	3 (4.5%)	-	-	1	1 (2.9%)	4	4 (2.8%)
	Flatulence	1	1 (1.5%)	1	1 (2.4%)	2	2 (5.9%)	4	4 (2.8%)
	Gastrooesophageal reflux disease	1	1 (1.5%)	1	1 (2.4%)	2	2 (5.9%)	4	4 (2.8%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
	Rectal haemorrhage	1	1 (1.5%)	2	2 (4.8%)	1	1 (2.9%)	4	4 (2.8%)
	Haemorrhoids	1	1 (1.5%)	1	1 (2.4%)	1	1 (2.9%)	3	3 (2.1%)
	Hiatus hernia	1	1 (1.5%)	-	-	2	2 (5.9%)	3	3 (2.1%)
	Tooth disorder	2	2 (3%)	1	1 (2.4%)	-	-	3	3 (2.1%)
	Abdominal pain lower	2	2 (3%)	-	-	-	-	2	2 (1.4%)
	Dry mouth	-	-	-	-	2	2 (5.9%)	2	2 (1.4%)
	Dysphagia	2	2 (3%)	-	-	-	-	2	2 (1.4%)
	Eructation	-	-	1	1 (2.4%)	1	1 (2.9%)	2	2 (1.4%)
	Functional gastrointestinal disorder	1	1 (1.5%)	1	1 (2.4%)	-	-	2	2 (1.4%)
	Gastric ulcer	-	-	1	1 (2.4%)	1	1 (2.9%)	2	2 (1.4%)
	Inguinal hernia	1	1 (1.5%)	1	1 (2.4%)	-	-	2	2 (1.4%)
	Oesophagitis	-	-	1	1 (2.4%)	1	1 (2.9%)	2	2 (1.4%)
	Reflux gastritis	1	1 (1.5%)	1	1 (2.4%)	-	-	2	2 (1.4%)
	Abdominal discomfort	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Abdominal hernia	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Abdominal rigidity	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Aerophagia	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
	Anal fissure	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Anorectal discomfort	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Cheilitis	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Chronic gastritis	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Eosinophilic colitis	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Erosive duodenitis	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Faecaloma	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Faeces soft	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Gastritis	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Gastroduodenal ulcer	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Gastrointestinal angiodysplasia	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Gastrointestinal motility disorder	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Gingival bleeding	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Glossodynia	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Haemorrhoidal haemorrhage	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Intestinal obstruction	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Intestinal polyp	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
	Melaena	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Mouth haemorrhage	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Oral discomfort	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Oral lichen planus	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Oral mucosa erosion	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Rectal polyp	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Salivary hypersecretion	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Toothache	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
General disorders and administration site conditions	**ALL**	**74**	**37 (56.1%)**	**41**	**21 (50%)**	**29**	**18 (52.9%)**	**144**	**76 (53.5%)**
	Asthenia	24	19 (28.8%)	12	10 (23.8%)	6	4 (11.8%)	42	33 (23.2%)
	Fatigue	8	7 (10.6%)	6	5 (11.9%)	3	3 (8.8%)	17	15 (10.6%)
	Oedema peripheral	9	8 (12.1%)	2	2 (4.8%)	6	6 (17.6%)	17	16 (11.3%)
	Chest pain	9	8 (12.1%)	4	4 (9.5%)	2	2 (5.9%)	15	14 (9.9%)
	Drug ineffective	3	3 (4.5%)	2	1 (2.4%)	1	1 (2.9%)	6	5 (3.5%)
	Pyrexia	-	-	1	1 (2.4%)	5	5 (14.7%)	6	6 (4.2%)
	Therapeutic response decreased	3	2 (3%)	1	1 (2.4%)	1	1 (2.9%)	5	4 (2.8%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
	Chills	2	2 (3%)	-	-	1	1 (2.9%)	3	3 (2.1%)
	Drug intolerance	2	2 (3%)	1	1 (2.4%)	-	-	3	3 (2.1%)
	General physical health deterioration	2	2 (3%)	-	-	1	1 (2.9%)	3	3 (2.1%)
	Influenza like illness	2	2 (3%)	1	1 (2.4%)	-	-	3	3 (2.1%)
	Oedema	2	2 (3%)	1	1 (2.4%)	-	-	3	3 (2.1%)
	Face oedema	1	1 (1.5%)	-	-	1	1 (2.9%)	2	2 (1.4%)
	Gait disturbance	1	1 (1.5%)	1	1 (2.4%)	-	-	2	2 (1.4%)
	Inflammation	-	-	1	1 (2.4%)	1	1 (2.9%)	2	2 (1.4%)
	Malaise	-	-	2	1 (2.4%)	-	-	2	1 (0.7%)
	Pain	2	2 (3%)	-	-	-	-	2	2 (1.4%)
	Reduced drug effect	-	-	1	1 (2.4%)	1	1 (2.9%)	2	2 (1.4%)
	Treatment noncompliance	2	1 (1.5%)	-	-	-	-	2	1 (0.7%)
	Chest discomfort	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Feeling cold	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Generalised oedema	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Hernia	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Hyperthermia	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
	Ill-defined disorder	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Ulcer	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
Infections and infestations	**ALL**	**66**	**37 (56.1%)**	**29**	**20 (47.6%)**	**33**	**15 (44.1%)**	**128**	**72 (50.7%)**
	Bronchitis	13	12 (18.2%)	1	1 (2.4%)	3	3 (8.8%)	17	16 (11.3%)
	Urinary tract infection	2	2 (3%)	4	4 (9.5%)	6	5 (14.7%)	12	11 (7.7%)
	Corona virus infection	8	8 (12.1%)	1	1 (2.4%)	1	1 (2.9%)	10	10 (7%)
	Nasopharyngitis	6	6 (9.1%)	2	2 (4.8%)	2	2 (5.9%)	10	10 (7%)
	Infection	2	2 (3%)	2	2 (4.8%)	3	2 (5.9%)	7	6 (4.2%)
	Erysipelas	3	3 (4.5%)	-	-	3	1 (2.9%)	6	4 (2.8%)
	Influenza	2	2 (3%)	1	1 (2.4%)	2	2 (5.9%)	5	5 (3.5%)
	Folliculitis	3	3 (4.5%)	1	1 (2.4%)	-	-	4	4 (2.8%)
	Gastroenteritis	2	2 (3%)	1	1 (2.4%)	1	1 (2.9%)	4	4 (2.8%)
	Pneumonia	1	1 (1.5%)	1	1 (2.4%)	2	2 (5.9%)	4	4 (2.8%)
	Cystitis	1	1 (1.5%)	-	-	2	2 (5.9%)	3	3 (2.1%)
	Fungal infection	1	1 (1.5%)	2	2 (4.8%)	-	-	3	3 (2.1%)
	Herpes zoster	2	2 (3%)	1	1 (2.4%)	-	-	3	3 (2.1%)
	Laryngitis	3	3 (4.5%)	-	-	-	-	3	3 (2.1%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
	Candida infection	-	-	-	-	2	2 (5.9%)	2	2 (1.4%)
	Diverticulitis	-	-	2	2 (4.8%)	-	-	2	2 (1.4%)
	Ear infection	1	1 (1.5%)	-	-	1	1 (2.9%)	2	2 (1.4%)
	Herpes simplex	2	2 (3%)	-	-	-	-	2	2 (1.4%)
	Localised infection	-	-	1	1 (2.4%)	1	1 (2.9%)	2	2 (1.4%)
	Onychomycosis	2	1 (1.5%)	-	-	-	-	2	1 (0.7%)
	Oral fungal infection	1	1 (1.5%)	1	1 (2.4%)	-	-	2	2 (1.4%)
	Rhinitis	2	2 (3%)	-	-	-	-	2	2 (1.4%)
	Upper respiratory tract infection	1	1 (1.5%)	1	1 (2.4%)	-	-	2	2 (1.4%)
	Vulvovaginal mycotic infection	-	-	1	1 (2.4%)	1	1 (2.9%)	2	2 (1.4%)
	Abdominal abscess	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Anal abscess	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Conjunctivitis	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Genital infection female	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Gingivitis	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Hepatitis E	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Klebsiella infection	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
	Orchitis	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Otitis media acute	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Pharyngitis	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Sepsis	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Sinusitis	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Skin infection	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Tooth abscess	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Tooth infection	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Urinary tract infection bacterial	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Vaginal infection	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
Musculoskeletal and connective tissue disorders	**ALL**	**57**	**34 (51.5%)**	**45**	**22 (52.4%)**	**25**	**14 (41.2%)**	**127**	**70 (49.3%)**
	Arthralgia	11	9 (13.6%)	7	7 (16.7%)	7	6 (17.6%)	25	22 (15.5%)
	Myalgia	7	6 (9.1%)	6	5 (11.9%)	2	2 (5.9%)	15	13 (9.2%)
	Back pain	6	6 (9.1%)	3	3 (7.1%)	3	3 (8.8%)	12	12 (8.5%)
	Muscle spasms	2	2 (3%)	6	5 (11.9%)	4	4 (11.8%)	12	11 (7.7%)
	Musculoskeletal pain	3	3 (4.5%)	3	2 (4.8%)	3	3 (8.8%)	9	8 (5.6%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
	Pain in extremity	4	4 (6.1%)	3	3 (7.1%)	2	2 (5.9%)	9	9 (6.3%)
	Osteoarthritis	2	2 (3%)	3	2 (4.8%)	1	1 (2.9%)	6	5 (3.5%)
	Arthritis	3	3 (4.5%)	2	2 (4.8%)	-	-	5	5 (3.5%)
	Neck pain	1	1 (1.5%)	2	2 (4.8%)	-	-	3	3 (2.1%)
	Tendonitis	2	2 (3%)	1	1 (2.4%)	-	-	3	3 (2.1%)
	Bone pain	1	1 (1.5%)	1	1 (2.4%)	-	-	2	2 (1.4%)
	Chondrocalcinosis	1	1 (1.5%)	1	1 (2.4%)	-	-	2	2 (1.4%)
	Intervertebral disc disorder	2	2 (3%)	-	-	-	-	2	2 (1.4%)
	Intervertebral disc protrusion	2	2 (3%)	-	-	-	-	2	2 (1.4%)
	Musculoskeletal chest pain	-	-	-	-	2	2 (5.9%)	2	2 (1.4%)
	Spinal osteoarthritis	2	2 (3%)	-	-	-	-	2	2 (1.4%)
	Spinal pain	2	1 (1.5%)	-	-	-	-	2	1 (0.7%)
	Tendon pain	1	1 (1.5%)	-	-	1	1 (2.9%)	2	2 (1.4%)
	Back disorder	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Flank pain	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Groin pain	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Intervertebral disc degeneration	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
	Joint ankylosis	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Joint effusion	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Limb discomfort	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Osteoporosis	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Periarthritis	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Rhabdomyolysis	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Rotator cuff syndrome	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Scoliosis	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
Respiratory, thoracic and mediastinal disorders	**ALL**	**53**	**25 (37.9%)**	**33**	**18 (42.9%)**	**16**	**9 (26.5%)**	**102**	**52 (36.6%)**
	Dyspnoea	10	8 (12.1%)	11	10 (23.8%)	5	5 (14.7%)	26	23 (16.2%)
	Pleural effusion	11	7 (10.6%)	2	2 (4.8%)	3	3 (8.8%)	16	12 (8.5%)
	Dyspnoea exertional	7	5 (7.6%)	2	2 (4.8%)	1	1 (2.9%)	10	8 (5.6%)
	Cough	6	5 (7.6%)	2	2 (4.8%)	1	1 (2.9%)	9	8 (5.6%)
	Sleep apnoea syndrome	3	3 (4.5%)	3	3 (7.1%)	-	-	6	6 (4.2%)
	Asthma	4	3 (4.5%)	-	-	-	-	4	3 (2.1%)
	Chronic obstructive pulmonary disease	2	2 (3%)	2	2 (4.8%)	-	-	4	4 (2.8%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
	Dysphonia	1	1 (1.5%)	3	3 (7.1%)	-	-	4	4 (2.8%)
	Rhinorrhoea	1	1 (1.5%)	1	1 (2.4%)	1	1 (2.9%)	3	3 (2.1%)
	Epistaxis	1	1 (1.5%)	-	-	1	1 (2.9%)	2	2 (1.4%)
	Lung disorder	1	1 (1.5%)	-	-	1	1 (2.9%)	2	2 (1.4%)
	Oropharyngeal pain	1	1 (1.5%)	-	-	1	1 (2.9%)	2	2 (1.4%)
	Productive cough	1	1 (1.5%)	-	-	1	1 (2.9%)	2	2 (1.4%)
	Pulmonary pain	-	-	2	2 (4.8%)	-	-	2	2 (1.4%)
	Acute respiratory failure	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Haemoptysis	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Hypoventilation	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Hypoxia	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Orthopnoea	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Pleural fibrosis	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Pulmonary embolism	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Rales	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Upper respiratory tract congestion	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Vocal cord polyp	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
Skin and subcutaneous tissue disorders	**ALL**	**56**	**29 (43.9%)**	**24**	**16 (38.1%)**	**20**	**14 (41.2%)**	**100**	**59 (41.5%)**
	Dry skin	11	11 (16.7%)	2	2 (4.8%)	-	-	13	13 (9.2%)
	Pruritus	7	6 (9.1%)	2	2 (4.8%)	4	3 (8.8%)	13	11 (7.7%)
	Rash	5	3 (4.5%)	5	4 (9.5%)	1	1 (2.9%)	11	8 (5.6%)
	Eczema	6	4 (6.1%)	1	1 (2.4%)	1	1 (2.9%)	8	6 (4.2%)
	Skin lesion	1	1 (1.5%)	1	1 (2.4%)	3	3 (8.8%)	5	5 (3.5%)
	Actinic keratosis	2	2 (3%)	1	1 (2.4%)	1	1 (2.9%)	4	4 (2.8%)
	Erythema	1	1 (1.5%)	3	3 (7.1%)	-	-	4	4 (2.8%)
	Rash pruritic	3	3 (4.5%)	1	1 (2.4%)	-	-	4	4 (2.8%)
	Alopecia	1	1 (1.5%)	1	1 (2.4%)	1	1 (2.9%)	3	3 (2.1%)
	Dermatitis bullous	3	2 (3%)	-	-	-	-	3	2 (1.4%)
	Hyperhidrosis	-	-	1	1 (2.4%)	2	2 (5.9%)	3	3 (2.1%)
	Intertrigo	2	2 (3%)	-	-	1	1 (2.9%)	3	3 (2.1%)
	Ecchymosis	1	1 (1.5%)	1	1 (2.4%)	-	-	2	2 (1.4%)
	Night sweats	-	-	-	-	2	2 (5.9%)	2	2 (1.4%)
	Purpura	1	1 (1.5%)	-	-	1	1 (2.9%)	2	2 (1.4%)
	Urticaria	2	2 (3%)	-	-	-	-	2	2 (1.4%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
	Acne	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Decubitus ulcer	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Dermatitis	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Dermatitis contact	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Dermatitis exfoliative	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Lichenoid keratosis	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Nail pigmentation	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Onychoclasis	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Pityriasis	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Prurigo	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Psoriasis	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Rash maculo-papular	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Rash vesicular	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Scab	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Skin necrosis	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Skin odour abnormal	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Skin reaction	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Stasis dermatitis	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
Nervous system disorders	**ALL**	**33**	**22 (33.3%)**	**19**	**11 (26.2%)**	**15**	**10 (29.4%)**	**67**	**43 (30.3%)**
	Headache	6	6 (9.1%)	6	6 (14.3%)	6	5 (14.7%)	18	17 (12%)
	Dizziness	5	5 (7.6%)	3	3 (7.1%)	4	3 (8.8%)	12	11 (7.7%)
	Sciatica	3	3 (4.5%)	2	2 (4.8%)	-	-	5	5 (3.5%)
	Tremor	2	2 (3%)	-	-	1	1 (2.9%)	3	3 (2.1%)
	Balance disorder	-	-	1	1 (2.4%)	1	1 (2.9%)	2	2 (1.4%)
	Head discomfort	-	-	2	1 (2.4%)	-	-	2	1 (0.7%)
	Hypoaesthesia	1	1 (1.5%)	-	-	1	1 (2.9%)	2	2 (1.4%)
	Memory impairment	2	2 (3%)	-	-	-	-	2	2 (1.4%)
	Neuropathy peripheral	2	2 (3%)	-	-	-	-	2	2 (1.4%)
	Somnolence	-	-	1	1 (2.4%)	1	1 (2.9%)	2	2 (1.4%)
	Anosmia	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Areflexia	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Carotid arteriosclerosis	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Carotid artery stenosis	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Cognitive disorder	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Coma	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
	Disturbance in attention	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Dysgeusia	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Hypersomnia	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Migraine	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Nervous system disorder	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Neuralgia	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Paraesthesia	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Presyncope	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Sensory disturbance	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Transient ischaemic attack	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Trigeminal neuralgia	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
Metabolism and nutrition disorders	**ALL**	**21**	**15 (22.7%)**	**30**	**18 (42.9%)**	**13**	**10 (29.4%)**	**64**	**43 (30.3%)**
	Decreased appetite	6	5 (7.6%)	6	6 (14.3%)	3	3 (8.8%)	15	14 (9.9%)
	Iron deficiency	2	2 (3%)	3	3 (7.1%)	3	3 (8.8%)	8	8 (5.6%)
	Vitamin D deficiency	3	3 (4.5%)	2	2 (4.8%)	2	2 (5.9%)	7	7 (4.9%)
	Dyslipidaemia	4	4 (6.1%)	1	1 (2.4%)	-	-	5	5 (3.5%)
	Hypertriglyceridaemia	3	3 (4.5%)	-	-	2	2 (5.9%)	5	5 (3.5%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
	Folate deficiency	-	-	4	4 (9.5%)	-	-	4	4 (2.8%)
	Gout	1	1 (1.5%)	2	2 (4.8%)	1	1 (2.9%)	4	4 (2.8%)
	Hyperkalaemia	-	-	3	3 (7.1%)	-	-	3	3 (2.1%)
	Hypokalaemia	-	-	2	2 (4.8%)	1	1 (2.9%)	3	3 (2.1%)
	Malnutrition	1	1 (1.5%)	1	1 (2.4%)	1	1 (2.9%)	3	3 (2.1%)
	Diabetes mellitus	-	-	2	2 (4.8%)	-	-	2	2 (1.4%)
	Diabetes mellitus inadequate control	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Fluid retention	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Hypercalcaemia	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Hyperphagia	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Type 2 diabetes mellitus	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
Vascular disorders	**ALL**	**17**	**14 (21.2%)**	**15**	**14 (33.3%)**	**10**	**7 (20.6%)**	**42**	**35 (24.6%)**
	Hypertension	3	3 (4.5%)	6	6 (14.3%)	3	3 (8.8%)	12	12 (8.5%)
	Hot flush	4	4 (6.1%)	1	1 (2.4%)	-	-	5	5 (3.5%)
	Hypotension	2	1 (1.5%)	2	2 (4.8%)	-	-	4	3 (2.1%)
	Pallor	2	2 (3%)	2	2 (4.8%)	-	-	4	4 (2.8%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
	Arteriosclerosis	1	1 (1.5%)	1	1 (2.4%)	1	1 (2.9%)	3	3 (2.1%)
	Phlebitis	1	1 (1.5%)	1	1 (2.4%)	1	1 (2.9%)	3	3 (2.1%)
	Haematoma	-	-	-	-	2	1 (2.9%)	2	1 (0.7%)
	Hypertensive crisis	1	1 (1.5%)	1	1 (2.4%)	-	-	2	2 (1.4%)
	Varicose vein	1	1 (1.5%)	1	1 (2.4%)	-	-	2	2 (1.4%)
	Arterial disorder	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Arteritis	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Intermittent claudication	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Peripheral arterial occlusive disease	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Subclavian artery stenosis	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
Investigations	**ALL**	**10**	**8 (12.1%)**	**24**	**17 (40.5%)**	**6**	**6 (17.6%)**	**40**	**31 (21.8%)**
	Weight decreased	2	2 (3%)	5	5 (11.9%)	-	-	7	7 (4.9%)
	Blood creatinine increased	2	2 (3%)	2	2 (4.8%)	1	1 (2.9%)	5	5 (3.5%)
	Alanine aminotransferase increased	2	2 (3%)	-	-	-	-	2	2 (1.4%)
	Blood thyroid stimulating hormone increased	1	1 (1.5%)	-	-	1	1 (2.9%)	2	2 (1.4%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
	Breath sounds abnormal	-	-	2	2 (4.8%)	-	-	2	2 (1.4%)
	Lipase increased	-	-	2	2 (4.8%)	-	-	2	2 (1.4%)
	Liver function test abnormal	-	-	2	2 (4.8%)	-	-	2	2 (1.4%)
	Weight increased	-	-	1	1 (2.4%)	1	1 (2.9%)	2	2 (1.4%)
	Aspartate aminotransferase increased	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Blood glucose abnormal	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Blood parathyroid hormone increased	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Blood pressure decreased	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Blood thyroid stimulating hormone decreased	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Blood urea increased	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Blood uric acid increased	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Cardiac murmur	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Coronavirus test positive	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Electrocardiogram ST segment depression	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
	Gamma-glutamyltransferase increased	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Intestinal transit time increased	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Pulse absent	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Serum ferritin normal	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Transaminases increased	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Troponin increased	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
Renal and urinary disorders	**ALL**	**20**	**15 (22.7%)**	**8**	**5 (11.9%)**	**10**	**8 (23.5%)**	**38**	**28 (19.7%)**
	Renal failure	4	4 (6.1%)	2	2 (4.8%)	3	2 (5.9%)	9	8 (5.6%)
	Pollakiuria	3	3 (4.5%)	-	-	2	2 (5.9%)	5	5 (3.5%)
	Acute kidney injury	2	1 (1.5%)	1	1 (2.4%)	-	-	3	2 (1.4%)
	Chronic kidney disease	3	3 (4.5%)	-	-	-	-	3	3 (2.1%)
	Dysuria	1	1 (1.5%)	1	1 (2.4%)	-	-	2	2 (1.4%)
	Haematuria	1	1 (1.5%)	1	1 (2.4%)	-	-	2	2 (1.4%)
	Nephrolithiasis	1	1 (1.5%)	-	-	1	1 (2.9%)	2	2 (1.4%)
	Renal artery stenosis	1	1 (1.5%)	1	1 (2.4%)	-	-	2	2 (1.4%)
	Renal colic	-	-	-	-	2	2 (5.9%)	2	2 (1.4%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
	Renal cyst	1	1 (1.5%)	1	1 (2.4%)	-	-	2	2 (1.4%)
	Chromaturia	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Micturition urgency	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Nocturia	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Oliguria	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Polyuria	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Urinary tract disorder	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
Cardiac disorders	**ALL**	**15**	**7 (10.6%)**	**10**	**8 (19%)**	**7**	**6 (17.6%)**	**32**	**21 (14.8%)**
	Cardiac failure	6	3 (4.5%)	1	1 (2.4%)	1	1 (2.9%)	8	5 (3.5%)
	Atrial fibrillation	4	2 (3%)	1	1 (2.4%)	-	-	5	3 (2.1%)
	Palpitations	2	2 (3%)	1	1 (2.4%)	-	-	3	3 (2.1%)
	Pericardial effusion	1	1 (1.5%)	1	1 (2.4%)	1	1 (2.9%)	3	3 (2.1%)
	Pericarditis	-	-	3	3 (7.1%)	-	-	3	3 (2.1%)
	Tachycardia	-	-	1	1 (2.4%)	2	2 (5.9%)	3	3 (2.1%)
	Arrhythmia	1	1 (1.5%)	-	-	1	1 (2.9%)	2	2 (1.4%)
	Extrasystoles	-	-	1	1 (2.4%)	1	1 (2.9%)	2	2 (1.4%)
	Arrhythmia supraventricular	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
	Bradycardia	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Cardiomegaly	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
Psychiatric disorders	**ALL**	**13**	**12 (18.2%)**	**8**	**8 (19%)**	**6**	**6 (17.6%)**	**27**	**26 (18.3%)**
	Anxiety	3	3 (4.5%)	2	2 (4.8%)	2	2 (5.9%)	7	7 (4.9%)
	Depression	4	4 (6.1%)	3	3 (7.1%)	-	-	7	7 (4.9%)
	Insomnia	2	2 (3%)	2	2 (4.8%)	1	1 (2.9%)	5	5 (3.5%)
	Affective disorder	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Depressed mood	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Irritability	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Libido decreased	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Mental disorder	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Morose	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Nervousness	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Sleep disorder	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
Blood and lymphatic system disorders	**ALL**	**11**	**8 (12.1%)**	**5**	**5 (11.9%)**	**8**	**7 (20.6%)**	**24**	**20 (14.1%)**
	Anaemia	8	7 (10.6%)	3	3 (7.1%)	5	4 (11.8%)	16	14 (9.9%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
	Iron deficiency anaemia	-	-	2	2 (4.8%)	1	1 (2.9%)	3	3 (2.1%)
	Agranulocytosis	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Lymphopenia	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Neutropenia	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Thrombocytopenia	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Thrombocytosis	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
Hepatobiliary disorders	**ALL**	**13**	**11 (16.7%)**	**8**	**5 (11.9%)**	**3**	**3 (8.8%)**	**24**	**19 (13.4%)**
	Hepatocellular injury	7	6 (9.1%)	4	4 (9.5%)	2	2 (5.9%)	13	12 (8.5%)
	Cholelithiasis	1	1 (1.5%)	1	1 (2.4%)	-	-	2	2 (1.4%)
	Cholestasis	2	2 (3%)	-	-	-	-	2	2 (1.4%)
	Hepatic steatosis	1	1 (1.5%)	1	1 (2.4%)	-	-	2	2 (1.4%)
	Hepatomegaly	1	1 (1.5%)	1	1 (2.4%)	-	-	2	2 (1.4%)
	Hepatic fibrosis	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Hepatic pain	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Jaundice cholestatic	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
Eye disorders	**ALL**	**14**	**12 (18.2%)**	**6**	**4 (9.5%)**	**3**	**3 (8.8%)**	**23**	**19 (13.4%)**

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
	Cataract	4	3 (4.5%)	1	1 (2.4%)	-	-	5	4 (2.8%)
	Eyelid oedema	3	3 (4.5%)	1	1 (2.4%)	-	-	4	4 (2.8%)
	Blepharitis	1	1 (1.5%)	1	1 (2.4%)	-	-	2	2 (1.4%)
	Conjunctival haemorrhage	-	-	1	1 (2.4%)	1	1 (2.9%)	2	2 (1.4%)
	Cystoid macular oedema	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Dry eye	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Eye swelling	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Eyelid disorder	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Eyelid ptosis	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Lacrimation increased	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Periorbital oedema	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Photopsia	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Retinal haemorrhage	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Uveitis	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
Injury, poisoning and procedural complications	**ALL**	**11**	**9 (13.6%)**	**3**	**3 (7.1%)**	**9**	**8 (23.5%)**	**23**	**20 (14.1%)**
	Omissions of a medication dose	2	1 (1.5%)	-	-	2	2 (5.9%)	4	3 (2.1%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
	Fall	2	2 (3%)	-	-	1	1 (2.9%)	3	3 (2.1%)
	Limb injury	1	1 (1.5%)	-	-	1	1 (2.9%)	2	2 (1.4%)
	Wound	1	1 (1.5%)	1	1 (2.4%)	-	-	2	2 (1.4%)
	Accident at work	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Ankle fracture	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Arthropod bite	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Fractured coccyx	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Head injury	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Overdose	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Scratch	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Spinal compression fracture	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Tendon rupture	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Thermal burn	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Tooth fracture	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Toxicity to various agents	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
Reproductive system and breast disorders	**ALL**	**7**	**6 (9.1%)**	**8**	**7 (16.7%)**	**2**	**2 (5.9%)**	**17**	**15 (10.6%)**
	Benign prostatic hyperplasia	1	1 (1.5%)	2	2 (4.8%)	-	-	3	3 (2.1%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
	Gynaecomastia	1	1 (1.5%)	2	2 (4.8%)	-	-	3	3 (2.1%)
	Prostatitis	2	2 (3%)	-	-	-	-	2	2 (1.4%)
	Vulvovaginal burning sensation	2	2 (3%)	-	-	-	-	2	2 (1.4%)
	Erectile dysfunction	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Genital burning sensation	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Ovarian cyst	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Pelvic discomfort	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Pelvic pain	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Prostatism	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Testicular pain	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
Endocrine disorders	**ALL**	**3**	**3 (4.5%)**	**5**	**5 (11.9%)**	**3**	**2 (5.9%)**	**11**	**10 (7%)**
	Hypothyroidism	-	-	3	3 (7.1%)	1	1 (2.9%)	4	4 (2.8%)
	Hyperthyroidism	1	1 (1.5%)	-	-	1	1 (2.9%)	2	2 (1.4%)
	Basedow's disease	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Haemorrhagic thyroid cyst	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Hyperparathyroidism	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
	Hyperparathyroidism secondary	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Thyroid mass	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**ALL**	**7**	**7 (10.6%)**	**2**	**2 (4.8%)**	**2**	**2 (5.9%)**	**11**	**11 (7.7%)**
	Acrochordon	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Benign pancreatic neoplasm	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Leiomyoma	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Lipoma	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Melanocytic naevus	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Meningioma	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Monoclonal gammopathy	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Neoplasm progression	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Prostatic adenoma	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Seborrhoeic keratosis	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Uterine leiomyoma	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
Ear and labyrinth disorders	**ALL**	**5**	**4 (6.1%)**	**2**	**2 (4.8%)**	**2**	**2 (5.9%)**	**9**	**8 (5.6%)**

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
	Vertigo	2	2 (3%)	-	-	1	1 (2.9%)	3	3 (2.1%)
	Tinnitus	-	-	1	1 (2.4%)	1	1 (2.9%)	2	2 (1.4%)
	Deafness unilateral	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Ear discomfort	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Hypoacusis	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Vestibular disorder	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
Immune system disorders	**ALL**	**3**	**3 (4.5%)**	**-**	**-**	**2**	**2 (5.9%)**	**5**	**5 (3.5%)**
	Hypersensitivity	2	2 (3%)	-	-	2	2 (5.9%)	4	4 (2.8%)
	Food allergy	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
Congenital, familial and genetic disorders	**ALL**	**2**	**2 (3%)**	**-**	**-**	**-**	**-**	**2**	**2 (1.4%)**
	Dilatation intrahepatic duct congenital	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Gene mutation	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
Social circumstances	**ALL**	**-**	**-**	**1**	**1 (2.4%)**	**-**	**-**	**1**	**1 (0.7%)**
	Physical disability	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
Surgical and medical procedures	**ALL**	**-**	**-**	**-**	**-**	**1**	**1 (2.9%)**	**1**	**1 (0.7%)**
	Vasectomy	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)

Table 15.3.5b Adverse Events by System Organ Class and Preferred Term (All Causalities and grade 1-2) - SAF (n=142)

Table 73: Adverse Events by System Organ Class and Preferred Term (All Causalities and grade 3-4) - SAF (n=142)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
ALL		**100**	**34 (51.5%)**	**56**	**29 (69%)**	**77**	**25 (73.5%)**	**233**	**88 (62%)**
Infections and infestations	**ALL**	**9**	**8 (12.1%)**	**7**	**6 (14.3%)**	**5**	**3 (8.8%)**	**21**	**17 (12%)**
	Pyelonephritis	-	-	1	1 (2.4%)	1	1 (2.9%)	2	2 (1.4%)
	Sepsis	2	2 (3%)	-	-	-	-	2	2 (1.4%)
	Staphylococcal infection	1	1 (1.5%)	-	-	1	1 (2.9%)	2	2 (1.4%)
	Abdominal abscess	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Bacterial infection	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Bronchitis	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Escherichia infection	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Gastroenteritis	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Gastrointestinal infection	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Herpes ophthalmic	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Influenza	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
	Paronychia	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Perineal abscess	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Pneumonia	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Pneumonia aspiration	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Pneumonia fungal	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Tooth abscess	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Urinary tract infection	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
Respiratory, thoracic and mediastinal disorders	**ALL**	**8**	**8 (12.1%)**	**4**	**3 (7.1%)**	**9**	**5 (14.7%)**	**21**	**16 (11.3%)**
	Pleural effusion	1	1 (1.5%)	2	2 (4.8%)	3	2 (5.9%)	6	5 (3.5%)
	Dyspnoea	2	2 (3%)	-	-	1	1 (2.9%)	3	3 (2.1%)
	Lung disorder	2	2 (3%)	-	-	1	1 (2.9%)	3	3 (2.1%)
	Acute pulmonary oedema	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Acute respiratory distress syndrome	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Bronchopulmonary disease	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Chronic obstructive pulmonary disease	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
	Pleurisy	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Pulmonary arterial hypertension	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Pulmonary hypertension	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Respiratory distress	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Sleep apnoea syndrome	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
Hepatobiliary disorders	**ALL**	**10**	**10 (15.2%)**	**5**	**5 (11.9%)**	**5**	**4 (11.8%)**	**20**	**19 (13.4%)**
	Hepatocellular injury	7	7 (10.6%)	3	3 (7.1%)	2	2 (5.9%)	12	12 (8.5%)
	Hepatitis	1	1 (1.5%)	-	-	1	1 (2.9%)	2	2 (1.4%)
	Cholecystitis	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Cholecystitis acute	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Cholecystitis chronic	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Cholelithiasis	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Cholelithiasis obstructive	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Hepatotoxicity	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
Blood and lymphatic system disorders	**ALL**	**4**	**4 (6.1%)**	**6**	**3 (7.1%)**	**9**	**5 (14.7%)**	**19**	**12 (8.5%)**

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
	Anaemia	2	2 (3%)	2	2 (4.8%)	6	3 (8.8%)	10	7 (4.9%)
	Iron deficiency anaemia	-	-	3	1 (2.4%)	1	1 (2.9%)	4	2 (1.4%)
	Thrombocytopenia	1	1 (1.5%)	1	1 (2.4%)	1	1 (2.9%)	3	3 (2.1%)
	Pancytopenia	1	1 (1.5%)	-	-	1	1 (2.9%)	2	2 (1.4%)
Gastrointestinal disorders	**ALL**	**6**	**6 (9.1%)**	**7**	**5 (11.9%)**	**6**	**4 (11.8%)**	**19**	**15 (10.6%)**
	Diarrhoea	4	4 (6.1%)	2	2 (4.8%)	2	2 (5.9%)	8	8 (5.6%)
	Vomiting	-	-	1	1 (2.4%)	2	2 (5.9%)	3	3 (2.1%)
	Abdominal pain	1	1 (1.5%)	1	1 (2.4%)	-	-	2	2 (1.4%)
	Anal fistula	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Constipation	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Intestinal obstruction	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Nausea	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Pancreatitis acute	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Rectal haemorrhage	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
Cardiac disorders	**ALL**	**6**	**5 (7.6%)**	**4**	**3 (7.1%)**	**7**	**4 (11.8%)**	**17**	**12 (8.5%)**
	Cardiac failure	3	3 (4.5%)	3	2 (4.8%)	3	3 (8.8%)	9	8 (5.6%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
	Angina pectoris	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Atrial fibrillation	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Coronary artery insufficiency	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Coronary artery stenosis	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Left ventricular failure	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Myocardial infarction	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Pericarditis	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Tachyarrhythmia	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
General disorders and administration site conditions	**ALL**	**7**	**4 (6.1%)**	**4**	**4 (9.5%)**	**5**	**4 (11.8%)**	**16**	**12 (8.5%)**
	Malaise	2	1 (1.5%)	1	1 (2.4%)	-	-	3	2 (1.4%)
	Asthenia	1	1 (1.5%)	-	-	1	1 (2.9%)	2	2 (1.4%)
	Chest pain	2	1 (1.5%)	-	-	-	-	2	1 (0.7%)
	General physical health deterioration	-	-	-	-	2	2 (5.9%)	2	2 (1.4%)
	Pain	-	-	1	1 (2.4%)	1	1 (2.9%)	2	2 (1.4%)
	Oedema	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Polyp	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
	Pyrexia	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Reduced drug effect	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Treatment noncompliance	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
Renal and urinary disorders	**ALL**	**10**	**7 (10.6%)**	**3**	**3 (7.1%)**	**2**	**2 (5.9%)**	**15**	**12 (8.5%)**
	Renal failure	4	4 (6.1%)	2	2 (4.8%)	-	-	6	6 (4.2%)
	Acute kidney injury	3	3 (4.5%)	-	-	-	-	3	3 (2.1%)
	Chronic kidney disease	1	1 (1.5%)	-	-	1	1 (2.9%)	2	2 (1.4%)
	Prerenal failure	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Renal artery stenosis	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Renal impairment	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Urinary retention	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
Musculoskeletal and connective tissue disorders	**ALL**	**9**	**7 (10.6%)**	**2**	**2 (4.8%)**	**2**	**2 (5.9%)**	**13**	**11 (7.7%)**
	Osteoarthritis	4	3 (4.5%)	-	-	1	1 (2.9%)	5	4 (2.8%)
	Arthralgia	2	2 (3%)	-	-	-	-	2	2 (1.4%)
	Arthritis	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
	Back pain	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Chondrocalcinosis	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Musculoskeletal pain	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Myalgia	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Neck pain	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
Metabolism and nutrition disorders	**ALL**	**7**	**5 (7.6%)**	**3**	**3 (7.1%)**	**2**	**2 (5.9%)**	**12**	**10 (7%)**
	Diabetes mellitus inadequate control	1	1 (1.5%)	1	1 (2.4%)	-	-	2	2 (1.4%)
	Hypokalaemia	-	-	2	2 (4.8%)	-	-	2	2 (1.4%)
	Decreased appetite	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Dehydration	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Folate deficiency	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Hyperkalaemia	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Hypocalcaemia	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Hyponatraemia	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Iron deficiency	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Malnutrition	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
Investigations	**ALL**	**3**	**1 (1.5%)**	**5**	**3 (7.1%)**	**3**	**3 (8.8%)**	**11**	**7 (4.9%)**
	Alanine aminotransferase increased	1	1 (1.5%)	2	2 (4.8%)	1	1 (2.9%)	4	4 (2.8%)
	Aspartate aminotransferase increased	2	1 (1.5%)	2	2 (4.8%)	-	-	4	3 (2.1%)
	Lipase increased	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Transaminases increased	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Weight increased	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
Injury, poisoning and procedural complications	**ALL**	**5**	**5 (7.6%)**	**2**	**1 (2.4%)**	**3**	**3 (8.8%)**	**10**	**9 (6.3%)**
	Limb injury	1	1 (1.5%)	-	-	1	1 (2.9%)	2	2 (1.4%)
	Animal bite	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Arteriovenous fistula occlusion	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Fall	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Hip fracture	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Maternal exposure during pregnancy	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
	Post procedural complication	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Procedural pain	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Vascular graft occlusion	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
Nervous system disorders	**ALL**	**5**	**3 (4.5%)**	**2**	**2 (4.8%)**	**3**	**2 (5.9%)**	**10**	**7 (4.9%)**
	Carotid artery stenosis	1	1 (1.5%)	-	-	2	1 (2.9%)	3	2 (1.4%)
	Axonal neuropathy	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Carpal tunnel syndrome	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Cervicobrachial syndrome	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Headache	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Nerve compression	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Petit mal epilepsy	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Ulnar tunnel syndrome	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
Vascular disorders	**ALL**	**4**	**4 (6.1%)**	**-**	**-**	**5**	**5 (14.7%)**	**9**	**9 (6.3%)**
	Hypertension	3	3 (4.5%)	-	-	1	1 (2.9%)	4	4 (2.8%)
	Peripheral artery stenosis	-	-	-	-	2	2 (5.9%)	2	2 (1.4%)
	Arterial occlusive disease	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
	Haemorrhage	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Hypertensive crisis	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
Skin and subcutaneous tissue disorders	**ALL**	**-**	**-**	**-**	**-**	**5**	**4 (11.8%)**	**5**	**4 (2.8%)**
	Skin ulcer	-	-	-	-	2	1 (2.9%)	2	1 (0.7%)
	Angioedema	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Dermatitis	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Vascular skin disorder	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**ALL**	**2**	**2 (3%)**	**2**	**2 (4.8%)**	**-**	**-**	**4**	**4 (2.8%)**
	Bowen's disease	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Chronic myeloid leukaemia	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Gastrointestinal stromal tumour	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Prostate cancer	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
Surgical and medical procedures	**ALL**	**1**	**1 (1.5%)**	**-**	**-**	**3**	**2 (5.9%)**	**4**	**3 (2.1%)**
	Foot amputation	-	-	-	-	2	1 (2.9%)	2	1 (0.7%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
	Angioplasty	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Thyroidectomy	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
Psychiatric disorders	**ALL**	**1**	**1 (1.5%)**	**-**	**-**	**2**	**2 (5.9%)**	**3**	**3 (2.1%)**
	Depression	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Insomnia	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Paranoia	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
Ear and labyrinth disorders	**ALL**	**1**	**1 (1.5%)**	**-**	**-**	**-**	**-**	**1**	**1 (0.7%)**
	Hypoacusis	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
Eye disorders	**ALL**	**1**	**1 (1.5%)**	**-**	**-**	**-**	**-**	**1**	**1 (0.7%)**
	Retinal vein occlusion	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
Immune system disorders	**ALL**	**1**	**1 (1.5%)**	**-**	**-**	**-**	**-**	**1**	**1 (0.7%)**
	Anaphylactic shock	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
Pregnancy, puerperium and perinatal conditions	**ALL**	**-**	**-**	**-**	**-**	**1**	**1 (2.9%)**	**1**	**1 (0.7%)**
	Complication of pregnancy	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)

Table 15.3.5c Adverse Events by System Organ Class and Preferred Term (All Causalities and grade 3-4) - SAF (n=142)

Table 74: Adverse Events by System Organ Class and Preferred Term (All Causalities and grade 5 or missing) - SAF (n=142)

Patient No.	Treatment lines	Date of initiation of bosutinib treatment	SOC name	PT name	CTCAE grade	Date of occurrence	Is the event serious?	Status	Date of recovery	Is it reasonably possible that the event may be related to the study medication?	Is it reasonably possible that the event may be related to a concomitant drug?	yes, specify the concomitant drug	Name of the drug (1)	Action taken (1)	Name of the drug (2)	Action taken (2)
01-01	4L+	24/02/2016	Infections and infestations	Sepsis	Grade 5	10/01/2017	Yes	Subject not recovered		No	No		BOSULIF	Not applicable		.
03-01	2L	19/05/2016	Injury, poisoning and procedural complications	Intentional product misuse	.	NK/NK/2018	No	Recovery	01/09/2018	No	No		BOSULIF	Not applicable		.
04-09	3L	10/10/2019	Injury, poisoning and procedural complications	Hip fracture	.	NK/NK/2021	Yes	Recovery	NK/NK/2021	No	No		BOSULIF	Not applicable	PONATINIB	No dose modification
09-10	2L	21/09/2017	General disorders and administration site conditions	General physical health deterioration	Grade 5	01/02/2018	Yes	Subject not recovered		No	No		BOSULIF	No dose modification		.
09-14	2L	12/11/2018	Social circumstances	Miscarriage of partner	.	UK/08/2020	Yes	Recovery	UK/08/2020	No	No		BOSULIF	Not applicable	DASATINIB	No dose modification
			Social circumstances	Pregnancy of partner	.	UK/09/2020	Yes	Recovery	UK/06/2021	No	No		BOSULIF	Not applicable	DASATINIB	No dose modification
			General disorders and administration site conditions	Ill-defined disorder	.	14/09/2020	No	Subject not recovered		No	Yes	DASATINIB	BOSULIF	Not applicable	DASATINIB	No dose modification

Patient No.	Treatment lines	Date of initiation of bosutinib treatment	SOC name	PT name	CTCAE grade	Date of occurrence	Is the event serious?	Status	Date of recovery	Is it reasonably possible that the event may be related to the study medication?	Is it reasonably possible that the event may be related to a concomitant drug?	yes, specify the concomitant drug	Name of the drug (1)	Action taken (1)	Name of the drug (2)	Action taken (2)
11-02	4L+	14/04/2016	Injury, poisoning and procedural complications	Maternal exposure during pregnancy	.	15/05/2017	No	Recovery	21/01/2018	No	No		BOSUTINIB	Withdrawal (temporary or permanent, or deferred administration)		.
13-01	4L+	26/03/2016	General disorders and administration site conditions	General physical health deterioration	Grade 5	26/07/2016	Yes	Subject not recovered		No	No			Withdrawal (temporary or permanent, or deferred administration)		.
13-04	4L+	15/03/2018	General disorders and administration site conditions	Condition aggravated	Grade 5	02/02/2020	Yes	Subject not recovered		No	No			Unknown		.
16-03	4L+	24/07/2016	General disorders and administration site conditions	Multiviceral failure	Grade 5	30/10/2018	Yes	Subject not recovered		No	No		BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.
16-08	3L	30/01/2019	Infections and infestations	Pneumonia	Grade 5	18/06/2021	Yes	Subject not recovered		Yes	No			No dose modification		.

Patient No.	Treatment lines	Date of initiation of bosutinib treatment	SOC name	PT name	CTCAE grade	Date of occurrence	Is the event serious?	Status	Date of recovery	Is it reasonably possible that the event may be related to the study medication?	Is it reasonably possible that the event may be related to a concomitant drug?	yes, specify the concomitant drug	Name of the drug (1)	Action taken (1)	Name of the drug (2)	Action taken (2)
23-01	3L	07/07/2016	General disorders and administration site conditions	General physical health deterioration	.	07/08/2019	.	Recovery	13/09/2019	No	No		BOSULIF	No dose modification		.
23-02	2L	01/10/2016	General disorders and administration site conditions	General physical health deterioration	Grade 5	20/10/2016	Yes	Subject not recovered		No	No		BOSULIF	Withdrawal (temporary or permanent, or deferred administration)	PREVISCAN	Withdrawal (temporary or permanent, or deferred administration)

Listing 15.3.5d Adverse Events by System Organ Class and Preferred Term (All Causalities and grade 5 or missing) - SAF (n=142)

10.6.2. Serious adverse event

Overall, 246 SAEs were reported in 86 (60.6%) patients. Similar profiles were observed regardless of subgroup, 39 (59.1%) patients in the 2L group, 28 (66.7%) patients from the 3L group and 19 (55.9%) 4L+ group. All SAEs are summarized in Table 75. Additionally, measures taken to prevent AE and SAE are presented in **Appendix 7.7** and according to the safety narrative plan all reports of SAE leading to treatment interruption are provided in **APPENDIX 8.**

Considering all SAE regardless of grade, the SOC for which the most SAE were recorded were Respiratory, thoracic and mediastinal disorders (14.8%) with mostly pleural effusion (7.7%), Infections and infestations (13.4%), Cardiac disorders (11.3%) with mostly cardiac failure (6.3%) and General disorders and administration site conditions reported in 18 (12.7%) patients. As well as renal and urinary disorders which occurred in 13 (9.2%) patients (mainly renal failure (4.2%)) and musculoskeletal and connective tissues disorders which occurred in 13 (9.2%) patients.

Regarding grade 1-2 SAEs, 87 SAEs were reported in 46 (32.4%) patients (Table 76). The SOC for which the most SAEs were reported were Respiratory, thoracic and mediastinal disorders observed in 13 (9.2%) patients (mostly pleural effusion and dyspnea), and gastrointestinal disorders observed in 9 (6.3%) patients. Additionally, cardiac disorders, infections and infestations as well as general disorders and administration sites conditions SAEs were reported in 4.9% of the SAF population each. Overall, There were slightly less grade 1-2 SAEs in the 4L+ group (23.5%) compared to the 2L group (33.3%) and the 3L group (38.1%).

Regarding SAEs of grade 3 to 4 summarized in Table 77, 67 (47.2%) patients experienced an SAE grade 3-4 for a total of 149 SAEs reported. The SOC for which the most grade 3-4 SAEs were reported were cardiac disorders observed in 12 (8.5%) patients, mostly cardiac failure (5.6%); Infections and infestations observed in 14 (9.9%) patients and respiratory, thoracic and mediastinal disorders reported in 14 (9.9%) patients. There were slightly less grade 3-4 SAEs in the 2L group (40.9%) compared to the 3L group (52.4%) and the 4L+ group (52.9%).

Finally, 7 patients experienced a grade 5 SAE. Three patients had a general physical health deterioration, two had an infection/ infestation related SAE (one patient developed a sepsis and another one a pneumonia), one patient had an aggravation of his condition and finally a patient had a multi visceral failure (Table 78).

Additionally, 2 SAEs grade were missing (Table 78).

Table 75: Serious Adverse Events by System Organ Class and Preferred Term (All grade) - SAF (n=142)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
ALL		**102**	**39 (59.1%)**	**68**	**28 (66.7%)**	**76**	**19 (55.9%)**	**246**	**86 (60.6%)**
Respiratory, thoracic and mediastinal disorders	**ALL**	**12**	**9 (13.6%)**	**11**	**5 (11.9%)**	**11**	**7 (20.6%)**	**34**	**21 (14.8%)**
	Pleural effusion	3	3 (4.5%)	3	3 (7.1%)	6	5 (14.7%)	12	11 (7.7%)
	Dyspnoea	3	3 (4.5%)	1	1 (2.4%)	1	1 (2.9%)	5	5 (3.5%)
	Lung disorder	2	2 (3%)	-	-	1	1 (2.9%)	3	3 (2.1%)
	Chronic obstructive pulmonary disease	-	-	1	1 (2.4%)	1	1 (2.9%)	2	2 (1.4%)
	Sleep apnoea syndrome	1	1 (1.5%)	1	1 (2.4%)	-	-	2	2 (1.4%)
	Acute pulmonary oedema	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Acute respiratory distress syndrome	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Acute respiratory failure	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Hypoventilation	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Pleurisy	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
	Pulmonary arterial hypertension	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Pulmonary embolism	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Pulmonary pain	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Respiratory distress	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Vocal cord polyp	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
Cardiac disorders	**ALL**	**12**	**6 (9.1%)**	**8**	**4 (9.5%)**	**9**	**6 (17.6%)**	**29**	**16 (11.3%)**
	Cardiac failure	7	3 (4.5%)	3	2 (4.8%)	4	4 (11.8%)	14	9 (6.3%)
	Atrial fibrillation	2	1 (1.5%)	-	-	1	1 (2.9%)	3	2 (1.4%)
	Pericarditis	-	-	3	2 (4.8%)	-	-	3	2 (1.4%)
	Pericardial effusion	-	-	1	1 (2.4%)	1	1 (2.9%)	2	2 (1.4%)
	Angina pectoris	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Arrhythmia supraventricular	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Coronary artery insufficiency	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Coronary artery stenosis	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Left ventricular failure	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Myocardial infarction	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
	Tachyarrhythmia	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
Infections and infestations	**ALL**	**8**	**8 (12.1%)**	**11**	**7 (16.7%)**	**8**	**4 (11.8%)**	**27**	**19 (13.4%)**
	Bronchitis	3	3 (4.5%)	1	1 (2.4%)	1	1 (2.9%)	5	5 (3.5%)
	Sepsis	1	1 (1.5%)	1	1 (2.4%)	1	1 (2.9%)	3	3 (2.1%)
	Pneumonia	-	-	1	1 (2.4%)	1	1 (2.9%)	2	2 (1.4%)
	Pyelonephritis	-	-	1	1 (2.4%)	1	1 (2.9%)	2	2 (1.4%)
	Staphylococcal infection	1	1 (1.5%)	-	-	1	1 (2.9%)	2	2 (1.4%)
	Urinary tract infection	1	1 (1.5%)	1	1 (2.4%)	-	-	2	2 (1.4%)
	Abdominal abscess	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Bacterial infection	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Erysipelas	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Escherichia infection	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Gastrointestinal infection	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Infection	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Influenza	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Perineal abscess	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Pneumonia aspiration	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
	Pneumonia fungal	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Tooth abscess	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
General disorders and administration site conditions	**ALL**	**10**	**6 (9.1%)**	**5**	**4 (9.5%)**	**9**	**8 (23.5%)**	**24**	**18 (12.7%)**
	Chest pain	5	4 (6.1%)	1	1 (2.4%)	-	-	6	5 (3.5%)
	General physical health deterioration	2	2 (3%)	-	-	3	3 (8.8%)	5	5 (3.5%)
	Malaise	2	1 (1.5%)	1	1 (2.4%)	-	-	3	2 (1.4%)
	Pyrexia	-	-	1	1 (2.4%)	1	1 (2.9%)	2	2 (1.4%)
	Asthenia	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Condition aggravated	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Generalised oedema	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Multiviceral failure	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Oedema	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Oedema peripheral	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Pain	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Polyp	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
Gastrointestinal disorders	**ALL**	**7**	**7 (10.6%)**	**4**	**3 (7.1%)**	**7**	**2 (5.9%)**	**18**	**12 (8.5%)**
	Inguinal hernia	1	1 (1.5%)	1	1 (2.4%)	-	-	2	2 (1.4%)
	Abdominal pain	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Anal fissure	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Anal fistula	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Dysphagia	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Erosive duodenitis	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Gastric ulcer	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Gastroduodenal ulcer	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Gastrointestinal disorder	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Hiatus hernia	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Intestinal obstruction	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Nausea	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Oesophagitis	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Pancreatitis acute	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Rectal haemorrhage	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Tooth disorder	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Vomiting	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
Renal and urinary disorders	**ALL**	**12**	**7 (10.6%)**	**4**	**4 (9.5%)**	**2**	**2 (5.9%)**	**18**	**13 (9.2%)**
	Renal failure	5	4 (6.1%)	2	2 (4.8%)	-	-	7	6 (4.2%)
	Acute kidney injury	4	3 (4.5%)	-	-	-	-	4	3 (2.1%)
	Renal artery stenosis	2	2 (3%)	-	-	-	-	2	2 (1.4%)
	Chronic kidney disease	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Dysuria	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Prerenal failure	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Renal colic	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Urinary retention	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
Musculoskeletal and connective tissue disorders	**ALL**	**10**	**8 (12.1%)**	**3**	**3 (7.1%)**	**2**	**2 (5.9%)**	**15**	**13 (9.2%)**
	Osteoarthritis	3	3 (4.5%)	1	1 (2.4%)	1	1 (2.9%)	5	5 (3.5%)
	Arthralgia	3	3 (4.5%)	-	-	-	-	3	3 (2.1%)
	Arthritis	1	1 (1.5%)	1	1 (2.4%)	-	-	2	2 (1.4%)
	Chondrocalcinosis	1	1 (1.5%)	1	1 (2.4%)	-	-	2	2 (1.4%)
	Back pain	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
	Myalgia	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Pain in extremity	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
Nervous system disorders	**ALL**	**1**	**1 (1.5%)**	**6**	**5 (11.9%)**	**4**	**3 (8.8%)**	**11**	**9 (6.3%)**
	Carotid artery stenosis	1	1 (1.5%)	-	-	2	1 (2.9%)	3	2 (1.4%)
	Axonal neuropathy	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Cervicobrachial syndrome	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Coma	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Somnolence	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Transient ischaemic attack	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Tremor	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Trigeminal neuralgia	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Ulnar tunnel syndrome	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
Blood and lymphatic system disorders	**ALL**	**2**	**2 (3%)**	**4**	**2 (4.8%)**	**4**	**3 (8.8%)**	**10**	**7 (4.9%)**
	Anaemia	-	-	1	1 (2.4%)	3	3 (8.8%)	4	4 (2.8%)
	Iron deficiency anaemia	-	-	3	1 (2.4%)	-	-	3	1 (0.7%)
	Pancytopenia	1	1 (1.5%)	-	-	1	1 (2.9%)	2	2 (1.4%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
	Thrombocytopenia	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
Injury, poisoning and procedural complications	**ALL**	**3**	**3 (4.5%)**	**3**	**3 (7.1%)**	**3**	**3 (8.8%)**	**9**	**9 (6.3%)**
	Hip fracture	-	-	1	1 (2.4%)	1	1 (2.9%)	2	2 (1.4%)
	Limb injury	1	1 (1.5%)	-	-	1	1 (2.9%)	2	2 (1.4%)
	Fall	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Post procedural complication	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Procedural pain	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Tendon rupture	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Vascular graft occlusion	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
Vascular disorders	**ALL**	**4**	**4 (6.1%)**	**1**	**1 (2.4%)**	**4**	**4 (11.8%)**	**9**	**9 (6.3%)**
	Peripheral artery stenosis	-	-	-	-	2	2 (5.9%)	2	2 (1.4%)
	Arterial occlusive disease	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Haemorrhage	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Hypertension	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Hypotension	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
	Peripheral arterial occlusive disease	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Phlebitis	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Subclavian artery stenosis	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
Hepatobiliary disorders	**ALL**	**4**	**4 (6.1%)**	**1**	**1 (2.4%)**	**2**	**2 (5.9%)**	**7**	**7 (4.9%)**
	Hepatocellular injury	2	2 (3%)	-	-	-	-	2	2 (1.4%)
	Cholecystitis	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Cholecystitis acute	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Cholecystitis chronic	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Cholelithiasis	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Cholelithiasis obstructive	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
Metabolism and nutrition disorders	**ALL**	**4**	**3 (4.5%)**	**1**	**1 (2.4%)**	**1**	**1 (2.9%)**	**6**	**5 (3.5%)**
	Diabetes mellitus inadequate control	1	1 (1.5%)	1	1 (2.4%)	-	-	2	2 (1.4%)
	Folate deficiency	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Hypocalcaemia	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Hyponatraemia	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
	Malnutrition	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**ALL**	**2**	**2 (3%)**	**2**	**2 (4.8%)**	**-**	**-**	**4**	**4 (2.8%)**
	Bowen's disease	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Chronic myeloid leukaemia	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Gastrointestinal stromal tumour	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Uterine leiomyoma	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
Skin and subcutaneous tissue disorders	**ALL**	**-**	**-**	**-**	**-**	**4**	**3 (8.8%)**	**4**	**3 (2.1%)**
	Skin ulcer	-	-	-	-	2	1 (2.9%)	2	1 (0.7%)
	Angioedema	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Dermatitis	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
Surgical and medical procedures	**ALL**	**1**	**1 (1.5%)**	**-**	**-**	**3**	**2 (5.9%)**	**4**	**3 (2.1%)**
	Foot amputation	-	-	-	-	2	1 (2.9%)	2	1 (0.7%)
	Angioplasty	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Thyroidectomy	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
Eye disorders	**ALL**	**3**	**3 (4.5%)**	**-**	**-**	**-**	**-**	**3**	**3 (2.1%)**
	Blepharitis	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Cataract	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Retinal vein occlusion	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
Investigations	**ALL**	**-**	**-**	**2**	**1 (2.4%)**	**1**	**1 (2.9%)**	**3**	**2 (1.4%)**
	Alanine aminotransferase increased	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Aspartate aminotransferase increased	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Lipase increased	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
Social circumstances	**ALL**	**2**	**1 (1.5%)**	**1**	**1 (2.4%)**	**-**	**-**	**3**	**2 (1.4%)**
	Miscarriage of partner	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Physical disability	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Pregnancy of partner	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
Ear and labyrinth disorders	**ALL**	**1**	**1 (1.5%)**	**-**	**-**	**1**	**1 (2.9%)**	**2**	**2 (1.4%)**

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
	Hypoacusis	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Vertigo	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
Immune system disorders	**ALL**	**2**	**2 (3%)**	**-**	**-**	**-**	**-**	**2**	**2 (1.4%)**
	Anaphylactic shock	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Food allergy	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
Congenital, familial and genetic disorders	**ALL**	**1**	**1 (1.5%)**	**-**	**-**	**-**	**-**	**1**	**1 (0.7%)**
	Gene mutation	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
Endocrine disorders	**ALL**	**-**	**-**	**1**	**1 (2.4%)**	**-**	**-**	**1**	**1 (0.7%)**
	Hypothyroidism	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
Pregnancy, puerperium and perinatal conditions	**ALL**	**-**	**-**	**-**	**-**	**1**	**1 (2.9%)**	**1**	**1 (0.7%)**
	Complication of pregnancy	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
Reproductive system and breast disorders	**ALL**	**1**	**1 (1.5%)**	**-**	**-**	**-**	**-**	**1**	**1 (0.7%)**

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
	Prostatitis	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)

Table 15.3.6a Serious Adverse Events by System Organ Class and Preferred Term (All grade) - SAF (n=142)

Table 76: Serious Adverse Events by System Organ Class and Preferred Term (Grade 1-2) - SAF (n=142)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
ALL		**40**	**22 (33.3%)**	**28**	**16 (38.1%)**	**19**	**8 (23.5%)**	**87**	**46 (32.4%)**
Respiratory, thoracic and mediastinal disorders	**ALL**	**6**	**6 (9.1%)**	**7**	**4 (9.5%)**	**4**	**3 (8.8%)**	**17**	**13 (9.2%)**
	Pleural effusion	2	2 (3%)	1	1 (2.4%)	3	3 (8.8%)	6	6 (4.2%)
	Dyspnoea	2	2 (3%)	1	1 (2.4%)	1	1 (2.9%)	4	4 (2.8%)
	Acute respiratory failure	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Chronic obstructive pulmonary disease	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Hypoventilation	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Pulmonary embolism	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Pulmonary pain	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Sleep apnoea syndrome	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Vocal cord polyp	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
Cardiac disorders	**ALL**	**6**	**2 (3%)**	**4**	**3 (7.1%)**	**2**	**2 (5.9%)**	**12**	**7 (4.9%)**

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
	Cardiac failure	4	1 (1.5%)	-	-	1	1 (2.9%)	5	2 (1.4%)
	Atrial fibrillation	2	1 (1.5%)	-	-	-	-	2	1 (0.7%)
	Pericardial effusion	-	-	1	1 (2.4%)	1	1 (2.9%)	2	2 (1.4%)
	Pericarditis	-	-	2	2 (4.8%)	-	-	2	2 (1.4%)
	Arrhythmia supraventricular	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
Gastrointestinal disorders	**ALL**	**5**	**5 (7.6%)**	**2**	**2 (4.8%)**	**5**	**2 (5.9%)**	**12**	**9 (6.3%)**
	Inguinal hernia	1	1 (1.5%)	1	1 (2.4%)	-	-	2	2 (1.4%)
	Anal fissure	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Dysphagia	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Erosive duodenitis	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Gastric ulcer	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Gastroduodenal ulcer	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Gastrointestinal disorder	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Hiatus hernia	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Nausea	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Oesophagitis	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Tooth disorder	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
Infections and infestations	**ALL**	**3**	**3 (4.5%)**	**3**	**3 (7.1%)**	**2**	**1 (2.9%)**	**8**	**7 (4.9%)**
	Bronchitis	2	2 (3%)	1	1 (2.4%)	1	1 (2.9%)	4	4 (2.8%)
	Erysipelas	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Infection	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Sepsis	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Urinary tract infection	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
General disorders and administration site conditions	**ALL**	**3**	**3 (4.5%)**	**2**	**2 (4.8%)**	**2**	**2 (5.9%)**	**7**	**7 (4.9%)**
	Chest pain	3	3 (4.5%)	1	1 (2.4%)	-	-	4	4 (2.8%)
	Generalised oedema	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Oedema peripheral	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Pyrexia	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
Musculoskeletal and connective tissue disorders	**ALL**	**5**	**3 (4.5%)**	**1**	**1 (2.4%)**	**-**	**-**	**6**	**4 (2.8%)**
	Osteoarthritis	1	1 (1.5%)	1	1 (2.4%)	-	-	2	2 (1.4%)
	Arthralgia	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
	Arthritis	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Chondrocalcinosis	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Pain in extremity	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
Renal and urinary disorders	**ALL**	**4**	**3 (4.5%)**	**1**	**1 (2.4%)**	**1**	**1 (2.9%)**	**6**	**5 (3.5%)**
	Acute kidney injury	2	1 (1.5%)	-	-	-	-	2	1 (0.7%)
	Dysuria	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Renal artery stenosis	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Renal colic	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Renal failure	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
Nervous system disorders	**ALL**	**-**	**-**	**4**	**3 (7.1%)**	**1**	**1 (2.9%)**	**5**	**4 (2.8%)**
	Coma	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Somnolence	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Transient ischaemic attack	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Tremor	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Trigeminal neuralgia	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
Vascular disorders	**ALL**	**2**	**2 (3%)**	**1**	**1 (2.4%)**	**1**	**1 (2.9%)**	**4**	**4 (2.8%)**
	Hypotension	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Peripheral arterial occlusive disease	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Phlebitis	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Subclavian artery stenosis	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
Eye disorders	**ALL**	**2**	**2 (3%)**	**-**	**-**	**-**	**-**	**2**	**2 (1.4%)**
	Blepharitis	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Cataract	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
Congenital, familial and genetic disorders	**ALL**	**1**	**1 (1.5%)**	**-**	**-**	**-**	**-**	**1**	**1 (0.7%)**
	Gene mutation	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
Ear and labyrinth disorders	**ALL**	**-**	**-**	**-**	**-**	**1**	**1 (2.9%)**	**1**	**1 (0.7%)**
	Vertigo	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
Endocrine disorders	**ALL**	**-**	**-**	**1**	**1 (2.4%)**	**-**	**-**	**1**	**1 (0.7%)**

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
	Hypothyroidism	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
Immune system disorders	**ALL**	**1**	**1 (1.5%)**	**-**	**-**	**-**	**-**	**1**	**1 (0.7%)**
	Food allergy	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
Injury, poisoning and procedural complications	**ALL**	**-**	**-**	**1**	**1 (2.4%)**	**-**	**-**	**1**	**1 (0.7%)**
	Tendon rupture	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**ALL**	**1**	**1 (1.5%)**	**-**	**-**	**-**	**-**	**1**	**1 (0.7%)**
	Uterine leiomyoma	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
Reproductive system and breast disorders	**ALL**	**1**	**1 (1.5%)**	**-**	**-**	**-**	**-**	**1**	**1 (0.7%)**
	Prostatitis	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
Social circumstances	**ALL**	**-**	**-**	**1**	**1 (2.4%)**	**-**	**-**	**1**	**1 (0.7%)**

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
	Physical disability	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)

Table 15.3.6b Serious Adverse Events by System Organ Class and Preferred Term (Grade 1-2) - SAF (n=142)

Table 77: Serious Adverse Events by System Organ Class and Preferred Term (Grade 3-4) - SAF (n=142)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
ALL		**58**	**27 (40.9%)**	**38**	**22 (52.4%)**	**53**	**18 (52.9%)**	**149**	**67 (47.2%)**
Cardiac disorders	**ALL**	**6**	**5 (7.6%)**	**4**	**3 (7.1%)**	**7**	**4 (11.8%)**	**17**	**12 (8.5%)**
	Cardiac failure	3	3 (4.5%)	3	2 (4.8%)	3	3 (8.8%)	9	8 (5.6%)
	Angina pectoris	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Atrial fibrillation	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Coronary artery insufficiency	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
	Coronary artery stenosis	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Left ventricular failure	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Myocardial infarction	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Pericarditis	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Tachyarrhythmia	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
Infections and infestations	**ALL**	**5**	**5 (7.6%)**	**7**	**6 (14.3%)**	**5**	**3 (8.8%)**	**17**	**14 (9.9%)**
	Pyelonephritis	-	-	1	1 (2.4%)	1	1 (2.9%)	2	2 (1.4%)
	Staphylococcal infection	1	1 (1.5%)	-	-	1	1 (2.9%)	2	2 (1.4%)
	Abdominal abscess	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Bacterial infection	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Bronchitis	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Escherichia infection	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Gastrointestinal infection	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Influenza	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Perineal abscess	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Pneumonia	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Pneumonia aspiration	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
	Pneumonia fungal	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Sepsis	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Tooth abscess	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Urinary tract infection	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
Respiratory, thoracic and mediastinal disorders	**ALL**	**6**	**6 (9.1%)**	**4**	**3 (7.1%)**	**7**	**5 (14.7%)**	**17**	**14 (9.9%)**
	Pleural effusion	1	1 (1.5%)	2	2 (4.8%)	3	2 (5.9%)	6	5 (3.5%)
	Lung disorder	2	2 (3%)	-	-	1	1 (2.9%)	3	3 (2.1%)
	Acute pulmonary oedema	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Acute respiratory distress syndrome	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Chronic obstructive pulmonary disease	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Dyspnoea	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Pleurisy	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Pulmonary arterial hypertension	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Respiratory distress	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
	Sleep apnoea syndrome	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
General disorders and administration site conditions	**ALL**	**5**	**2 (3%)**	**3**	**3 (7.1%)**	**4**	**4 (11.8%)**	**12**	**9 (6.3%)**
	Malaise	2	1 (1.5%)	1	1 (2.4%)	-	-	3	2 (1.4%)
	Chest pain	2	1 (1.5%)	-	-	-	-	2	1 (0.7%)
	General physical health deterioration	-	-	-	-	2	2 (5.9%)	2	2 (1.4%)
	Asthenia	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Oedema	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Pain	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Polyp	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Pyrexia	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
Renal and urinary disorders	**ALL**	**8**	**6 (9.1%)**	**3**	**3 (7.1%)**	**1**	**1 (2.9%)**	**12**	**10 (7%)**
	Renal failure	4	4 (6.1%)	2	2 (4.8%)	-	-	6	6 (4.2%)
	Acute kidney injury	2	2 (3%)	-	-	-	-	2	2 (1.4%)
	Chronic kidney disease	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Prerenal failure	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
	Renal artery stenosis	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Urinary retention	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
Blood and lymphatic system disorders	**ALL**	**2**	**2 (3%)**	**4**	**2 (4.8%)**	**4**	**3 (8.8%)**	**10**	**7 (4.9%)**
	Anaemia	-	-	1	1 (2.4%)	3	3 (8.8%)	4	4 (2.8%)
	Iron deficiency anaemia	-	-	3	1 (2.4%)	-	-	3	1 (0.7%)
	Pancytopenia	1	1 (1.5%)	-	-	1	1 (2.9%)	2	2 (1.4%)
	Thrombocytopenia	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
Musculoskeletal and connective tissue disorders	**ALL**	**5**	**5 (7.6%)**	**2**	**2 (4.8%)**	**2**	**2 (5.9%)**	**9**	**9 (6.3%)**
	Osteoarthritis	2	2 (3%)	-	-	1	1 (2.9%)	3	3 (2.1%)
	Arthralgia	2	2 (3%)	-	-	-	-	2	2 (1.4%)
	Arthritis	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Back pain	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Chondrocalcinosis	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Myalgia	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
Hepatobiliary disorders	**ALL**	**4**	**4 (6.1%)**	**1**	**1 (2.4%)**	**2**	**2 (5.9%)**	**7**	**7 (4.9%)**
	Hepatocellular injury	2	2 (3%)	-	-	-	-	2	2 (1.4%)
	Cholecystitis	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Cholecystitis acute	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Cholecystitis chronic	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Cholelithiasis	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Cholelithiasis obstructive	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
Injury, poisoning and procedural complications	**ALL**	**3**	**3 (4.5%)**	**1**	**1 (2.4%)**	**3**	**3 (8.8%)**	**7**	**7 (4.9%)**
	Limb injury	1	1 (1.5%)	-	-	1	1 (2.9%)	2	2 (1.4%)
	Fall	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Hip fracture	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Post procedural complication	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Procedural pain	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Vascular graft occlusion	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
Gastrointestinal disorders	**ALL**	**2**	**2 (3%)**	**2**	**2 (4.8%)**	**2**	**1 (2.9%)**	**6**	**5 (3.5%)**

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
	Abdominal pain	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Anal fistula	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Intestinal obstruction	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Pancreatitis acute	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Rectal haemorrhage	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Vomiting	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
Metabolism and nutrition disorders	**ALL**	**4**	**3 (4.5%)**	**1**	**1 (2.4%)**	**1**	**1 (2.9%)**	**6**	**5 (3.5%)**
	Diabetes mellitus inadequate control	1	1 (1.5%)	1	1 (2.4%)	-	-	2	2 (1.4%)
	Folate deficiency	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Hypocalcaemia	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Hyponatraemia	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Malnutrition	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
Nervous system disorders	**ALL**	**1**	**1 (1.5%)**	**2**	**2 (4.8%)**	**3**	**2 (5.9%)**	**6**	**5 (3.5%)**
	Carotid artery stenosis	1	1 (1.5%)	-	-	2	1 (2.9%)	3	2 (1.4%)
	Axonal neuropathy	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
	Cervicobrachial syndrome	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Ulnar tunnel syndrome	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
Vascular disorders	**ALL**	**2**	**2 (3%)**	**-**	**-**	**3**	**3 (8.8%)**	**5**	**5 (3.5%)**
	Peripheral artery stenosis	-	-	-	-	2	2 (5.9%)	2	2 (1.4%)
	Arterial occlusive disease	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Haemorrhage	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Hypertension	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
Skin and subcutaneous tissue disorders	**ALL**	**-**	**-**	**-**	**-**	**4**	**3 (8.8%)**	**4**	**3 (2.1%)**
	Skin ulcer	-	-	-	-	2	1 (2.9%)	2	1 (0.7%)
	Angioedema	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Dermatitis	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
Surgical and medical procedures	**ALL**	**1**	**1 (1.5%)**	**-**	**-**	**3**	**2 (5.9%)**	**4**	**3 (2.1%)**
	Foot amputation	-	-	-	-	2	1 (2.9%)	2	1 (0.7%)
	Angioplasty	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
	Thyroidectomy	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
Investigations	**ALL**	**-**	**-**	**2**	**1 (2.4%)**	**1**	**1 (2.9%)**	**3**	**2 (1.4%)**
	Alanine aminotransferase increased	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Aspartate aminotransferase increased	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Lipase increased	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**ALL**	**1**	**1 (1.5%)**	**2**	**2 (4.8%)**	**-**	**-**	**3**	**3 (2.1%)**
	Bowen's disease	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
	Chronic myeloid leukaemia	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
	Gastrointestinal stromal tumour	-	-	1	1 (2.4%)	-	-	1	1 (0.7%)
Ear and labyrinth disorders	**ALL**	**1**	**1 (1.5%)**	**-**	**-**	**-**	**-**	**1**	**1 (0.7%)**
	Hypoacusis	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
Eye disorders	**ALL**	**1**	**1 (1.5%)**	**-**	**-**	**-**	**-**	**1**	**1 (0.7%)**

SOC AND PT		2L N=66		3L N=42		4L+ N=34		Total N=142	
		n	n(%)	n	n(%)	n	n(%)	n	n(%)
	Retinal vein occlusion	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
Immune system disorders	**ALL**	**1**	**1 (1.5%)**	**-**	**-**	**-**	**-**	**1**	**1 (0.7%)**
	Anaphylactic shock	1	1 (1.5%)	-	-	-	-	1	1 (0.7%)
Pregnancy, puerperium and perinatal conditions	**ALL**	**-**	**-**	**-**	**-**	**1**	**1 (2.9%)**	**1**	**1 (0.7%)**
	Complication of pregnancy	-	-	-	-	1	1 (2.9%)	1	1 (0.7%)

Table 15.3.6c Serious Adverse Events by System Organ Class and Preferred Term (Grade 3-4) - SAF (n=142)

Table 78: Serious Adverse Events by System Organ Class and Preferred Term (Grade 5 or missing) - SAF (n=142)

Patient No.	Date of initiation of bosutinib treatment	SOC name	PT name	CTCAE grade	Date of occurrence	Is the event serious?	Status	Date of recovery	Is it reasonably possible that the event may be related to the study medication?	Is it reasonably possible that the event may be related to a concomitant drug?	Name of the drug (1)	Action taken (1)	Name of the drug (2)	Action taken (2)
01-01	24/02/2016	Infections and infestations	Sepsis	Grade 5	10/01/2017	Yes	Subject not recovered		No	No	BOSULIF	Not applicable		.
04-09	10/10/2019	Injury, poisoning and procedural complications	Hip fracture	.	NK/NK/2021	Yes	Recovery	NK/NK/2021	No	No	BOSULIF	Not applicable	PONATINIB	No dose modification
09-10	21/09/2017	General disorders and administration site conditions	General physical health deterioration	Grade 5	01/02/2018	Yes	Subject not recovered		No	No	BOSULIF	No dose modification		.
09-14	12/11/2018	Social circumstances	Miscarriage of partner	.	UK/08/2020	Yes	Recovery	UK/08/2020	No	No	BOSULIF	Not applicable	DASATINIB	No dose modification
		Social circumstances	Pregnancy of partner	.	UK/09/2020	Yes	Recovery	UK/06/2021	No	No	BOSULIF	Not applicable	DASATINIB	No dose modification

Patient No.	Date of initiation of bosutinib treatment	SOC name	PT name	CTCAE grade	Date of occurrence	Is the event serious?	Status	Date of recovery	Is it reasonably possible that the event may be related to the study medication?	Is it reasonably possible that the event may be related to a concomitant drug?	yes, specify	Name of the drug (1)	Action taken (1)	Name of the drug (2)	Action taken (2)
13-01	26/03/2016	General disorders and site administration conditions	General physical health deterioration	Grade 5	26/07/2016	Yes	Subject not recovered		No	No			Withdrawal (temporary or permanent, or deferred administration)		.
13-04	15/03/2018	General disorders and site administration conditions	Condition aggravated	Grade 5	02/02/2020	Yes	Subject not recovered		No	No			Unknown		.
16-03	24/07/2016	General disorders and site administration conditions	Multiviceral failure	Grade 5	30/10/2018	Yes	Subject not recovered		No	No		BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.

Patient No.	Date of initiation of bosutinib treatment	SOC name	PT name	CTCAE grade	Date of occurrence	Is the event serious?	Status	Date of recovery	Is it reasonably possible that the event may be related to the study medication?	Is it reasonably possible that the event may be related to a concomitant drug?	yes, specify	Name of the drug (1)	Action taken (1)	Name of the drug (2)	Action taken (2)
16-08	30/01/2019	Infections and infestations	Pneumonia	Grade 5	18/06/2021	Yes	Subject not recovered		Yes	No			No dose modification		.
23-02	01/10/2016	General disorders and administration site conditions	General physical health deterioration	Grade 5	20/10/2016	Yes	Subject not recovered		No	No		BOSULIF	Withdrawal (temporary or permanent, or deferred administration)	PREVISCAN	Withdrawal (temporary or permanent, or deferred administration)

Listing 15.3.6d Serious Adverse Events by System Organ Class and Preferred Term (Grade 5 or missing) - SAF (n=142)

11. DISCUSSION

11.1. Key results

From October 15, 2015, to December 19, 2019, 146 patients were included in 23 centers for this non-interventional study.

Among the total set of patients, 142 were included in the safety population, while 4 patients were excluded from the SAF population (Table 5). Reasons for exclusion was that the principal investigator from center #24 decided to abandon his center's participation in the study, and so without proposing a PI replacement; thus, study data were not signed and cleaned. Three patients from the SAF population were excluded from the FAS population, which finally included 139 patients; regarding the 3 patients, we report an excessive delay in initiating treatment for one patient, and inclusion criterion #3 not complied for two patients. In the FAS population, 19 patients (13.6%) were prematurely withdrawn from the study.

Regarding baseline characteristics of patients and according to the number of previous lines of treatment, it was observed that patients were aged 62.0 ± 13.6 years in the 2L group, 62.0 ± 11.1 years in the 3L group, and 61.8 ± 15.0 years in the 4L+ group. Overall, men were more represented with a proportion of 56.1% in the FAS population. The mean BMI (kg/m²) was 28.98 ± 6.41 in the 2L group, 28.00 ± 5.40 in the 3L group, and 26.01 ± 4.59 in the 4L+ group. Finally, the ECOG scores were similar between groups, with 64 (57.1%) patients in total having a score of 0, and 48 (42.9%) patients having a score of 1.

Regarding initial diagnosis of CML, the mean time between initial diagnosis and initiation of bosutinib was 3.19 ± 4.24 years in the 2L groups, 7.37 ± 6.40 years in the 3L group, and 9.82 ± 6.44 years in the 4L+ group, and all patients were diagnosed with a chronic phase, except one patient in the 2L group, diagnosed with an accelerated phase. Bone marrow karyotype was performed in 88.5% of patients, among which 89.4% had a t(9,22) translocation rearrangement. Additionally, molecular analyses by qRT-PCR revealed that most patients had an expression of the ABL 81.2%, followed by 13.7% of patients having a BCR expression.

The main objective of this non-interventional study was to describe the use of bosutinib under real-life conditions of use to determine the proportion of patients with CP, AP or BP Ph+/- CML presenting AEs considered related to bosutinib by the participating doctor, according to the type of adverse event and grade of event.

The proportion of patients who permanently discontinued bosutinib following an AE considered related to bosutinib by the participating doctor were also described to precise the safety profile of bosutinib.

Regarding the safety characteristics of bosutinib, overall, 88% patients experienced an AE related to bosutinib, which led to a treatment change in 59.9% of the cases. Most patients (84.5%) experienced mild or moderate bosutinib-related AEs (grade 1-2), while grade 3-4 bosutinib-related AEs were reported in 31.7% of patients. Regarding grade 1-2 bosutinib-related AEs, the SOC for which the most AEs were reported was gastrointestinal disorders, with diarrhea affecting 50.7% of patients and nausea 14.1%, while grade 3-4 diarrhea was only observed in 4.2% patients. Additionally, grade 1-2 general disorders and administration site conditions AEs were also noted, affecting 22.5% of patients, as asthenia and fatigue were commonly reported (9.2% and 4.9% respectively).

Considering grade 3-4 AE, the SOC for which the most drug-related AEs were recorded was hepatobiliary disorders (9.9%), mostly hepatocellular injury (8.5%). Gastrointestinal disorders were also notable, affecting 7% of patients (including diarrhea (4.2%)). Lastly, only one patient presented with grade 5 drug-related pneumonia.

Regarding the AEs leading to permanent discontinuation of bosutinib, the design of the eCRF did not enable to differentiate when an AE led to a temporary discontinuation or a permanent discontinuation. Accordingly, it has been necessary to perform a medical review and cross-checked the eCRF forms related to discontinuation for intolerance and the AE forms for patients who discontinued permanently bosutinib, in order to identify the AEs leading to permanent discontinuation of bosutinib. The concordance between intolerance and the AEs leading to permanent discontinuation was verified according to the date of permanent discontinuation and of the occurrence of AE. For few patients a medical review and interpretation has been necessary

because of discordances in the eCRF which have not been noticed during the monitoring or the data review.

Accordingly, we observed that among the total SAF population, 63 (44.4%) patients permanently discontinued bosutinib, among who 46 (32.4%) due to AE. Indeed, 39 (27.5%) patients permanently discontinued due to bosutinib-related AE define as intolerance, 3 (2.1%) patients due to suboptimum response of bosutinib, 1 (0.7%) patient due to lack of efficacy of bosutinib and 3 (2.1%) for other reasons.

Considering AE related to bosutinib and leading to permanent discontinuation because of intolerance, most frequent were diarrhea observed in 11 (7.7%) patients, pleural effusion in 7 (4.9%) patients and hepatocellular injury observed in 7 (4.9%) patients (Table 19).

Our findings are in line with previous study which reported that bosutinib exhibited an acceptable safety profile; the most common treatment-emergent adverse event were primarily gastrointestinal adverse events (diarrhea [83-84%], nausea [45-48%], vomiting [37-38%] (Cortes, Khoury et al. 2016), which were mostly mild to moderate and typically transient.

The initial median dosage prescribed for patients in the 2L group was 200 [100; 200] (mg/day), for the 3L group it was 200 [100 , 300] (mg/day), and for the 4L+ group, it was 200 [100 , 300] (mg/day). Thus, across the entire population, the median dosage was 200 [100 , 300] (mg/day). However, the median dosage during treatment was higher, with patients in the 2L group receiving 326.20 [282.80 ; 440.40] (mg/day), those in the 3L group receiving 306.20 [270.60 ; 391.40] (mg/day), and those in the 4L+ group receiving 264.00 [201.20 ; 303.20] (mg/day). Consequently, the overall median dosage during treatment was 300.00 [252.00 ; 396.80] (mg/day). Regarding dose intensity, median dose appears to be higher in the 2L group, 207.40 [105.10 ; 311.80] %, compared to 3L group and 4L+ group with a mean dose intensity at 148.60 [100.00 ; 245.80] % and 151.60 [100.00 ; 199.20] %, respectively. Relative dose intensity was 65.24 [56.56 ; 88.08] % in the 2L group, 61.240 [54.12 ; 78.28] % in the 3L group and 52.80 [40.24 ; 60.64] % in the 4L+ group.

A majority of patients underwent dose modifications during the study, with 76.1% requiring an increase and 50% requiring a reduction. Specifically, a dose increase was observed in 52 (78.8%)

patients in the 2L group, 33 (78.6%) in the 3L group, and 23 (67.6%) in the 4L+ group. Main reason for dose increase was dose optimization, which reflects the routine practice of bosutinib administration. Indeed, in order to optimize the benefit/risk ratio of bosutinib it is recommended to increase the dose progressively. This strategy was assessed in study ({Isfort, 2023 #24}) which evaluated the efficacity and safety of initiating bosutinib at a low dose followed by an increase during the first months until the recommended dose was reached. Additionnaly, in our study loss of response was also a frequent reason for dose increase.

Conversely, a dose reduction was noted in 30 (45.5%) patients in the 2L group, 22 (52.4%) in the 3L group, and 19 (55.9%) in the 4L+ group, mostly due to AE (80.4% of the events).

Temporary discontinuation of treatment was necessary for 43.7% of patients, lasting an average of 29.4 ± 35.3 days. Although the mean duration was similar across groups, ranging from 26.8 ± 30.3 days in the 3L group to 33.1 ± 44.4 days in the 4L+ group, the median time varied, with durations of 18 (1 ; 123) days in the 2L group, 16 (1 ; 97) in the 3L group, and 7 (1 ; 160) in the 4L+ group, indicating differences in treatment discontinuation patterns according to the treatment line. The main reason for temporary discontinuation was occurrence of AE (76.5%).

Moreover, permanent discontinuation was recorded for 63 (44.4%) patients, with 30 (45.5%) in the 2L group, 21 (50%) in the 3L group, and 12 (35.3%) in the 4L+ group. The primary reasons for permanent discontinuation were intolerance for 39 (61.9%) patients and suboptimal response for 15 (23.8%) patients, while discontinuation due to disease progression or death were reported for only 2 patients each.

Overall, the median time to treatment failure was 3.29 [2.53-Not evaluable] years. At 2 year and 3 years there were 38% and 44% patients respectively, which had a treatment failure, which is consistent with previous results regarding efficacy and safety of bosutinib over a five-year period (Gambacorti-Passerini, Cortes et al. 2018).

Most patients (128/139 (92.1%)) had a hematological response to bosutinib, 127 (91.4%) patients had a complete hematological response while one (0.7%) patient had a partial response (Table 23). Considering hematological response according to bosutinib's dose, similar proportions of patients

with response have been observed regardless of the dose. Overall, the median time to hematological response was 0.24 [0.23-0.25] year. As of the data cutoff, 92% of the evaluable patients who achieved a HR still retained their response, with a median duration of HR not reached.

Overall, 18 (12.9%) patients from the FAS population had cytogenetic response, 8 (12.5%) patients had a major response in the 2L group, 6 (14.3%) patients in the 3L group, and 2 (6.1%) patients in the 4L+ group. Only 1 (1.6%) patient in the 2L group, and 1 (2.4%) in the 3L group had a minor response. Nevertheless, it is important to note that cytogenetic response was only recorded in 21 patients (15.1%) from the FAS population. Indeed, the measure of cytogenetic response required an invasive procedure to extract bone narrow, which is not performed in routine medical practice unless it is necessary. Therefore, it is difficult to conclude on the results reported in our study. However, regarding the proportion of patients having a cytogenetic response among patients which were tested, a high percentage had a cytogenetic response (85.7%).

Most patients (98/139 (70.5%)) had a cumulative molecular response, among these patients, 21 (15.1%) had a major molecular response (MMR) best response, 14 (10.1%) had a MR4 best response, 22 (15.8%) had a MR4.5 best response, 41 (29.5%) had a MR5 best response. In addition, 55.4% and 45.3% of patients reached a cumulative MR4 and MR4.5 respectively. Interestingly, only 14 (10.1%) of patients did not have a measurement of molecular response. The molecular response rate in total was 70.5% and was similar in subgroups. Considering molecular response according to bosutinib's dose, it has been observed that 56.3% of patients who received a dose ≤ 200 mg/day had a response, 74% of patients having a dose comprised between 200 and 300 mg/day had a complete response. For patients who received a dose comprised between 300 and 400 mg/day, 69.7% had a cytogenetic response. Finally, for patients who received a dose above 400 mg/day, 69% had a major response. Accordingly, the molecular response appeared to be more important with dose superior to 200 mg/day of bosutinib.

The median time to molecular response was 0.28 [0.25-0.45] year and was similar between subgroups. At 1 year, only 81% of patients reached a molecular response, and at 2 year and 3 years, there were 86% of patients who had a molecular response. The median time duration for molecular response was not reached at the end of the study, with 89% of patients still responding after 1 year of initiation of treatment, and 81% at 3 years.

According to previous studies, bosutinib induces a good significant response in patients previously treated with TKI ranging from 85% to 86% for CHR, 35% to 41% for MMR, 31% to 57% for MCyR (Cortes, Kantarjian et al. 2011, Gambacorti-Passerini, Brummendorf et al. 2014). In our study, rates of hematological and molecular response were consistent with the literature. However, due to a low proportion of cytogenetic testing we observed an inferior response rate (12.9%) compared to what is reported in the literature. When regarding the proportions of patients with cytogenetic testing however, the response rate is much higher (85.7%) and more consistent with previous studies.

The median time of PFS was not reached at the cutoff date. At 1 and 2 years, 96% and 95% of patients respectively were progression-free. Overall, 5 (3.6%) patients had a progression disease during the study: one patient from the 2L group progressed from AP to AP, 2 progressed from CP to AP, and 1 from CP to BP and one patient from 4L+ group progressed from CP to AP.

The median OS time was not reached at the cutoff date. At 1 and 2 years, 98% and 96% of patients respectively, were alive. At 3 years, 95% of patients were still alive.
Our results are in line regarding a previous phase 1/2 study evaluating the PSF and OS of patients treated by bosutinib, which found that PFS rate at 1 year was 91% and 2 years 79%, while OS was 97% at 1 year and 92% at 2 years (Cortes, Kantarjian et al. 2011). Interestingly, another study found similar results with two-year probabilities of PFS and OS at 81% and 91%, respectively (Gambacorti-Passerini, Brummendorf et al. 2014).

Treatment adherence was assessed using the Morisky score during each follow-up visit, revealing that the majority of patients demonstrated high adherence to treatment. This ranged from a minimum of 54.9% at 3 months to a maximum of 78.1% at 15 months during the 36 months of the study. However, data for 51 patients were missing at the 3-month mark, increasing to 113 missing data points at 36 months.

One of the secondary objectives of the study was to determine the safety profile of bosutinib, illustrated by AEs that occurred during treatment with bosutinib, AEs which required changes to treatment with bosutinib and biological and hematological toxicities that occurred with bosutinib.

Our results highlighted the fact that the vast majority of patient experienced at least one AE during the treatment, since 141 patients among the 142 patients of the SAF population experienced one AE. Among these patients 86 (60.6%) had at least one SAE, equally distributed regardless of the previous number of treatment line.

Moreover, 85 (59.9%) patients exhibited AE which led to treatment change, more frequently in the 4L+ group were 25 (73.5%) patients had a treatment change due to AE compared to 36 (54.5%) patients in the 2L group, and 24 (57.1%) in the 3L group.

Regarding AEs grade, most patients (140 [98.6%]) experienced an AE grade 1-2. Mainly gastrointestinal disorders observed in 113 (79.6%) patients, with diarrhea, nausea, constipation, and abdominal pain. General disorders and administration site conditions related AE were also reported in more than half of the population (53.5%) with asthenia and fatigue and peripheral oedema, as well as infection and infestations (50.7%) such as bronchitis and other infections.

Collected data showed that 88 (62%) patients experienced an AE grade 3-4. The most experienced grade 3-4 AEs were hepatobiliary disorders observed in 19 (13.4%) patients, infection and infestations observed in 17 (12%) patients, respiratory, thoracic and mediastinal disorders reported in 16 (11.3%) patients, as well as gastrointestinal disorders observed in 15 (10.6%) patients.

Rates of cross-intolerance between bosutinib and prior TKI were low as only 7 patients have a cross intolerance between bosutinib and a previous TKI treatment, suggesting that most of patients who were intolerant to previous therapy may be successfully treated with bosutinib. Pleural effusion was the most prevalent AE similarly found in bosutinib and dasatinib or imatinib. Indeed, patients 01-04, 15-05, 33-08 and 38-01 developed a pleural effusion with dasatinib therapy and similarly developed a bosutinib-related pleural effusion leading to discontinuation. Drug related pleural effusion was also observed for imatinib for patient 38-01. For patient 13-06 renal and cardiac failure occurred with Imatinib and a cardiac failure related to Bosutinib was also observed.The patient 15-05 developed a dypsnea with Dasatinib therapy and a pleural effusion with Bosutinib leading to discontinuation.

Moreover, the patient 15-02 developed diarrhea with imatinib and bosutinib leading to discontinuation, and the patient 16-05 experienced arthralgia/myalgia with nilotinib, then lower back pain with imatinib, and finally pain with bosutinib, which was leading to discontinuation.

In terms of quality of life, severity of symptoms appeared stable throughout the study for the overall population, regarding physical, emotional, social and functional well-being, which is consistent with a previous study evaluating the long-term patient-reported outcomes in patients treated with bosutinib with CML (Kantarjian, Mamolo et al. 2018). Nevertheless, the mixed model with repeated measures revealed a significant effect of visit (p-value = 0.0020) on the FACT-leukemia trial outcome index with an increased score over time; reflecting an improvement of the quality of life over time.

11.2. Limitations

Considering AEs leading to discontinuation, the major limitation of our study concerns the fact that the reporting of AE leading to discontinuation did not allow to differentiate if it was a temporary discontinuation or a permanent discontinuation. Therefore, it was not possible to identify precisely the AE leading to permanent discontinuation. For this reason, considering the date of permanent discontinuation we could provide a listing of all AE on going at that time, but we could not determine which one causes the permanent discontinuation automatically. Therefore, a medical review was performed in order to cross-check the permanent discontinuation due to intolerance and the AE which were considered for this intolerance according to the date of discontinuation, the date of AE occurrence and the medical interpretation for some patients were the relation was not obvious. Accordingly, it appears that 46 patients did permanently discontinue due to AE, among who 39 due to intolerance to bosutinib and 4 due to AE-related to bosutinib considered as suboptimum response or lack of efficacy (patient 9-19; 11-03; 16-01 and 33-01).

Regarding patients who were ticked for permanent discontinuation due to bosutinib intolerance it is important to note that patient 11-12, stopped bosutinib due to a resection syndrome of the rectum, deemed unrelated to bosutinib according to the investigator. Despite this, based on the investigator decision to report intolerance in the eCRF and the fact that no other AE for this patient was related to intolerance, we considered after the medical review to include this patient in the population with permanent discontinuation due to intolerance. For patient 16-10, the investigator reported a permanent discontinuation due to intolerance, however, no AE related could be found in the eCRF. Nonetheless, regarding the investigator decision we considered this patient in the population of patient who permanently discontinued due to intolerance but no AE related could be described in the relevant table.

Furthermore, patient 08-02 discontinued due to intolerance according to the investigator on the 26-12-2017. Regarding AEs ongoing at that date, 2 AEs were related to a discontinuation: vomiting and hepatic pain reported on the NK-12-2017 both. Nevertheless, during medical review it appears that hepatocellular injury occurred the 13-09-2017 inducing a temporary discontinuation. However, a medical review revealed hepatocellular injury occurring on 13-09-2017, leading to temporary discontinuation. Considering the resolution date of hepatocellular injury post-permanent discontinuation and the relatedness of vomiting and hepatic pain to this AE, hepatocellular injury was considered the causative AE leading to permanent discontinuation.

Regarding patient 09-10, the investigator reported a permanent discontinuation due to intolerance on the 05-06-2018, two AEs considered related to bosutinib and leading to a discontinuation by the investigator, vomiting and diarrhea reported the 04-06-2018 and the 09-02-2018 respectively and after the cross-check done by the medical team the bronchitis reported the 19-05-2018 but not considered related to bosutinib by the investigator was also considered related to permanent discontinuation. Indeed, the treatment was not resume after bronchitis, the influence of bronchitis could not then be minimized on the decision to discontinue bosutinib.

These discrepancies were not identified during monitoring or data review.

Additionally, among the 46 patients, 3 permanently discontinued due to AEs unrelated to bosutinib: patient 16-03 due to multivisceral decompensation, patient 23-02 due to adenocarcinoma, and patient 09-21 due to a non-programmed pregnancy leading to temporary discontinuation.

However, considering patient 09-21, a non-programmed pregnancy was reported the 03-06-2021 leading to a temporary discontinuation. Bosutinib was restarted in February 2022, followed by diarrhea reported on 22-02-2022, deemed treatment-related. However, the patient experienced depression in April 2022 unrelated to bosutinib, leading to discontinuation. During the medical review, it was concluded that the non-programmed pregnancy was the primary AE leading to bosutinib discontinuation.

These discrepancies underscore the limitations of our study, necessitating medical interpretation to analyze AEs leading to permanent bosutinib discontinuation, potentially introducing bias into the results.

Participating doctors have been recruited from a baseline survey representative of different centres specializing in management of CML in France. However, the voluntary characteristic of participation of doctors in the study is a usual selection bias for this type of study. Therefore, the comparison of the two populations of doctors (those accepting and those refusing to participate) would have been beneficial.

It is also noteworthy that we observed few patients having a cytogenetic testing. Cytogenetic testing is the examination of chromosome abnormalities which is done on bone narrow and as such required an invasive procedure not performed in medical routine. Therefore, our results considering cytogenetic response do not allow us to conclude about the efficacy on bosutinib on this response.

Efficacy results about response to bosutinib may have been confounded by the fact that data of patients with newly attained response and maintained from baseline were pooled and analysed without distinction. Indeed, in previous studies the probability to maintain or improve the response appeared to be higher than the probability to obtain a response (Garcia-Gutierrez, Martinez-Trillos et al. 2015, Gambacorti-Passerini, Cortes et al. 2018, Garcia-Gutierrez, Milojkovic et al. 2019).

Because this study was an observational study, the dosage and changes in dosage of bosutinib were not controlled; therefore, analyses of effectiveness and safety of bosutinib vary according to the individual approach applied to all patients; indeed, treatment protocols are adapted to each individual. Thus, it would be of interest to integrate as a core parameter the dosage of bosutinib administered in order to analyse effectiveness and safety.

Additionally, while evaluation of quality has been assessed all along the study for patients under treatment, numerous missing data have been noted, therefore it could have influenced the results. Similarly, for the assessment of biological and hematological parameters while most data were available for early study visits, it became relatively sparse during the course of the study, as such results could not be fully analysed as planned.

11.3. Interpretation

Our results showed that drug-related AEs were mostly mild or moderate and mainly gastrointestinal (diarrhea, nausea, vomiting), similar to what was recorded in phase I/II/III trials (Cortes, Kantarjian et al. 2011, Gambacorti-Passerini, Brummendorf et al. 2014, Cortes, Khoury et al. 2016, Gambacorti-Passerini, Cortes et al. 2018). Overall, 27.5% of patients had to discontinue due to drug-related AEs intolerance, mainly diarrhea, pleural effusion, and hepatocellular injury. Only 1 patient had a grade 5 drug-related AE, confirming the safety of bosutinib. Additionally, the majority of patients demonstrated high adherence to treatment and 54.2% patients were still treated at the end of the study reflecting a good tolerability of bosutinib. Rates of cross-intolerance between bosutinib and prior TKI were low, suggesting that most patients intolerant to previous therapy may be successfully treated with bosutinib.

Moreover, the majority of patients exhibited a hematological and a molecular response in the early phase of the treatment which lasted, as reflected by 92% and 81% of patients, respectively, still responding at the end of the study. However, we could not conclude on cytogenetic response due to the low percentage of tested patients. Nevertheless, when looking at the proportion of patient who had a cytogenetic response among those who were tested for cytogenetic response, we observed a high percentage of response (85.7%), which is more consistent with the literature. Moreover, considering the proportion of major molecular response, one could suggest that patient having major

molecular response, which correspond to a decrease of at least 3-log of BCR-ACL, had also cytogenetic response. Indeed, molecular response measures the level of BCR-ACL transcript and is an indicator of the number of circulating leukemic cells. MMR is then considered as the most sensitive method of testing minimal residual disease in CML patients.

Regarding PFS and OS, at 1 and 2 years, 96% and 95% of patients respectively were progression-free and 98% and 96% of patients respectively, were alive. The median PFS and OS time were not reached at the cut-off date. Thus, our study confirmed the efficacy of bosutinib.

Taken together, our data confirmed previous findings showing that bosutinib is effective and tolerable in patients with chronic phase TKI-resistant or intolerant CML.

11.4. Generalizability

This study is an observational study which included patients with chronic myeloid leukemia previously treated with TKI, the aim was to evaluate the safety and efficacy of bosutinib in real condition of use. Our results thus are extracted from the overall population treated with bosutinib in the usual standard of care. Therefore, the result exhibits a high external validity considering data source and characteristic of the study population for patients with CML resistant or intolerant to previous TKI.

12. OTHER INFORMATION

Not applicable

13. CONCLUSIONS

Taken together, our data confirmed that bosutinib demonstrates durable efficacy and a toxicity profile similar to previous bosutinib studies in CP CML patients resistant/intolerant to multiple TKIs in the real condition of use.

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15. LIST OF SOURCE TABLES AND FIGURES

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APPENDIX 1. SIGNATURES

NI Study Report signature page signed by all parties with DocuSign provided into a separate document.

APPENDIX 2.PROTOCOL

NON-INTERVENTIONAL (NI) STUDY PROTOCOL

PASS information

Title	BOSEVAL: An observational study - Evaluation of efficacy and safety of Bosulif® under real life conditions of use
Protocol number	B1871047
Identifier of protocol version	*Version 2.0*
Date	*15-FEB-2019*
EU Post Authorization Study (PAS) registration number	ENCEPP/SDPP/8231
Active substance	*Bosutinib*
Medicinal product	*Bosulif®*
Product reference	**BOSULIF 100 mg** film-coated tablet, 28 tablets per box, no. 34009 269 935 2 8 (EU no. 1/13/818/001)

	BOSULIF 400 mg film-coated tablet, 28 tablets per box, no. 34009 301 462 2 4 (EU no. 1/13/818/006) **BOSULIF 500 mg** film-coated tablet, 28 tablets per box, no. 34009 269 937 5 7 (EU no. 1/13/818/003)
Procedure number	*EMA/H/C/002373*
Marketing authorization holder (MAH)	Pfizer Europe MA EEIG Boulevard de la Plaine 17 1050 Brussels, Belgium
Common PASS	*No*
Question and study objectives	This non-interventional study is designed to evaluate safety, efficacy, as well as modalities of use of Bosulif® under real life conditions of use.
Country of study	FRANCE
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LIST OF ABBREVIATIONS

Abbreviation	Definition
(e)CRF	(Electronic) Case Report Form
(S)AE	(Serious) Adverse Events
ANSM	French National Agency for Medicines and Health Products Safety
AP	Accelerated phase
BP	Blast phase
BCR-ABL	Breakpoint Cluster Region – Abelson
CCTIRS	Consultative Committee for Processing of Information in Field of Scientific research
CI	Confidence interval
CML	Chronic Myeloid Leukemia
CNIL	National Commission on Data Processing and Freedoms
CP	Chronic phase
CPP	Ethics Committee
CRA	Clinical Research Associate
ECOG	Eastern Cooperative Oncology Group
ELN	European Leukemia Net
EMA	European Medicines Agency
ENCEPP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
FACT-leu	Functional Assessment of Cancer Therapy – Leukemia
FISH	Fluorescence In Situ Hybridization
FPFV	First Patient First Visit
GPP	Good Pharmacoepidemiologic Practice
GVP	Guidelines on good pharmacovigilance practices
ICN	Information and Consent Note
IFNα	Interferon alpha
ISEP	International Society for Pharmacoepidemiology
LPLV	Last Patient Last Visit

MA	Marketing authorization
MCR-C/P/m	Major Cytological Response - Complete/Partial/Minor
MHR-C/P	Major Hematological Response - Complete/Partial
MMR-C/P	Major Molecular Response - Complete/Partial
NMC	National Medical Council
PASS	Post Authorization Safety Study
Ph-	Philadelphia chromosome negative
Ph+	Philadelphia chromosome positive
Ph1	Philadelphia chromosome
PHC	Public Health Code
PV	Pharmacovigilance
QC	Quality Control
RT-PCR	Reverse Transcriptase Polymerase Chain Reaction
SmPC	Summary of Product Characteristics
TKI	Tyrosine Kinase Inhibitor
WHO	World Health Organization
WMA	World Medical Association

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SYNOPSIS

Title	BOSEVAL: An observational study - Evaluation of efficacy and safety of Bosulif® under real life conditions of use
Identifier of protocol version	*Version 2.0*
Date	*15-FEB-2019*
RATIONALE:	In spite of recent advances in treatment and management of patients with chronic myeloid leukemia (CML), an important unmet medical need persists for many patients who are resistant or intolerant to one or more tyrosine kinase inhibitors (TKI). Treatment with bosutinib offers an additional alternative for patients with CML resistant or intolerant to one or more previous therapies with TKI. In light of the availability of several targeted therapies for treatment of CML, each of which has a specific safety and tolerability profile, it is important to evaluate the efficacy, safety and modalities for use of these treatments under real-life conditions in France. This non-interventional study will make it possible to obtain data under real-life conditions of use of bosutinib in treatment of CML (all phases combined) in patients previously treated with one or more TKI and for whom imatinib, dasatinib or nilotinib are not considered as appropriate treatments.
OBJECTIVES:	**Primary objectives:**

	- To determine the percentage of patients with chronic phase (CP) Ph+/- CML or blast phase CML presenting with AE considered related to bosutinib by the participating doctor. - To evaluate the percentage of patients who permanently discontinued bosutinib after an AE considered related to bosutinib by the participating doctor. **Secondary objectives:** - To determine the safety profile of bosutinib. - To evaluate adherence of patients to treatment with bosutinib. - To evaluate quality of life of patients treated with bosutinib. - To describe modalities of treatment with bosutinib under real life conditions of use. - To evaluate the efficacy of treatment with bosutinib. - To describe the hematological, cytogenetic and molecular responses. - To describe the characteristics of patients treated with bosutinib. - To evaluate cross intolerance between bosutinib and previously prescribed tyrosine kinase inhibitors.
Study Design	Non-interventional observational multicentric prospective study not affecting the patient's medical care.
POPULATION CONCERNED:	**Criteria for inclusion:** • Male or female patient 18 years of age or older;

	• Patient with Philadelphia chromosome positive or negative CML, or BCR-ABL positive, chronic, accelerated or blast phase; • Patient resistant or intolerant to previous therapy with a TKI for CP, AP or BP CML other than bosutinib; • Patient initiating bosutinib for treatment of CP, AP or BP Ph+/- CML, at the end of the inclusion visit or during the month preceding it; • Patient who has been informed that a method of contraception must be used if a risk of pregnancy exists; • Patient who has been informed about the study and who signed his or her consent form. Criteria for non-inclusion: • *Patient with Philadelphia chromosome negative CML, BRC-ABL negative chronic, accelerated or blast phase CML.* • *Patient recently diagnosed with CML and who has not received previous treatment with TKI;* • *Patient currently treated with a treatment other than bosutinib* • *Patient of childbearing potential not using a method of contraception;* • *Patient treated in the setting of an interventional study for another disease (outside of follow-up period);*

	• *Patient who refuses computer processing of his/her medical data.*
NATURE AND DURATION OF STUDY	This is a national, observational, descriptive, prospective, multi-centre study conducted in Metropolitan France in adult patients treated for chronic phase, accelerated or blast phase Philadelphia chromosome positive (Ph+/-) CML, previously treated with one or more TKIs and for whom imatinib, dasatinib or nilotinib are not considered as appropriate treatments. The study will be conducted in all centres involved in management of CML, i.e. about twenty (20) centres are expected. The study will be offered to all patients who satisfy criteria for eligibility up to the end of the recruitment period. Eligible patients but not included in the study will be recorded in a non-inclusion registry. Patients will be followed prospectively throughout the duration of the study (3-year follow-up) starting from their inclusion in the study. Follow-up data will be collected at follow-up visits conducted in the setting of usual management, estimated at every 3 months independently of discontinuations, changes or discontinuations of treatment possibly implemented. Therapeutic management of the patient will not be changed by participation in the study.
ORIGIN AND NATURE OF DATA COLLECTED	Patients will undergo collection of medical data indirectly by name at inclusion and during follow-up. Data collection will involve the following information: - Compliance with criteria for inclusion and non-inclusion

	- Demographic characteristics (year of birth, gender, weight, height, ECOG performance status) - Description of CML (date of diagnosis and phase of CML at time of diagnosis, tests performed for diagnosis) - History of therapeutic management: Descriptions of previous treatments of CML (type, dose, dosage, duration; better response to previous treatment; reasons for change in lines of treatment; type and grade of AEs which resulted in change of the previous line of treatment, better response obtained) - Characteristics of patients at time of initiation of treatment with bosutinib: comorbidities and previous conditions, performance status, concomitant treatments - Biochemistry and hematological assessments (at time of inclusion and follow-up) - Description of CML at time of initiation of bosutinib (phase at initiation, responses to treatments and types of tests performed) - Description of initiation of treatment with bosutinib (date of initiation, dose, dosage) - Description of changes to treatments (bosutinib: changes to dose or dosage, temporary or permanent discontinuation of treatment; change to concomitant treatments) - Safety and tolerability and management of toxicities related to bosutinib (concomitant treatments, additional corrective medical measures) - Hematological, cytogenetic and molecular tests performed for monitoring of response to treatment

	- Compliance with treatment - Quality of life
Number of patients	Since CML is a rare disease, a minimum number of patients is not expected. Therefore, in this context about 100 patients included in the study appears to be a reasonable objective, which will make it possible to have acceptable precision for estimates measured.
DATA ANALYSIS	All tests will be performed with a type 1 error α = 5%. A descriptive analysis of qualitative and ordinal variables will consist of the sample size and frequency of each modality with its 95% confidence interval (CI). Quantitative variables will be described for the overall population and for each cohort (chronic phase, accelerated phase, blast phase) of patients analyzed, in terms of sample size, mean and medium, standard deviation (SD), confidence interval, as well as number of missing data. An estimate of progression-free survival (PFS) and of overall survival (OS) will be measured by the Kaplan-Meier method. The survival function S(t) will be the probability that the event of interest (progression or death respectively) does not occur before date t. The percent survival will be estimated and described in each of the cohorts of interest. Data will be evaluated separately for patients presenting with chronic phase, accelerated phase or blast phase Philadelphia chromosome +/- CML and depending on treatment line. Interim analyses will be performed if necessary.

AMENDMENTS AND UPDATES

Amendment number	Date	Section(s) of protocol changed	Summary of amendment(s)	Reason
1	22-JAN-2019	Liste 2. LIST OF ABBREVIATIONS 3. PARTIES RESPONSABLES 4. RÉSUMÉ 6. ÉVÉNEMENTS IMPORTANTS 9.1. Schéma de l'étude 9.2.1. Critères d'inclusion 9.4.1. Données patient 9.7. Analyse des données 9.8. Contrôle qualité 11. PRISE EN CHARGE ET NOTIFICATION DES ÉVÉNEMENTS INDÉSIRABLES / DES EFFETS INDÉSIRABLES	The amendment has been written in order to include Ph(-) patients in the analysis. To specify criteria for inclusion in order to facilitate understanding by the investigators and the Clinical Research Associateds. The inclusion period has been extended by 24 months. Update of the CRF and precision of data following on-site monitoring. Update of all documents relating to the study following effective application of the GDPR law. Update the AEM form.	

IMPORTANT EVENTS

Table 1: Provisional schedule

Important event	Planned date
Conduct of evaluation of feasibility	*December 2014 – January 2015*
Submission of the study to the CNOM (National Medical Council)	*23-DEC-2014*
Authorization of the CNIL	*22-JUL-2015*
Start of data collection	*22-OCT-2015*
End of data collection	*DEC 2019*
Recording in the EU PAS registry	*November 2014*
Study final report	*DEC 2023*

1. RATIONALE AND GENERAL CONSIDERATIONS

1.1. Chronic myeloid leukemia

Chronic myeloid leukemia (CML) is a malignant hematological disease which belongs to the group of myeloproliferative syndromes (or myeloproliferative neoplasia according to WHO classification 2008 [1]). This hematologic disease is a rare disease, with 600 to 700 new cases per year (the incidence in France is estimated at 1 or 2 cases per 100,000 persons, and increasing with age) [2], accounting for

15% to 20% of all cases of leukemia [3]. Mean age at time of diagnosis is 54 years and the disease affects 1.4 males vs. 1 female patient. The prevalence, on the order of 6000 to 7000 patients in France, is on the increase because of a frank decrease in mortality rate, at least during the first 6 years after the diagnosis [2].

CML results from a specific chromosomal anomaly which occurs in hematopoietic stem cells, although the principal cause of this anomaly is not yet understood. It is characterized by the presence of a chromosomal marker in hematopoietic cells, the Philadelphia chromosome (Ph1 chromosome), which can be detected in 95% of patients with CML [4]. The chimeric protein BCR-ABL (Breakpoint Cluster Region – Abelson), resulting from translocation t(9; 22) at the origin of the Philadelphia chromosome positive (Ph+), has a high tyrosine kinase activity responsible for leukemic transformation by resulting in excessive and persistent production of white blood cells.

The disease, referred to as chronic, develops gradually and evolves slowly in three successive phases, becoming increasingly resistant to treatments with progression of disease: chronic phase (CP CML), accelerated phase (AP CML) and blast phase (blast crisis) (BP CML). The majority of patients are diagnosed during the chronic phase. Without treatment, patients in chronic phase CML will progress to the accelerated phase in 4 to 6 years. Patients diagnosed during the accelerated phase have a life expectancy estimated at less than 12 months in the absence of treatment. Following the blast phase, patients live on average 2 to 4 months if they are not treated [4].

1.2. *Therapeutic management of CML*

Management of CML has appreciably improved over the last 20 years, in particular since introduction of the oral tyrosine kinase inhibitors BCR-ABL, more than a decade ago. Before the introduction of targeted therapies – tyrosine kinase inhibitors (TKI) – median survival of patients with CML was estimated at 6 years [5].

Based on results of the phase III study entitled “IRIS” (International Randomized Interferon versus STI571) published in 2003, imatinib (Glivec®, Novartis, 2001 [6]), the first TKI marketed for treatment of CML in 2001, quickly replaced interferon alpha (IFNα) as the 1st line treatment of reference of CML, whether in chronic phase (CP), accelerated phase (AP) or blast phase (BP) with a progression-free

survival rate to accelerated phase of 83% at 7 years, and an overall survival rate of 88% during the same period [7].

However, imatinib is commonly associated with a certain number of toxicities and resistance. After 8 years follow-up in the IRIS study, only 55% of patients randomized to the imatinib-treatment arm were still under treatment, with discontinuations related to a lack of efficacy (17%), a loss of complete cytogenetic response (15%) or intolerance to imatinib (7%) [8, 9].

Second generation TKIs such as dasatinib (Spyrcel®, Bristol-Myers Squibb, 2006 [10]) and nilotinib (Tasigna®, Novartis, 2007 [11]) subsequently have been developed for 2nd line treatment of CML in patients intolerant or resistant to imatinib. Dasatinib obtained marketing authorization (MA) as 2nd line treatment for all phases of CML: chronic, accelerated and blast phase. Nilotinib obtained MA as 2nd line treatment for patients in chronic and accelerated phase of CML. These two therapies have recently obtained MA as 1st line treatment of chronic phase CML. In France, only nilotinib (chronic phase) and imatinib (all phases) are reimbursed as 1st line treatment [*12]. Like imatinib, resistance or intolerance exist to these treatments, which require changes to treatments [13, 14].*

In spite of recent advances in treatment and management of patients who have CML, an important unmet medical need persists for many patients who are resistant or intolerant to one or more TKI. Approximately one third of CML patients treated with imatinib do not achieve an optimum response to treatment [15]. Among patients who are resistant or intolerant to imatinib and who require treatment with dasatinib or nilotinib, approximately half do not maintain a durable cytogenetic response. A clinical study evaluating 2nd line treatment with dasatinib (n=91) or nilotinib (n=25) in 119 patients with CP CML for whom treatment with imatinib has failed, showed that 52% of patients discontinued treatment following development of resistance or intolerance [16, 17].

Treatment with bosutinib (Bosulif®, Pfizer, 2013 [18]) offers an additional alternative for patients with CML (all phases) resistant or intolerant to one or more previous therapies with TKI, and in whom imatinib, nilotinib and dasatinib are not considered as appropriate treatments.

1.3. Bosutinib (Bosulif ®, Pfizer)

*Bosutinib is a TKI indicated in treatment of adult patients with Philadelphia chromosome positive CML (Ph+ CML) in chronic phase (CP), in accelerated phase (AP) or in blast phase (BP), previously treated with one or more TKI and for whom imatinib, dasatinib and nilotinib are not considered as appropriate treatments. Bosutinib has demonstrated its activity against the majority of mutations in the BCR/ABL domain resistant to imatinib, to dasatinib or to nilotinib, except for the T315I mutation. The European Medicines Agency (EMA) has granted marketing authorization, valid in the entire European Union, for Bosulif® in this indication on 27 March 2013 in the category of an orphan medicinal product [19]. This approval is based on results of a single-arm, phase II, multicentre clinical trial conducted on 570 patients resistant or intolerant to a previous targeted therapy with TKI (Study 200). Efficacy data observed are listed below [*Table 1*] according to phase of disease and treatment lines [20, 21]:*

Table 1: Efficacy results of study 200 [20]

Phase	***Treatments***	***CHR***	***MCyR***	***CCyR***
CP CML (n=288)	*Imatinib 1st line Bosutinib 2nd line*	*86%*	*53% (at 24 weeks: 31%)*	*41%*
CP CML (n=118)	*Several TKI and then bosutinib*	*73%*	*32%*	*24%*
AP CML (n=76)	*One or more TKI and then bosutinib*	*35%*	*35%*	*25%*
BP CML (n=76)	*One or more TKI and then bosutinib*	*15%*	*30%*	*64%*

Concerning the safety profile of bosutinib, the most common grade 1 or 2 non-hematological adverse events (AE) during this trial were diarrhea, nausea, vomiting and rash. 8% and 4% of patients had grade 3 / 4 diarrhea respectively. The most common grade 3 / 4 hematological adverse events were: thrombocytopenia (25%), neutropenia (19%), and anaemia (8%). In addition, bosutinib was associated with a low impact on prolongation of the QT interval, a low incidence of pleural effusions, muscle

cramps, musculoskeletal events or cardiac toxicities which can be observed with other TKIs. Approximately 20% of patients in this trial permanently discontinued their treatment with bosutinib following an AE [20, 21, 13]. Data from this study suggest that bosutinib has a favourable efficacy and safety profile in patients with CML (all phases) pre-treated with one or more TKIs.

In addition, cross-intolerance between bosutinib and a previous targeted therapy with TKI in 570 patients included in the study 200 suggest that patients intolerant to previous treatment with imatinib, dasatinib or nilotinib did not present the same toxicities in treatment with bosutinib. In this study, cross-hematological intolerance between treatment with bosutinib and a previous therapy with imatinib or dasatinib was of relatively low incidence in such patients, although many patients presented with the same grade 3 / 4 cytopenia adverse events during treatment with Bosulif®. Non-hematological cross-intolerance, including diarrhea, remained rare. In conclusion, these results suggest that, a CML patient intolerant to previous treatment with a TKI, will not necessarily have a recurrence or enhancement of this intolerance during treatment with Bosulif®. Generally, cross-intolerance between imatinib, dasatinib or nilotinib and bosutinib seems low [17].

*In 2006, in 2009 and more recently in 2013, the European Leukemia Net (ELN) group developed a series of basic definitions and recommendations which guide the diagnosis, the treatment approach and the follow-up that is appropriate to adopt for patients depending on progression of the disease [10]. Monitoring of response to treatment, successively characterized by a hematological response, a cytogenetic response and then a molecular response should be performed regularly in order to set up appropriate management. Blood sample collection, as well as bone marrow samples collected at regular intervals make it possible to monitor the course of the white blood cell count, the number of cells that are carriers of the Philadelphia chromosome and the BCR-ABL load [*Table 2*]. Concomitantly, regular consultations with a hematologist and a clinical examination that he/she performs enable to control the patient's overall health condition.*

Table 2 – Diagnostic tests and monitoring of response to treatment (ELN 2013)

Type of response	***Diagnostic test***	***Type of sample***	***Monitoring period***

HR	*Blood cell count*	*Blood sample*	*At time of diagnosis, and then every 2 weeks up to obtainment of confirmed CHR, and then at least every 3 months or as needed.*
CyR	*FISH*	*Bone marrow blood*	*At time of diagnosis, at 3 months, at 6 months and at 12 months up to obtainment of a CCyR, and then every 12 months.* *The karyotype can be replaced with FISH (in blood) only with the CCyR is reached.*
	Karyotype	*Bone marrow*	
MR	*RT-PCR*	*Blood sample*	*At time of diagnosis, and then every 3 months up to obtainment of an MMR, and then every 3 to 6 months.*

1.4. *Study rationale*

The evolution of treatments and management of patients with CML have made it a treatable chronic disease associated with possible functional cure. In the same capacity as choice of 1st line treatment, the choice of the treatment sequence should take into account previous lines of therapy, comorbidities and individual preferences.

In light of the availability of several targeted therapies for treatment of CP, AP or BC Ph+/CML, each with their own specific safety of use and tolerability profiles and their own concomitant mechanisms of resistance, it is important to evaluate the efficacy, safety, cross intolerance and current modalities for use (dose adjustment, temporary discontinuations, permanent discontinuations of treatment) of these treatments under real life conditions of use in France.

Adherence of patients to their treatment is essential in order to maintain the response to treatment. For the purpose of optimizing adherence to treatment, it is also important to evaluate the strategies used in clinical practice in terms of therapeutic management and management of adverse events related to treatment.

This study will make it possible to obtain data on the real-life conditions of use of bosutinib in treatment of CP, AP or BP Ph+/- CML, in patients previously treated with one or more TKIs and for whom imatinib, dasatinib and nilotinib are not considered as appropriate treatments.

This non-interventional study is designed as a PASS (Post-Authorization Safety Study) and it is conducted voluntarily by Pfizer.

2. STUDY QUESTION AND OBJECTIVES

This observational study, whose primary objective is to evaluate the safety and the rate of discontinuation of treatment because of intolerance, is going to make it possible to describe management of adverse events (dose adjustment, temporary discontinuation, permanent discontinuation of treatment) under real life conditions of use in France.

2.1. *Primary objectives*

Under real life conditions of use:

- *To determine the proportion of patients with CP, AP or BP Ph+/- CML presenting with AEs considered related to bosutinib by the participating doctor according to:*
    - *type of adverse event;*
    - *grade of event: 1, 2, 3, 4 or 3/4.*
- *To evaluate the proportion of patients who permanently discontinued bosutinib following an AE considered related to bosutinib by the participating doctor.*

2.2. *Secondary objectives*

Under real life conditions of use:

- *To determine the safety profile of bosutinib: AEs that occurred during treatment with bosutinib, AEs which required changes to treatment with bosutinib, biological and hematological toxicities that occurred with bosutinib.*
- *To evaluate adherence of patients to treatment of bosutinib, with the aid of a self-questionnaire completed by patients (Morisky Questionnaire).*

- *To evaluate quality of life of patients treated with bosutinib, with a self-questionnaire completed by patients (FACT-leu version 4 - Questionnaire specific for leukemia)*
- *To describe the modalities of treatment with bosutinib under real life conditions of use (dose adjustment and reason for adjustment, dose intensity, relative dose intensity; duration of treatment, temporary discontinuations/permanent discontinuations and reasons for such discontinuations).*
- *To evaluate the cumulative response rates: hematological (PHR/CHR), cytogenetic (CCyR / MCyR/ PCyR) and molecular response (MMR/CMR).*
- *To evaluate efficacy of treatment with bosutinib:*
    - *Progression-free survival at 1, 2 and 3 years of patients treated with bosutinib*
    - *Overall survival (OS) at 1, 2 and 3 years in patients treated with bosutinib*
    - *The percent transformation to AP/BC*
- *To describe the modalities of hematological, cytogenetic and molecular responses: median time to occurrence of response, median duration of response, type of response according to dose.*
- *To describe characteristics of patients treated with bosutinib (demographic characteristics; previous medical conditions, comorbidities; duration between time of diagnosis and initiation of treatment; previous treatments and better response under these treatments; duration of previous treatments, reasons for discontinuation of previous treatments; the last hematological, cytogenetic or molecular responses known).*
- *To evaluate cross intolerance between bosutinib and tyrosine kinase inhibitors prescribed previously.*

3. STUDY METHODS

This non-interventional study protocol has been submitted to an internal validation committee in conformity with Pfizer standard procedures.

3.1. *Study design*

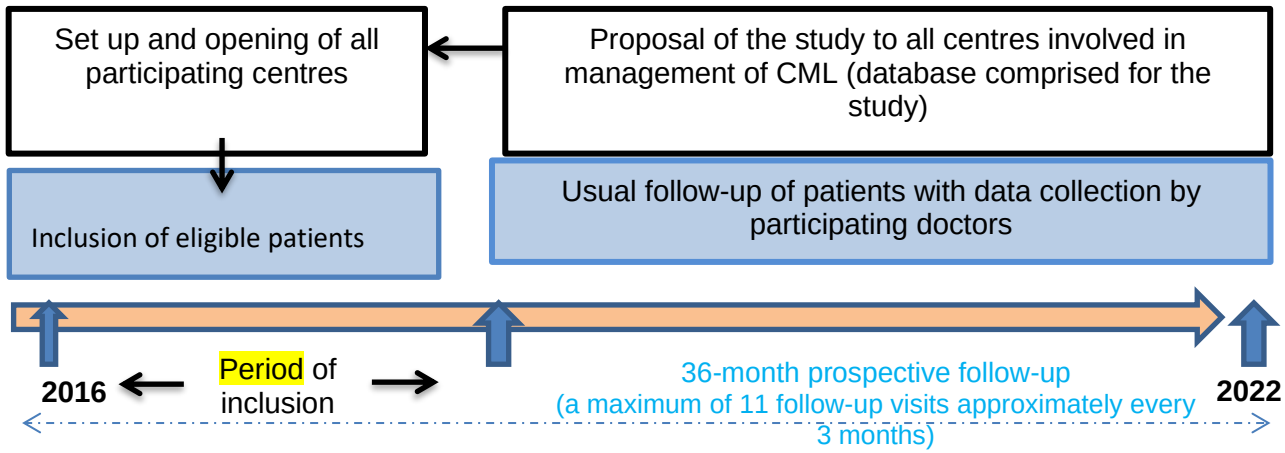
This is a national, observational, descriptive, prospective, multicentre study conducted in metropolitan France in adult patients treated for accelerated or blast phase Philadelphia chromosome positive chronic myeloid leukemia, previously treated with one or more TKIs and for whom imatinib, nilotinib and dasatinib are not considered as appropriate treatments. The study will be conducted in all centres involved in management of CML, i.e. about twenty (20) in expected centres.

The study will be offered to the totality of patients who satisfy criteria for inclusion and for non-inclusion up to the end of the inclusion period defined as 4 years. About one hundred (100) patients included are expected in the study. Therapeutic management of a patient will not be changed by participation in the study and will depend on decisions taken by doctors in agreement with current international recommendations (European Leukemia Net, ELN network [13]) (see paragraph 7.3).

Patients will be followed prospectively over a 3-year period starting with their inclusion in the study. The inclusion visit will be performed at time of inclusion of the patient in the study, after which the patient has been informed and has accepted to participate by signing the consent form. Follow-up visits will be performed after usual consultation, estimated at about every 3 months. No visit or additional examination will be requested by the protocol: modalities for follow-up and treatment will be left up to the entire judgement of the participating doctor. Data will be recorded during the 3 years of the patient's participation, except in case of withdrawal of consent, death of a patient or termination of the study before its planned end.

Total duration of the study is estimated at 7 years with an inclusion period of 4 years and a follow-up period of 3 years (see Figure 1). Throughout the study, at least one monitoring visit per year will be performed.

Figure 13 – Overall study flowchart



3.2. Context

This study, conducted in metropolitan France, will include patients who satisfy eligibility criteria defined below.

Eligible patients but not included in the study will be reported in a registry of non-inclusion with a minimum collection of information (see 9.4.1.7 Registry of non-inclusion).

3.2.1. Criteria for inclusion

Patients must satisfy all of the following criteria for inclusion in order to be eligible.

- Male or female patient 18 years of age or older;
- Patient with BCR-ABL Philadelphia chromosome positive or negative CML, in chronic, accelerated or blast phase;
- Patient resistant or intolerant to previous therapy with TKI for CP, AP or CB CML other than bosutinib;
- Patient initiating treatment with bosutinib for treatment of CP, AP or BP phase Ph+ / - CML at the end of the inclusion visit or during the one monthprior to it;
- Patient who has been informed that a method of contraception must be used if a risk of pregnancy exists.

- Patients who have been informed about the study and who signed the informed consent form.

3.2.2. Criteria for non-inclusion

Patients who satisfy one of the following criteria will not be included in the study:

- *Patient with chronic, accelerated or blast phase BRC-ABL Philadelphia chromosome negative CML;*
- *Patient recently diagnosed with CML and who has not received previous treatment with a TKI;*
- *Patient currently treated with a treatment other than bosutinib;*
- *Patient of childbearing potential not using a method of contraception;*
- *Patient treated in the setting of an interventional study for another disease (outside of follow-up period);*
- *Patient who refuses computer processing of his/her medical data.*

3.3. Variables

Patients will be identified indirectly via a unique number in the study (the centre no., patient no. pair).

The following "patient" data will be collected in the setting of the study at the usual consultation of patients in the centres.

Data	Role	Source
Compliance with criteria for inclusion and non-inclusion	Baseline characteristics	Inclusion visit

Demographic characteristics (year of birth, gender, weight, height, ECOG performance status)	Baseline characteristics	Inclusion visit
Diagnosis of CML (date of diagnosis, phase of CML at time of diagnosis, tests performed for diagnosis)	Baseline characteristics	Inclusion visit
Transcription of BCR-ABL gene at time of diagnosis	Baseline characteristics	Inclusion visit
Previous treatments of CML (type, dose, dosage, duration of previous treatment)	Baseline characteristics	Inclusion visit
Best response to previous treatments	Baseline characteristics	Inclusion visit
Reasons for change of previous treatments (if discontinuation for toxicity, description of the AE: type and grade)	Baseline characteristics	Inclusion visit
Phase of CML in the estimate of the participating doctor, at time of initiation of treatment with bosutinib	Baseline characteristics	Inclusion visit Follow-up visit
Evolution of mutational profile of BCR-ABL gene at time of initiation of treatment with bosutinib	Baseline characteristics	Inclusion visit Follow-up visit
Concomitant treatments at time of inclusion in the setting of management of CML	Baseline characteristics	Inclusion visit
Biological and hematological assessment data	Baseline characteristics Evaluation end point	Inclusion visit Follow-up visit
Hematological, cytogenetic and molecular response at time of inclusion and results	Baseline characteristics	Inclusion visit
Description of initiation of treatment with bosutinib (date of initiation, dose, dosage)	Baseline characteristics	Inclusion visit
Change to concomitant treatments in the setting of management of CML	Evaluation end point	Inclusion visit Follow-up visit
Description of treatment with bosutinib (changes to dose or dosage, temporary or permanent discontinuations of treatment)	Evaluation end point	Follow-up visit
Safety in treatment with bosutinib	Evaluation end point	Follow-up visit
Management of toxicities related to bosutinib (concomitant treatments, additional corrective medical measures)	Evaluation end point	Follow-up visit

Hematologic, cytogenetic and molecular tests performed for monitoring of response to treatment (type and frequency of monitoring, results of tests)	Evaluation end point	Follow-up visit
Compliance with treatment with bosutinib (Morisky Questionnaire) *	Evaluation end point	Follow-up visit
Quality of life (FACT-leu_v4)*	Baseline characteristics Evaluation end point	Inclusion visit Follow-up visit
Patient status and date of last news (date of death if applicable)	Evaluation end point	End of study
Last hematological, cytogenetic and molecular responses known	Evaluation end point	End of study
Status of treatment with bosutinib	Evaluation end point	End of study

* Morisky medication adherence scale and fact leu self-questionnaire are intended solely for patients under treatment with bosutinib.

3.4. Sources of data

A case report form (CRF) will be used for recording data. In the setting of this protocol, the CRFs are the reference for collection of medical data in electronic format or in paper format. Data will be collected according to two methods:

- By doctors in an electronic case report form (eCRF),
- By patients in paper format questionnaires.

Questionnaires collected at the different times of measurement are:

- At time of inclusion of patients: a questionnaire at inclusion competed by the doctors; questionnaires on compliance and quality of life completed by patients
- During follow-up of patients: a questionnaire on follow-up completed by the doctor; questionnaires on compliance and quality of life completed by patients
- In case of a premature end of study: end of study questionnaire completed by the doctor for patients lost to follow-up and/or withdrawal of consent.

3.4.1. *Patient data*

Social and medical data collected will be obtained from patients' medical dossiers at follow-up visits usually performed in centres in the setting of routine management of the patient, estimated at every 3 months in the setting of evaluation of response to treatment.

Patients will also be asked to complete questionnaires on measurement of compliance with treatment, the Morisky medication adherence scale (completed at all follow-up visits, estimated at every 3 months) and measurement of quality of life, the FACT-leu questionnaire version 4 (completed only at visits corresponding to months *M0, M3, M6, M12, M18, M24 and M36) in paper format, that they will complete on site and will return to the doctors at the corresponding visit.*

Morisky and Fact LEU questionnaires will be completed only if the patient is under treatment with bosutinib. They will no longer be completed in long-term follow-up visits.

Table 4 – Estimated schedule of data collection

Estimated visits:	**M 0**	**M 3**	**M 6**	**M 9**	**M1 2**	**M1 5**	**M1 8**	**M2 1**	**M2 4**	**M2 7**	**M3 0**	**M3 3**	**M3 6**
Visits completed by the doctor (eCRF)													
Inclusion visit	**x**												
Follow-up visit		**X**	**x**	**x**	**x**	**X**	**x**	**x**	**x**	**x**	**x**	**X**	**x**
Self-questionnaires completed by patients (paper)													
Compliance (Morisky)		**X**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**X**	**x**
Quality of life (FACT-leu)	**x**	**X**	**x**		**x**		**x**		**x**				**x**

3.4.1.1. Inclusion visit

Patients included will undergo collection of medical data indirectly by name (patients' questionnaires completed by the doctor *via* the eCRF).

3.4.1.2. Follow-up visit

At each follow-up visit, conducted in the setting of usual management estimated every 3 months in conformity with recommendations on management of CML, doctors will complete *via* the eCRF a follow-up visit for all patients.

3.4.1.3. Long-term follow-up visit

Patients who have permanently discontinued their treatment with bosutinib will be followed according to their usual management, estimated at every 3 months in conformity with recommendations of management of CML. Doctors will complete via eCRF a long-term follow-up visit for all these patients.

At this visit, the following information will be provided:

- Outcome of the CML Phase
- Therapeutic management of CML

3.4.1.4. End of study questionnaire

An end of study visit will be completed by the participating doctor for all patients who discontinued the study before 36 months follow-up planned by the protocol (patient lost to follow-up, patient died or patient who withdrew their consent).

3.4.1.5. Measurement of compliance with treatment

Compliance with treatment will be evaluated directly in patients using a Morisky standardized validated questionnaire (Annex 3). This generic questionnaire on evaluation of adherence with treatment consists of 7 questions for which the rating scale is 0 for "YES" (reflection of poor compliance) and 1 for "NO" (reflection of good compliance), and an 8th question with 5

response modalities ranging from “never/rarely” to “all of the time” which makes it possible to qualify the degree of agreement [23].

This questionnaire will be returned by the patient to the participating doctor at the end of the visit. All adverse events identified by the participating doctor via these questionnaires (if the patient has ticked YES to questions **3, 6**) must be reported in the study database and be reported through the Pfizer Pharmacovigilance department (*see section* 11 **Error! Reference source not found.**.

3.4.1.6. Measurement of quality of life

Patient quality of life depends on treatments received and on complications encountered. It will be measured at the inclusion visit and at certain follow-up visits (M3, M6, M12, M18, M24, M36), by completion of a standardized questionnaire and validated in French FACT-leu (Functional Assessment of Cancer-Therapy-Leukemia, version 4 November 2007) in paper format for all patients in the study (Annex 3).

The FACT-leu questionnaire is a 44-item questionnaire with 5 modalities ranging from 0 (“not at all”) to 4 (“enormously”), evaluating 5 major dimensions of quality of life in the last 7 days: physical well-being (7 questions, score of 0 to 28), social/familial well-being (7 questions, score of 0 to 28), emotional well-being (6 questions, score of 0 to 24), functional well-being (7 questions, score of 0 to 28), and other subjects of concern (17 specific questions on leukemia, score of 0 to 68). A total score (of 0 to 176) can be calculated; a high score reflects good quality of life [24].

This questionnaire will be returned by the patient to the participating doctor at the end of the visit. All adverse events identified by the participating doctor via these questionnaire (e.g. “I have nausea” scored between 1 (a little) and 4 (enormously)) should be recorded in the study database and be reported to the Pfizer Pharmacovigilance department *(see* 11 **Error! Reference source not found.Error! Reference source not found.**).

3.4.1.7. Registry of non-inclusion:

Patients eligible but not included must be recorded in a non-inclusion registry (*see* **Error! Reference source not found.***Registry of non-inclusion),* with a minimum of parameters collected:

- Demographic characteristics (year of birth, gender),
- Reason for non-inclusion.

3.5. Study sample size

Since the descriptive objective of this study does not involve the hypothesis of specific research, it is not necessary to calculate a minimum sample size population of participating patients. Furthermore, since CML is a rare disease, a minimum number of patients is not expected.

Based on the number of monthly prescriptions of Bosulif® (sponsor data) and taking into account the future start-up of a competitive study, a total of one hundred (100) patients included in the study appears to be a reasonable objective. Participating doctors should include on average 5 patients in the study, with no distinction between phases of CML at inclusion.

However, it is shown that about one hundred patients would make it possible to have acceptable precision, precision corresponding to half of a 95% confidence interval (CI):

- ≤ 10% to estimate a percent of patients presenting with a given event (Wald asymptotic method without a continuity correction – hypothesis of a 50% rate)
- Of 10% in order to estimate median survival (Greenwood formula under the hypothesis of absence of data censured at the right before median survival and occurrence of a single event at a time.

Consecutive inclusion of patients who satisfy eligibility criteria up to the end of the inclusion period estimated at 2 years will ensure the representativeness of patients in the study.

In order to ensure compliance with this consecutiveness, a registry of non-inclusion will be set up. Patients eligible but not included in the study must be recorded in this registry and throughout the period of inclusion. A minimum of parameters will be collected.

3.6. Data management

Data will exist in electronic format for data collected from doctors at visits (e-CRF), and in paper format (CRF) for data collected from patients.

All operations of data management will be performed in agreement with requirements of Pfizer and Standard Operating Procedures of the CRO in charge of data management. The database and a data management manual enabling to define and to describe all activities of biometry will be developed by the CRO and then validated by Pfizer.

3.6.1. Case report forms (CRF)/tools for data collection (e-CRF)/electronic recording of data

As used in this protocol, the term case report forms (CRF)*/e-CRF* should be understood as referring to a paper support medium or to electronic recording of data, or both, depending on method of data collection used in this study.

Data of interest will be recorded in a case report form in electronic format (e-CRF).

A CRF/e-CRF is required and must be completed for each patient included. Original CRF/e-CRF completed are the sole property of Pfizer and must not be made available to any third party in whatever form, except for certified representatives of Pfizer, of appropriate regulatory authorities, without the written authorization of Pfizer. The participating doctor must make certain that CRF/e-CRF are stored in a secure manner on the study site in encrypted electronic format or paper format and will be protected by a password or secured in a locking room in order to prevent unauthorized third parties from accessing them.

The participating doctor is responsible as the last resort for collection and reporting of all clinical data, safety and biological data recorded in the CRF*/e-CRF* and in all other media for data collection (source documents) and to ensure that they are accurate, authentic/original, attributable, complete, consistent, legible and available if applicable. CRF*/e-CRF* must be signed by the participating doctor or by a certified member of the research team in order to ensure the authenticity of data entered in the CRF*/e-CRF*. Any correction made to entries performed in the CRF*/e-CRF* or source documents must

be dated, accompanied by the author's initials and explained (if applicable), and should not conceal the original data entry.

In the majority of cases, source documents are comprised of hospital dossiers or the doctor's dossiers. In this case, data collected in the CRF/e-CRF should correspond to these dossiers.

In some cases, the CRF/e-CRF can also be used as a source document. In this case, a document, available in the participating doctor's centre or at Pfizer, must clearly identify the data which have been recorded in the CRF/e-CRF, and for which the CRF/e-CRF will comprise the source document.

3.6.1.1. Channel of CRF and data entry

Data collected by the participating doctor at time of inclusion and in the follow-up of patient visits will be recorded directly in the eCRF of the study.

For each centre, a registry will be made available to investigators to list patients eligible but not included: reason for non-inclusion, age, gender, and disease. Only one order number will be used to designate such patients in a manner so that they may be identified. Patients not included will be compared to patients included in the database of characteristics recorded in order to verify the absence of a selection bias or of inclusion bias.

Adverse events will be collected *via* the eCRF by doctors at the usual follow-up consultations, for all patients in the study. When applicable, requests for further information form the Pfizer pharmacovigilance department will be sent to the person who reported the event (participating doctor). All reports (initial and follow-up reports) will be grouped together via a centre number and patient number.

Patients' questionnaires on measurement of compliance and patients' questionnaires on measurement of quality of life will be sent to the CRO in charge of their data entry.

After validation of the database by Pfizer, paper questionnaires will undergo double data entry with the CRO's own software for patients' questionnaires in paper format. Periodic update reports on progression of data entry will be edited by the CRO and sent to Pfizer.

3.6.1.2. Construction of the database

An annotated questionnaire will be prepared by the CRO in charge of data management. This document will contain the names of tables and names of variables. Each variable will be associated with its type, its length and possible format. The annotated questionnaire will be submitted to Pfizer for validation.

The CRO then will build a database using its own software. The structure of the database will be documented and verified in listings by comparing the attributes of variables in the database with specifications noted in the annotated questionnaire.

Before entry of real data, the structure of the database and the data entry screens will be tested and validated in agreement with the Standard Operating Procedures of the CRO and those of Pfizer. In order to do this, fictitious questionnaires will be completed and entered. Validation will be performed by a complete examination in listing of these data and then their comparison with data recorded in the questionnaires. A validation report will be sent to Pfizer. The final structure of the database must be submitted to Pfizer for validation before entry of real data.

An audit file will be created to record all changes made to the database. The original data, the modified data, the date and time of the change, the person who made the change and reason for the change will be recorded in the audit file. The operation of the audit file will be tested by change to fictional data. A report will be written and sent to Pfizer.

3.6.1.3. Control of data

A list of controls of consistency enabling detection of inconsistencies and of aberrant responses present in the questionnaires will be edited by the CRO and validated by Pfizer. Such controls will be scheduled with the CRO's own software and then tested with fictitious data. These fictitious data and the documentation relating to the test will be kept in the study binder by the CRO and available for review by Pfizer.

After data entry, controls will be executed continuously. A specific request for each inconsistency will be generated electronically by the data control system. In order to limit the number of queries to submit to participating doctors, a guide on obvious corrections prepared by the CRO and validated by Pfizer may be compiled.

The CRO will make available the documentation on control of data upon simple request from Pfizer. Periodic update reports on data control will be edited by the CRO and sent to Pfizer.

3.6.1.4. Access to data

The database and servers on which they are stored will be located in locking facilities. Only the staff dedicated to the study will have access to the databases.

3.6.1.5. Locking of the database

Locking of the database will be performed only after data entry, control of data and possible coding has been completed by the CRO. Locking of the database will be performed in agreement with Pfizer procedure CT-24. After validation by Pfizer, the database will be locked by the CRO and readied for statistical analysis.

3.6.1.6. Data management report

A data management report will be edited by the CRO after locking of the database and sent to Pfizer.

9.6.2. Saving of dossiers

To enable evaluation and/or inspection/audits by the regulatory authorities or by Pfizer, the participating doctor accepts to save dossiers, including the identity of all participating patients (sufficient information to be able to make a link with the dossiers, for example CRF/eCRF and hospital dossiers), all original signed informed consent documents, copies of all CRF/e-CRF, pharmacovigilance report forms, source documents, detailed dossiers on distribution of treatments and adequate documentation on relevant correspondence (for example, letters, minutes of meetings and phone call reports). Dossiers must be saved by the participating doctor in conformity with local regulation or according to specification of the study contract, depending on the longer duration. The participating

doctor must make certain that the dossiers continue to be stored in a secure manner as long as they must be stored.

If the participating doctor no longer is able, for whatever reason, to continue to save study dossiers during the period required (for example, in case he retires or moves away), Pfizer must be notified in advance. The study dossiers must be transferred by a person designated by Pfizer, for example another investigator, another institution, or an independent third party named by Pfizer.

The participating doctor's dossiers must be stored for a minimum duration of 15 years after the end or discontinuation of the study or longer if local regulations in force so require.

The participating doctor must obtain written authorization form Pfizer before disclosing any dossier, even if requirements for storage have been satisfied.

3.7. Analysis of data

The detailed methodology for descriptive and statistical analyses of data collected in this study will be documented in a statistical analysis plan (SAP) which will be dated, classified and saved by the sponsor. The SAP can change the plans indicated in the protocol; any major change in definition of the primary evaluation criteria and of their analysis must be translated by a protocol amendment.

Management and statistical analysis of data will be performed using SAS software (version 9.4 or later, SAS Institute, North Carolina USA).

Interim analyses may be performed once a year, if necessary. In case of absence of a test hypothesis, no adjustment for multiplicity therefore is justified.

3.7.1. Statistical methods

Description of data

Patients' characteristics will be evaluated overall and then separately for patients with CP, AP or BP Ph+/- CML, and by line of treatment. Other data will be separately evaluated for patients presenting with CP, AP or BP Ph+/- CML and then by treatment line.

A descriptive analysis of qualitative and ordinal variables will consist of the sample size and the frequency of each modality with its 95% confidence interval (CI). Quantitative variables will be described in terms of sample size, mean and median, standard deviation, SD, confidence interval.

The description of variables collected during follow-up of each patient will contain a presentation of parameters for each of the times of measurement.

Overall survival data and progression-free survival (PFS) will be described with Kaplan Meier curves. Median survival will be estimated and presented with its 95% CI.

The sample size of missing values for each variable analysed will be indicated in the tables of results. Key data will be made obligatory in the electronic CRF in order to control the percent of missing data, if applicable, with models based on maximization of the function of probability or of techniques of attribution will be used.

Modelling

- Linear mixed model

Linear mixed models for repeated data will be used in the setting of analysis of continuous repeated data (longitudinal analyses). This approach will enable (1) to take into account all data from patients, and (2) to estimate at each measurement time the mean parameter on all of the patients, adjusted to the phase of CML and to treatment line. It will apply to analysis of biological and hematological parameters. The outcome in comparison to baseline (M0) will be estimated by appropriate contrasts.

- Logistical regression

Multivariate logistical regressions (binary variables) or polynomial (multi-categorical variables) will make it possible to estimate the association of qualitative parameters studied (e.g. response) and of explanatory variables (without notion of time). All models used will be adjusted to potential confounding factors or changes to effect.

3.7.2. Analysis of the primary objectives

The following parameters will be evaluated in order to respond to the primary objectives:

- The percent of patients presenting with adverse events considered related to bosutinib by the participating doctor will be described overall (all grades of seriousness combined, all types of events combined), depending on grade: 1, 2, 3 and 4 and grades 3/4, and by type of event.
- The percent of patients who permanently discontinued treatment with bosutinib following an AE considered related to bosutinib by the participating doctor will be described overall.

Analysis of the primary objectives will be detailed in the statistical analysis plan.

3.7.3. Analyses of secondary objectives

Safety profile with bosutinib:

- *The following percent will be described by System Organ Class (SOC) overall and according to grade of event whether it is considered as related to bosutinib or not (grade 1, 2, 3, 4, or grades 3/4):*
    - *percent of patients presenting with AE that occurred with bosutinib*
    - *percent of patients presenting with AE which required a change to treatment with bosutinib (a reduction of dose and/or temporary or permanent discontinuation)*
- *The percent of patients presenting with biological or hematological toxicities during treatment with bosutinib, whether considered related to bosutinib or not, will be described overall and according to grade of the event (grade 1, 2, 3, 4, or grade 3/4).*

  The biological and hematological events will be estimated by the CTCAE v4.03 criteria of June 2010, with all values greater than the upper normal value, or lower than the lower normal value of the parameter considered.
- *Measures taken to prevent AE will be described (supportive therapy, etc.).*
- *Biochemical and hematological parameters will be described in follow-up using a linear mixed model for repeated data.*

***Adherence to treatment (Morisky Questionnaire)**.*

The MMAS-8 rating scale consists of eight items with a "Yes" = 0 and "No" = 1 rating system for the first seven items and a 5-point response for the last item. Items will be added in order to obtain a score.

- *The score will be described continuously and categorically (0 = high adherence, 1-2 = average adherence, ≥3 = low adherence) at each measurement time.*

Quality of life (FACT-leu version 4 – Specific questionnaire on leukemia)

- *Scores obtained based on the FACT-leu questionnaire will be calculated at each measurement time according to rules on calculation provided in Annex 3.5.*
- *The gain in quality of life, defined by the difference between the best score recorded for a patient and his baseline score, will be calculated.*

Describing treatment modalities for bosutinib under real life conditions of use

- *Dosage: mean dosage prescribed at time of initiation and average dosage during treatment.*
- *Change to dose and reasons: percent of patients with dose reduction/percent of patients with a dose increase and if applicable, description of the reason .*
- *Maintenance of dose intensity and relative dose intensity (defined as the result of the ratio of the dose received over the expected dose): percent of patients with a dose intensity/relative dose intensity maintained over time and at different measurement times.*
- *Temporary discontinuation of treatment: percent of patients with temporary discontinuation of treatment and description of the reason; cumulative duration of temporary discontinuations.*
- *Permanent discontinuation of treatment: percent of patients with a permanent discontinuation of treatment and description of reason for discontinuation.*
- *Duration of treatment: duration of initiation up to discontinuation of treatment will be calculated for all causes of discontinuation combined and by cause of discontinuation (Kaplan-Meier survival curves).*

Cumulative response to treatment (hematological, cytogenetic and molecular results) and duration up to response and response time

<u>Response rate for patients in CP, AP or BP according to treatment line:</u>

- *Cumulative hematological response:*

- *percent of patients presenting with a CHR during treatment with bosutinib (best response according to the participating doctor's judgement)*
- *percent of patients presenting with a PHR during treatment with bosutinib (best response according to the participating doctor's judgement)*

- *Cumulative cytogenetic response:*
  - *percent of patients presenting with CCyR during treatment with bosutinib (best response according to the participating doctor's judgement)*
  - *percent of patients presenting with MCyR during treatment with bosutinib (best response according to the participating doctor's judgement)*
  - *percent of patients presenting with PCyR during treatment with bosutinib (best response according to the participating doctor's judgement)*
  - *percent of patients presenting with mCyR during treatment with bosutinib (best response according to the participating doctor's judgement)*

- *Cumulative molecular response:*
  - *percent of patients presenting with CMR (MR^4; $MR^{4.5}$; MR^5) during treatment with bosutinib (best response according to the participating doctor's judgement)*
  - *percent of patients presenting with an MMR (MR^3) during treatment with bosutinib (best response according to the participating doctor's judgement)*

Suboptimal response (after dose escalation or without dose escalation due to ongoing toxicities):

- *Patient with chronic phase CML, refer to ELN guidelines 2013.*
- *Patient with accelerated phase or blast phase CML, loss of all hematological response.*

Median time to response:

For each response (hematological, cytogenetic, molecular), the median time to occurrence of response will correspond to the median duration between date of initiation of bosutinib and the first date of response as defined in the aforementioned (Kaplan Meier method).

Median duration of response

For each response (hematological, cytogenetic, molecular), the median duration of response will correspond to the median duration between first date of response as defined in the aforementioned and the confirmed loss of response, the progression of disease or death of the patient (Kaplan Meier method).

Response according to mean dose received

- *For each response (hematological, cytogenetic, molecular), the percent of patients with a response according to mean dose received in period of follow-up up to response will be described (stratification based on dose)*
- *Logistic regression on each response (hematological, cytogenetic, molecular) according to mean dose received in the period of follow-up up to the (quantitative) response*

Progression

Defined as passage from the chronic phase to the accelerated phase or to blast phase. This progression must be validated by two consecutive evaluations less than one week apart. Patients presenting an increase in leukocyte count in at least one period greater than or equal to one month, with second assay measurement > 20 x 10^9/L and confirmed at least one week later. Patients presenting a loss of major hematological response (with hematological confirmation within a time greater than or equal to 2 weeks after loss of initial response) or non-confirmation of major cytogenetic response (with a Ph+ rate increased by 30%).

Progression-free survival at 1, 2 and 3 years of patients treated with bosutinib:

Progression-free survival will be defined as the duration between initiation of bosutinib and date of progression estimated by the participating doctor or death of patient (all causes combined) (Kaplan Meier method).

Overall survival at 1, 2 and 3 years of patients treated with bosutinib:

Overall survival will be defined as the duration between initiation of bosutinib and date of death (all causes combined) (Kaplan Meier method).

Describing the characteristics of patients treated with bosutinib:

The description of the population covered will present the characteristics of patients at time of initiation of treatment:

- *demographic characteristics;*
- *medical history and comorbidities, duration between diagnosis and initiation of treatment and latest hematological, cytogenetic or molecular responses known (cytogenetic and molecular responses will be mentioned only if patient is in chronic phase);*
- *previous treatments: number of lines of treatment, medicinal products, better response during treatment, reasons for discontinuation of previous treatments.*

Evaluating cross-intolerance between bosutinib and previous targeted therapies:

Cross-intolerance will be defined by percent of patients who permanently discontinued bosutinib because of an adverse event which had resulted in discontinuation of a previous treatment (imatinib, dasatinib, nilotinib). Cross intolerance will be estimated for all AEs, but also by type of adverse event.

Analysis of secondary objectives will be detailed in the statistical analysis plan.

3.7.4. *Representativeness of participating centres*

A description of a sample of centres will be made post hoc based on data on identification of participating doctors in each centre (gender, age, geographical location). It then will be verified that the sample of participating doctors is representative of hematologists in France in terms of sample size and type of centre in order to ensure outside validity of the study.

3.8. Quality control

3.8.1. Set up of participating doctors

It will be offered to doctors preselected to participate in this study. This participation will be made tangible by signature of the financial agreement. Validation of the latter, a visit for set up of study on site will be organized by the Clinical Research Associate in order to present the study and all related documents to the participating doctor, as well as to members of his staff that he has designated, if applicable.

3.8.2. Logistics and monitoring of participating centres

Throughout the study, participating doctors will be contacted to ensure the understanding and compliance with the protocol and the electronic questionnaire. All contacts will be documented.

Study Monitors will be in charge of performing at least one monitoring visit per year and per centre, as well as one closing visit. At these visits, the monitors will be in charge of ensuring the understanding and compliance of the protocol by the doctor, the existence of patients included, that the data recorded in the case report form are in fact identical to source data (verification of a minimum number of clinically relevant and major data defined beforehand in agreement with the scientific committee), of verifying the good keeping up-to-date of the Site Master File (SMF), and of verifying the reporting of AE to the Pfizer pharmacovigilance department (*see* 11 **Error! Reference source not found.**)

Key indicators of proper conduct of this study (number of active centres, number of patients included, number of follow-ups performed, etc.) will be generated using the study database. This database will make it possible to edit study progress reports which will enable to generate the sending of reminders to centres.

3.8.3. *Quality and accuracy of data*

The participating doctor will be responsible for collection of reports of all clinical data, of safety data and laboratory data entered in the eCRF and/or other forms of data collection (source documents), and must ensure that they are accurate, authentic, attributable to the patient, complete, consistent, readable, contemporaneous and available if needed.

In order to enable controls and/or audits by the regulatory authorities or by Pfizer, the participating doctor accepts to keep registries including the identity of all participating patients (sufficient information to review the dossiers (e.g. eCRF and hospital medical dossiers)). The participating doctor will keep all original signed informed consent forms, copies of serious adverse event reports, source documents and medical results leading to decisions on treatment.

3.9. Limitations of study methods

This protocol has been built in a manner so as to best respond to the objective set for this observational study. However, the latter has certain limitations which must be discussed and which should be taken into account at time of the initiation of the study and utilization of results.

3.9.1. Selection bias of participating doctors

Participating doctors will be recruited from a baseline survey representative of different centres specializing in management of CML in France. However, the voluntary characteristic of participation of doctors in the study is a usual selection bias for this type of study. This is why the two populations of doctors (those accepting and those refusing to participate) will be compared. In the event that major deviations in comparison with the survey database are observed, this will be taken into account by making corrections and or by discussing results of the study with regard to the differences observed.

3.9.2. Selection bias of patients

The representativeness of the sample of the study compared to the target population is basic in order to be able to extrapolate results of the study to the target population. The representativeness of the sample depends on internal validity (precision of estimates and selection criteria of study population – the patients) and the outside validity (plan and fluctuations of sampling).

The representativeness of patients included is a potential selection bias in observational studies. Conscious selection or not of patients in the study by participating doctors is inevitable. Participating doctors will be asked to include sequentially and exhaustively all patients who satisfy eligibility criteria for the study up until the end of the inclusion period in order to limit this bias. Parameters on representativeness of patients included will be controlled by the set-up of a registry of non-inclusion up until the end of the inclusion period.

3.9.3. *Patients lost to follow-up during follow-up*

Special attention will be paid to patients who discontinue the study or that the participating doctor has not seen in a visit as the results of the observational characteristic of the study (frequency of visits for follow-up of patients can vary depending on doctors and patients). For patients lost to follow-up,

a questionnaire on last news from the patient (end of study) will be completed by the participating doctor. Statistical analyses will compare characteristics of patients included and who participated in the entire duration of the study in patients included and lost to follow-up and/or who discontinued the study before the end of follow-up.

3.9.4. Measurement bias

Special attention will be paid to patients who discontinue the study or that the participating doctor does not see at a visit as a result of the observational characteristic of the study (the frequency of visits for follow-up of patients can vary depending on doctors and patients). For patients lost to follow-up, a questionnaire on the patient's last news/end of study will be completed by the participating doctor. Statistical analyses will compare the characteristics of patients included and who participated in the entire duration of the study in patients included and lost to follow-up and/or who discontinue the study before the end of follow-up.

3.10. Other aspects

Insofar as no additional examination will be performed compared to the usual management of patients with CML, the medical services provided and the medicinal products prescribed will be reimbursed by the social security system. The fixed reimbursement is paid in the capacity of work load invested in the documentation and completion of the study questionnaires.

4. PROTECTION OF PATIENTS

4.1. Information leaflet for patients

All parties will comply with legislation in force, in particular laws concerning the implementation of organizational and technical measures designed to ensure the protection of patients' personal data. These measures will include omission of the names of patients or of other data enabling to identify them directly in all reports, all publications and all other disclosures, except for requirements imposed by legislation in force.

Personal data will be kept in the study centre in encrypted electronic or paper format and will be protected by a password or secured in a locking room in order to ensure that only study certified staff can have access to it. The study centre will set up appropriate technical and organizational measures

in order to ensure that personal data can be recovered in the eventual case of an accident. In the eventuality of potential violation of personal data, the study centre will assume responsibility to determine if this violation was really produced and, in this case, to carry out the notifications required by law.

In order to protect the rights and freedoms of physical persons with respect to the processing of personal data, when study data are compiled in order to be transferred to Pfizer and to other certified parties, patients' names will be removed and replaced by a unique specific code number, based on a numbering system defined by Pfizer. All other data enabling identification of patients which will be transferred to Pfizer or to other certified parties will be identified by a specific unique code for each patient. The participating doctor's centre will keep a confidential list of patients who participated in the study, with a link between the numerical codes of each patient and the real identity of each of them. In case of transfer of data, Pfizer will maintain high standards of confidentiality and protection of patients' personal data in conformity with conditions of the study contract and laws in force on protection of private life.

4.2. Consent of patients

Informed consent documents and all materials intended for recruitment of patients must comply with regulatory and local legislative requirements, in particular laws in force on respect of private life.

Informed consent documents used in the process for obtaining informed consent and all materials enabling recruitment of patients must be examined and approved by Pfizer, approved by the ethics committee (CPP – Committee for Protection of Persons)/independent ethics committee (IEC) with their use, and must be available for inspection.

The participating doctor must ensure that all patients in the study are fully informed about the nature and objectives of the study, on communication of data relating to the study, and on possible risks associated with their participation, in particular risks associated with the processing of personal data of patients. The participating doctor must also make certain that all patients in the study have been fully informed of their rights of access and correction of their personal data, and of withdrawal of their consent for processing of their personal data.

4.3. Withdrawal of a patient

Patients can withdraw from the study at any time at their own request or may be withdrawn at any time based on the judgement of the participating doctor or the sponsor for reasons of safety of use, behavior or administrative reasons. In all circumstances, every effort must be made to document the outcome of the patient whenever applicable. The participating doctor will collect information on the reason for a patient's withdrawal and follow-up with the patient, concerning all unresolved adverse events.

If a patient withdraws from the study and also withdraws his consent for disclosure of future information, no other evaluation should be made and no other data should be collected. The sponsor can keep and continue to use all data collected before the withdrawal of consent.

4.4. Committee for Protection of Persons (CPP)/Public Health Code Law no. "2004-806 of 9 August 2004"

This trial is an observational study that does not in any way modify the usual medical management of persons entering the study, and does not harm the physical or psychological integrity and does not require a specific follow-up visit for persons entering the study. All procedures are performed and products used in the usual manner with no unusual or additional diagnostic or monitoring procedure.

Under these conditions, the study does not fall within the scope of application of law of program no. 2006-450 of 18 April 2006 for research nor law no. 2004-806 of 9 August 2004 article 88 chapter II article L1121-1 and therefore the project is not subject to submission to the National Agency for Medicines and Health Products Safety (ANSM), nor to a Committee for Protection for Persons (CPP) (ethics committee).

In this regard, for an opinion which has been issued prior to 16 November 2017, the Ethics Committee is not competent for substantial changes on this project.

4.5. National Medical Council

Participating doctors and experts in the scientific committee will be compensated for their participation in the study. The study protocol and the financial agreements will be submitted to the National Medical Council (article L4113-6 of the Public Health Code and articles R4113-104 and R4113-105).

Each participating doctor and scientific expert must send to the National Medical Council a copy of his/her contract (articles L4113-9, L4113-10 and L4163-10 of the Public Health Code).

4.6. Ethical conduct of the study Protection of Data: National Committee on Data Processing and Freedoms "CNIL"

In compliance with law 78-17 of 6 January 1978 relating to data processing, computer files and freedoms, as modified by law 2004-801 of 6 August 2004 relating to protection of physical persons with regard to processing of personal data, this protocol has been submitted in a request for an opinion from the Consultative Committee on Data Processing in the Area of Research in the Field of Health (CCTIRS). Upon receipt of a favorable opinion from this committee, the computer file used to write the present study has been the subject of a request for authorization form the National Committee for Data Processing and Freedoms (CNIL). This computer file can be used only after receipt of authorization from the CNIL.

Since this involves the potential competence of the Consultative Committee on Data Processing in the Area of Research in the Field of Health (CCTIRS) which has been eliminated on 5 May 2017, date of a decision concerning creation of the Expert Committee on Research, Studies and Evaluations in the Field of Health (CEREES) in application of French law no. 2016-41 of modernization of the health system of 26 January 2016, and of the application decision of the so-called Jardé law no. 2016-1537 of 16 November 2016, the departments of the ministry of research are no longer competent for analysis of corrections made to research projects.

Also, in compliance with law 78-17 of 6 January 1978 relating to data processing, files and freedoms modified by law 2004-801 of 6 August 2004 relating to protection of physical persons regarding processing of personal data, the protocol has been submitted in a request for authorization from the National Commission on Data Processing and Freedoms (CNIL). This computer file may be implemented only after receipt of authorization from CNIL.

4.7. Ethical conduct of study

The study will be conducted in compliance with legislative and regulatory requirements, in conformity with its objective, scientific value and rigorousness and will follow the practices of research generally accepted and described in the following documents:

- Recommendations on Good Pharmacoepidemiologic Practice (GPP) published by International Society for Pharmacoepidemiology (ISPE), https://www.pharmacoepi.org/resources/guidelines_08027.cfm

- Recommendations on Good Epidemiological Practice (GEP) published by the International Epidemiological Association (IEA), http://ieaweb.org/2010/04/good-epidemiological-practice-gep/

- Good practice of research on results on results published by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), http://www.ispor.org/workpaper/practices_index.asp

- Recommendations on Good Practice for studies on health data under real life conditions concerning a treatment and/or comparative efficacy: recommendations of the joint working group ISPOR-ISPE on concrete evidence in decision making in the area of healthcare https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5639372/

- International ethical recommendations for epidemiological research published by the Council for International Organizations of Medical Sciences (CIOMS) http://ieaweb.org/wp-content/uploads/2012/06/cioms.pdf

- European Medicines Agency (EMA) European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology

- The ENCePP Code of Conduct for scientific independence and transparency in conduct of studies of pharmacoepidemiology and pharmacovigilance http://www.encepp.eu/code_of_conduct/documents/ENCePPCodeofConduct_Rev3.pdf

- Guide of methodological standards in pharmacoepidemiology, guidelines of the Food and Drug Administration (FDA) for industry: Good Practice of pharmacovigilance and of pharmacoepidemiologic evaluation (Good Pharmacovigilance and Pharmacoepidemiologic Assessment), https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm071696.pdf

- FDA guidelines for industry and FDA staff: Good Practice of conduct and reporting of pharmacoepidemiologic studies of safety using all electronic medical data http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM243537.pdf

- Guidelines for industry: Measures evolution recorded by the patient: Use in development of medical products to support labelling of the label. http://www.fda.gov/downloads/Drugs/Guidances/UCM193282.pdf

5. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

5.1. Single reference document in safety of use

The Summary of Product Characteristics (SmPC) in force in France will be the unique reference document on safety in this study. It will be used by the Pfizer pharmacovigilance department to evaluate all events concerning safety of use reported to the Pfizer pharmacovigilance department by the participating doctor during the study.

This unique reference document on safety must be used by the participating doctor for prescribing information and recommendations.

5.2. Requirement in terms of pharmacovigilance

Table 5 in the following summarizes the requirements for recording of adverse events in the electronic case report forms and for reporting adverse events via the adverse event report form of non-interventional studies to Pfizer *pharmacovigilance* (NIS AEM Report Form). These requirements are defined for three types of events: (1) serious adverse events (SAE), (2) non-serious adverse events (AE) (if applicable), and (3) situations involving exposure to a medicinal product including exposure in pregnancy, exposure during lactation, medicinal product errors, overdose, misuse, extravasation, lack of efficacy and occupational exposure. These events are defined in the section entitled “Definition of an adverse event”.

Table 5: Requirements for recording of adverse events

Adverse event	Recorded in the electronic CRF of the study	Reported via NIS AEM Report Form to Pfizer Pharmacovigilance within 24hr following awareness of the event
SAE	All	All
Non-serious AE	All	All

Adverse event	Recorded in the electronic CRF of the study	Reported via NIS AEM Report Form to Pfizer Pharmacovigilance within 24hr following awareness of the event
Situations involving exposure to a study medicinal product including exposure in pregnancy, exposure during lactation, medicinal product errors, overdose, misuse, extravasation; lack of efficacy and occupational exposure	All (independently of presence of a concomitant AE) **except for occupational exposure**	All (independently of presence of an associated AE) Note: Any associated AE is reported together with the exposure scenario.

For each AE, the participating doctor must look for and obtain sufficient information both to determine the outcome of the adverse event and to evaluate if it satisfies criteria for classification of an SAE (see section entitled “Serious adverse event” in the following).

Adverse events must be reported to Pfizer within 24 hours following awareness of the event by the participating doctor, **whether the event has been considered as related to the study medicinal product or not by the participating doctor**.

In particular, if a serious adverse event is fatal or life-threatening, its reporting to Pfizer must be done immediately, whatever the information available on the adverse event. This time period also applies to all new information (follow-up) relating to reports of previously transmitted adverse events. In rare cases where the participating doctor is not immediately informed of occurrence of an adverse event, the participating doctor must report the event

within 24 hours after he/she has become aware of it and report the time when he/she became aware of this adverse event for the first time.

For adverse events considered as serious or identified in the right column of the aforementioned table which are to be reported to Pfizer within 24 hours following awareness of it, the participating doctor is required to look for and to provide all additional information to Pfizer in conformity with this time period of 24hr. Furthermore, Pfizer can request from a participating doctor to obtain urgently information on specific additional follow-up. This information can be more detailed than that recorded in the study case report forms. Generally, such information will include a description of the adverse event in a sufficiently detailed manner to enable medical evaluation of the case, and independent determination of possible causal relation. All relevant information concerning the event, such as concomitant treatments or disorders, must be provided. In the event of death of a patient, a summary of results of an autopsy available must be sent as soon as possible to Pfizer or to its certified representative.

5.3. Period of reporting

For each patient, the period of reporting of adverse events starts from the time when the patient received the first dose of the study medicinal product or starting from the date on which the patient provided his/her informed consent if he/she has already been exposed to the study medicinal product, and ends at the end of the observation period of the study, i.e. at least at the end of a period of 28 calendar days after the last administration of the study medicinal product (bosutinib); a report must be sent to the PFIZER Pharmacovigilance department or its certified representative for all types of adverse events listed in the abovementioned table and which occurred during this period. If the patient received the study medicinal product on the last day of the observational period, the period of reporting will be extended by 28 calendar days after the end of the observation period. Most often, the date of signature of the consent form corresponds to the date of inclusion of the patient in the study.

In some cases, there may be a difference between the date of signature of the consent form and date of inclusion in the study.

In the event that the patient provided his/her consent but was never included in the study (for example, a patient changed his / her mind on participation; screening failure), the period of reporting ends on the date of decision of non-inclusion of patient.

If the participating doctor becomes aware of a SAE that occurred at any time after the end of the observational period and that is considered related to the study medicinal product (bosutinib), this SAE must also be reported to the Pfizer Pharmacovigilance department.

5.4. Evaluation of causal relation

The participating doctor must evaluate and report the causal relationship. For all adverse events, sufficient information must be obtained by the participating doctor in order to determine the causal relation of each adverse event. For AE considered as related to the study medicinal product (bosutinib), the participating doctor is required to perform follow-up up to resolution or stabilization of the event and/or of its sequelae to a level considered acceptable by the participating doctor, and that Pfizer is in agreement with this evaluation.

The evaluation of the causal relation by the participating doctor is the determination of the fact that there is a reasonable possibility that the study medicinal product (bosutinib) has caused or has contributed to an adverse event. If final determination of the causal relation is “unknown” and the participating doctor cannot determine if the study medicinal product (bosutinib) has caused the event, then the event must be reported within 24 hours.

If the participating doctor cannot determine the aetiology of the event but that he/she has determined that the study medicinal product (bosutinib) was not the cause of the event, this should be clearly mentioned in the case report forms and in the adverse event report form for non-interventional studies.

5.5. Definition of an adverse event

5.5.1. Adverse event

An adverse event is any unwanted manifestation that occurred in a patient to whom a medicinal product was administered. It is not necessary for the event to have a causal relation with the treatment or use. Examples of adverse events include, without this list having a limited characteristic:

- Abnormal test results (see in the following for circumstances in which an abnormal test result is an AE);
- Clinically significant symptoms and signs;
- Changes to results of the clinical examination;
- Hypersensitivity;
- Lack of efficacy;
- Drug abuse;
- Medicinal product dependence.

Furthermore, for medicinal products, they can include resultant signs and symptoms of:

- an overdose;
- withdrawal;
- misuse;
- off-label use;
- drug interaction;
- extravasation;
- exposure during pregnancy;
- exposure during lactation;
- a medicinal product error;

- occupational exposure.

Abnormal test results

The criteria enabling to determine if abnormal test data in an objective test should be reported as an adverse event are as follows:

- The test result is associated with symptoms, and/or
- The test result requires additional diagnostic investigations or a medical/surgical intervention, and/or
- The test result leads to a change to dosage or withdrawal of the patient from the study, to administration of a significant additional concomitant treatment or another treatment, and/or
- The test result is considered as an adverse event by the participating doctor or the sponsor.

The simple repetition of an abnormal test, in the absence of the aforementioned conditions, does not constitute an adverse event. Any abnormal test result which proves to result from an error does not need to be reported as an adverse event.

5.5.2. Serious adverse events

A SAE is any untoward medical occurrence in a patient administered a medicinal or nutritional product (including pediatric formulas) at any dose that:

:

- Causes death;
- Is life threatening;
- Requires hospitalization of the patient or prolongation of hospital stay (see below for circumstances under which it does not constitute an adverse event);
- Results in permanent or important disability or incapacity (important alteration of ability to perform acts of daily living);

- Results in a congenital anomaly or malformation.

Progression of the malignancy during the study (including signs and symptoms of disease progression) should not be reported as a serious adverse event, unless the outcome is fatal during the study or during the period of reporting adverse events. Hospitalization due to signs and symptoms of disease progression should not be reported as a serious adverse event. If the malignant condition has a fatal outcome during the study or during the period for reporting adverse events, then the event leading to death should be reported as an adverse event, and as a grade 5 serious adverse event.

An event will be defined as a medically important event based on medical and scientific judgement. A medically important event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is established that the event can be life-threatening for the patient and/or require an intervention in order to prevent one of the aforementioned outcomes, the medically important event should be reported as serious.

Cases which enter into this category of medically important events are, for example, allergic bronchospasm, requiring intensive care in the emergency room of a hospital or at home, coagulation disorders, seizures which have not resulted in hospitalization, or development of medicinal product dependence or medicinal product abuse.

Furthermore, any suspicion of transmission of an infectious agent, pathogenic or not, by a Pfizer product is considered as a serious adverse event. This event can be suspected by clinical symptoms or test results indicating an infection in a patient exposed to a Pfizer product. The terms “suspicion of transmission” and “transmission” are considered as synonymous.

These cases are considered as unexpected and should be managed as serious cases by the Pfizer Pharmacovigilance Department. These cases can also be reported as a product defect, if applicable.

Hospitalization

Hospitalization is defined as any initial admission (even for a duration less than 24 hours) into a health institution or any prolongation of an admission.

An admission also includes transfer within the hospital to an intensive care unit (for example, from a psychiatric department to a medical department, from a medical department to a coronary care unit, from a neurology department to an intensive care unit for tuberculosis).

A consultation in the ER does not necessarily constitute a hospitalization; however, an event leading to a consultation in the ER should be evaluated as medically important.

Hospitalization in the absence of an adverse event does not constitute an adverse event in itself and does not need to be reported. For example, the following reasons for hospitalization without an AE are to be reported.

- An admission for social reasons (for example, a patient who has no place to sleep)
- An administrative admission (for example, for a yearly examination)
- An optional admission not associated with a triggering AE (for example, for a scheduled cosmetic surgery procedure)
- Hospitalization for observation in absence of an AE
- Admission for treatment of a pre-existing disorder not associated with development of a new AE nor worsening of a pre-existing condition (for example, for an assessment following persistence of laboratory test abnormalities pre-existing treatment)
- An admission planned by the protocol during the clinical study (for example, for a procedure required by the study protocol)

5.6. Situation requiring reporting to pharmacovigilance within 24hr.

Situations involving exposure during pregnancy, exposure during lactation, a medicinal product error, an overdose, misuse, extravasation, lack of efficacy and occupational exposure are described in the following.

<u>Exposure during pregnancy (or exposure in utero)</u>

Exposure in pregnancy occurs if:

1. A woman becomes pregnant or it turns out that she is pregnant while she is receiving or is exposed to the study medicinal product (bosutinib) (for example, environmental exposure), or a woman becomes pregnant or turns out to be pregnant after having discontinued and/or having been exposed to the study medicinal product (bosutinib) (maternal exposure);

   An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (for example, a registered nurse reports that she is pregnant and has been exposed to chemotherapy products).

2. A man has been exposed, in the setting of treatment or of environmental exposure, to the study medicinal product (bosutinib) before or around the time period of conception and/or has been exposed during the pregnancy of his partner (paternal exposure).

Generally, cases of prospective and retrospective exposure during pregnancy, whatever the source, are to be reported, whether a concomitant adverse event is present or not, according to procedure for reporting serious adverse events.

If a female patient in the study or the partner of a male patient in the study becomes pregnant or it turns out that she is pregnant during treatment of the patient in the study with the study medicinal product (bosutinib), the participating doctor must report this information to Pfizer, whether an adverse event has occurred or not, in addition to the adverse event report form for non-interventional studies as well as the additional form entitled “Exposure during pregnancy”.

Furthermore, information relating to environmental exposure to the study medicinal product (bosutinib) of a pregnant woman (for example, a female patient reports that she is pregnant and that she has been exposed to a cytotoxic product by inhalation or after having accidentally spilled the product) must be reported to Pfizer, whether an adverse event has occurred or not, in addition to the adverse event report form for non-interventional studies as well as the additional form “Exposure during pregnancy”.

The information transmitted must include the expected date of term of pregnancy (see below for information concerning term of pregnancy).

Follow-up should be initiated to obtain general information on the pregnancy.

Furthermore, follow-up should be initiated to obtain information on the outcome of the pregnancy for all cases which are subject to reporting of exposure during pregnancy whose outcome is unknown.

A pregnancy must be followed up to its full term or up to discontinuation of pregnancy (for example, voluntary termination of pregnancy), and Pfizer must be informed of its outcome.

This information will be provided in the capacity of follow-up of the initial report of exposure during pregnancy. In case of birth of a baby, the structural integrity of the neonate cannot be evaluated at time of birth.

In case of a termination of pregnancy, the reason must be specified and, if possible clinically, the structural integrity of the foetus must be evaluated by visual inspection (unless the results of tests performed before the procedure have concluded in a congenital anomaly and that these results have been reported).

If the outcome of pregnancy corresponds to the criteria of an SAE (for example, an ectopic pregnancy, a spontaneous abortion, fetal death in utero, neonatal death, or a congenital anomaly [for a viable baby, an aborted fetus, fetal death in utero or neonatal death]), the procedures for reporting SAE should be followed.

Additional information on the outcome of pregnancy which are reported as SAE are as follows:

- A spontaneous abortion which includes a miscarriage and fetal retention;
- Neonatal deaths which occur during the month following birth must be reported as SAE, whatever the causal relation. Furthermore, the death of an infant above one month of age should be reported as an SAE when the participating doctor evaluates the death of the infant as related or possibly related to exposure to the study product.

Additional information on exposure during pregnancy can be requested. Follow-ups on outcome at birth will be processed on a case-by-case basis (for example, follow-up of a pre-term birth, of young age to identify developmental retardation).

In the case of paternal exposure, the communication form for information intended for the pregnant partner will be given to the patient participating in the study for his partner. It should be documented that this document has been given to the patient participating in the study for transmission to his partner.

Exposure during lactation

Situations of exposure during lactation should be reported, independently of presence of a concomitant AE.

A report of exposure during lactation does not have to be performed when a Pfizer product specifically indicated for use in a breastfeeding woman (for example, vitamins) is administered in agreement with the MA.

However, if the infant presents an AE associated with administration of such a medicinal product, the AE must be reported with exposure during lactation.

Medicinal product error

A medicinal product error means any unintentional error in prescription, in dispensing or administration of a medicinal product, which can cause or lead to inappropriate use of a medicinal product or harm for the patient, even though it occurs under control of a health care professional, of the patient or the consumer. Such events can be related to professional practice, to products, to procedures and to systems in particular: in prescribing; transmission of an order; product information; packaging and nomenclature of a product; composition; dispensing; distribution; administration; training in product; monitoring and use.

Medicinal product errors include the following:

- "Almost" adverse events, involving a patient directly or not (for example, inadvertent or erroneous administration, which is the accidental use of a product off-label or prescription by a health care professional or a patient/consumer);
- Confusion concerning the product name (for example, tradename, brand name).

The participating doctor must report the following medicinal product errors to Pfizer, independently of presence of a concomitant AE/SAE:

- Medicinal product errors involving exposure of a patient to the product, whether the medicinal product is accompanied by an adverse event or not.
- Medicinal product errors not involving a patient directly (for example, potential or almost accidental medicinal product errors). Whenever a medicinal product error does not involve exposure of a patient to the product, the following minimum criteria comprise a case of a medicinal product error:
  - An identifiable notifying party;
  - A suspect product;
  - A medicinal product error.

Overdose, Misuse, Extravasation

Cases of overdose, misuse and extravasation associated with use of a Pfizer product must be reported to Pfizer by the participating doctor, independently of the presence of an associated AE/SAE.

Lack of efficacy

Cases of lack of efficacy of a Pfizer product must be reported to Pfizer by the participating doctor, independently of the existence of an associated AE/SAE or of the indication of the Pfizer product.

Occupational exposure

Cases of occupational exposure to a Pfizer product must be reported to Pfizer by the participating doctor independently of the presence of an associated AE/SAE.

6. PLANS FOR DISCLOSURE AND COMMUNICATION OF RESULTS OF STUDY

6.1. Confidentiality

All data on patients participating in the study must be collated with appropriate precautions to ensure confidentiality of such data, according to applicable laws and regulations on protection of personal data (French law 78-17 of 6 January 1978, modified by law 2004-801 of 6 August 2004).

In all presentations of study results, at meetings or in publications, the identity of patients will remain confidential and all data will be issued anonymously.

6.2. Ownership of data

Pfizer will retain ownership of all forms of case reports, data analyses and reports which result from the study.

6.3. Communications and publications

All information obtained from this study will be considered confidential, up until analysis and final review by Pfizer and by members of the scientific committee have been completed.

Results of the study can be edited or presented by members of the scientific committee after the review and agreement of Pfizer, and such as confidential information or industrial property are not disclosed. Before publication of presentation, a copy of the final text must be sent by the member(s) of the scientific committee to Pfizer, for comment. Such comments will seek to ensure the scientific content of publications and/or of proposed presentations and to ensure that the data and material relating to Pfizer products and activities received an equitable, precise and reasonable presentation.

6.4. Communication of problems

In the eventual case of prohibition or a restriction imposed (for example, suspension of the clinical trial) by responsible competent authority in whatever region of the world, or if the participating doctor becomes aware of new information which may affect the evaluation of the benefits and risks of a Pfizer product, Pfizer must immediately be informed of it.

Furthermore, the participating doctor will immediately inform Pfizer of all urgent measures of safety taken by the participating doctor in order to protect patients in the study against any immediate hazard, and of all serious violations of the NI study protocol for which the participating has become aware.

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8. LIST OF TABLES

9. LIST OF FIGURES

APPENDIX 3. INVESTIGATORS AND CORRESPONDING INDEPENDENT ETHICS COMMITTEES (IECS) OR INSTITUTIONAL REVIEW BOARDS (IRBS)

For studies that involved sites registered in the Corporate Clinical Trials Registry (CCTR)*, the listings in Appendix 3 are generated from available data in the* CCTR by the NI study report author (NIS) (or delegate) and sent to the NI study lead (NIS) (or delegate).

For studies involving sites that were not registered in CCTR (eg, primary data collection studies with protocols approved by Pfizer before July 2012), *these listings are created and quality controlled (QC'd) by members of the study team/study team (NIS) (eg, NI study lead [NIS] delegate) using site and IEC/IRB information stored in the study master file.*

For studies that did not involve sites but had more than 2 IEC/IRB approvals, include "Refer to section 3 Investigators" in the header for Appendix 3.1 and complete Appendix 3.2.

For studies that did not involve sites and had no more than 2 IEC/IRB approvals, include "Refer to section 3 Investigators and section 5 Milestones" in the Appendix 3 header and omit the headers for Appendix 3.1 and Appendix 3.2. The applicable information is completed in sections 3 and 5 of the study report.

Where appendices do not apply to the study, include the appendix heading and state as "Not applicable" in the description.

Appendix 3.1. List of Investigators by Country

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OLIVIER	Gaelle	Doctor	CH DE SAINT BRIEUC _ HOPITAL YVES LE FOLL, 10 RUE MARCEL PROUST, 22027 SAINT BRIEUC
ROBERT	Daniel	Doctor	CH DE SAINT BRIEUC _ HOPITAL YVES LE FOLL, 10 RUE MARCEL PROUST, 22027 SAINT BRIEUC
LAUNAY	Vincent	Doctor	CH DE SAINT BRIEUC _ HOPITAL YVES LE FOLL, 10 RUE MARCEL PROUST, 22027 SAINT BRIEUC
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COURBY	Stephane	Doctor	CH DE GRENOBLE, AVENUE DES MAQUIS DU GRESIVAUDAN, 38700 GRENOBLE
MEUNIER	Mathieu	Doctor	CH DE GRENOBLE, AVENUE DES MAQUIS DU GRESIVAUDAN, 38700 GRENOBLE
CORM	Selim	Doctor	MEDIPOLE DE SAVOIE, AVENUE DES MASSETTES, 73190 CHALLES LES EAUX
COSTELLO	REGIS	Professor	APHM HOPITAL DE LA CONCEPTION, 147, boulevard Baille, 13005 MARSEILLE
IVANOV	VADIM	Doctor	APHM HOPITAL DE LA CONCEPTION, 147, boulevard Baille, 13005 MARSEILLE
TURLURE	Pascal	Doctor	HOPITAL DUPUYTREN, 2 AVENUE MARTIN LUTHER KING, 87042 LIMOGES
FOUILLARD	Loic	Doctor	CH MEAUX CEDEX, 6 8 RUE SAINT FIACRE, 77104 MEAUX

ABARAH	Wajed	Doctor	CH MEAUX CEDEX, 6 8 RUE SAINT FIACRE, 77104 MEAUX
ABRAHAM	Julie	Doctor	HOPITAL DUPUYTREN, 2 AVENUE MARTIN LUTHER KING, 87042 LIMOGES
DMYTRUK	Natalia	Doctor	HOPITAL DUPUYTREN, 2 AVENUE MARTIN LUTHER KING, 87042 LIMOGES
GIRAULT	Stéphane	Doctor	HOPITAL DUPUYTREN, 2 AVENUE MARTIN LUTHER KING, 87042 LIMOGES
GOURIN	Marie-Pierre	Doctor	HOPITAL DUPUYTREN, 2 AVENUE MARTIN LUTHER KING, 87042 LIMOGES
JACCARD	Arnaud	Doctor	HOPITAL DUPUYTREN, 2 AVENUE MARTIN LUTHER KING, 87042 LIMOGES
KENNEL	Céline	Doctor	HOPITAL DUPUYTREN, 2 AVENUE MARTIN LUTHER KING, 87042 LIMOGES
MOREAU	Stéphane	Doctor	HOPITAL DUPUYTREN, 2 AVENUE MARTIN LUTHER KING, 87042 LIMOGES
PENOT	Amélie	Doctor	HOPITAL DUPUYTREN, 2 AVENUE MARTIN LUTHER KING, 87042 LIMOGES
REMENIERAS	Liliane	Doctor	HOPITAL DUPUYTREN, 2 AVENUE MARTIN LUTHER KING, 87042 LIMOGES
TOUATI	Mohamed	Doctor	HOPITAL DUPUYTREN, 2 AVENUE MARTIN LUTHER KING, 87042 LIMOGES
CAHN	Jean Yves	Doctor	CH DE GRENOBLE, AVENUE DES MAQUIS DU GRESIVAUDAN, 38700 GRENOBLE
BULABOIS	Claude Eric	Doctor	CH DE GRENOBLE, AVENUE DES MAQUIS DU GRESIVAUDAN, 38700 GRENOBLE
GARBAN	Frédéric	Doctor	CH DE GRENOBLE, AVENUE DES MAQUIS DU GRESIVAUDAN, 38700 GRENOBLE

GRESSIN	Rémy	Doctor	CH DE GRENOBLE, AVENUE DES MAQUIS DU GRESIVAUDAN, 38700 GRENOBLE
CARRE	Martin	Doctor	CH DE GRENOBLE, AVENUE DES MAQUIS DU GRESIVAUDAN, 38700 GRENOBLE
MARIETTE	Clara	Doctor	CH DE GRENOBLE, AVENUE DES MAQUIS DU GRESIVAUDAN, 38700 GRENOBLE
MOLINA	Lysiane	Doctor	CH DE GRENOBLE, AVENUE DES MAQUIS DU GRESIVAUDAN, 38700 GRENOBLE
PEGOURIE BANDELIER	Brigitte	Doctor	CH DE GRENOBLE, AVENUE DES MAQUIS DU GRESIVAUDAN, 38700 GRENOBLE
PARK	Sophie	Professor	CH DE GRENOBLE, AVENUE DES MAQUIS DU GRESIVAUDAN, 38700 GRENOBLE
THIEBAUT BERTRAND	Anne	Doctor	CH DE GRENOBLE, AVENUE DES MAQUIS DU GRESIVAUDAN, 38700 GRENOBLE

Appendix 3.2. List of Independent Ethics Committee (IEC) or Institutional Review Board (IRB) and Corresponding Protocol Approval Dates

NA

APPENDIX 4. STATISTICAL ANALYSIS PLAN

Non-Interventional Study Protocol

B1871047

BOSEVAL: An Observational Study - Evaluation of Efficacy and Safety of Bosulif® Under Real Life Conditions of Use

Statistical Analysis Plan

(SAP)

Version: 1

Author: Lespinasse, Jérémie (eXYSTAT)

Date: 31-Aug-2023

TABLE OF CONTENTS

ABBREVIATIONS

Abbreviation	Term
AE	Adverse Event
CI	Confidence Interval
CRF/eCRF	(electronic) Case Report Form
EFS	Event-Free Survival
FAS	Full Analysis Set
HR	Hazard Ratio
NI/NIS	Non-Interventional (Study)
OS	Overall Survival
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SOC	System Organ Class

10. AMENDMENTS FROM PREVIOUS VERSION(S)

Version	Effective Date	Change Type (New, Revise, Admin)	Summary of Revisions
1	*31-Aug-2023*	*New*	

11. INTRODUCTION

Note: in this document, any text taken directly from the non-interventional (NI) study protocol is ***italicised***.

Chronic myeloid leukemia (CML) is a malignant hematological disease which belongs to the group of myeloproliferative syndromes. This hematologic disease is a rare disease, with 600 to 700 new cases per year, accounting for 15% to 20% of all cases of leukemia. Mean age at time of diagnosis is 54 years and the disease affects 1.4 males vs. 1 female patient.

The disease, referred to as chronic, develops gradually and evolves slowly in three successive phases, becoming increasingly resistant to treatments with progression of disease: chronic phase (CP CML), accelerated phase (AP CML) and blast phase (blast crisis) (BP CML).

In spite of recent advances in treatment and management of patients with chronic myeloid leukemia (CML), an important unmet medical need persists for many patients who are resistant or intolerant to one or more tyrosine kinase inhibitors (TKI). Treatment with bosutinib offers an additional alternative for patients with CML resistant or intolerant to one or more previous therapies with TKI. In light of the availability of several targeted therapies for treatment of CML, each of which has a specific safety and tolerability profile, it is important to evaluate the efficacy, safety and modalities for use of these treatments under real-life conditions in France. This non-interventional study will make it possible to obtain data under real-life conditions of use of

bosutinib in treatment of CML (all phases combined) in patients previously treated with one or more TKI and for whom imatinib, dasatinib or nilotinib are not considered as appropriate treatments.

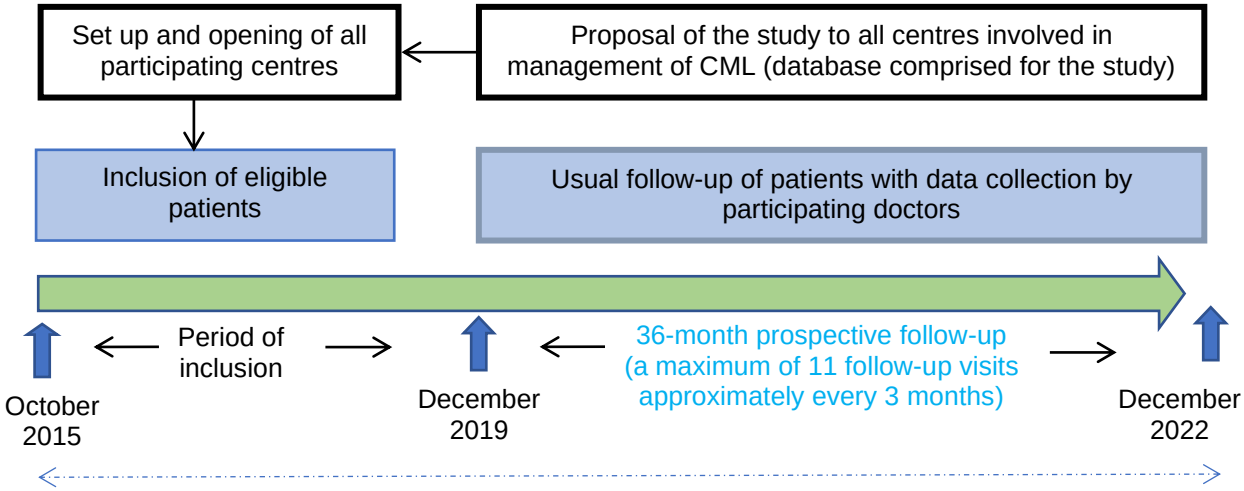
11.1. Study Design

This is a non-interventional, national, observational, descriptive, prospective, multi-centre study conducted in Metropolitan France in adult patients treated for chronic phase, accelerated or blast phase Philadelphia chromosome positive and negative (Ph+/-) CML, previously treated with one or more TKIs and for whom imatinib, dasatinib or nilotinib are not considered as appropriate treatments. The study will be conducted in all centres involved in management of CML, i.e. about twenty (20) centres are expected.

The study will be offered to all patients who satisfy criteria for eligibility up to the end of the recruitment period. Eligible patients but not included in the study will be recorded in a non-inclusion registry.

Follow-up

Patients will be followed prospectively throughout the duration of the study (3-year follow-up) starting from their inclusion in the study. Follow-up data will be collected at



follow-up visits conducted in the setting of usual management, estimated at every 3 months independently of discontinuations, changes or discontinuations of treatment possibly implemented. Therapeutic management of the patient will not be changed by participation in the study.

Figure 14 – Overall study flowchart

Study population

Since CML is a rare disease, a minimum number of patients is not expected. Therefore, in this context about 100 patients included in the study appears to be a reasonable objective, which will make it possible to have acceptable precision for estimates measured.

Inclusion criteria

Patients must satisfy all of the following criteria for inclusion in order to be eligible.

- *Male or female patient 18 years of age or older;*
- *Patient with Philadelphia chromosome positive or negative CML, or BCR-ABL positive, chronic, accelerated or blast phase;*
- *Patient resistant or intolerant to previous therapy with TKI for CP, AP or CB CML other than bosutinib;*
- *Patient initiating treatment with bosutinib for treatment of CP, AP or BP phase Ph+ / - CML at the end of the inclusion visit or during the one month prior to it;*
- *Patient who has been informed that a method of contraception must be used if a risk of pregnancy exists.*
- *Patients who have been informed about the study and who signed the informed consent form.*

Non-inclusion criteria

Patients who satisfy one of the following criteria will not be included in the study:

- *Patient with Philadelphia chromosome negative CML, BRC-ABL negative chronic, accelerated or blast phase CML;;*
- *Patient recently diagnosed with CML and who has not received previous treatment with a TKI;*
- *Patient currently treated with a treatment other than bosutinib;*
- *Patient of childbearing potential not using a method of contraception;*
- *Patient treated in the setting of an interventional study for another disease (outside of follow-up period);*
- *Patient who refuses computer processing of his/her medical data.*

Data sources

Social and medical data collected will be obtained from patients' medical dossiers at follow-up visits usually performed in centres in the setting of routine management of the patient, estimated at every 3 months in the setting of evaluation of response to treatment.

Patients will also be asked to complete questionnaires on measurement of compliance with treatment, the Morisky medication adherence scale (completed at all follow-up visits, estimated at every 3 months) and measurement of quality of life, the FACT-leu questionnaire version 4 (completed only at visits corresponding to months M0, M3, M6, M12, M18, M24 and M36) in paper format, that they will complete on site and will return to the doctors at the corresponding visit.

The following data will be collected as part of the study during patients' regular visits to the centers (estimated every 3 months).

Table 3 - Patient Data Collected

	Inclusion visits	Follow-up visits

Type of data	Prior to bosutinib	Bosutinib Initiation	During bosutinib	After bosutinib	Latest news
Data completed by the doctor (questionnaires via eCRF)					
Verification of eligibility criteria		X			
Demographic data	X				
Initial diagnosis of CML	X				
Therapeutic management of CML (previous treatments, best responses to treatment, tests)	X				
Description of pathology at initiation of bosutinib (CML phase, treatment responses and examination, reason for previous line change)		X			
Patient status at baseline (ECOG performance index, history and comorbidities)		X			
Mutational analyses		X			
Biochemical and haematological assessments		X	X		
Description of initiation of bosutinib treatment		X			
Concomitant treatments		X	X		
Description of treatment with bosutinib (changes to terms of use, best answers, reviews)			X		
Modification of concomitant treatments			X		
Pharmacovigilance			X	X	
Evolution of the pathology				X	

Post-bosutinib therapeutic care				X	
Patient status at last new					X
Data completed by the patient (self-questionnaires in paper format)					
Adherence (Morisky 8 items)**			X		
Quality of life (FACT-leu v4)**		X	X*		

* The patient self-questionnaire measuring quality of life will only be issued at certain follow-up visits (M3, M6, M12, M18, M24, M36).

** The Quality of Life and Compliance self-questionnaires will only be completed when the patient is on treatment. (The questionnaires will therefore not be completed during long-term follow-up visits).

11.2. Study Objectives

The aim of this observational study, whose primary objective is to evaluate the safety and the rate of discontinuation of treatment because of intolerance, is going to make it possible to describe management of adverse events (dose adjustment, temporary discontinuation, permanent discontinuation of treatment) under real life conditions of use of Bosutinib in France.

Primary objectives

Under real life conditions of use:

- *To determine the proportion of patients with CP, AP or BP Ph+/- CML presenting with AEs considered related to bosutinib by the participating doctor according to:*
  - *type of adverse event;*
  - *grade of event: 1, 2, 3, 4 or 3/4.*
- *To evaluate the proportion of patients who permanently discontinued bosutinib following an AE considered related to bosutinib by the participating doctor.*

Secondary objectives

Under real life conditions of use:

- *To determine the safety profile of bosutinib: AEs that occurred during treatment with bosutinib, AEs which required changes to treatment with bosutinib, biological and hematological toxicities that occurred with bosutinib.*
- *To evaluate adherence of patients to treatment of bosutinib, with the aid of a self-questionnaire completed by patients (Morisky Questionnaire).*
- *To evaluate quality of life of patients treated with bosutinib, with a self-questionnaire completed by patients (FACT-leu version 4 - Questionnaire specific for leukemia)*
- *To describe the modalities of treatment with bosutinib under real life conditions of use (dose adjustment and reason for adjustment, dose intensity, relative dose intensity; duration of treatment, temporary discontinuations/permanent discontinuations and reasons for such discontinuations).*
- *To evaluate the cumulative response rates: hematological /CHR), cytogenetic (CCyR / MCyR/ PCyR) and molecular response (MMR/CMR).*
- *To evaluate effectiveness of treatment with bosutinib:*
    - *Progression-free survival at 1, 2 and 3 years of patients treated with bosutinib*
    - *Overall survival (OS) at 1, 2 and 3 years in patients treated with bosutinib*
    - *The percent transformation to AP/BC*
- *To describe the modalities of hematological, cytogenetic and molecular responses: median time to occurrence of response, median duration of response, type of response according to dose.*
- *To describe characteristics of patients treated with bosutinib (demographic characteristics; previous medical conditions, comorbidities; duration between time of diagnosis and initiation of treatment; previous treatments and better response under these treatments; duration of previous treatments, reasons for*

discontinuation of previous treatments; the last hematological, cytogenetic or molecular responses known).

- *To evaluate cross intolerance between bosutinib and tyrosine kinase inhibitors prescribed previously.*

12. INTERIM ANALYSES

Descriptive interim analyses were performed for publication purpose.

13. HYPOTHESES AND DECISION RULES

13.1. Statistical Hypotheses

This study is a non-interventional and uncontrolled study. In that sense, there is no inferential hypothesis that will serve for a claim.

13.2. Statistical Decision Rules

The analysis of this study will be mainly descriptive. However, predictive factors of treatment response will be identified using univariable and multivariable modelling that will be carried out by testing whether the corresponding estimated parameters are significantly non-zero. All these statistical tests will be exploratory in nature and no correction will be applied for multiplicity.
The level of type I error (α) will be set at 5% for all statistical tests, excepted for univariable analysis where the type I error will be set at 10%. Ninety-five percent confidence intervals (95%CI) will be provided when appropriate.

14. ANALYSIS SETS/POPULATIONS

14.1. Full Analysis Set

The full analysis set (FAS) will be defined as all patients who received at least one dose of bosutinib and who are eligible (compliance with inclusion and exclusion criteria).

14.2. Safety Analysis Set

The safety analysis set (SAF) will be defined as all patients who received at least one dose of bosutinib.

14.3. Other Analysis Set

Eligible patients but not included in the study will be reported in a registry of non-inclusion with a minimum collection of information.

14.4. Subgroups

Descriptive statistics will be provided overall and by subgroup defined by the CML phase defined at study inclusion:

- chronic phase (CP),
- accelerated phase (AP)
- blast phase (blast crisis) (BP)

Descriptive statistics will be provided overall and by subgroup defined by treatment lines. Expected treatment lines are:

- 2^{L},
- 3^{L},

- 4L+

A change in dosage or combination of CML treatment does not constitute a change in line.

15. ENDPOINTS AND COVARIATES

15.1. Effectiveness Endpoints

Responses

In this section, some endpoints have been deleted or modified compared to the initial protocol in order to be as consistent as possible with the study design.

Cumulative response rate (at least one time)

- *Cumulative hematological response,* complete (CHR) *:*
    - *percent of patients presenting with a CHR at any time during treatment with bosutinib (best response according to the participating doctor's judgement)*
- *Cumulative cytogenetic response,* major (MCyR), complete (CCyR), partial (PCyR), or minor (mCyR)*:*
    - *percent of patients presenting with CCyR at any time during treatment with bosutinib (best response according to the participating doctor's judgement)*
    - *percent of patients presenting with PCyR at any time during treatment with bosutinib (best response according to the participating doctor's judgement)*

- *percent of patients presenting with mCyR at any time during treatment with bosutinib (best response according to the participating doctor's judgement)*

**Major response (MCyR) percent of patients presenting with MCyR at any time during treatment with bosutinib (best response according to the participating doctor's judgement) will be derived from the complete and partial response.*

- *Cumulative molecular response,* MR3, MR4, MR4.5, MR5*:*
  - *percent of patients presenting with MR3, MR4; MR4.5; MR5 at any time during treatment with bosutinib (best response according to the participating doctor's judgement)*

Suboptimal response ***(after dose escalation or without dose escalation due to ongoing toxicities):***

- *Patient with chronic phase CML, refer to ELN guidelines 2013.*
- *Patient with accelerated phase or blast phase CML, loss of all hematological response.*

Time to response

For each response (hematological, cytogenetic, molecular), the time to response will correspond to the duration between date of initiation of bosutinib and the first date of response.

* if the patient is already in response at initiation, time to response should be defined as the time between the first date of response to a better response or the maintenance with bosutinib.

Event Date and Outcome for time to response

Scenario	**Date of Event/Censoring**	**Outcome**
Response to bosutinib (all types)	Date of response	Event

Death during bosutinib	Date of death	Censored
Discontinuation of bosutinib	Date of discontinuation	Censored
Lost to follow-up	Date of last contact	Censored

Duration of response

For each response (hematological, cytogenetic, molecular), the duration of response will correspond to the duration between first date of response as defined in the aforementioned and the confirmed loss of response, the progression of disease or death of the patient.

* if the patient is already in response at initiation, duration of response should be defined as the duration between the first date of response and the confirmed loss of response, the progression of disease or death of the patient. to a better response or the maintenance with bosutinib.

Event Date and Outcome for duration of response

Scenario	**Date of Event/Censoring**	**Outcome**
Loss of response	Date of loss of response	Event
Disease progression	Date of disease progression	Event
Death while responding	Date of death	Event
Alive at end of follow-up	Date of last contact	Censored
Lost to follow-up	Date of last contact	Censored

Type of response according to dose

Percent of patients with a response according to mean dose received in period of follow-up to response. Proportions are calculated for each type of response (HR, CyR or MR) and strata of dose a day (e.g. strata could be $\leqslant$ 200, >200 to $\leqslant$ 400, >400 to $\leqslant$

600, >600 but may be changed to provide relevant information based on the number of observations)

Progression

The proportion of patients with progression of CML defined as passage from CP phase to AP or BP phases. This progression is validated by two consecutive evaluation less than one week apart.

- *Patients presenting an increase in leukocyte count in at least one period greater than or equal to one month, with second assay measurement > 20 x 109/L and confirmed at least one week later.*
- *Patients presenting a loss of major hematological response (with hematological confirmation within a time greater than or equal to 2 weeks after loss of initial response) or non-confirmation of major cytogenetic response (with a Ph+ rate increased by 30%).*

The proportion of patients with at least one change in disease phase, and patient progressor from CP to AP, from CP to BP, and from AP to BP.

Progression Free Survival (PFS)

PFS is defined as the time from first day of treatment with bosutinib to date of progression estimated by the participating doctor or death of patient (all causes combined). The censoring and event date options to be considered for the PFS analysis are defined as follows:

Event Date and Outcome for PFS

Scenario	Date of Event/Censoring	Outcome
Death during bosutinib	Date of death	Event
Death after treatment discontinuation	Date of death	Event
Disease progression during bosutinib	Date of disease progression	Event
Disease progression after treatment discontinuation	Date of disease progression	Event
Alive without disease progression at end of follow-up	Date of last contact	Censored
Lost to follow-up	Date of last contact	Censored

Overall Survival (OS)

OS is defined as the time from first day of treatment with bosutinib to date of death, all causes combined. The censoring and event date options to be considered for the OS analysis are defined as follows:

Event Date and Outcome for OS

Scenario	Date of Event/Censoring	Outcome
Death during bosutinib	Date of death	Event
Death after treatment discontinuation	Date of death	Event
Alive at end of follow-up	Date of last contact	Censored
Lost to follow-up	Date of last contact	Censored

15.2. Safety Endpoints

Exposure to Bosutinib

Describing treatment modalities for bosutinib under real life conditions of use will include:

- *Dosage: mean dosage prescribed at time of initiation and average dosage during treatment.*
- *Change to dose and reasons: percent of patients with dose reduction/percent of patients with a dose increase and if applicable, description of the reason.*
- *Maintenance of dose intensity and relative dose intensity (defined as the result of the ratio of the dose received over the expected dose): percent of patients with a dose intensity/relative dose intensity maintained over time and at different measurement times.*
- *Temporary discontinuation of treatment: percent of patients with temporary discontinuation of treatment and description of the reason; cumulative duration of temporary discontinuations.*
- *Permanent discontinuation of treatment: percent of patients with a permanent discontinuation of treatment and description of reason for discontinuation.*
- *Duration of treatment: duration of initiation up to discontinuation of treatment will be calculated for all causes of discontinuation combined and by cause of discontinuation.*

Event Date and Outcome for Duration of treatment

Scenario	**Date of Event/Censoring**	**Outcome**
Bosutinib discontinuation (all causes)	Date of treatment discontinuation	Event
Death during bosutinib	Date of death	Censored

Alive and treated with bosutinib	Date of last news	Censored
Lost to follow-up	Date of last contact	Censored

- Cumulative duration of treatment defined as duration of treatment minus cumulative duration of temporary discontinuations.
- Time to treatment failure (TTF): Duration of treatment from initiation up to permanent discontinuation for all causes

Event Date and Outcome for TTF

Scenario	**Date of Event/Censoring**	**Outcome**
Permanent Bosutinib discontinuation (all causes)	Date of permanent treatment discontinuation	Event
Death during bosutinib	Date of death	Censored
Alive and treated with bosutinib	Date of last news	Censored
Lost to follow-up	Date of last contact	Censored

<u>Average dose during the treatment</u>

The average dose during the treatment is the mean of the doses indicated to the patient during their follow-up (in mg/day):

- If the treatment dose remains unchanged during the follow-up, the average dose is equal to the prescribed dose at initiation.
- If the treatment dose is modified, the average dose is equal to the sum of the products of the prescribed doses (in mg/day) by the number of days treated at those doses, divided by the total number of actual treatment days.

<u>Dose intensity</u>

The dose intensity is defined as the treatment dose received per unit of time. For this study, the received dose is the prescribed dose at initiation (in mg/day) or, in case of treatment modification, the new prescribed dose defined by the physician.
The relative dose intensity is the result of the ratio of the dose received per unit of time (dose intensity) to the expected dose per unit of time (recommended dose according to the bosutinib Summary of Product Characteristics: 500 mg/day). The relative dose intensity will be calculated at each timepoints.

Adverse Events

All AEs will be coded using the MedDRA dictionary by System Organ Class (SOC) and grade of event according to the CTCAE v4.03 (1, 2, 3, 4 or 3-4). Safety endpoints will be analysed for the whole study duration from M0 to M36 (overall and by subgroups).

Primary endpoints:

- The proportion of patients presenting with AE considered related to bosutinib by the participating doctor (overall, by types of event and by grade of event)
- The proportion of patients who permanently discontinued bosutinib following an AE considered related to bosutinib by the participating doctor (overall).

Secondary endpoints:

- The proportion of patients presenting AE that occurred during treatment with bosutinib by SOC (overall and by grade of event)
- The proportion of patients presenting AE which required changes to treatment with bosutinib by SOC (overall and by grade of event)
- The proportion of patients presenting biological and hematological toxicities that occurred with bosutinib

- The proportion of patients who permanently discontinued bosutinib because of an AE which had resulted in discontinuation of a previous treatment (imatinib, dasatinib, nilotinib). Cross intolerance will be estimated for all AEs, but also by type of adverse event.
- Measures taken to prevent AE

Biological and Hematological Parameters

Biological and hematological parameters are collected as continuous variables.

15.3. Other Endpoints

Characteristics of the Patients Treated with Bosutinib

The description of the population covered will present the characteristics of patients at time of initiation of treatment:

- *demography;*
- *medical history and comorbidities, duration between diagnosis and initiation of Bosutinib treatment and latest hematological, cytogenetic or molecular responses known (cytogenetic and molecular responses will be mentioned only if patient is in chronic phase);*
- *previous treatments: number of lines of treatment, medicinal products, best response during treatment (hematological, cytogenetic or molecular responses), reasons for discontinuation of previous treatments.*

Data at the time of initiation of treatment are data collected at last inclusion visit (M0) or previous inclusion visit before bosutinib initiation. Description will be provided overall and by subgroups.

Quality of Life

The quality of life (QoL) of the patient will be assess with the FACT-leu version 4, a specific questionnaire on Leukemia for Functional Assessment of Cancer Therapy. The questionnaire includes 44 items on a 5-point Likert-type scale scored 0 to 4 (“Not at all”, “A little”, “Moderately”, “Much”, “Enormously”). Items are organized in 5 subscale domains:

- Physical Well-Being or PWB (7 items from 1 to 7): sum score ranges from 0 to 28, Likert-type scale need to be reverse from item 1 to 7.

$$PWB = 7 * \frac{\sum_1^{\mathrm{i}} \mathrm{GP(i)}}{\text{Number of GPi items answered}}$$

- Social/Family Well-Being or SWB (7 items from 8 to 14): sum score ranges from 0 to 28.

$$SWB = 7 * \frac{\sum_1^{\mathrm{i}} \mathrm{GS(i)}}{\text{Number of GSi items answered}}$$

- Emotional Well-Being or EWB (6 items from 15 to 20): sum score ranges from 0 to 24, Likert-type scale need to be reverse for item 15, 17, 18, 19, 20.

$$EWB = 6 * \frac{\sum_1^{\mathrm{i}} \mathrm{GE(i)}}{\text{Number of GEi items answered}}$$

- Functional Well-Being or FWB (7 items from 21 to 27): sum score ranges from 0 to 28.

$$FWB = 7 * \frac{\sum_1^{\mathrm{i}} \mathrm{GF(i)}}{\text{Number of GFi items answered}}$$

- Leukemia Subscale or LeuS (17 items from 28 to 44): sum score ranges from 0 to 68, Likert-type scale need to be reverse for the items from 28 to 37 and from 40 to 44.

$$LEUS = 17 * \frac{\sum \begin{matrix}(\text{BRM3, P2, BRM2, ES3, LEU1, TH1, TH2, HI12,} \\ \text{BMT6, C2, C6, An7, N3, LEU5, LEU6, BRM9, LEU7})\end{matrix}}{\text{Number of Leus items answered}}$$

Each subscale score (PWB, SWB, EWB, FWB ans LeuS) is computed as the sum score multiply by the number of items in the domain divided by the number of items answered.

Then the following scores will be derived where the higher the score, the better the QoL:

- FACT-Leukemia Trial Outcome Index (TOI) as the sum of PWB, FWB and LeuS range from 0 to 124.

$$TOI = PWB + FWB + LeuS$$

- FACT-G total score as the sum of PWB, SWB, EWB and FWB range from 0 to 108.

$$FACT - G = PWB + SWB + EWB + FWB$$

- FACT-Leukemia total score as the sum of PWB, SWB, EWB, FWB and LeuS range from 0 to 176.

$$FACT - Leukemia = PWB + SWB + EWB + FWB + LeuS$$

Derived scores will be calculated at each measurement time and the change in QoL will be defined by the difference between the best score recorded for a patient during follow-up visits (M3, M6, M12, M18, M24, M36) and his baseline score (M0 = inclusion visit).

Adherence to Treatment

The MMAS-8 (Morisky Questionnaire) rating scale consists of eight items added to obtain a total score. Items from 1 to 7 are scored with a “Yes” = 0 and “No” = 1. Item 8 is a 5-point response scored with A = 0 and B, C, D or E = 1. The total score will be

described continuously and categorically (0 = high adherence, 1-2 = average adherence, ⩾3 = low adherence) at each measurement visit (M3, M6, M9, M12, M15, M18, M21, M24, M27, M30, M33, M36).

15.4. Covariates

Predictive factors of the treatment response will be investigated and are listed hereafter:

- baseline characteristics of the patient (age, sex, weight, height, IMC, ECOG),
- medical history and comorbidities,
- baseline characteristics of the disease (phase, treatment line, BCR-ABL mutations, transplant history, previous response to treatment in particular TKIs, SOKAL score, time between diagnosis and treatment initiation),
- baseline biological and hematological parameters.

ECOG grade (from 0 to 5) and SOKAL scores (low, intermediate, or high) are categorical variables collected by the investigator.

16. HANDLING OF MISSING VALUES

For all analyses, only partially missing dates will be imputed. If the day of the month is missing for any date used in a calculation of time to event endpoints, the first of the month will be used to replace the missing date unless the calculation results in a negative time duration (eg, date of resolution cannot be prior to date of onset; if replacing resolution date with the first of the month results in a negative duration, the resolution date will be set to the onset date). If both month and day are missing, the date will be imputed to January 1 unless it results in negative time duration. For time-to-

event analyses if conventions result in a negative duration, duration will be reset to 1 day.

For data where start and stop dates are collected (eg, adverse events): for missing start dates, the rules above will be applied. For missing stop dates, if the day of the month is missing, the last day of the month will be used to replace the missing date. If both day and month are missing, December 31 of the non-missing year will be used to replace the missing date.

In a rare case when the exact death date is unknown, but the date of death is known to be between two dates, the earlier date will be used as the death date.

Missing data will be described as specified in section 0. No imputation methods will be used. Restricted maximum likelihood (REML) estimator that will be used for the analyses of available longitudinal continuous data and will assume that data are missing at random (MAR).

For time-to-event data, subjects who will drop out or complete the study without meeting the event criteria will be treated as censored at the last visit. Therefore, all subjects will be included in the survival analyses.

Other statistical tests or other statistical models will be performed on complete cases.

17. STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

17.1. Statistical Methods

Descriptive Statistics

Quantitative variables will be described using number of filled and missing data, mean, standard deviation, median, 1st and 3rd quartiles, minimum and maximum.
Qualitative variables will be described using number of filled and missing data and, for each modality, the frequency and percentage (referring to filled data).
Ordinal variables will be described using the most appropriate method (continuous variables or categorical variables).

Unless otherwise specified, the following conventions will be applied to all analyses:

- Mean, standard deviation (SD), median, first and third quartiles (Q1 and Q3) values will be formatted to 1 more decimal place than the measured value. Minimum and maximum values will be presented with the same number of decimal places as the measured value.
- Percentages will be rounded to 1 decimal place. Number and percentage values will be presented as xx (xx.x%).
- P-values will be rounded to 3 decimal places. P-values that round to 0.000 will be presented as '< 0.001' and p-values that round to 1.000 will be presented as '> 0.999'.

Means and percentage will be further described with 95CI% where appropriate.

When specified, absolute change from baseline will be used and defined as follow:
Absolute change from baseline B at visit V (unit) = Value at V (unit) – Value at B (unit)

Analyses of Time-to-Event Data

Kaplan-Meier estimates (product-limit estimates) will be presented together with a summary of associated statistics including the median survival time with 95%CI at the specified timepoints (yearly).

The CIs for the median will be calculated according to Brookmeyer and Crowley (Brookmeyer, 1982) and the CIs for the survival function estimates at the time points will be derived using the log-log transformation according to Kalbfleisch and Prentice (Kalbfleisch and Prentice 1980) (conftype=loglog default option in SAS Proc LIFETEST) with back transformation to a CI on the untransformed scale. The estimate of the standard error will be computed using Greenwood's formula(Kalbfleisch and Prentice 2002). Frequency (number and percentage) of participants with each event type and censoring reasons will be presented.

The follow-up duration will also be assessed using a Kaplan-Meier method reversing the censoring and event indicators.

Longitudinal Analyses of Continuous Data

Changes from baseline at specified follow-up assessment time points will be analyzed using a mixed model for repeated measures (MMRM) under the MAR framework. Analyses will include the fixed, categorical visit (including baseline). An unstructured (co)variance structure will be used to model the within-participant errors. If this analysis fails to converge, the following structures will be tested: *a heterogeneous Toeplitz covariance structure followed by the heterogeneous first-order autoregressive covariance structure will be considered*. The covariance structure converging to the best fit, as determined by Akaike's information criterion, will be used as the primary analysis. The Kenward-Roger approximation will be used to estimate de-nominator degrees of freedom. Mean changes from baseline will be assessed using appropriate contrasts of least-squares means. Two-sided 95% confidence intervals will be provided.

Code SAS:

```
proc mixed data=<infile> method=reml;
  class patid visit;
  model eval = visit / ddfm=kr;
  repeated visit / subject=patid type=un;
  lsmeans visit / cl;
  estimate 'Change t1 - 0' visit -1 1 0 0 ..0 / cl;
  estimate 'Change t2 - 0' visit -1 0 1 0 ..0 / cl;

  estimate 'Change tx - 0' visit -1 0 0 0 ..1 / cl;
run;
```

Multivariable Analyses of Binary and Categorical Variables

Multivariable logistic regression and multivariable multinomial logistic regressions will be used to estimate by maximum likelihood (ML) the association of a qualitative parameters (response to treatment) with predictive factors. Multinomial logistic regressions will only be performed if the number of collected observations is sufficient for each modality to estimate the models.
Results will be report in term of ORs with their 95%CI for each categorical and continuous variable implemented in the models.

SAS syntax for logistic regression

PROC LOGISTIC DATA=*dataset****;***
CLASS *response <predictive_factor>****;***
MODEL response *=predictive_factor* ***/ LINK=LOGIT;***
ODDSRATIO *predictive_factor* ***/ CL=PL;***
RUN;

SAS syntax for multinomial logistic regression

PROC LOGISTIC DATA=*dataset;*

CLASS *response <predictive_factor>;*

MODEL *response = predictive_factor* ***/ LINK=GLOGIT;***

ODDSRATIO *predictive_factor* ***/ CL=PL;***

RUN;

<predictive_factor> only specified in the CLASS statement if it corresponds to a categorical variable.

Predictive factors associated to an outcome of interest () will be identified using univariable logistic regression models. A separate logistic regression model will be created for each factor listed in section 15.4. If the variable is significantly associated to the outcome at the 10% level then the factor will be put forward into a multivariable model. Once the univariable model selection is complete, backwards selection will be used to remove factors from the multivariable model which do not have a significant p value at the 5% level. The covariate with the highest p value will be removed in turn until all factors have a p value less than 0.05. If a significant interaction is found then the individual factors of this interaction will be kept in the model, regardless of their p value. A significant interaction is tested for between all variables in the multivariable model. Furthermore, a table showing all the 95% confidence intervals and p values for the odds ratios coming from the univariable and multivariable models will be provided.

Standardized differences

Standardized comparisons will be performed to assess the imbalance across specific groups and described the representativeness of the Study.

Effect size (ES, quantifying the size of the difference between two groups) will be used for continuous factor,

$$ES = \frac{|m_1 - m_2|}{S} ; S = \sqrt{\frac{(n_1-1)s_1^2+(n_2-1)s_2^2}{n_1+n_2-2}};$$

and Cramer's V transformed in an ES for categorical factors

$$ES = \frac{2V/1.253}{\sqrt{1-\left(\frac{V}{1.253}\right)^2}} ; V = \frac{\mathrm{X}^2}{n \times df} ; df = \min(r-1, c-1) ,$$

with r, c respectively the number off groups and number of categories.

The ES and Cramer's V transformed in an ES can be interpreted on the basis of thresholds proposed by Cohen': Small (⩽0.2), Medium (⩽0.5), Large (⩽0.8).

17.2. Statistical Analyses

Primary analyses will concern two safety analyses only, all other analyses are secondary.

Safety Analyses

All safety analyses will be performed in the SAF (See definition in section 14.2).

Exposure to Bosutinib

A summary table will be provided with the descriptive statistics of the variables which describe the treatment modalities for bosutinib under real life conditions of use by subgroups.

Duration of treatment will be described with a figure and summary table according to the methodology detailed in section 9.9.2.3 by subgroups (overall and by cause of discontinuation).

TTF will be described with a figure and summary table according to the methodology detailed in section 8.1.2 by subgroups.

Adverse Events

All safety analysis will be performed on the SAF population and will be reported overall and by subgroups (CML phases, treatment lines). All AEs will be listed.

Primary analyses

A summary table will be provided with the descriptive statistics for the number and proportion of patients presenting with AEs considered related to bosutinib by the participating doctor (overall, by type of adverse event; by grade of event: 1, 2, 3, 4 or 3-4).
A summary table will be provided with the descriptive statistics for the number and proportion of patients who permanently discontinued bosutinib following an AE considered related to bosutinib by the participating doctor.

Secondary analyses

A summary table of AEs will be provided with the descriptive statistics of the number and percentage for the following categories:

- AEs that occurred during treatment with bosutinib
- AEs which required changes to treatment with bosutinib

A summary table for cross intolerance will be provided overall and by type of AE with the descriptive statistics of the number and proportion of patients who permanently discontinued bosutinib because of an AE which had resulted in discontinuation of a previous treatment (imatinib, dasatinib, nilotinib).

A listing of the measures taken to prevent AE will be provided.

Biological and Hematological Parameter

Considering the sparsity of biological and hematological data that will be collected in this study, the longitudinal analysis initially planned in the protocol will not be conducted. A summary table with only descriptive statistics will only be provided at each time point.

Effectiveness Analyses

All effectiveness analyses will be performed in the FAS (See definition in section 14.1).

Analyses of the Responses to Bosutinib

Cumulative responses will be summarized by subgroups for:

- the number and percent of patients presenting with a CHR
- the number and percent of patients presenting with CCyR
- the number and percent of patients presenting with PCyR
- the number and percent of patients presenting with mCyR
- the number and percent of patients presenting with CMR
- the number and percent of patients presenting with an MMR

Time to response and duration of response will be described using the methodology presented in section 9.9.2.1.

Type of response according to dose will be described with the number and percentage of each type of response by dose and subgroups.

Predictive factors of the response will be investigated according to the methodology described in section 9.9.2.3. Summary tables with univariable and multivariable estimates of the ORs and 95%CI will be provided for 3 logistic models (one for each type of response: HR, CyR, MR) or 1 multinomial logistic model.

Progression of CML

A summary table will be provided with descriptive statistics of the number and percentage of patient which change in disease phase at least one time, and patient progressor from CP to AP, from CP to BP, and from AP to BP (overall and by treatment line)

Progression free survival

PFS will be described with a figure and summary table according to the methodology detailed in section 8.1.2 by subgroups.

Overall survival

OS will be described with a figure and summary table according to the methodology detailed in section 8.1.2 by subgroups.

Other Analyses

Analyses of Baseline Characteristics

A summary table of the baseline characteristics collected until initiation of bosutinib will be report with descriptive statistics overall, by CML phase and by treatment line. Data of variables that cannot be summarized using statistics will be listed.

Analyses of Long-Term Follow-up and Latest News Data

Description of Long-Term Follow-up Data

Data collected during long-term follow-up visits for patients who have permanently discontinued their bosutinib treatment will be described by visit as follows:

- Evolution of the CML phase
- Proportion of patients in AP
- Proportion of patients in CP
- Proportion of patients with changes in therapeutic management
- Prescribed treatment(s), line, status (ongoing/discontinued), and reason for discontinuation

Description of Latest News Data

Data collected in the latest news questionnaires will be described as follows:

- Patient status
- Cause of death
- Average duration of treatment before the last contact

Analyses of Morisky Scores

A summary table will be provided by subgroups with

- the descriptive statistics of the total score, and absolute change in total score from previous timepoints described continuously.
- The descriptive statistics of the total score described categorically at each measurement timepoints.

Analyses of Quality of Life

A summary table will be provided by subgroups with the descriptive statistics of the scores TOI, FACT-G and FACT-Leukemia at each timepoints and descriptive statistics of the maximum absolute positive change from baseline (as described in the section 0) and the absolute change from previous timepoints. A summary table of the LSMeans with 95%CI and LSMeans change from baseline (M0) with 95%CI, will be provided at each time point. Estimations will be reported overall and by subgroups according to the longitudinal analysis methodology detailed in section 8.1.3.

Analyses of Representativeness of the Study

Representativeness of the study will be assess with data from registry of non-inclusion, characteristics of participating centes and characteristics of lost to follow-up patient with standardized differences (as described in secio 8.1.5)

Registry of non-inclusion

A summary table with descriptive statistics for age and sex will be provided for patients reported in the registry of non-inclusion and patients included.
Number and proportion of patient refusal will be provided, other reasons for non-inclusion will be listed.

Representativeness of the participating centres

A summary table with descriptive statistics will be provided for:
Data on identification of participating doctors in each centre (gender, age, geographical location). It then will be verified that the sample of participating doctors is representative of hematologists in France in terms of sample size and type of centre in order to ensure outside validity of the study.
Verification will made by using an appropriate database with relevant information about haematologists in France. The database needs to be identified.

Assessment of the attrition bias

A summary table with descriptive statistics will be provided for baseline characteristics of the patients:

- included and who participated in the entire duration of the study
- included and lost to follow-up and/or who discontinued the study before the end of follow-up

Summary of Analyses

Outcome	Analysis Set	Supports Protocol Objective Number	Subgroups	Statistical Method	Covariates/ Strata	Missing Data
Treatment modalities for bosutinib under real life	SAF	6 (secondary)		Descriptive statistics		NA
Duration of treatment	SAF	6 (secondary)	CML phase, treatment line	Time-to-event data	Cause of discontinuation	NA
Time-to-treatment failure	SAF	6 (secondary)	CML phase, treatment line	Time-to-event data		NA
Number and proportion of patients presenting with AEs considered related to bosutinib	SAF	1 (primary)	CML phase, treatment line	Descriptive statistics	AE types / AE grades	NA
Number and Proportion of patients who permanently discontinued bosutinib following an AE considered related to bosutinib	SAF	2 (primary)	CML phase, treatment line	Descriptive statistics		NA
Number and proportion of AEs that occurred during treatment with bosutinib and AEs which required changes to treatment with bosutinib	SAF	3 (secondary)	CML phase, treatment line	Descriptive statistics		NA
Number and proportion of patients who permanently diconstinued bosutinib because of an AE which had resulted in	SAF	11 (secondary)	CML phase, treatment line	Descriptive statistics	AE types	NA

discontinuation of a previous treatment (imatinibn dasatinib, nilotinib)						
Number and proportion of patients pesenting with response	FAS	? (secondary)	CML phase, treatment line	Descriptive statistics	Response types	NA
Time to response	FAS	(secondary)		Time-to-event data	Response type	NA
Duration of response	FAS	(secondary)		Time-to-event data	Response type	NA
Number and proportion of response by dose	FAS	(secondary)	CML phase, treatment line	Descriptive statistics	Response type	NA
Predictive factors of the response	FAS	(secondary)	?	Multivariable analyses	Response type	NA
Number and proportion of patients which change in disease phase at least one time, of patients progressor from CP to AP, from CP to BP, and from AP to BP	FAS	(secondary)	Treatment line	Descriptive statistics		NA
Progression Free Survival	FAS	(secondary)	CML phase, treatment line	Time-to-event data		NA
Overall Survival	FAS	(secondary)	CML phase, treatment line	Time-to-event data		NA
Baseline characteristics collected until initiation of bosutinib	FAS	10 (secondary)	CML phase, treatment line	Descriptive statistics		NA

In long-term follow-up data: number and proportion of patients in AP, in CP, with changes in therapeutic management; number and proportions of prescribed treatment and characteristics.	FAS	(secondary)		Descriptives statistics	Visit number	NA
In latest news data: number and proportion of patient by status, cause of death; average duration of treatment before last contact	FAS	(secondary)		Descriptive statistics		NA
Total Morisky score and aboslute change from previous time point	FAS	4 (secondary)		Descriptive statistics		NA
TOI, FACT-G and FACT-Leukemia scores at each timepoints and maximum absolute change from baseline	FAS	5 (secondary)	CML phase, treatment line	Descriptive statistics		NA
LSMeans change from baseline at each timepoint	FAS	5 (secondary)	CML phase, treatment line	Longitudinal data		NA
Registry of non-inclusion	FAS	5 (secondary)		Descriptive statistics	Included and non-included	NA
Description of the participating centres	FAS	(secondary)		Descriptive statistics	Participating center and national references	NA
Description of attrition bias	FAS	(secondary)		Descriptive statistics	Complete follow-up and Incomplete follow-up	NA

18. LIST OF TABLES AND TABLE SHELLS

A list of tables (LOT) will be provided in a separate document.

19. REFERENCES

Kalbfleisch, J. D., & Prentice, R. L. (1980). *The Statistical Analysis of Failure Time Data.* New York: John Wiley & Sons.

Kalbfleisch, J. D., & Prentice, R. L. (2002). *The Statistical Analysis of Failure Time Data* (2nd ed.). New York: John Wiley and Sons.

20. APPENDICIES

20.1. Appendix 1: Data Derivation Details

20.1.1. A1.1 Definition and Use of Visit Windows in Reporting

Data will be summarized in tables by visit (timepoint) when applicable. The following visit labels and visit windows will be applied for the analysis of repeated measures:

Variables	***Visit Label***	***Target Day***	***Visit Window***
Quality of Life	*Baseline*	*1*	*Day 1 or before*
	Month 3	*91*	*Day 45 to Day 137*
	Month 6	*183*	*Day 138 to Day 274*
	Month 12	*365*	*Day 273 to Day 457*
	Month 18	*548*	*Day 458 to Day 639*
	Month 24	*730*	*Day 640 to Day 913*
	Month 36	*1095*	*Day 914 to Day 1278*
	Baseline	*1*	*Day 1 or before*

Variables	***Visit Label***	***Target Day***	***Visit Window***
Biological and Haematological *Variables*	*Month 3*	*91*	*Day 45 to Day 137*
	Month 6	*183*	*Day 138 to Day 229*
	Month 9	*274*	*Day 230 to Day 320*
	Month 12	*365*	*Day 321 to Day 411*
	Month 15	*456*	*Day 412 to Day 502*
	Month 18	*548*	*Day 503 to Day 594*
	Month 21	*639*	*Day 595 to Day 685*
	Month 24	*730*	*Day 686 to Day 776*
	Month 27	*821*	*Day 776 to Day 867*
	Month 30	*913*	*Day 868 to Day 959*
	Month 33	*1004*	*Day 960 to Day 1050*

In case of multiple observations falling within a given window, the observations selected for analysis will be identified as follows:

1. *The observation closest to the target day will be used.*
2. *If the observations are at equal distance from the target day in absolute value, the one with a correct nominal visit label will be used.*
3. *If neither (1) nor (2) can be used to identify the observation windowing, then the latest observation within the analysis window will be used.*

APPENDIX 5. Case Report Form

Case Report Form

Project number: 1179

Etude observationnelle

« Evaluation de l'efficacité et de la tolérance de Bosulif® en conditions réelles d'utilisation »

Data-management : **EURAXI-PHARMA**

Unité Biométrie

10, rue Gutenberg, BP 80325

37303 Joué Les Tours

Tel : +33 2 47 74 30 47 - Fax : +33 2 47 74 30 49

Promoteur : **Pfizer**

23-25, avenue du Dr Lannelongue

75668 Paris Cedex 14 France

Final version 3.2, 2023-12-04

HISTORIQUE DES MODIFICATIONS

Après l'édition de la version initiale du plan CRF, toutes les modifications de document doivent apparaitre dans un n° de version (débutant avec 0.1) comme défini ci-dessous :

→ Modification mineur (1.y): corrections d'orthographe, corrections de format et clarifications mineures apparaitront dans une version avec incrémentation du y (ex., version 1.0 à 1.1)

→ Modification majeure (x.0): changement dans les objectifs, dans l'assignation des responsabilités et les changements significatifs des activités de data-management apparaitront dans une version avec incrémentation du x (ex., version 1.0 à 2.0)

Le CRF est un document unique pouvant renvoyer vers plusieurs annexes séparées. Les annexes sont développées, revues et éventuellement approuvées de manière indépendante.

Le CRF sera conserve électroniquement au niveau de l'arborescence Data-management du projet.

Le Clinical Data Manager (CDM) s'assure qu'une copie de toutes les différentes versions est bien stockée au niveau du dossier électronique du projet.

L'historique des modifications décrira toutes les différentes versions du CRF, contenant une synthèse des changements et les numéros des versions amendés.

Une copie papier de la version en vigueur sera stockée dans le TMF. La version finale du CRF sera noté "Version finale" et sera classée dans le TMF, une fois le projet terminé.

Version	Date	Préparé par	Commentaires
2.4	2017-07-10	AA (Euraxi Pharma)	Ajout de l'unité log ou % pour « **Transcrit BCR-ABL »**

3.0	2019-06-26	JB (Euraxi Pharma)	Modification conformément à l'amendement du protocole v2 du 15/02/2019
3.1	2022-01-07	JB (Euraxi Pharma)	Suite demande Pfizer
3.2	2023-12-04	PMLM (Euraxi Pharma)	Correction de l'intitulé du CNI 4 avant amendement n°1

PAGE DE SIGNATURE

Les cosignataires déclarent avoir examiné le CRF et être en accord sur sa forme et son contenu.

Préparé par :

Pierre-Marie Le Meur

Euraxi-Pharma

Data-Manager	*Signature*	*Date*

Approuvé par :

Camille Cathary

Pfizer

Chef de projet	*Signature*	*Date*

C A H I E R D ' O B S E R V A T I O N

Identifiant Centre _|_|

Identifiant patient _|_|

VISITE D'INCLUSION

PATIENT N° |____|____|-|____|____|

N° de centre **N° du patient**

Critères d'éligibilité

Version applicable avant amendement n°1 (23 avril 2019)

CRITERES D'INCLUSION		
Homme ou femme âgé de 18 ans ou plus.	❑ Oui	❑ Non
Patient atteint d'une LMC à chromosome Philadelphie positif ou négatif, BCR-ABL positif, en phase chronique, accélérée ou blastique.	❑ Oui	❑ Non
Patient résistant ou intolérant à une thérapie antérieure par ITK pour une LMC PC, PA ou CB autre que bosutinib.	❑ Oui	❑ Non
Patient ayant initié un traitement par bosutinib pour le traitement d'une LMC Ph positive ou négative en phase PC, PA ou CB le jour de l'inclusion ou dans les 7 jours précédents.	❑ Oui	❑ Non
Patient en âge de procréer utilisant obligatoirement une méthode de contraception.	❑ Oui	❑ Non
Patient ayant été informé de l'étude et ayant signé son consentement.	❑ Oui	❑ Non

Un seul « non » à l'un des critères empêche l'éligibilité du patient dans l'étude

CRITERES D'EXCLUSION		
Patient atteint d'une LMC à chromosome Philadelphie négatif BCR-ABL négatif en phase chronique, avancée ou blastique.	❑ Oui	❑ Non
Patient récemment diagnostiqué pour une LMC et n'ayant pas reçu de traitement antérieur par ITK.	❑ Oui	❑ Non
Patient actuellement traité pour une LMC à chromosome Philadelphie positif par un traitement validé par l'EMA ou en cours d'expérimentation, autre que bosutinib.	❑ Oui	❑ Non
Patient en âge de procréer n'utilisant pas une méthode de contraception	❑ Oui	❑ Non
Patient déjà inclus dans une autre étude interventionnelle ou observationnelle, au moment de son screening.	❑ Oui	❑ Non
Patient refusant l'informatisation de ses données médicales.	❑ Oui	❑ Non

Un seul « oui » à l'un des critères empêche l'éligibilité du patient dans l'étude

Si le patient n'est pas inclus dans l'étude, merci de compléter le registre de non-inclusion

VISITE D'INCLUSION

PATIENT N° |____|____|-|____|____|

N° de centre **N° du patient**

Critères d'éligibilité

Version applicable après amendement n°1 (23 avril 2019)

CRITERES D'INCLUSION		
Homme ou femme âgé de 18 ans ou plus.	❑ Oui	❑ Non
Patient atteint d'une LMC à chromosome Philadelphie positif ou négatif, BCR-ABL positif, en phase chronique, accélérée ou blastique.	❑ Oui	❑ Non
Patient résistant ou intolérant à une thérapie antérieure par ITK pour une LMC PC, PA ou CB autre que bosutinib.	❑ Oui	❑ Non
Patient initiant un traitement par bosutinib pour le traitement d'une LMC Ph positive ou négative en phase PC, PA ou CB à l'issue de la visite d'inclusion ou dans le mois précédent celle-ci.	❑ Oui	❑ Non
Patient ayant été informé qu'une méthode de contraception doit être utilisée s'il existe un risque de grossesse.	❑ Oui	❑ Non
Patient ayant été informé de l'étude et ayant signé son consentement.	❑ Oui	❑ Non

Un seul « non » à l'un des critères empêche l'éligibilité du patient dans l'étude

CRITERES D'EXCLUSION		
Patient atteint d'une LMC à chromosome Philadelphie négatif BCR-ABL négatif en phase chronique, avancée ou blastique.	❑ Oui	❑ Non
Patient récemment diagnostiqué pour une LMC et n'ayant pas reçu de traitement antérieur par ITK.	❑ Oui	❑ Non
Patient n'ayant pas été informé qu'une méthode de contraception doit être utilisée s'il existe un risque de grossesse.	❑ Oui	❑ Non
Patient actuellement traité par un traitement autre que bosutinib.	❑ Oui	❑ Non
Patient traité dans le cadre d'une étude interventionnelle pour une autre pathologie (hors période de follow up).	❑ Oui	❑ Non

Patient refusant l'informatisation de ses données médicales.	❑ Oui	❑ Non

Un seul « oui » à l'un des critères empêche l'éligibilité du patient dans l'étude

Si le patient n'est pas inclus dans l'étude, merci de compléter le registre de non-inclusion

VISITE D'INCLUSION

PATIENT N° |____|____|-|____|____|

N° de centre **N° du patient**

Caractéristiques démographiques

Date de la visite d'inclusion : _|_| / _|_| / _|_| _|_| (JJ/MM/AAAA)

(Date de signature du consentement par le patient)

Date de naissance : _|_| / _|_|_|_| (MM/AAAA)

Sexe : ○ **Masculin** ○ **Féminin**

VISITE D'INCLUSION **PATIENT N°** |____|____|-|____|____|

N° de centre **N° du patient**

Diagnostic initial de la LMC

Diagnostic initial

Date du diagnostic initial : _|_| / _|_| / _|_|_|_| (JJ/MM/AAAA) ☐ **Date non connue**

Phase de la LMC au diagnostic : ⩔ **Chronique**

⩔ **Accélérée**

⩔ **Blastique**

⩔ **Non connue**

Examens réalisés pour l'établissement du diagnostic initial de la LMC

a. Caryotype médullaire : ○ **Oui** ○ **Non** ○ **Inconnu**

Si oui, **le réarrangement t (9,22) est – il présent ?** **Oui** **Non** **Inconnu**

b. FISH : ○ **Oui** ○ **Non** ○ **Inconnu**

Si oui**, Source de l'échantillon :** ☐ **Moelle osseuse** ☐ **Sang périphérique**

Pourcentage de noyaux positifs :_|_|_|,_| **%**

c. Analyses moléculaires par qRT-PCR : ○ **Oui** ○ **Non** ○ **Inconnu**

Si oui**, Préciser :** **Gène contrôle :** ⩔ **BCR**

⩔ **ABL**

⩔ **GSUB**

⩔ **Autre, préciser : _____**

Transcrit BCR-ABL : __|__|__|,__|__|__|__|__| ⩗% ⩗Log

VISITE D'INCLUSION

PATIENT N° |____|____|-|____|____|

N° de centre **N° du patient**

Caractéristiques du patient

Score de SOKAL au diagnostic connu : ○ **Oui** ○ **Non**

***Si oui*, score :** ○ **Faible** ○ **Intermédiaire** ○ **Elevé**

Affichage : un lien sera ajouté pour permettre de consulter la définition du score de SOKAL

Evolution de la phase de la LMC depuis le diagnostic initial : ○ **Oui** ○ **Non**

Si oui, **Phase(s) :** ☐ **Accélérée, date d'évolution** : _|_| / _|_| / _|_|_|_| (JJ/MM/AAAA)

☐ **Blastique, date d'évolution** : _|_| / _|_| / _|_|_|_| (JJ/MM/AAAA)

VISITE D'INCLUSION **PATIENT N° |____|____|-|____|____|**

N° de centre N° du patient

Antécédent de greffe

Antécédent de greffe : ○ **Oui** ○**Non**

Si oui, **merci de décrire toutes les transplantations reçues par le patient dans le cadre de la prise en charge de la LMC (y compris ce jour) :**

Date de la transplantation	Type	Source
_|_|/_|_|/_|_|_|_| (JJ/MM/AAAA)	☐allogénique ☐autologue	☐moelle osseuse (CSH) ☐sang périphérique (CSSP)
_|_|/_|_|/_|_|_|_| (JJ/MM/AAAA)	☐allogénique ☐autologue	☐moelle osseuse (CSH) ☐sang périphérique (CSSP)
_|_|/_|_|/_|_|_|_| (JJ/MM/AAAA)	☐allogénique ☐autologue	☐moelle osseuse (CSH) ☐sang périphérique (CSSP)
_|_|/_|_|/_|_|_|_| (JJ/MM/AAAA)	☐allogénique ☐autologue	☐moelle osseuse (CSH) ☐sang périphérique (CSSP)
_|_|/_|_|/_|_|_|_| (JJ/MM/AAAA)	☐allogénique ☐autologue	☐moelle osseuse (CSH) ☐sang périphérique (CSSP)

(Ajout de lignes possible si plus de transplantations sont observées)

VISITE D'INCLUSION

PATIENT N° |____|____|-|____|____|

N° de centre **N° du patient**

Thérapies antérieures par ITK

Ligne _|_|

Thérapie :
- ⩔ **Imatinib**
- ⩔ **Dasatinib**
- ⩔ **Nilotinib**
- ⩔ **Ponatinib**
- ⩔ **Autre, préciser :_____**

Dose : _|_|_|,_| **mg**

Fréquence :
- ⩔ **1 / jour**
- ⩔ **2 / jour**
- ⩔ **Autre, préciser : _____**

Date de début : _|_| / _|_| / _|_|_|_| (JJ/MM/AAAA)

Date de fin : _|_| / _|_| / _|_|_|_| (JJ/MM/AAAA)

Motif de changement de ligne :
- ⩔ **Absence de réponse**
- ⩔ **Perte de la réponse**
- ⩔ **Réponse suboptimale**
- ⩔ **Progression de la maladie (changement de phase)**
- ⩔ **Intolérance**
- ⩔ **Autre, préciser : ___**

Si Intolérance :

Merci de renseigner le grade dans la case correspondant à l'évènement indésirable

Gastro-intestinale
- _| Diarrhée
- _| Nausée
- _| Douleurs abdominales
- _| Vomissements
- _| Pancréatite

Troubles généraux
- _|Fatigue
- _| Œdème

Hépatique
- _| Augmentation ALAT
- _|Augmentation ASAT

Hématologique
- _| Anémie
- _| Thrombocytopénie
- _| Neutropénie

Troubles vasculaires
- _| Artériopathie oblitérant périphérique
- _| Ischémie périphérique
- _| Thromboses veineuse

☐ HTA

☐ Thrombose veineuse périphérique

Cardio-pulmonaire

☐ Allongement QTc

☐ HTAP

☐ Epanchement péricardique

☐ Epanchement pleural

Musculo-squelettique

☐ Arthralgie

☐ Douleurs lombaires

☐ Myalgie

Autre

☐ Autre, préciser : ___

Meilleure réponse ☐ Inconnue ☐ Absence de réponse ☐ Progression de la maladie (changement de phase)

Hématologique

- Complète
- Partielle
- Pas de réponse
- Inconnue/Pas évaluée

Cytogénétique

- Complète
- Partielle
- Majeure
- Mineure/Minimale
- Pas de réponse
- Inconnue/Pas évaluée

Moléculaire

- Majeure : RM^3
- RM^4
- $RM^{4.5}$
- RM^5
- Pas de réponse
- Inconnue/Pas évaluée

VISITE D'INITIATION DU TRAITEMENT

PATIENT N° |____|____|-|____|____|

N° de centre **N° du patient**

Initiation du traitement

Date d'initiation du traitement bosutinib : _|_| / _|_| / _|_|_|_| (JJ/MM/AAAA)

Posologie à l'initiation :

- **100mg/jour**
- **200mg/jour**
- **300mg/jour**
- **400mg/jour**
- **500mg/jour**
- **600mg/jour**
- **Autre, précisez: _|_|_| mg/jour**

Affichage : message concernant un sur dosage

Caractéristiques du patient à l'initiation de bosutinib

Poids : _|_|_|,_| **kg** **Taille :** _|_|_| **cm** **IMC :** _|_|,_| (auto)

Indice de performance ECOG à l'inclusion : ○ **Oui** ○ **Non**

Si oui, **Date :** _|_| / _|_| / _|_|_|_| (JJ/MM/AAAA)

Score : ○ **0** ○ **1** ○ **2** ○ **3** ○ **4**

Affichage : un lien sera ajouté pour permettre de consulter la définition de l'indice ECOG

Analyse mutationnelle du gène BCR-ABL réalisée depuis le diagnostic de la LMC

○ **Oui** ○ **Non**

Si oui, **Date de la dernière analyse mutationnelle :** _|_|/_|_|/_|_|_|_| (JJ/MM/AAAA)

☐ **Date non connue**

Mutation(s) identifiée(s) : ○ **Oui, préciser** _____

○ **Non**

VISITE D'INITIATION DU TRAITEMENT

PATIENT N° |____|____|-|____|____|

N° de centre **N° du patient**

Antécédents

Antécédents et comorbidités à l'initiation de bosutinib : ○**Oui** ○**Non**

***Si oui,* merci de décrire tous les antécédents et comorbidités du patient :**

Aide au remplissage du tableau 3 :

1) *Sélectionner l'antécédent ou la comorbidité que présente votre patient (si votre patient présente plusieurs antécédents ou comorbidités, merci de remplir une ligne pour chacun).*
2) *Précisez si le statut de l'antécédent ou la comorbidité est en cours ou terminé.*
3) *Est-ce que cet antécédent ou comorbidité est lié ou non à la thérapie antérieure par un ITK?*
4) *Est-ce que cet antécédent/comorbidités est actuellement pris en charge ou non?*

Antécédents et comorbidités	Statut	Causalité	Prise en charge
⩛**Affection cardiaque** ⩛Allongement de l'intervalle QTc ⩛**Affection vasculaire** ⩛Maladie artérielle périphérique ⩛Accident thrombotique ⩛HTA ⩛**Trouble métabolique** ⩛Diabète (tous types) ⩛**Affection rénale** ⩛Affection rénale ⩛**Maladie hépatique** ⩛Maladie hépatique ⩛**Affection pulmonaire** ⩛Hypertension pulmonaire ⩛Epanchement pleural ⩛BPCO ⩛**Affection hématologique** ⩛Myélosuppression	⩛ En cours ⩛Terminé	⩛Lié à une thérapie antérieure par ITK ⩛ Non lié à un ITK antérieur ***Si lié,*** préciser : ⩛Imatinib ⩛Dasatinib ⩛Nilotinib ⩛Autre, précisez : _____	⩛Actuellement traité ⩛Pas de traitement en cours

⮛**Troubles généraux**			
⮛Œdème			
⮛Fatigue			
⮛**Affection musculo-squelettiques**			
⮛Douleurs lombaires			
⮛Arthralgie			
⮛Myalgie			
⮛**Affection gastro-intestinale**			
⮛Pancréatite			
⮛**Autre affection**			
⮛Autre, préciser ____			

(Tableau dynamique : ajout de lignes possible si plus de comorbidités sont observées)

VISITE D'INITIATION DU TRAITEMENT

PATIENT N° |____|____|-|____|____|

N° de centre **N° du patient**

Description de la pathologie

Phase de la LMC à l'initiation du traitement par bosutinib

Date d'évaluation : _|_| / _|_| / _|_|_|_| (JJ/MM/AAAA)

Phase actuelle :

- ⩛ **Chronique**
- ⩛ **Accélérée**
- ⩛ **Blastique**
- ⩛ **Non connue**

Statut de la réponse au traitement précédent à l'initiation par bosutinib

a. * **Evaluation moléculaire réalisée :** ○ **Oui** ○ **Non** ○ **Evaluation non faite**

Si oui, **Date de l'évaluation :** _|_| / _|_| / _|_|_|_| (JJ/MM/AAAA)

Réponse :

- ⩛ **Majeure : RM[3]**
- ⩛ **RM[4]**
- ⩛ **RM[4.5]**
- ⩛ **RM[5]**
- ⩛ **Pas de réponse**

b. * **Evaluation cytogénétique réalisée :** ○ **Oui** ○ **Non** ○ **Evaluation non faite**

Si oui, **Date de l'évaluation :** _|_| / _|_| / _|_|_|_| (JJ/MM/AAAA)

Réponse :

- ⩛ **Complète**
- ⩛ **Partielle**
- ⩛ **Majeure**
- ⩛ **Mineure/Minimale**

⮟Pas de réponse

c. Evaluation hématologique réalisée : ○ Oui ○ Non

Si oui, **Date de l'évaluation : __/__/____ (JJ/MM/AAAA)**

Réponse : ⮟Complète

⮟Partielle

⮟ Pas de réponse

***** ***Le statut de la réponse moléculaire ou cytogénétique au traitement précédant l'initiation par bosutinib ne sera à renseigner qu'en cas de Phase chronique.***

VISITE D'INITIATION DU TRAITEMENT

PATIENT N° |____|____|-|____|____|

N° de centre **N° du patient**

Bilan biochimique

Bilan biochimique à l'inclusion : ○**Oui** ○**Non**

Si oui, **Date du dernier bilan biochimique :** __/__/__/__/__/__/__/__ (JJ/MM/AAAA)

Paramètres	Valeur obtenue	Valeur CS/NCS	Valeur Num	Unité
ALAT	○Oui ○Non	⩛Cliniquement significative ⩛Non cliniquement significative	|__|__|__| |	⩛UI/L ⩛Autre, préciser :
ASAT	○Oui ○Non	⩛Cliniquement significative ⩛Non cliniquement significative	|__|__|__| |	⩛UI/L ⩛Autre, préciser :
Bilirubine totale	○Oui ○Non	⩛Cliniquement significative ⩛Non cliniquement significative	|__|__|__| |	⩛mg/dL ⩛µmol/L ⩛g/dL ⩛Autre, préciser :
Bilirubine conjuguée	○Oui ○Non		|__|__|__| |	⩛mg/L ⩛µmol/L ⩛Autre, préciser :
LDH	○Oui ○Non		|__|__|__| |	⩛UI/L ⩛Autre, préciser :
Albumine	○Oui ○Non		|__|__|__| |	⩛ g/dL ⩛g/L ⩛Autre, préciser :
Amylase	○Oui ○Non	⩛Cliniquement significative ⩛Non cliniquement significative	|__|__|__| |	⩛UI/L ⩛Autre, préciser :
Lipase	○Oui ○Non	⩛Cliniquement significative ⩛Non cliniquement significative	|__|__|__| |	⩛UI/L ⩛Autre, préciser :
Créatinine sérique	○Oui ○Non	⩛Cliniquement significative ⩛Non cliniquement significative	|__|__|__| |	⩛mg/dL ⩛µmol/L ⩛mg/L ⩛Autre, préciser :
Glycémie (à jeun)	○Oui ○Non	⩛Cliniquement significative ⩛Non cliniquement significative	|__|__|__| |	⩛mg/dL ⩛mmol/L ⩛g/L ⩛Autre, préciser :
Glycémie (non à jeun)	○Oui ○Non	⩛Cliniquement significative ⩛Non cliniquement significative	|__|__|__| |	⩛mg/dL ⩛mmol/L ⩛g/L ⩛Autre, préciser :
Magnésium	○Oui ○Non		|__|__|__| |	⩛mg/L ⩛Autre, préciser :

Calcium	○Oui ○Non		|__|__|__|	⮟mg/L ⮟mmol/L ⮟Autre, préciser :
Urée sanguine	○Oui ○Non		|__|__|__|	⮟mmol/L ⮟g/L ⮟Autre, préciser :
Acide urique	○Oui ○Non		|__|__|__|	⮟mg/dL ⮟mg/L ⮟Autre, préciser :

**** Si Cliniquement significative, merci de déclarer un événement indésirable.***

☐ ***Je ne souhaite pas être contacté par le service de pharmacovigilance de Pfizer concernant le report ou suivi d'événements indésirables.***

VISITE D'INITIATION DU TRAITEMENT

PATIENT N° |____|____|-|____|____|

N° de centre **N° du patient**

Bilan hématologique

Bilan hématologique à l'inclusion : ○ **Oui** ○**Non**

Si oui, **Date du dernier bilan hématologique :** _|_| / _|_| / _|_|_|_| (JJ/MM/AAAA)

Paramètres	Valeur obtenue	Valeur CS/NCS	Valeur Num	Unité
Hémoglobine	○ Oui ○Non		|__|__|__|	⩛g/dL ⩛mmol/L ⩛g/L ⩛Autre, préciser :
Hématocrite	○ Oui ○Non		|__|__|__|	⩛% ⩛Autre, préciser : ___
Leucocytes	○ Oui ○Non		|__|__|__|	⩛ 10^9/L ⩛G/L ⩛Autre, préciser : ___
Plaquettes	○ Oui ○Non	⩛Cliniquement significative ⩛Non cliniquement significative	|__|__|__|	⩛ 10^9/L ⩛10^{12}/L ⩛G/L ⩛/mm^3 ⩛Autre, préciser : ___
Blastes (sang périphérique)	○ Oui ○Non	⩛Cliniquement significative ⩛Non cliniquement significative	|__|__|__|	⩛% ⩛Autre, préciser : ___
Basophiles	○ Oui ○Non		|__|__|__|	⩛ 10^9/L ⩛G/L ⩛/mm^3 ⩛% ⩛Autre, préciser : ___
Eosinophiles	○ Oui ○Non		|__|__|__|	⩛ 10^9/L ⩛G/L ⩛/mm^3 ⩛% ⩛Autre, préciser : ___
Neutrophiles	○ Oui ○Non	⩛Cliniquement significative ⩛Non cliniquement significative	|__|__|__|	⩛ 10^9/L ⩛G/L ⩛/mm^3 ⩛% ⩛Autre, préciser : ___
Monocytes	○ Oui ○Non		|__|__|__|	⩛ 10^9/L ⩛G/L ⩛/mm^3 ⩛% ⩛Autre, préciser : ___
Lymphocytes	○ Oui ○Non		|__|__|__|	⩛ 10^9/L ⩛G/L ⩛/mm^3 ⩛% ⩛Autre, préciser : ___

**** Si Cliniquement significative, merci de déclarer un événement indésirable.***

☐ ***Je ne souhaite pas être contacté par le service de pharmacovigilance de Pfizer concernant le report ou suivi d'événements indésirables.***

VISITE D'INITIATION DU TRAITEMENT

PATIENT N° |____|____|-|____|____|

N° de centre **N° du patient**

Informations complémentaires 1/2

Qualité de vie à l'inclusion

Un questionnaire d'évaluation de la qualité de vie a-t-il été complété par le patient à l'issu de la visite d'inclusion ?

○ Oui **○Non**

***Si oui*, merci d'envoyer le questionnaire au Centre Logistique (adresse)**

***Si oui*, avez-vous relevé des évènements indésirables cliniquement significatifs ?** **○ Oui ○Non**

Si oui, les événements indésirables cliniquement significatifs identifiés dans le cadre de l'auto-questionnaire ont-ils été déclarés au service de pharmacovigilance de Pfizer via l'eCRF ?

○ Oui **○Non**

Si non, merci de compléter la fiche de déclaration d'évènement indésirable.

☐ ***Je ne souhaite pas être contacté par le service de pharmacovigilance de Pfizer concernant le report ou suivi d'événements indésirables.***

***Si non,* motif de non complétion : _____**

VISITE D'INITIATION DU TRAITEMENT

PATIENT N° |____|____|-|____|____|

N° de centre **N° du patient**

Informations complémentaires 2/2

Traitements concomitants

Modification des traitements concomitants en cours ou prescrits lors de la première visite ?

○ **Oui** ○**Non**

Si oui, merci de décrire l'ensemble des traitements concomitants du patient dans la section Traitements Concomitants.

Tolérance – survenue d'événements indésirables **(recueil rétrospectif)**

La période de notification des événements indésirables commence à partir du moment où le patient reçoit la première dose du médicament de l'étude ou à partir de la date à laquelle le patient fournit son consentement éclairé s'il a déjà été exposé au médicament de l'étude

Le patient a-t-il présenté des événements indésirables graves ou non graves depuis l'initiation ?

○ **Oui** ○**Non**

Si oui, merci de décrire l'ensemble des événements du patient dans la section Evénements Indésirables

VISITE DE SUIVI

PATIENT N° |____|____|-|____|____|

N° de centre **N° du patient**

Paramètres cliniques

Date de la visite de suivi : _|_| / _|_| / _|_| _|_| (JJ/MM/AAAA)

Evolution de la phase de la LMC depuis la dernière visite : ○**Oui** ○**Non**

Si oui, **Phase(s) :** ☐ **Accélérée, date d'évolution** : _|_| / _|_| / _|_|_|_| (JJ/MM/AAAA)

☐ **Blastique, date d'évolution** : _|_| / _|_| / _|_|_|_| (JJ/MM/AAAA)

VISITE DE SUIVI

PATIENT N° |____|____|-|____|____|

N° de centre **N° du patient**

Modification du traitement par Bosutinib

Est-ce que la dose du traitement par bosutinib a été modifiée depuis la dernière visite (y compris lors de la visite du jour) : ○**Oui** ○**Non**

Si oui, **merci de décrire toutes les modifications observées depuis la dernière visite :**

Date	Changement de dose	Nouvelle dose	Raison de la modification
___ / ___ / _____ (JJ/MM/AAAA)	⩛Augmentation ⩛Diminution	⩛100 mg/jour ⩛200 mg/jour ⩛300 mg/jour ⩛400 mg/jour ⩛500 mg/jour ⩛600 mg/jour ⩛Autre, préciser : ____ mg/jour	⩛ EI : ⩛EI# Nom de l'EI <AUTO> ***Si EI, AE Form complété :*** ○**Oui** ○**Non** ⩛Manque d'efficacité / Réponse suboptimale* ⩛ Perte de la réponse * ⩛Autre, _____
___ / ___ / _____ (JJ/MM/AAAA)	⩛Augmentation ⩛Diminution	⩛100 mg/jour ⩛200 mg/jour ⩛300 mg/jour ⩛400 mg/jour ⩛500 mg/jour ⩛600 mg/jour ⩛Autre, préciser : ____ mg/jour	⩛ EI : ⩛EI# Nom de l'EI <AUTO> ***Si EI, AE Form complété :*** ○**Oui** ○**Non** ⩛Manque d'efficacité / Réponse suboptimale* ⩛ Perte de la réponse * ⩛Autre, _____
___ / ___ / _____ (JJ/MM/AAAA)	⩛Augmentation ⩛Diminution	⩛100 mg/jour ⩛200 mg/jour ⩛300 mg/jour ⩛400 mg/jour ⩛500 mg/jour ⩛600 mg/jour	⩛ EI : ⩛EI# Nom de l'EI <AUTO> ***Si EI, AE Form complété :*** ○**Oui** ○**Non** ⩛Manque d'efficacité / Réponse suboptimale*

		⮟Autre, préciser : ____ mg/jour	⮟ Perte de la réponse * ⮟Autre, _____
___ / ___ / _____ (JJ/MM/AAAA)	⮟Augmentation ⮟Diminution	⮟100 mg/jour ⮟200 mg/jour ⮟300 mg/jour ⮟400 mg/jour ⮟500 mg/jour ⮟600 mg/jour ⮟Autre, préciser : ____ mg/jour	⮟ EI : ⮟EI# Nom de l'EI <AUTO> ***Si EI, AE Form complété :*** **○Oui ○Non** ⮟Manque d'efficacité / Réponse suboptimale* ⮟ Perte de la réponse * ⮟Autre, _____
___ / ___ / _____ (JJ/MM/AAAA)	⮟Augmentation ⮟Diminution	⮟100 mg/jour ⮟200 mg/jour ⮟300 mg/jour ⮟400 mg/jour ⮟500 mg/jour ⮟600 mg/jour ⮟Autre, préciser : ____ mg/jour	⮟ EI : ⮟EI# Nom de l'EI <AUTO> ***Si EI, AE Form complété :*** **○Oui ○Non** ⮟Manque d'efficacité / Réponse suboptimale* ⮟ Perte de la réponse * ⮟Autre, _____

(Tableau dynamique : ajout de lignes possible si plus de modifications sont observées)

* *A reporter dans la section Evènements Indésirables de l'eCRF uniquement si le patient est à la dose recommandée de 500mg de Bosutinib et/ou considéré comme imputable au produit par l'investigateur* ➔ Fenêtre pop-up : déclaration EI

VISITE DE SUIVI

PATIENT N° |____|____|-|____|____|

N° de centre **N° du patient**

Interruption du traitement par Bosutinib

Est-ce que le traitement par bosutinib a été interrompu temporairement depuis la dernière visite (y compris lors de la visite du jour) : ○**Oui** ○**Non**

Si oui, **merci de décrire chaque interruption :**

Date	Durée	Si oui, raison de l'interruption
__|__| / __|__| / __|__|__|__| (JJ/MM/AAAA)	__|__| jours ☐ En cours	⮟ EI : ⮟EI# Nom de l'EI <AUTO> ***Si EI, AE Form complété :*** ○**Oui** ○**Non** ⮟ Interaction médicamenteuse * ⮟ Autre, préciser : _______
__|__| / __|__| / __|__|__|__| (JJ/MM/AAAA)	__|__| jours ☐ En cours	⮟ EI : ⮟EI# Nom de l'EI <AUTO> ***Si EI, AE Form complété :*** ○**Oui** ○**Non** ⮟ Interaction médicamenteuse * ⮟ Autre, préciser : _______
__|__| / __|__| / __|__|__|__| (JJ/MM/AAAA)	__|__| jours ☐ En cours	⮟ EI : ⮟EI# Nom de l'EI <AUTO> ***Si EI, AE Form complété :*** ○**Oui** ○**Non** ⮟ Interaction médicamenteuse * ⮟ Autre, préciser : _______
__|__| / __|__| / __|__|__|__| (JJ/MM/AAAA)	__|__| jours ☐ En cours	⮟ EI : ⮟EI# Nom de l'EI <AUTO> ***Si EI, AE Form complété :*** ○**Oui** ○**Non** ⮟ Interaction médicamenteuse * ⮟ Autre, préciser : _______
	__|__| jours	⮟ EI : ⮟EI# Nom de l'EI <AUTO>

__ / __ / _____ (JJ/MM/AAAA)	☐ En cours	***Si EI, AE Form complété :*** **○Oui ○Non** ➢ Interaction médicamenteuse * ➢ Autre, préciser : _____

(Tableau dynamique : ajout de lignes possible si plus d'interruptions sont observées)

* *Merci de reporter l'événement indésirable dans la section Evènements Indésirables de l'eCRF* ➔ Fenêtre pop-up : déclaration EI

VISITE DE SUIVI

PATIENT N° |____|____|-|____|____|

N° de centre **N° du patient**

Arrêt du traitement par Bosutinib

Le traitement par bosutinib a-t-il été arrêté définitivement : ○**Oui** ○**Non**

Si oui, **Date d'arrêt :** _|_| / _|_| / _|_|_|_| (JJ/MM/AAAA)

Motif de l'arrêt :

☐ **Progression de la maladie,** **Date** _|_|/_|_|/_|_|_|_| (JJ/MM/AAAA)

☐ **Crise Blastique** ☐ **Phase accélérée** ☐ **Phase chronique**

☐ **Réponse suboptimale** *

☐ **Perte de réponse** *

☐ **Intolérance** *

☐ **Choix du patient**

☐ **Perdu de vue**

☐ **Décès,** **Date :** _|_| / _|_| / _|_|_|_| (JJ/MM/AAAA)

Cause du décès : ○ **Relié à la maladie**

○ **Relié au traitement**

○ **Autre, préciser :** _____

* *A reporter dans la section Evènements Indésirables de l'eCRF uniquement si le patient est à la dose recommandée de 500mg de Bosutinib et/ou considéré comme imputable au produit par l'investigateur* ➔ Fenêtre pop-up : déclaration EI

* *Merci de reporter l'arrêt définitif dans la section arrêt du Bosutinib de l'eCRF.*

VISITE DE SUIVI

PATIENT N° |____|____|-|____|____|

N° de centre **N° du patient**

Evaluation de la réponse au traitement

Y a-t-il eu une nouvelle évaluation de la réponse au traitement depuis la dernière visite ? : (OPTIONNEL)

○ **Oui** ○**Non**

Date d'évaluation : _|_| / _|_| / _|_|_|_| (JJ/MM/AAAA)

Statut de la réponse au traitement depuis la dernière visite

a. * **Evaluation moléculaire réalisée :** ○ **Oui** ○**Non**

Si oui, **Date de la dernière évaluation :** _|_| / _|_| / _|_|_|_| (JJ/MM/AAAA)

Réponse :
- ⩛**Majeure : RM^{3}**
- ⩛**RM^{4}**
- ⩛**RM$^{4.5}$**
- ⩛**RM^{5}**
- ⩛**Pas de réponse**

Si évaluation non faite, date de la dernière évaluation _|_| / _|_| / _|_|_|_| **(OPTIONNEL)**

b. * **Evaluation cytogénétique réalisée :** ○ **Oui** ○**Non**

Si oui, **Date de la dernière évaluation :** _|_| / _|_| / _|_|_|_| (JJ/MM/AAAA)

Réponse :
- ⩛**Complète**
- ⩛**Partielle**
- ⩛**Majeure**
- ⩛**Mineure/minimale**
- ⩛**Pas de réponse**

Si évaluation non faite, date de la dernière évaluation _|_| / _|_| / _|_|_|_| **(OPTIONNEL)**

c. Evaluation hématologique réalisée : ○**Oui** ○ **Non**

Si oui, **Date de la dernière évaluation :** _|_| / _|_| / _|_|_|_| (JJ/MM/AAAA)

Réponse : ⩛**Complète** ⩛**Partielle**

⩛ **Pas de réponse**

Si évaluation non faite, date de la dernière évaluation _|_| / _|_| / _|_|_|_| **(OPTIONNEL)**

* ***Le statut de la réponse moléculaire ou cytogénétique au traitement précédant l'initiation par bosutinib ne sera à renseigner qu'en cas de Phase chronique.***

VISITE DE SUIVI

PATIENT N° |____|____|-|____|____|

N° de centre **N° du patient**

Bilan biochimique

Bilan biochimique depuis la dernière visite : ○**Oui** ○**Non**

Si oui, **Date du dernier bilan biochimique :** _|_| / _|_| / _|_|_|_| (JJ/MM/AAAA)

Paramètres	Valeur obtenue	Valeur CS/NCS	Valeur Num	Unité
ALAT	○Oui ○Non	⩛Cliniquement significative ⩛Non cliniquement significative	|__|__|__ |	⩛UI/L ⩛Autre, préciser :
ASAT	○Oui ○Non	⩛Cliniquement significative ⩛Non cliniquement significative	|__|__|__ |	⩛UI/L ⩛Autre, préciser :
Bilirubine totale	○Oui ○Non	⩛Cliniquement significative ⩛Non cliniquement significative	|__|__|__ |	⩛mg/dL ⩛µmol/L ⩛g/dL ⩛Autre, préciser :
Bilirubine conjuguée	○Oui ○Non		|__|__|__ |	⩛mg/L ⩛µmol/L ⩛Autre, préciser :
LDH	○Oui ○Non		|__|__|__ |	⩛UI/L ⩛Autre, préciser :
Albumine	○Oui ○Non		|__|__|__ |	⩛ g/dL ⩛g/L ⩛Autre, préciser :
Amylase	○Oui ○Non	⩛Cliniquement significative ⩛Non cliniquement significative	|__|__|__ |	⩛UI/L ⩛Autre, préciser :
Lipase	○Oui ○Non	⩛Cliniquement significative ⩛Non cliniquement significative	|__|__|__ |	⩛UI/L ⩛Autre, préciser :
Créatinine sérique	○Oui ○Non	⩛Cliniquement significative ⩛Non cliniquement significative	|__|__|__ |	⩛mg/dL ⩛µmol/L ⩛mg/L ⩛Autre, préciser :
Glycémie (à jeun)	○Oui ○Non	⩛Cliniquement significative ⩛Non cliniquement significative	|__|__|__ |	⩛mg/dL ⩛mmol/L ⩛g/L ⩛Autre, préciser :
Glycémie (non à jeun)	○Oui ○Non	⩛Cliniquement significative ⩛Non cliniquement significative	|__|__|__ |	⩛mg/dL ⩛mmol/L ⩛g/L ⩛Autre, préciser :

Magnésium	○Oui ○Non		|__|__|__ |	⮟mg/L ⮟Autre, préciser :
Calcium	○Oui ○Non		|__|__|__ |	⮟mg/L ⮟mmol/L ⮟Autre, préciser :
Urée sanguine	○Oui ○Non		|__|__|__ |	⮟mmol/L ⮟g/L ⮟Autre, préciser :
Acide urique	○Oui ○Non		|__|__|__ |	⮟mg/dL ⮟mg/L ⮟Autre, préciser :

**** Si Cliniquement significative, merci de déclarer un événement indésirable.***

☐ ***Je ne souhaite pas être contacté par le service de pharmacovigilance de Pfizer concernant le report ou suivi d'événements indésirables.***

VISITE DE SUIVI

PATIENT N° |____|____|-|____|____|

N° de centre **N° du patient**

Bilan hématologique

Bilan hématologique depuis la dernière visite : ○ **Oui** ○**Non**

Si oui, **Date du dernier bilan hématologique :** _|_| / _|_| / _|_|_|_| (JJ/MM/AAAA)

Paramètres	Valeur obtenue	Valeur CS/NCS	Valeur Num	Unité
Hémoglobine	○ Oui ○Non		|__|__|__|	⩛g/dL ⩛mmol/L ⩛g/L ⩛Autre, préciser :
Hématocrite	○ Oui ○Non		|__|__|__|	⩛% ⩛Autre, préciser : ___
Leucocytes	○ Oui ○Non		|__|__|__|	⩛ 10^9/L ⩛G/L ⩛Autre, préciser : ___
Plaquettes	○ Oui ○Non	⩛Cliniquement significative ⩛Non cliniquement significative	|__|__|__|	⩛ 10^9/L ⩛10^{12}/L ⩛G/L ⩛/mm^3 ⩛Autre, préciser : ___
Blastes (sang périphérique)	○ Oui ○Non	⩛Cliniquement significative ⩛Non cliniquement significative	|__|__|__|	⩛% ⩛Autre, préciser : ___
Basophiles	○ Oui ○Non		|__|__|__|	⩛ 10^9/L ⩛G/L ⩛/mm^3 ⩛% ⩛Autre, préciser : ___
Eosinophiles	○ Oui ○Non		|__|__|__|	⩛ 10^9/L ⩛G/L ⩛/mm^3 ⩛% ⩛Autre, préciser : ___
Neutrophiles	○ Oui ○Non	⩛Cliniquement significative ⩛Non cliniquement significative	|__|__|__|	⩛ 10^9/L ⩛G/L ⩛/mm^3 ⩛% ⩛Autre, préciser : ___
Monocytes	○ Oui ○Non		|__|__|__|	⩛ 10^9/L ⩛G/L ⩛/mm^3 ⩛% ⩛Autre, préciser : ___
Lymphocytes	○ Oui ○Non		|__|__|__|	⩛ 10^9/L ⩛G/L ⩛/mm^3 ⩛% ⩛Autre, préciser : ___

**** Si Cliniquement significative, merci de déclarer un événement indésirable.***

☐ ***Je ne souhaite pas être contacté par le service de pharmacovigilance de Pfizer concernant le report ou suivi d'événements indésirables.***

VISITE DE SUIVI

PATIENT N° |____|____|-|____|____|

N° de centre **N° du patient**

Transplantations

Transplantation pendant le traitement par bosutinib :

○ **Oui** ○**Non**

Date de la transplantation	Type	Source
⎿⎿/ ⎿⎿/ ⎿⎿⎿⎿ (JJ/MM/AAAA)	⋎allogénique ⋎autologue	⋎moelle osseuse (CSH) ⋎sang périphérique (CSSP)
⎿⎿/ ⎿⎿/ ⎿⎿⎿⎿ (JJ/MM/AAAA)	⋎allogénique ⋎autologue	⋎moelle osseuse (CSH) ⋎sang périphérique (CSSP)
⎿⎿/ ⎿⎿/ ⎿⎿⎿⎿ (JJ/MM/AAAA)	⋎allogénique ⋎autologue	⋎moelle osseuse (CSH) ⋎sang périphérique (CSSP)
⎿⎿/ ⎿⎿/ ⎿⎿⎿⎿ (JJ/MM/AAAA)	⋎allogénique ⋎autologue	⋎moelle osseuse (CSH) ⋎sang périphérique (CSSP)
⎿⎿/ ⎿⎿/ ⎿⎿⎿⎿ (JJ/MM/AAAA)	⋎allogénique ⋎autologue	⋎moelle osseuse (CSH) ⋎sang périphérique (CSSP)

(Tableau dynamique : ajout de lignes possible si plus de transplantations sont observées)

VISITE DE SUIVI

PATIENT N° |____|____|-|____|____|

N° de centre **N° du patient**

Informations complémentaires 1/2

Observance au traitement

Nombre de jours de traitement par bosutinib manqués par le patient depuis la dernière visite :

_|_|_| **Jours (hors interruption de traitement décidé avec le médecin)**

Un questionnaire d'évaluation de l'observance au traitement a-t-il été complété par le patient à l'issu de la visite du jour ? ○ **Oui** ○**Non**

***Si oui*, merci d'envoyer le questionnaire au Centre Logistique (adresse)**

***Si oui*, avez-vous relevé des évènements indésirables cliniquement significatifs ?** ○ **Oui** ○**Non**

Si oui, les événements indésirables cliniquement significatifs identifiés dans le cadre de l'auto-questionnaire ont-ils été déclarés au service de pharmacovigilance de Pfizer via l'eCRF ?

○ **Oui** ○**Non**

Si non, merci de compléter la fiche de déclaration d'évènement indésirable.

☐ ***Je ne souhaite pas être contacté par le service de pharmacovigilance de Pfizer concernant le report ou suivi d'événements indésirables.***

***Si non,* motif de non complétion : _____**

Qualité de vie

(Pour les visites à M3, M6, M12, M18, M24 et M36 uniquement)

Un questionnaire d'évaluation de l'observance au traitement a-t-il été complété par le patient à l'issu de la visite du jour ? ○ **Oui** ○**Non**

***Si oui*, merci d'envoyer le questionnaire au Centre Logistique (adresse)**

***Si oui*, avez-vous relevé des évènements indésirables cliniquement significatifs ?** ○ **Oui** ○**Non**

Si oui, les événements indésirables cliniquement significatifs identifiés dans le cadre de l'auto-questionnaire ont-ils été déclarés au service de pharmacovigilance de Pfizer via l'eCRF ?

○ **Oui** ○**Non**

Si non, merci de compléter la fiche de déclaration d'évènement indésirable.

☐ ***Je ne souhaite pas être contacté par le service de pharmacovigilance de Pfizer concernant le report ou suivi d'événements indésirables.***

***Si non,* motif de non complétion : _____**

VISITE DE SUIVI

PATIENT N° |____|____|-|____|____|

N° de centre **N° du patient**

(Pour les visites à M9, M15, M21, M27, M30 et M33)

Informations complémentaires 1/2

Observance au traitement

Nombre de jours de traitement par bosutinib manqués par le patient depuis la dernière visite :

_|_|_| **Jours (hors interruption de traitement décidé avec le médecin)**

Un questionnaire d'évaluation de l'observance au traitement a-t-il été complété par le patient à l'issu de la visite du jour ? ○ **Oui** ○**Non**

***Si oui*, merci d'envoyer le questionnaire au Centre Logistique (adresse)**

***Si oui*, avez-vous relevé des évènements indésirables cliniquement significatifs ?**

○ **Oui** ○**Non**

Si oui, les événements indésirables cliniquement significatifs identifiés dans le cadre de l'auto-questionnaire ont-ils été déclarés au service de pharmacovigilance de Pfizer via l'eCRF ?

○ **Oui** ○**Non**

Si non, merci de compléter la fiche de déclaration d'évènement indésirable.

☐ ***Je ne souhaite pas être contacté par le service de pharmacovigilance de Pfizer concernant le report ou suivi d'événements indésirables.***

***Si non,* motif de non complétion : _____**

VISITE DE SUIVI

PATIENT N° |____|____|-|____|____|

N° de centre **N° du patient**

Informations complémentaires 2/2

Traitements concomitants

✱ **Y a-t-il eu modifications des traitements concomitants en cours ou prescrits depuis la dernière visite ?**

○ **Oui** ○ **Non**

Si oui, merci de décrire l'ensemble des traitements concomitants du patient dans la section Traitements Concomitants.

✱ **Y a-t-il eu mise en place de nouvelles lignes de traitement de la LMC depuis l'arrêt définitif de bosutinib ?**

○ **Oui** ○ **Non**

Si oui, merci de décrire l'ensemble de ces lignes dans la section Nouvelles Lignes de traitement de la LMC.

Tolérance – survenue d'événements indésirables

Le patient a-t-il présenté des événements indésirables graves ou non graves depuis la dernière visite?

○ **Oui** ○ **Non**

Si oui, merci de décrire l'ensemble des événements du patient dans la section Evénements Indésirables

VISITE DE SUIVI A LONG TERME – APRES ARRET DEFINITIF DU BOSUTINIB

PATIENT N° |____|____|-|____|____|

N° de centre **N° du patient**

Paramètres cliniques

Date de la visite de suivi : _|_| / _|_| / _|_| _|_| **(JJ/MM/AAAA)**

Evolution de la phase de la LMC depuis la dernière visite : ○**Oui** ○**Non**

Si oui, **Phase(s) :** ☐ **Accélérée, date d'évolution** : _|_| / _|_| / _|_|_|_| (JJ/MM/AAAA)

☐ **Blastique, date d'évolution** : _|_| / _|_| / _|_|_|_| (JJ/MM/AAAA)

VISITE DE SUIVI A LONG TERME – APRES ARRET DEFINITIF DU BOSUTINIB

PATIENT N° |____|____|-|____|____|

N° de centre **N° du patient**

Informations complémentaires

Prise en charge thérapeutique

Y a-t-il eu mise en place ou modification de nouvelles lignes de traitement de la LMC depuis l'arrêt définitif de bosutinib ?

○ Oui **○Non**

Si oui, merci de décrire l'ensemble de ces lignes dans la section Nouvelles Lignes de traitement de la LMC.

Tolérance – survenue d'événements indésirables

Le patient a-t-il présenté des événements indésirables graves ou non graves depuis la dernière visite ?

○ Oui **○Non**

Si oui, merci de décrire l'ensemble des événements du patient dans la section Evénements Indésirables

VISITE DE DERNIERES NOUVELLES

PATIENT N° |____|____|-|____|____|

N° de centre **N° du patient**

Statut du patient aux dernières nouvelles

Le patient a-t-il été suivi pendant les 36 mois de l'étude ? ○ **Oui** ○ **Non**

Si non, Statut du patient aux dernières nouvelles :

○ **Vivant, arrêt d'étude par choix du patient,**

Date de dernier contact : _|_|/_|_|/_|_|_|_| (JJ/MM/AAAA)

○ **Perdu de vue,**

Date de dernier contact : _|_|/_|_|/_|_|_|_| (JJ/MM/AAAA)

○ **Décédé** *

Date de décès : _|_| / _|_| / _|_|_|_| (JJ/MM/AAAA)

Cause du décès :

○ **Relié à la maladie**

○ **Relié au traitement**

○ **Autre, préciser : _____**

* ***En cas de décès, merci de remplir la section tolérance du CRF***

Sections Transverses

PATIENT N° |____|____|-|____|____|

N° de centre **N° du patient**

Lignes de traitement de la LMC

Nouvelle ligne ou modification de traitement de la LMC initiée depuis l'arrêt définitif de bosutinib :

○**Oui** ○**Non**

***Si oui*, merci de décrire chaque nouvelle ligne de traitement :**

Ligne : _|_| **Thérapie :** _____

Date de début : _|_|/_|_|/ _|_|_|_| **En cours :** ☐ **Date de fin :** _|_|/_|_|/ _|_|_|_|

Raison d'arrêt :

☐ **Progression, date :** _|_|/_|_|/ _|_|_|_|

☐ **Réponse suboptimale ***

☐ **Perte de réponse ***

☐ **Intolérance ***

☐ **Réponse optimale**

☐ **Choix du patient**

☐ **Perdu de vue**

☐ **Décès *, Date :** _|_|/_|_|/ _|_|_|_| **Cause :** ○ **Relié à la maladie**
○ **Relié au traitement**
○ **Autre, préciser ____**

☐ **Autre, préciser ____**

Meilleure réponse	**Hématologique**	**Cytogénétique**	☐ Pas de réponse
☐ Inconnue	☐ Complète	☐ Complète	☐ Inconnue/Pas évaluée
☐ Absence de réponse	☐ Partielle	☐ Partielle	
☐ Progression de la maladie	☐ Pas de réponse	☐ Majeure	
(changement de phase)	☐ Inconnue/Pas évaluée	☐ Mineure/Minimale	

Moléculaire	☐ RM[4]	☐ RM[5]*	☐ Inconnue/Pas évaluée
☐ Majeure : RM[3]	☐ RM[4.5]	☐ Pas de réponse	

Merci de reporter l'événement indésirable dans la section Evénements Indésirables de l'eCRF → Fenêtre pop-up : déclaration EI

**** Le statut de la réponse moléculaire ou cytogénétique au traitement précédent l'initiation par bosutinib ne sera à renseigner qu'en cas de Phase chronique.***

→ En cas d'arrêt définitif de traitement par bosutinib, le patient sera suivi durant les 3 ans prévus par le protocole (visite de suivi à long terme).

PATIENT N° |____|____|-|____|____|

N° de centre **N° du patient**

Traitements concomitants

DCI (nom commercial) : _____

Indication : _____

Motif de prescription : _____

(OPTIONNEL)

Dose prescrite : _|_|_|,_|

(OPTIONNEL)

Unité de dose : ⩒mg ⩒g ⩒µg ⩒ml ⩒% ⩒Autre : _____

(OPTIONNEL)

Fréquence : ○ **Par jour** ○ **Autre, préciser : _____ (OPTIONNEL)**

Date d'initiation : _|_| / _|_| / _|_|_|_| (JJ/MM/AAAA)

Statut ○ **En cours** ○ **Arrêté, Date :** _|_| / _|_| / _|_|_|_| (JJ/MM/AAAA)

(Ajout de pages possible si plus de traitements sont observés)

PATIENT N° |____|____|-|____|____|

N° de centre **N° du patient**

Caractéristiques des patients non inclus dans l'étude

	Date de la consultation	Date de naissance	Sexe	Motif de non inclusion
1			**⩛Homme** **⩛Femme**	**⩛Refus du patient** **⩛Autre, préciser :** _____
2			**⩛Homme** **⩛Femme**	**⩛Refus du patient** **⩛Autre, préciser :** _____
3			**⩛Homme** **⩛Femme**	**⩛Refus du patient** **⩛Autre, préciser :** _____
4			**⩛Homme** **⩛Femme**	**⩛Refus du patient** **⩛Autre, préciser :** _____
5			**⩛Homme** **⩛Femme**	**⩛Refus du patient** **⩛Autre, préciser :** _____
6			**⩛Homme** **⩛Femme**	**⩛Refus du patient** **⩛Autre, préciser :** _____

7			**⮟Homme** **⮟Femme**	**⮟Refus du patient** **⮟Autre, préciser :** **_____**
8			**⮟Homme** **⮟Femme**	**⮟Refus du patient** **⮟Autre, préciser :** **_____**
9			**⮟Homme** **⮟Femme**	**⮟Refus du patient** **⮟Autre, préciser :** **_____**
10			**⮟Homme** **⮟Femme**	**⮟Refus du patient** **⮟Autre, préciser :** **_____**

APPENDIX 6. SAMPLE STANDARD SUBJECT INFORMATION SHEET AND INFORMED CONSENT DOCUMENT (ICD)

Chère Madame, Cher Monsieur,

Merci de prendre le temps d'envisager de participer à cette étude. Ce consentement peut vous aider à prendre votre décision en vous expliquant **comment se déroulera cette étude**, également appelée étude observationnelle.

Votre participation à cette étude est **entièrement volontaire (c'est votre choix)**. Prenez le temps nécessaire pour prendre votre décision. Vous pouvez également choisir de prendre part à l'étude maintenant, puis changer d'avis à tout moment.

Nous vous encourageons **à discuter de votre participation à cette étude avec votre famille, le personnel soignant, votre médecin ou tout autre professionnel de santé ou l'équipe chargée de l'étude,** afin de savoir si cette participation vous conviendrait. L'équipe chargée de l'étude répondra aux questions que vous pourriez avoir au sujet de l'étude. Cette équipe comprend le médecin de l'étude, les infirmières et toute autre personne travaillant avec le médecin de l'étude.

Si vous choisissez de participer à cette étude, **vous devrez signer et parapher ce formulaire de consentement** avant de débuter l'étude afin de permettre aux personnes chargées de l'étude de connaître votre décision.

Vous recevrez une copie signée de ce formulaire de consentement à conserver dans vos archives personnelles. Veuillez conserver ce formulaire de consentement comme preuve de votre accord.

Nous apprécions que vous envisagiez de prendre part à cette étude.

Cordialement,

_____

Le médecin de l'étude

Table des matières

Cette table des matières décrit les différentes sections de ce formulaire de consentement. Veuillez s'il vous plaît lire toutes les sections du présent document de consentement avant de prendre la décision de participer ou non à cette étude.

1. Informations clés relatives à l'étude et coordonnées

L'équipe chargée de l'étude répondra aux questions, préoccupations ou plaintes que vous pourriez avoir avant, pendant et après avoir terminé l'étude. Cette équipe comprend le médecin de l'étude, les infirmières et toute autre personne travaillant avec le médecin de l'étude.

Si vous avez des questions générales sur vos droits en tant que participant à l'étude ou si vous souhaitez obtenir des informations ou des suggestions, ou si vous souhaitez parler avec quelqu'un qui n'est pas directement impliqué dans l'étude, vous pouvez contacter la Commission Nationale de l'Informatique et des Libertés (CNIL) mentionnée ci-dessous :

Nom de l'étude : **« BOSEVAL : Etude observationnelle – Evaluation de l'efficacité et de la tolérance de Bosulif® en conditions réelles d'utilisation »**

Numéro de version du consentement Promoteur (Etude/Pays/Centre): **B1871047 / France – Version 3.0 du 15 février 2019**

Numéro d'étude du Promoteur : **B1871047**

Nom du Promoteur de l'étude : **PFIZER**

Nom du médecin participant (Médecin de l'étude) :

Coordonnées du Centre :

Personne à contacter :

Adresse :

Numéro de téléphone (Heures d'ouverture):

Numéro de téléphone (En dehors des heures d'ouverture) :

Coordonnées du Comité de Protection des Personnes (CPP) : Non applicable

Personne à contacter :

Adresse :

Numéro de téléphone :

Coordonnées de la CNIL :

Adresse : 3 Place de Fontenoy - TSA 80715 - 75334 PARIS CEDEX 07

Numéro de téléphone : 01 53 73 22 22

2. Bref résumé de cette étude

Il vous est proposé de participer à une étude menée par Pfizer (le «Promoteur»). Le Promoteur rémunère le médecin de l'étude et/ou l'établissement pour leur participation à l'étude.

Ce document de consentement est destiné aux participants qui peuvent ou non avoir la capacité de consentir à leur participation. Si vous êtes un représentant légal autorisé, n'oubliez pas que "vous" désigne le patient participant à l'étude.

Votre médecin vous a proposé de participer à une étude sur la leucémie myéloïde chronique menée chez des patients résistants ou intolérants à une thérapie antérieure par ITK, intitulée BoSEVAL « Etude observationnelle – Evaluation de l'efficacité et de la tolérance de Bosulif® en conditions réelles d'utilisation ».

L'objectif de cette étude observationnelle sera d'évaluer la tolérance, l'efficacité, ainsi que les modalités d'utilisation de Bosulif® (bosutinib) dans des conditions réelles d'utilisation.

Le respect du traitement et la qualité de vie des patients seront également évalués.

Cette étude est « non-interventionnelle » car elle recueille uniquement de l'information. Votre médecin administrera vos soins de la même manière que si vous ne participiez pas à cette étude.

Vous participerez à cette étude pour une durée de 36 mois. Au cours de cette étude, vous effectuerez les visites correspondant à la prise en charge habituelle de votre maladie (12 visites de suivi au maximum). Il n'y a donc pas de visites supplémentaires relatives à cette étude.

Cette étude n'entraîne aucun changement dans votre traitement actuel et est réalisée à des fins de recherche uniquement. Cette étude est faite pour évaluer en vie réelle le traitement par Bosulif® (bosutinib) et votre une leucémie myéloïde chronique**.** Il n'y a aucun avantage direct pour vous à y participer, mais les informations tirées de l'étude pourraient aider à mieux prendre en charge les personnes traitées avec le même médicament à l'avenir.

Participer à cette étude est volontaire (c'est votre choix). Il n'y a aucune sanction ou modification de votre prise en charge médicale si vous décidez de ne pas participer. Vous pouvez choisir de participer à l'étude maintenant, puis changer d'avis plus tard, à tout moment, sans perdre les avantages ou les soins médicaux auxquels vous avez droit. Nous vous encourageons à discuter de votre participation à l'étude avec votre famille, le personnel soignant, votre médecin ou l'équipe chargée de l'étude, pour savoir si cela vous conviendrait. L'équipe chargée de l'étude répondra aux questions que vous pourriez avoir au sujet de l'étude.

Vous recevrez une copie signée de ce formulaire de consentement à conserver dans vos archives personnelles. Conservez-le pour pouvoir vous y référer.

3. Quel est le but de cette étude ?

Vous êtes invité(e) à participer à cette étude parce que vous recevez un traitement par Bosulif® (bosutinib). Le but de cette étude est d'en savoir plus sur les effets du Bosulif®

(bosutinib) dans la pratique clinique. Le respect du traitement et la qualité de vie des patients seront également évalués.

Pour cette raison, le Promoteur mène cette étude afin de recueillir des informations supplémentaires sur les effets positifs ou négatifs du Bosulif® (bosutinb).

Bosulif® (bosutinib) vous a été prescrit par votre médecin.

4. Combien de temps vais-je participer à cette étude ?

La durée maximale de votre participation à cette étude sera de 36 mois (3 ans). Au cours de cette étude, vous effectuerez les visites correspondant à la prise en charge habituelle de votre maladie (12 visites de suivi au maximum).). Il n'y a donc pas de visites supplémentaires relatives à cette étude.

5. Combien de personnes participeront à cette étude ?

Il est attendu qu'une centaine (100) de patients traités par Bosulif® (bosutinib) pour une leucémie myéloïde chronique participeront à cette étude qui sera réalisée auprès d'environ 40 hématologues ou cancérologues répartis en France et spécialisés dans la prise en charge de cette pathologie.

6. Que va-t-il se passer pendant cette étude ?

Avant de commencer toute activité en lien avec l'étude, il vous sera demandé de lire et de signer ce formulaire de consentement.

Dans le cadre de cette étude, votre médecin recueillera tous les 3 mois environ sur une période maximale de 3 ans ou jusqu'à votre sortie prématurée de l'étude, pour quelque motif que ce soit, des données médicales vous concernant (principalement : vos caractéristiques sociodémographiques et cliniques, votre réponse et tolérance au traitement par Bosulif® (bosutinib)).

Visite d'inclusion :

La visite au cours de laquelle votre médecin vous proposera de participer à cette étude constituera la visite d'inclusion dans l'étude que vous initiez le traitement par Bosulif® (bosutinib) lors de cette visite ou que vous l'ayez débuté au maximum dans les 30 jours la

précédant. Si vous décidez de participer à cette étude, vous serez invité(e) à signer ce consentement. Aucune information ne sera recueillie avant la signature de ce document.

Après signature du consentement, votre médecin collectera des informations vous concernant. Ces informations porteront sur :

- Votre âge
- Votre taille et votre poids
- Votre sexe
- Si vous souffrez d'autres maladies que celle pour laquelle vous consultez, ainsi que les traitements associés
- L'histoire de votre maladie (date du diagnostic, traitement)

Au cours de cette première visite, il vous sera demandé de compléter un questionnaire papier de mesure de la qualité de vie.

Visites de suivis, réalisées environ tous les 3 mois selon la prise en charge habituelle :

Dans le cadre de la prise en charge habituelle de votre maladie, vous reverrez votre médecin environ tous les 3 mois pendant 3 ans (soit 12 visites de suivi au maximum). Celui-ci évaluera l'évolution de votre maladie, les modifications éventuelles de votre traitement par Bosulif® (bosutinib) et/ou des traitements concomitants, et récupérera vos auto-questionnaires de mesure du respect du traitement et de la qualité de vie.

Les auto-questionnaires, devront être remis à votre médecin à l'issu de la visite. Cela lui permettra de valider qu'aucun événement indésirable non discuté durant la visite n'a été omis.

Votre médecin vous demandera également si des effets indésirables se sont produits depuis votre dernière visite.

Toutes les données de l'étude seront recueillies et saisies dans un questionnaire électronique directement par votre médecin ou par un technicien d'étude clinique dûment habilité et astreint au secret professionnel.

7. Quels sont les risques et les inconvénients éventuels liés à ma participation à cette étude ?

Le traitement Bosulif® (bosutinib) peut causer des effets secondaires, comprenant certains risques ou désagréments. Ces effets indésirables sont décrits dans la notice d'information fournie avec le médicament. Vous pouvez subir ces risques ou désagréments lorsque vous prenez du Bosulif® (bosutinib). Il est important que vous le signaliez si cela vous arrive. Si vous êtes confronté(e) à un événement indésirable grave, comme par exemple toute maladie pour laquelle vous êtes hospitalisé, signalez-le à votre médecin immédiatement ou dès que possible.

Il peut y avoir des risques non physiques associés à votre participation à cette étude, tels que le risque de divulgation accidentelle de vos données personnelles (y compris vos informations médicales).

Suivi de grossesse

Si vous ou votre partenaire venez à être enceinte durant l'étude, informez-en **immédiatement** le médecin de l'étude. Dites également au médecin qui vous suivra ou suivra votre partenaire pendant la grossesse que vous ou votre partenaire étiez en cours de traitement par Bosulif® (bosutinib) au moment de la grossesse. Le médecin de l'étude demandera si vous/votre partenaire ou le médecin qui suit la grossesse êtes disposé(e) à fournir des informations sur son déroulement et son terme. Si vous/votre partenaire êtes d'accord, ces informations seront transmises au Promoteur pour un suivi de la tolérance.

8. Quels sont les bénéfices éventuels de ma participation à cette étude ?

Cette étude n'est réalisée qu'à des fins de recherche. Il n'y a aucun avantage direct à participer à l'étude parce que vous continuerez à recevoir vos soins médicaux habituels.

Cependant, les informations issues de cette étude pourraient aider d'autres personnes à l'avenir.

9. Quel autre choix ai-je si je ne rejoins pas cette étude ?

Cette étude n'est réalisée qu'à des fins de recherche. Il est bien entendu que vous pouvez décider de ne pas y participer et de continuer à suivre votre traitement et vos soins habituels

10. Que se passe-t-il si je subis un préjudice pendant cette étude ?

Cette étude recueille uniquement des informations, il est donc peu probable que vous subissiez un préjudice lié à cette étude. Vous recevez un traitement par Bosulif® (bosutinib) dans le cadre de vos soins médicaux habituels. Toute réaction négative que vous pourriez ressentir en participant à cette étude ne sera pas considérée comme un préjudice lié à l'étude.

11. Que se passe-t-il si je rejoins cette étude et que je change d'avis ?

Si vous acceptez de participer à cette étude et que vous changez d'avis pour une raison quelconque, vous êtes libre d'arrêter de participer à tout moment. Votre décision n'affectera pas vos soins médicaux habituels ou les avantages auxquels vous avez droit. Informez votre médecin si vous songez à arrêter ou si vous décidez d'arrêter de participer.

Parfois, votre médecin ou le Promoteur peut décider de vous retirer de l'étude si :

- L'étude est arrêtée par le Promoteur, le comité d'éthique (Comité de Protection des Personnes, un groupe de personnes qui examinent l'étude pour protéger vos droits), ou par un gouvernement ou un organisme règlementaire.
- Non-respect des procédures de l'étude (critère inclusion ou non-inclusion non respecté)

L'équipe chargée de l'étude vous fournira un document complémentaire relatif aux données personnelles, faisant partie intégrante de ce formulaire de consentement. Il décrit ce qu'il

advient de vos données personnelles et comment elles peuvent être utilisées si vous vous retirez de l'étude.

12. Que devrai-je payer si je participe à cette étude ?

Il n'y a aucun coût supplémentaire pour votre participation à cette étude.

Cette étude recueille uniquement des informations et il n'y a aucun changement à vos soins médicaux habituels. Le Promoteur ne prendra pas en charge les traitements ou procédures susceptibles de vous être administrés pendant votre participation à l'étude y compris le Bosulif® (bosutinib).

13. Serai-je rémunéré pour ma participation à cette étude ?

Vous ne recevrez aucun paiement pour votre participation à cette étude. Le Promoteur peut utiliser les informations/données résultant de l'étude pour développer des produits ou des procédés à partir desquels il peut réaliser des bénéfices. Il n'est pas prévu de vous rémunérer ou de vous fournir des produits développés à partir de cette étude. Tout produit ou processus développé en utilisant les informations/données de l'étude demeurera la propriété du Promoteur.

14. Qu'adviendra-t-il de mes données personnelles ?

L'équipe chargée de l'étude vous fournira un document complémentaire relatif aux données personnelles, faisant partie de ce consentement. Le document complémentaire relatif aux données personnelles vous présente :

- Quelles données personnelles peuvent être collectées directement auprès de vous au cours de l'étude ?
- Comment vos données personnelles seront utilisées et par qui (y compris par le centre participant à l'étude, le Promoteur, et d'autres tiers en dehors du centre participant à l'étude) ;
- Comment vos échantillons et images biologiques seront traités (s'ils sont collectés) ;

- Comment vos données personnelles pourraient être utilisées pour d'autres recherches ;
- Comment vos données personnelles seront protégées pendant leur transfert ;
- Vos droits en matière de protection des données, et quelles sont les personnes ou autorités que vous pouvez contacter à propos de vos droits ou pour toute autre préoccupation ou réclamation ; et
- Ce qu'il advient de vos données personnelles si vous décidez d'arrêter de participer à l'étude

15. Où puis-je trouver des informations complémentaires sur cette étude ou les résultats de l'étude ?

Une description de cette étude sera disponible sur le site http://www.encepp.eu. .

Ce site web ne comprendra aucune donnée qui pourrait permettre de vous identifier. Tout au plus, le site inclura un résumé des résultats. Vous pouvez faire des recherches sur ce site web à tout moment.

Ce site web est en anglais uniquement. Si vous avez besoin d'aide pour comprendre, merci de demander à votre médecin.

16. Signatures

Accord pour participer et au traitement de données personnelles
1. Je confirme avoir lu (ou, si je ne peux pas lire, un membre de l'équipe chargée de l'étude m'a lu) et avoir compris ce formulaire de consentement pour l'étude décrite ci-dessus et avoir eu l'occasion de poser des questions. J'ai eu assez de temps pour lire ce formulaire de consentement. J'ai également eu l'occasion de poser des questions sur les détails de l'étude et de décider de participer ou non.
2. J'ai lu et compris le document complémentaire relatif aux données personnelles. Je comprends que la participation à l'étude nécessitera le traitement (y compris la collecte, l'utilisation, le transfert, le stockage, l'analyse et la production de rapports) de mes données personnelles, tel qu'expliqué dans le document complémentaire sur la protection des données personnelles. Je comprends et j'accepte le traitement de mes données personnelles à l'intérieur et à l'extérieur de mon pays de résidence à des fins de soins de santé, de recherche médicale et/ou règlementaire. .
3. Je comprends que ma participation est volontaire et que je suis libre d'arrêter de participer à cette étude ou de retirer mon consentement au traitement de mes données personnelles à tout moment. Je n'ai pas besoin de me justifier et mes soins médicaux habituels et mes droits légaux ne seront pas affectés. Cependant, même si je retire mon consentement au traitement de mes données, mes données personnelles collectées jusqu'à ce moment-là peuvent être conservées pour se conformer aux lois et règlements et pour maintenir l'intégrité de l'étude.
4. J'accepte que l'équipe chargée de l'étude accède à mes antécédents médicaux, y compris les informations contenues dans mes dossiers médicaux et mes résultats de tests et tout traitement médical reçu au cours de l'étude et, si nécessaire, je les autorise à contacter

mon médecin ou tout autre professionnel de santé me traitant, pour accéder à ce type d'information.
5. Je comprends que le Promoteur et / ou les autres personnes travaillant avec le Promoteur, les comités d'éthique (Comités de Protection des Personnes (CPP)) et les autorités règlementaires peuvent avoir besoin d'accéder aux données personnelles recueillies sur le site ou recueillies par les personnes chargées de l'étude, pour l'étude et toute autre recherche. J'accepte qu'ils puissent avoir accès à mes données personnelles.
6. Je ne renonce à aucun de mes droits légaux en signant ce formulaire de consentement. Il m'a été précisé que je recevrai une copie signée et datée de ce document.
7. J'accepte de participer à l'étude décrite dans ce document.

Signatures :

_____

Nom en caractère d'imprimerie du patient §

_____

_____

_

Signature du patient§ Date de signature§

(Si la participation du patient ne nécessite pas la signature d'un représentant légal)

_____ _____

Nom du représentant légal en caractère d'imprimerie Lien

_____ _____

Signature du représentant légal Date de signature§

Personne recueillant le consentement : (le médecin de l'étude)

_____

Nom en caractères d'imprimerie du médecin de l'étude

_____ _____

Signature du médecin de l'étude † Date de signature

Consentement d'un patient ne sachant pas lire :

☐ Non Applicable (*Cocher cette case si la signature d'un témoin impartial n'est pas nécessaire. La signature d'un témoin impartial est nécessaire si le patient ne sait pas lire).*

Le patient a indiqué qu'il ne savait pas lire. Un ou plusieurs membres de l'équipe de l'étude lit le document de consentement au patient, en discute avec lui et lui donne la possibilité de poser des questions.

_____

Nom d'un témoin impartial en caractères d'imprimerie ‡

_____ _____

Signature du témoin impartial Date de la signature §

§ Patient/représentant légal/témoin impartial doivent dater personnellement leur signature.

† Le médecin de l'étude pour conduire la procédure de consentement éclairé, doit signer et dater le document de consentement pendant l'entretien au cours duquel le patient signe le formulaire de consentement.

‡ Témoin impartial : Il s'agit d'une personne, indépendante de l'étude, qui ne peut pas être déloyalement influencée par des personnes participant à l'étude, qui assiste à la procédure de consentement éclairé si le participant ou le représentant légal du participant ne sait pas

lire, et qui lit le consentement éclairé et toutes les autres informations écrites fournies au participant. Voir Directive pour l'industrie E6

Bonnes pratiques cliniques : Directive consolidée.

DOCUMENT COMPLÉMENTAIRE RELATIF AUX DONNEES PERSONNELLES

Ce document complémentaire relatif aux données personnelles décrit comment nous collecterons, utiliserons et partagerons vos données personnelles. Il précise également vos droits en matière de données personnelles.

A. Quelles données personnelles pouvons-nous recueillir à votre sujet au cours de cette étude ?

L'équipe chargée de l'étude ainsi que les personnes les assistant dans la prise en charge de vos soins liés à l'étude collecteront ou fourniront des données vous concernant, dont certaines sont sensibles. Ces données peuvent inclure :

- **Des données qui vous identifient directement** telles que votre nom, votre adresse, votre numéro de téléphone et votre mois et année de naissance.

- **Des données personnelles sensibles** telles que vos antécédents médicaux, les données résultant de cette étude (y compris les résultats des tests et procédures de l'étude), des données démographiques (par exemple, votre âge et votre sexe) et d'autres données sensibles nécessaires pour cette étude telles que vos antécédents médicaux et les traitements qui vous ont été prescrits.

- **Les données provenant de tests et de l'analyse d'échantillons biologiques** (tels que le sang ou l'urine) **et d'images** (telles que les radiographies, les tomodensitométries (scanners) et les photographies médicales). Cela peut également inclure des données génétiques.

B. Qui utilisera mes données personnelles, comment seront-elles utilisées et où seront-elles stockées?

Toute donnée personnelle vous concernant, collectée au cours de cette étude, sera conservée par l'équipe chargée de l'étude dans votre centre participant. L'équipe chargée de l'étude doit garder vos données personnelles confidentielles.

Vos données personnelles seront accessibles par :

- Votre médecin de l'étude et les autres membres de l'équipe chargée de l'étude ;

- Le Promoteur et ses représentants (y compris les sociétés affiliées)

- Des personnes ou des organisations fournissant des services ou collaborant avec le Promoteur ;

- Toute organisation qui obtient tout ou partie des affaires ou des droits du Promoteur sur le produit à l'étude ;

- Les autorités gouvernementales ou réglementaires (y compris celles d'autres pays) ; et

- Le Comité Institutionnel d'Évaluation (CIE) ou le Comité(s) d'éthique indépendant(s) (Comité de Protection des Personnes (CPP)) supervisant cette étude.

Les personnes et les groupes énumérés ci-dessus utiliseront vos données personnelles pour conduire cette étude et se conformer aux exigences légales ou réglementaires, notamment :

- déterminer si vous êtes éligible à cette étude;
- vérifier que l'étude est conduite correctement et que les données de l'étude sont exactes;
- répondre aux questions des CPP, des CIE ou des organismes gouvernementaux ou des autorités règlementaires ;
- vous contacter pendant et après l'étude (si nécessaire);
- le suivi de votre état de santé, y compris l'utilisation de sources accessibles au public, au cas où l'équipe chargée de l'étude ne serait pas en mesure de vous contacter à l'aide des informations disponibles dans votre dossier ;
- protéger vos intérêts vitaux ou les intérêts de votre partenaire enceinte (par exemple, dans une situation médicale critique, nécessitant de de fournir des informations à un service d'urgences d'un hôpital où vous êtes traité) ; et
- répondre à vos demandes en matière de protection des données (le cas échéant).

Votre centre participant à l'étude conservera vos données personnelles pendant la période nécessaire pour remplir les objectifs décrits dans la note d'information qui pourrait aller jusqu'à 15 ans après la fin de l'étude.
Si vous fournissez les données personnelles d'un tiers (par exemple, un contact d'urgence ou des informations sur les antécédents médicaux de la famille), vous devrez les informer que vous nous avez fourni ces informations. Nous n'utiliserons ces données personnelles que conformément à cette note d'information.

C. Qu'advient-il de mes informations personnelles envoyées en dehors du centre d'étude ?

Avant que l'équipe chargée de l'étude ne transfère vos données personnelles en dehors du centre d'étude, le centre remplacera votre nom par un code unique et supprimera les données qui vous identifient directement. Nous appelons cela "**Informations codées**". Le centre gardera le lien entre le code et vos données personnelles et confidentielles, et le Promoteur n'aura pas accès à ce lien. Les employés et les représentants du Promoteur sont tenus de protéger vos informations codées et ne tenteront pas de vous identifier de nouveau.
Vos informations codées seront utilisées par :

- Le Promoteur et ses représentants (y compris les sociétés affiliées) ;

- Les personnes et/ou organisations qui fournissent des services ou collaborent avec le Promoteur ;
- Toute organisation qui obtient tout ou partie de l'activité du Promoteur ou les droits sur le produit à l'étude ;
- D'autres chercheurs ;
- Le CPP ou le CIE qui a approuvé cette étude ;
- les autorités gouvernementales ou réglementaires.

Les parties ci-dessus peuvent utiliser vos données personnelles aux fins suivantes :

- **Mener l'étude**, y compris :
    - Examiner votre réponse au Bosulif® (bosutinib) ;
    - Comprendre l'étude et les résultats de l'étude et en apprendre davantage sur la leucémie myéloïde chronique ; et
    - Évaluer l'innocuité et l'efficacité de Bosulif® (bosutinib).
- **Se conformer à des obligations légales et réglementaires** telles que **:**
    - S'assurer que l'étude est menée conformément aux bonnes pratiques cliniques et épidémiologiques ;
    - Faire les divulgations requises aux CPP, aux CIE ou aux autorités gouvernementales ou réglementaires ;
    - Demander l'autorisation du gouvernement ou des autorités de réglementation pour commercialiser Bosulif® (bosutinib) (il est possible que ces autorités gouvernementales ou réglementaires divulguent vos Informations codées à d'autres chercheurs pour la réalisation de futures recherches scientifiques); et
    - Partager les données de l'étude avec d'autres chercheurs non affiliés au Promoteur ou à l'équipe chargée de l'étude (y compris par publication sur Internet ou par d'autres moyens, mais les renseignements qui pourraient vous identifier directement ne seront pas mis à la disposition d'autres chercheurs).

- **Publier des résumés des résultats de l'étude** dans des revues médicales, sur Internet ou lors de réunions de formation d'autres chercheurs. Vous ne serez pas directement identifié dans une publication ou un rapport d'étude. Cependant, certains représentants d'une revue médicale peuvent avoir besoin d'accéder à vos Informations codées pour vérifier les résultats de l'étude et s'assurer que la recherche répond aux normes de qualité de la revue médicale. En outre, les revues médicales peuvent exiger que les informations génétiques et que d'autres informations provenant de l'étude qui ne vous identifient pas directement soient mises à la disposition d'autres chercheurs pour d'autres projets de recherche.

- **Améliorer la qualité, la conception et la sécurité** de cette étude et d'autres études.

Le Promoteur conservera vos Informations codées pendant la période nécessaire pour remplir les objectifs décrits la note d'information qui pourrait aller jusqu'à 15 ans après la fin de l'étude.

D. Comment sont traités mes échantillons biologiques et mes images ?

Si des échantillons biologiques ou des images de vous sont prises pendant l'étude, ces échantillons et images seront traités de la même manière que vos Informations codées. Tous les échantillons seront traités comme requis par la loi. Parfois, votre centre d'étude peut être dans l'incapacité de supprimer des informations qui peuvent vous identifier à partir de vos images avant de les envoyer au Promoteur et à ses représentants.

E. Mes informations personnelles peuvent-elles être utilisées pour d'autres recherches ?

Vos Informations codées peuvent être utilisées pour faire progresser la recherche scientifique et la santé publique dans d'autres projets qui auront lieu à l'avenir. Actuellement, nous ne connaissons pas les détails spécifiques de ces futurs projets de recherche.

Cette autre recherche peut être conduite (1) en combinaison avec des données provenant **d'autres sources**, (2) à des fins de **recherche scientifique supplémentaires** au-delà des objectifs de cette étude, et (3) sous réserve de **mesures de protection spécifiques**.

- **Autres sources** : Les Informations codées peuvent être combinées avec des données provenant d'autres sources en-dehors du cadre de la recherche. Ces sources peuvent inclure: des dossiers de santé électroniques codés, des données ou bases de données de réclamations et coûts de soins de santé et de paiement, des registres sur des produits et maladies, des données recueillies par vos téléphone, tablette ou autres appareils et applications mobiles, médias sociaux, données pharmaceutiques, bio-banques ou programmes d'engagement des patients.

- **Recherche scientifique supplémentaire** : Vos Informations codées peuvent être utilisées pour comprendre comment fabriquer de nouveaux médicaments, dispositifs, produits de diagnostics, outils et / ou autres thérapies qui traitent des maladies et pour améliorer la recherche future. Elles peuvent

également être utilisées pour évaluer la valeur, le rapport coût-efficacité et le prix, et pour optimiser l'accès aux médicaments.

- **Des mesures de protection spécifiques** seront utilisées pour protéger vos Informations codées, telles que :
    - Limiter l'accès aux Informations codées à des personnes spécifiques qui seront tenues de garder ces informations confidentielles et qui auront interdiction d'essayer de ré-identifier vos informations codées.
    - Utiliser des mesures de sécurité pour éviter l'altération des données, la perte et l'accès non autorisé.
    - Anonymiser les données en supprimant et/ou en remplaçant des informations de vos Informations codées et/ou en détruisant le lien vers vos Informations codées.
    - Évaluer les systèmes de protection des données pour identifier et atténuer les risques pour la vie privée, le cas échéant, associés à chaque objectif de recherche scientifique supplémentaire.
    - Lorsque c'est requis par la loi applicable, s'assurer que la recherche scientifique à l'approbation des CPP, des CEI ou d'autres groupes d'évaluation de la recherche similaires.

F. Comment mes données personnelles seront-elles protégées lorsqu'elles seront transférées du centre participant au Promoteur ?

Vos données personnelles seront traitées conformément aux lois applicables en matière de protection des données. Le Promoteur et le centre participant sont les responsables de traitement de vos informations personnelles. Le centre participant sera le responsable de traitement de vos données personnelles et le Promoteur sera le responsable de traitement de vos Informations codées.

Certaines personnes utilisant vos données personnelles, y compris vos Informations codées, peuvent être basées dans des pays autres que votre pays, y compris les États-Unis. Les lois sur la protection des données peuvent être différentes dans ces pays. La Commission européenne a considéré que certains de ces pays offrent un niveau adéquat de protection des données (la liste complète de ces pays est disponible sur ce site : http://ec.europa.eu/justice/data-protection/international-transfers/adequacy/index_fr.htm

Le Promoteur et les personnes travaillant avec le Promoteur prendront des mesures pour préserver la confidentialité de vos données personnelles. Si vos données personnelles sont transférées par le Promoteur de l'Union Européenne (UE), de l'Espace Économique Européen (EEE) et / ou de la Suisse vers d'autres pays qui ne

répondent pas aux exigences de protection des données personnelles selon les autorités européennes, le Promoteur a mis en place des accords de transfert pour protéger vos données personnelles. Veuillez contacter l'équipe chargée de l'étude pour obtenir une copie de ces accords de transfert de données.

G. Quels sont mes droits en matière de protection des données ? Qui puis-je contacter au sujet de ces droits ou pour toute préoccupation ou réclamation ?

Si vous souhaitez exercer l'un des droits décrits ci-dessous, ou si vous avez des inquiétudes quant à la manière dont vos données personnelles sont traitées, il est préférable de contacter le centre participant et non le Promoteur. Généralement, le Promoteur ne saura pas qui vous êtes (par votre nom) parce que le Promoteur, habituellement, détient uniquement vos Informations codées, ce qui n'inclut pas votre nom ou toute autre information qui permettrait de vous identifier facilement. Pour contacter le centre participant, le médecin de l'étude ou le délégué à la protection des données du centre participant, veuillez consulter **les coordonnées** dans la note d'information.

- Vous avez le droit d'accéder à vos données personnelles détenues par l'équipe chargée de l'étude. Pour assurer l'intégrité de l'étude, vous ne serez pas en mesure de réviser certaines des données jusqu'à ce que l'étude ait été achevée.

- Vous avez le droit de corriger ou de mettre à jour vos données personnelles.

- Vous avez le droit de limiter la collecte et l'utilisation de vos données personnelles dans certaines circonstances (par exemple, si les données sont inexactes).

- Vous avez le droit de recevoir vos données personnelles dans un format informatique commun et structuré (par exemple, dans un fichier texte électronique lisible) pour vos propres besoins ou pour le donner à d'autres, comme l'exigent les lois applicables sur la protection des données. Vous pouvez ne pas avoir le droit d'obtenir vos données personnelles qui ont été utilisées à des fins d'intérêt public (par exemple, pour signaler des cas de maladie aux autorités responsables de la santé publique) ou dans l'exercice de l'autorité officielle conférée au Promoteur ou au centre participant (par exemple, répondre aux demandes d'information des autorités publiques ou surveiller la sécurité des médicaments).

- Vous avez le droit de demander la suppression de vos données personnelles si vous ne participez plus à l'étude et que vous retirez votre consentement à l'utilisation de vos données personnelles telle que décrite dans le présent document. Toutefois, il existe des limites à la possibilité d'accepter une demande de suppression de vos données personnelles. Une partie ou la totalité de vos données personnelles peuvent être conservées et utilisées si la suppression compromet sérieusement l'étude

(par exemple, si la suppression affecte la cohérence des résultats de l'étude) ou si vos données personnelles sont nécessaires pour se conformer aux exigences légales.

- Vous disposez du droit de définir des directives relatives au sort de vos données personnelles après votre décès

- Vous avez le droit d'introduire une réclamation auprès d'une autorité de protection des données

(http://ec.europa.eu/justice/data-protection/article-29/structure/data-protection-authorities/index_en.htm).

H. Que se passe-t-il si je ne souhaite pas poursuivre l'étude ?

Comme indiqué dans la note d'information, vous êtes libre d'arrêter de prendre part à cette étude à tout moment en en informant l'équipe chargée de l'étude.

Si vous ne participez plus à l'étude et que vous n'en informez pas l'équipe chargée de l'étude, elle peut vous contacter et vérifier si vous souhaitez toujours participer à l'étude. Si le centre participant ne peut pas vous joindre, le Promoteur peut consulter des registres accessibles au public concernant votre santé pour surveiller la sécurité d'utilisation à long terme du médicament à l'étude. Cela ne sera fait que si la loi le permet.

Si vous mettez un terme à votre participation à l'étude sans retirer votre consentement, vos données personnelles continueront d'être utilisées conformément au présent document et à la loi applicable. Aucune nouvelle donnée ou échantillon vous concernant ne sera collecté par l'équipe chargée de l'étude, sauf si vous avez accepté de les fournir.

Si vous décidez de retirer votre consentement :

- Vous ne pourrez plus participer à l'étude.

- Aucune nouvelle information ou aucun échantillon vous concernant ne sera recueilli par l'équipe chargée de l'étude ;

- L'équipe chargée de l'étude doit systématiquement signaler tout événement indésirable que vous avez pu avoir lors de votre participation à l'étude auprès du Promoteur ;

- Vos données personnelles, y compris les Informations codés, qui ont été recueillies jusqu'au moment de votre sortie de l'étude seront conservées et utilisées par le Promoteur pour garantir l'intégrité de l'étude, pour déterminer les effets sur la sécurité du Bosulif® (bosutinib), pour satisfaire à des exigences légales ou réglementaires, et/ou à toute autre fin permise par les lois applicables en matière de protection des données et de vie privée;

- Vos données personnelles (y compris les Informations codées) ne seront pas utilisées pour d'autres recherches scientifiques. Cependant, si vos Informations personnelles ont été anonymisées, afin que vous ne puissiez pas être identifié personnellement, ces informations peuvent continuer à être utilisées pour d'autres recherches scientifiques (tel que décrit à la section E du présent document), tel que permis par la loi applicable ; et

- Les échantillons biologiques qui ont été prélevés mais non analysés ne seront plus utilisés, à moins que la loi applicable ne le permette ou ne l'exige. Vous avez également le droit de demander que tous vos échantillons restants qui ont été recueillis dans le cadre de l'étude soient détruits. Vous pouvez exercer ce droit en communiquant à l'équipe chargée de l'étude votre souhait de faire détruire vos échantillons. L'équipe enverra alors votre demande codée au Promoteur. Dans certains pays, les lois ou réglementations locales peuvent exiger que vos échantillons soient détruits ou anonymisés si vous vous retirez de l'étude, que vous fassiez spécifiquement ou non une telle demande. Cependant, nous ne pouvons pas garantir la destruction des échantillons car il se peut que l'échantillon ne puisse plus être retracé jusqu'à vous, qu'il ait été complètement utilisé ou qu'il ait été remis à un tiers. Dans ce cas, il ne sera pas possible d'effacer et de détruire vos échantillons biologiques et toutes les données connexes.

APPENDIX 7. LIST OF SUBJECT DATA LISTINGS

List any data listings (table number and title) to be appended to the study report under the appropriate category. For secondary data collection studies with protocol deviations, retain the appendix heading "List of Subject Data Listings" and state "Not applicable" for all sub-headers except 7.2 Protocol Deviations. For all other secondary data collection studies, include the appendix heading *"List of Subject Data Listings"* and state as "Not applicable" in the description.

Appendix 7.1 Withdrawn Subjects

Table 79: Withdrawn Subjects

Patient No.	Date of initiation bosutinib treatment	Was the patient monitored for the 36 months of the study?	Alive	Alive, Date of last contact	Lost to follow-up	Lost to follow-up, Date of last contact	Died	Date of death
01-01	24/02/2016	No	.	.			Ticked	23/01/2017
01-02	08/09/2017	Yes	.	.			.	
01-03	14/12/2017	Yes	.	.			.	
01-04	07/03/2018	Yes	.	.			.	
01-05	15/01/2019	Yes	.	.			.	
01-06	16/01/2019	Yes	.	.			.	
02-01	24/10/2015	Yes	.	.			.	
02-02	28/10/2015	Yes	.	.			.	
02-04	30/10/2015	Yes	.	.			.	
02-05	26/07/2016	Yes	.	.			.	
02-06	05/07/2017	Yes	.	.			.	
02-07	17/10/2018	Yes	.	.			.	
02-08	26/06/2019	Yes	.	.			.	
02-09	03/10/2019	Yes	.	.			.	
03-01	19/05/2016	Yes	.	.			.	
03-02	09/12/2019	Yes	.	.			.	
04-01	09/11/2016	Yes	.	.			.	

Patient No.	Date of initiation bosutinib treatment	Was the patient monitored for the 36 months of the study?	Alive	Alive, Date of last contact	Lost to follow-up	Lost to follow-up, Date of last contact	Died	Date of death
04-02	16/12/2016	No	.		Ticked	08/08/2019	.	
04-03	22/03/2018	Yes	.		.		.	
04-04	30/01/2019	Yes	.		.		.	
04-05	08/07/2019	Yes	.		.		.	
04-06	06/09/2019	Yes	.		.		.	
04-07	09/09/2019	Yes	.		.		.	
04-08	19/09/2019	Yes	.		.		.	
04-09	10/10/2019	Yes	.		.		.	
04-10	20/11/2019	Yes	.		.		.	
05-01	05/08/2016	Yes	Ticked	25/10/2019	.		.	
06-01	16/12/2015	Yes	.		.		.	
08-01	24/10/2016	Yes	.		.		.	
08-02	05/07/2017	Yes	.		.		.	
08-03	23/08/2017	Yes	.		.		.	
08-04	13/10/2018	No	Ticked	08/04/2019	.		.	
09-01	04/05/2016	Yes	.		.		.	
09-02	08/09/2016	Yes	.		.		.	
09-03	17/10/2016	Yes	.		.		.	
09-04	10/10/2016	Yes	.		.		.	
09-05	01/01/2017	Yes	.		.		.	
09-06	06/01/2017	Yes	.		.		.	
09-07	26/01/2017	Yes	.		.		.	
09-08	15/03/2017	Yes	.		.		.	
09-09	16/05/2017	Yes	.		.		.	
09-10	21/09/2017	No	.		.		Ticked	02/03/2019
09-11	04/09/2018	Yes	.		.		.	
09-12	25/09/2018	Yes	.		.		.	
09-14	12/11/2018	Yes	.		.		.	
09-15	04/02/2019	Yes	.		.		.	
09-16	19/03/2019	Yes	.		.		.	
09-17	01/04/2019	Yes	.		.		.	

Patient No.	Date of initiation bosutinib treatment	Was the patient monitored for the 36 months of the study?	Alive	Alive, Date of last contact	Lost to follow-up	Lost to follow-up, Date of last contact	Died	Date of death
09-18	15/05/2019	Yes	.		.	.		
09-19	23/05/2019	Yes	.		.	.		
09-20	08/08/2019	Yes	.		.	.		
09-21	19/11/2019	Yes	.		.	.		
09-22	13/11/2019	Yes	.		.	.		
09-23	19/12/2019	No	Ticked	11/01/2021	.	.		
10-01	17/03/2016	Yes	.		.	.		
10-02	20/04/2016	Yes	.		.	.		
10-03	31/08/2016	Yes	.		.	.		
10-04	07/11/2019	Yes	.		.	.		
11-01	21/03/2016	Yes	.		.	.		
11-02	14/04/2016	Yes	.		.	.		
11-03	18/04/2016	Yes	.		.	.		
11-04	02/09/2016	No	Ticked	15/02/2018	.	.		
11-05	09/02/2017	Yes	.		.	.		
11-06	17/03/2017	Yes	.		.	.		
11-07	29/03/2017	Yes	.		.	.		
11-08	24/03/2017	Yes	.		.	.		
11-09	03/06/2017	Yes	.		.	.		
11-10	01/09/2017	Yes	.		.	.		
11-11	23/11/2017	Yes	.		.	.		
11-12	07/03/2018	Yes	.		.	.		
11-13	22/04/2018	Yes	.		.	.		
11-15	09/07/2018	No	Ticked	11/09/2019	.	.		
11-16	06/07/2018	No	Ticked	06/10/2020	.	.		
11-17	15/12/2018	Yes	.		.	.		
11-18	12/11/2018	Yes	.		.	.		
11-19	08/11/2018	Yes	.		.	.		
11-20	20/05/2019	Yes	.		.	.		
11-21	06/07/2019	Yes	.		.	.		
11-22	10/11/2019	Yes	.		.	.		

Patient No.	Date of initiation bosutinib treatment	Was the patient monitored for the 36 months of the study?	Alive	Alive, Date of last contact	Lost to follow-up	Lost to follow-up, Date of last contact	Died	Date of death
11-23	09/12/2019	Yes	.		.		.	
11-24	29/12/2019	Yes	.		.		.	
11-25	16/12/2019	Yes	.		.		.	
12-01	31/05/2016	Yes	.		.		.	
12-02	03/06/2016	Yes	.		.		.	
12-03	30/06/2016	Yes	.		.		.	
12-04	13/09/2018	Yes	.		.		.	
12-05	14/11/2018	Yes	.		.		.	
12-06	02/04/2019	Yes	.		.		.	
13-01	26/03/2016	No	.		.		Ticked	29/07/2016
13-02	09/05/2016	Yes	.		.		.	
13-03	12/12/2016	Yes	.		.		.	
13-04	15/03/2018	No	.		.		Ticked	02/02/2020
13-05	07/02/2018	Yes	.		.		.	
13-06	12/04/2018	Yes	.		.		.	
13-07	02/05/2019	Yes	.		.		.	
15-01	04/04/2016	Yes	.		.		.	
15-02	23/05/2016	Yes	.		.		.	
15-03	12/04/2017	Yes	.		.		.	
15-05	14/05/2018	Yes	.		.		.	
15-06	14/01/2019	Yes	.		.		.	
15-07	30/04/2019	Yes	.		.		.	
15-08	06/11/2019	Yes	.		.		.	
16-01	21/03/2016	Yes	.		.		.	
16-02	03/06/2016	Yes	.		.		.	
16-03	24/07/2016	No	.		.		Ticked	30/10/2018
16-04	06/10/2016	Yes	.		.		.	
16-05	12/12/2016	Yes	.		.		.	
16-06	27/11/2017	Yes	.		.		.	
16-07	04/04/2018	Yes	.		.		.	
16-08	30/01/2019	No	.		.		Ticked	27/06/2021

Patient No.	Date of initiation bosutinib treatment	Was the patient monitored for the 36 months of the study?	Alive	Alive, Date of last contact	Lost to follow-up	Lost to follow-up, Date of last contact	Died	Date of death
16-09	02/05/2019	Yes	.		.		.	
16-10	17/10/2019	Yes	.		.		.	
17-01	18/12/2018	Yes	.		.		.	
22-01	24/08/2017	No	.		Ticked	07/08/2018	.	
22-02	24/11/2017	Yes	.		.		.	
23-01	07/07/2016	Yes	.		.		.	
23-02	01/10/2016	No	.		.		Ticked	02/11/2016
23-03	19/10/2018	Yes	.		.		.	
24-01	06/03/2017	Yes	.		.		.	
24-02	28/03/2017	Yes	.		.		.	
24-03	12/04/2017	Yes	.		.		.	
24-04	05/12/2017	Yes	.		.		.	
33-01	04/10/2016	Yes	.		.		.	
33-02	02/05/2017	Yes	.		.		.	
33-03	04/12/2017	Yes	.		.		.	
33-04	28/06/2018	Yes	.		.		.	
33-05	01/09/2018	Yes	.		.		.	
33-06	05/09/2018	Yes	.		.		.	
33-07	01/10/2018	Yes	.		.		.	
33-08	14/10/2019	Yes	.		.		.	
34-01	01/09/2017	Yes	.		.		.	
34-02	16/01/2019	Yes	.		.		.	
36-01	26/08/2019	Yes	.		.		.	
37-01	07/01/2019	Yes	.		.		.	
38-01	14/09/2017	Yes	.		.		.	
38-02	14/08/2018	Yes	.		.		.	
39-01	07/09/2018	Yes	.		.		.	
42-01	28/11/2017	Yes	.		.		.	
42-02	12/12/2018	Yes	.		.		.	
43-01	20/11/2018	No	Ticked	16/12/2019	.		.	
43-02	01/10/2019	Yes	.		.		.	

Patient No.	Date of initiation bosutinib treatment	Was the patient monitored for the 36 months of the study?	Alive	Alive, Date of last contact	Lost to follow-up	Lost to follow-up, Date of last contact	Died	Date of death
47-01	22/01/2019	Yes	.		.	.		
47-02	05/03/2019	No	Ticked	02/12/2019	.	.		
47-03	18/03/2019	No	Ticked	09/12/2019	.	.		
48-01	06/10/2018	No	Ticked	06/01/2020	.	.		
49-01	23/08/2017	No	Ticked	30/09/2019	.	.		

Appendix 7.6 Withdrawn Subjects (Subject discontinuation) - All Subjects

Appendix 7.2 Protocol Deviations

1. Pfizer Protocol Number	2. Site Number	3. Principal Investigator Last Name	4. Patient Number	5. Date (dd-Mmm-yyyy)	6. Description	7. Action Taken	8. Pfizer Project Manager Review Date (dd-Mmm-yyyy)	9. Pfizer NI Study Lead Review Date (dd-Mmm-yyyy)	10. Important * /Non-important	11. Include in Study Report (Yes/No)	12. Comments
B1871047	001	Dr Maloisel	01-01	31-janv-22	01-01 EI : candidose 08/04/16 à NK/04/16, baisse de moral NK/01/17 en cours, surinfection bronchique 17/11/16 à 24/11/16, toux NK/10/16 à NK/10/16, anorexie NK/10/16 en cours, sécheresse buccale NK/10/16 à NK/10/16, dyspnée d'effort NK/10/16 à NK/11/16, ulcère artériel jambe gauche 14/12/16 en cours EIG non déclarés dans les 24h où le centre en a eu connaissance	Revue avec la TRC déclaration faite immédiatement	25-Mar-2022	25-Mar-2022	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	001	Dr Maloisel	01-01	31-janv-22	01-01 EI : Anémie 06/03/16 en cours non déclaré en EIG (grade 4) mais en EI	Revue avec la TRC EIG car grade 4, déclaration faite immédiatement	25-Mar-2022	25-Mar-2022	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	001	Dr Maloisel	01-01	31-janv-22	01-01 EI : troubles digestifs 05/09/16 à 23/09/16 non déclaré en EIG mais seulement en EI	Revue avec la TRC déclaration faite immédiatement	25-Mar-2022	25-Mar-2022	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	001	Dr Maloisel	01-02	28-nov-17	01-02: EI dégradation de la fonction rénale 14/11/17 en cours non déclaré dans les 24h où l'investigateur en a eu connaissance	Rappel fait à la TRC ainsi que dans le mail post visite	3-Oct-2019	3-Oct-2019	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	001	Dr Maloisel	01-02	17-avr-19	01-02: Episode infectieux NK/ 01/19 à NK/01/19 non déclaré dans les 24h où l'investigateur en a eu connaissance	Rappel fait à la TRC ainsi que dans le mail post visite	3-Oct-2019	3-Oct-2019	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	001	Dr Maloisel	01-02	05-sept-18	01-02 :EI diarrhée NK/06/18 à 04/09/18 non déclaré dans les 24h où l'investigateur en a eu connaissance	Rappel fait à la TRC ainsi que dans le mail post visite	3-Oct-2019	3-Oct-2019	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	001	Dr Maloisel	01-02	09-janv-18	01-02: EI : constipation NK/11/17 à 09/01/18 non déclaré dans les 24h où l'investigateur en a eu connaissance	Rappel fait à la TRC ainsi que dans le mail post visite	3-Oct-2019	3-Oct-2019	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	001	Dr Maloisel	01-02	23-mars-21	01-02 : EIG rupture du talon d'Achille NK/08/19 à 16/08/19 non déclarés dans les 24h où le centre en a eu connaissance	Rappel fait à la TRC ainsi que dans le mail post visite	30-Apr-2021	30-Apr-2021	Non-important	YES	Late Serious Adverse Event (SAE) Reporting

B1871047	001	Dr Maloisel	01-03	20-déc-18	01-03 : EI : diabète mal équilibrée 22/11/18 à 20/12/18 non déclaré dans les 24h où l'investigateur en a eu connaissance	Rappel fait à la TRC ainsi que dans le mail post visite	3-Oct-2019	3-Oct-2019	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	001	Dr Maloisel	01-03	23-mars-21	01-03 : EI : extrasystoles 13/09/19 en cours non déclarés dans les 24h où l'investigateur en a eu connaissance	Rappel fait à la TRC ainsi que dans le mail post visite	30-Apr-2021	30-Apr-21	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	001	Dr Maloisel	01-04	05-juil-18	01-04 : EI AIT EIG NK/06/18 à NK/06/18 non déclaré dans les 24h où l'investigateur en a eu connaissance	Rappel fait à la TRC ainsi que dans le mail post visite	3-Oct-2019	3-Oct-2019	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	001	Dr Maloisel	01-04	10-août-18	01-04 : EI hypokaliémie 11/07/18 à 12/07/18 non déclaré dans les 24h où l'investigateur en a eu connaissance	Rappel fait à la TRC ainsi que dans le mail post visite	3-Oct-2019	3-Oct-2019	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	001	Dr Maloisel	01-04	10-août-18	01-04 : EI carence vitamine A, acide folique NK/07/18 à NK/07/18 non déclaré dans les 24h où l'investigateur en a eu connaissance	Rappel fait à la TRC ainsi que dans le mail post visite	3-Oct-2019	3-Oct-2019	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	001	Dr Maloisel	01-04	10-août-18	01-04 : aggravation anxiété et dépression 5/07/18 à NK/07/18 non déclaré dans les 24h où l'investigateur en a eu connaissance	Rappel fait à la TRC ainsi que dans le mail post visite	3-Oct-2019	3-Oct-2019	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	001	Dr Maloisel	01-04	17-avr-18	01-04 EI aggravation de l'HTA 21/03/18 à 29/03/18 non déclaré dans les 24h où l'investigateur en a eu connaissance	Rappel fait à la TRC ainsi que dans le mail post visite	3-Oct-2019	3-Oct-2019	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	001	Dr Maloisel	01-04	17-avr-18	01-04 : EI douleurs articulaires 5/04/18 à 14/04/18 non déclaré dans les 24h où l'investigateur en a eu connaissance	Rappel fait à la TRC ainsi que dans le mail post visite	3-Oct-2019	3-Oct-2019	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	001	Dr Maloisel	01-04	17-avr-18	01-04 : EI fatigue 17/04/18 à 29/05/18 non déclaré dans les 24h où l'investigateur en a eu connaissance	Rappel fait à la TRC ainsi que dans le mail post visite	3-Oct-2019	3-Oct-2019	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	001	Dr Maloisel	01-04	17-avr-18	01-04 : EI nausées 7/03/18 à 21/03/18 non déclaré dans les 24h où l'investigateur en a eu connaissance	Rappel fait à la TRC ainsi que dans le mail post visite	3-Oct-2019	3-Oct-2019	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	001	Dr Maloisel	01-04	17-avr-18	01-04 :EI essoufflement 17/04/18 à 29/05/18 non déclaré dans les 24h où l'investigateur en a eu connaissance	Rappel fait à la TRC ainsi que dans le mail post visite	3-Oct-2019	3-Oct-2019	Non-important	YES	Late Serious Adverse Event (SAE) Reporting

B1871047	001	Dr Maloisel	01-04	29-mai-18	01-04 : EI céphalées 27/05/18 à NK/06/18 non déclaré dans les 24h où l'investigateur en a eu connaissance	Rappel fait à la TRC ainsi que dans le mail post visite	3-Oct-2019	3-Oct-2019	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	001	Dr Maloisel	01-04	01-févr-22	01-04 : EI douleurs thoraciques NK/NK/19 à NK/NK/10, ostéoporose NK/09/19 en cours, douleur poumon NK/10/20 à NK/10/20 non déclarés dans les 24h où le centre en a eu connaissance et depuis que la saisie des EI à long terme a commencé dans le centre	Evènement indésirable à long terme, oubli de la TRC, demande de déclarer faite dans le mail post-visite	25-Mar-2022	25-Mar-2022	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	001	Dr Maloisel	01-05	15-avr-19	01-05 : EI épisode infectieux NK/04/19 à NK/04/19 non déclaré dans les 24h où l'investigateur en a eu connaissance	Rappel fait à la TRC ainsi que dans le mail post visite	3-Oct-2019	3-Oct-2019	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	001	Dr Maloisel	01-05	15-avr-19	01-05 EI engourdissement des doigts NK/04/19 en cours non déclaré dans les 24h où l'investigateur en a eu connaissance	Rappel fait à la TRC ainsi que dans le mail post visite	3-Oct-2019	3-Oct-2019	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	001	Dr Maloisel	01-05	23-mars-21	01-05 : EI Hémorragie rétinienne NK/NK/19 en cours non déclaré dans les 24h où l'investigateur en a eu connaissance	Rappel fait à la TRC ainsi que dans le mail post visite	30-Apr-2021	30-Apr-2021	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	001	Dr Maloisel	01-05	23-mars-21	01-05 : EI Gène respiratoire NK/10/20 à 19/10/20 non déclaré dans les 24h où l'investigateur en a eu connaissance	Rappel fait à la TRC ainsi que dans le mail post visite	30-Apr-2021	30-Apr-2021	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	001	Dr Maloisel	01-05	23-mars-21	01-05 : OMI 26/01/21 en cours non déclaré dans les 24h où l'investigateur en a eu connaissance	Rappel fait à la TRC ainsi que dans le mail post visite	30-Apr-2021	30-Apr-2021	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	001	Dr Maloisel	01-05	16-juil-19	01-05 : Sous Décalage ST 14/01/20 en cours non déclaré dans les 24h où l'investigateur en a eu connaissance	Rappel fait à la TRC ainsi que dans le mail post visite	30-Apr-2021	30-Apr-2021	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	001	Dr Maloisel	01-06	29/02/2019	01-06 : EI douleurs épigastriques NK/02/19 à 25/03/19 non déclaré dans les 24h où l'investigateur en a eu connaissance	Rappel fait à la TRC ainsi que dans le mail post visite	3-Oct-2019	3-Oct-2019	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	001	Dr Maloisel	01-06	25-mars-19	01-06 : EI cytolyse hépatique 2/03/19 à 6/04/19 non déclaré dans les 24h où l'investigateur en a eu connaissance	Rappel fait à la TRC ainsi que dans le mail post visite	3-Oct-2019	3-Oct-2019	Non-important	YES	Late Serious Adverse Event (SAE) Reporting

B1871047	001	Dr Maloisel	01-06	02-mars-19	01-06 : EI réaction cutanée NK/09/19 à 25/03/19 non déclaré dans les 24h où l'investigateur en a eu connaissance	Rappel fait à la TRC ainsi que dans le mail post visite	3-Oct-2019	3-Oct-2019	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	001	Dr Maloisel	01-06	02-févr-22	01-06 : EI douleurs épigastriques NK/05/19 à NK/04/20, nodule thyroïdien NK/04/20 à NK/10/20 EIG, troubles de la voix NK/10/20 à NK/12/20 non déclarés dans les 24h où le centre en a eu connaissance et depuis que la saisie des EI à long terme a commencé dans le centre	Evènement indésirable à long terme, oubli de la TRC, demande de déclarer faite dans le mail post-visite	25-Mar-2022	25-Mar-2022	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	002	Dr Hacini	02-01	25-juil-16	02-01 : la diarrhée n'a pas été déclarée à la PV dans les 24h où le médecin en a eu connaissance	Protocol PV declaration guidelines reminded in follow-up letter	28-Nov-2016	28-Nov-2016	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	002	Dr Hacini	02-02	15-déc-17	02-02 : l'érésipèle n'a pas été déclarée à la PV dans les 24h où le médecin en a eu connaissance	Protocol PV declaration guidelines reminded in follow-up letter	7-Feb-2018	7-Feb-2018	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	002	Dr Hacini	02-02	15-déc-17	02-02 : la dégradation dentaire n'a pas été déclarée à la PV dans les 24h où le médecin en a eu connaissance	Protocol PV declaration guidelines reminded in follow-up letter	7-Feb-2018	7-Feb-2018	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	002	Dr Hacini	02-02	24-mai-16	02-02 : la diarrhée n'a pas été déclarée à la PV dans les 24h où le médecin en a eu connaissance	Protocol PV declaration guidelines reminded in follow-up letter	21-juin-19	21-juin-19	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	002	Dr Hacini	02-04	18-janv-16	02-04 : la nausée n'a pas été déclarée à la PV dans les 24h où le médecin en a eu connaissance	Protocol PV declaration guidelines reminded in follow-up letter	7-Mar-2016	7-Mar-2016	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	002	Dr Hacini	02-04	10-oct-16	02-04 : l'anémie n'a pas été déclarée à la PV dans les 24h où le médecin en a eu connaissance	Protocol PV declaration guidelines reminded in follow-up letter	28-Nov-2016	28-Nov-2016	Non-important	YES	Late Serious Adverse Event (SAE) Reporting

B1871047	002	Dr Hacini	02-04	16-janv-17	02-04 : la diarrhée 14/12/16 n'a pas été déclarée à la PV dans les 24h où le médecin en a eu connaissance	Protocol PV declaration guidelines reminded in follow-up letter	7-Feb-2018	7-Feb-2018	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	002	Dr Hacini	02-04	22-janv-19	02-04 : l'hypokaliémie n'a pas été déclarée à la PV dans les 24h où le médecin en a eu connaissance	Protocol PV declaration guidelines reminded in follow-up letter	21-juin-19	21-juin-19	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	002	Dr Hacini	02-04	22-janv-19	02-04 : la carence martiale n'a pas été déclarée à la PV dans les 24h où le médecin en a eu connaissance	Protocol PV declaration guidelines reminded in follow-up letter	21-juin-19	21-juin-19	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	002	Dr Hacini	02-04	18-sept-18	02-04 : la diarrhée NK/NK/18 n'a pas été déclarée à la PV dans les 24h où le médecin en a eu connaissance	Protocol PV declaration guidelines reminded in follow-up letter	21-juin-19	21-juin-19	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	002	Dr Hacini	02-05	24-oct-16	02-05 : la diarrhée n'a pas été déclarée à la PV dans les 24h où le médecin en a eu connaissance	Protocol PV declaration guidelines reminded in follow-up letter	28-Nov-2016	28-Nov-2016	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	002	Dr Hacini	02-06	04-oct-18	02-06 : la cholécystite EIG n'a pas été déclarée à la PV dans les 24h où le médecin en a eu connaissance (remplissage de la 1ère page de l'EI par le médecin avec le nom de l'EIG : erreur donc non parti à la PV)	Protocol PV declaration guidelines reminded in follow-up letter	21-juin-19	21-juin-19	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	002	Dr Hacini	02-06	21-déc-18	02-06 : la diarrhée n'a pas été déclarée à la PV dans les 24h où le médecin en a eu connaissance	Protocol PV declaration guidelines reminded in follow-up letter	21-juin-19	21-juin-19	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	002	Dr Hacini	02-06	21-déc-18	02-06 : le bigéminisme n'a pas été déclaré à la PV dans les 24h où le médecin en a eu connaissance	Protocol PV declaration guidelines reminded in follow-up letter	21-juin-19	21-juin-19	Non-important	YES	Late Serious Adverse Event (SAE) Reporting

B1871047	002	Dr Hacini	02-06	02-nov-17	02-06 : La carence martiale n'a pas été déclarée à la PV dans les 24h où le médecin en a eu connaissance	Protocol PV declaration guidelines reminded in follow-up letter	7-Feb-2018	7-Feb-2018	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	002	Dr Hacini	02-06	26-août-20	02-06 : La diarrhée n'a pas été déclarée à la PV dans les 24h où le médecin en a eu connaissance	Déclaré le jour du monitoring, rappel fait au médecin	8-Feb-2021	8-Feb-2021	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	002	Dr Hacini	02-08	25-août-20	02-08 : La diminution de la TSH n'a pas été déclarée à la PV dans les 24h où le médecin en a eu connaissance	Déclaré le jour du monitoring, rappel fait au médecin	8-Feb-2021	8-Feb-2021	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	002	Dr Hacini	02-09	25-août-20	02-09 : Mauvaise version du consentement signé (V2.1 au lieu de V3)	Rappel fait au médecin, la bonne version sera signée lors de la prochaine visite du patient	8-Feb-2021	8-Feb-2021	Non-important	YES	Breaches in the informed consent or data privacy processes
B1871047	002	Dr Hacini	02-08	25-oct-22	02-08: Aggravation de l'Insuffisance rénale n'a pas été déclarée à la PV dans les 24h où le médecin en a eu connaissance	Déclaré le jour du monitoring, rappel fait au médecin	14-Jul-2023	14-Jul-2023	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	002	Dr Hacini	02-08	25-oct-22	02-08: Douleurs musculosquelettiques n'a pas été déclarée à la PV dans les 24h où le médecin en a eu connaissance	Déclaré le jour du monitoring, rappel fait au médecin	14-Jul-2023	14-Jul-2023	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	003	Dr Orfeuvre	03-01	29-août-16	03-01 : Nausées non déclarées dans les 24h où le centre en a eu connaissance	Rappel fait dans le mail post visite du 12/09/16	14-Sep-2016	14-Sep-2016	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	003	Dr Orfeuvre	03-01	24-sept-19	03-01 : Mésusage non déclaré dans les 24h où le centre en a eu connaissance	Rappel fait dans le mail post visite du 103/07/19	15-Jul-2019	15-Jul-2019	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	003	Dr Orfeuvre	03-01	05-avr-19	03-01 : Infection dentaire non déclarées dans les 24h où le centre en a eu connaissance	Rappel fait dans le mail post visite du 103/07/19	15-Jul-2019	15-Jul-2019	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	003	Dr Orfeuvre	03-02	16-déc-22	03-02 : Anémie ferriprive non déclarées dans les 24h où le centre en a eu connaissance	Rappel fait dans le mail post visite du 04/01/23	4-Jan-2023	4-Jan-2023	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	004	Dr Quittet	04-01	14-avr-17	Patient 04-01 : consentement non présent sur centre	Déclaré par le médecin + rappel fait	20-Apr-2017	20-Apr-2017	Non-important	YES	Breaches in the informed consent or data privacy processes, finally collected and filed on site, closed on 20Jun-2017

B1871047	004	Dr Quittet	04-01	06-déc-17	Patient 04-01 : nausées et vomissements du 6/11/17 non déclarés dans les 24h00 où le médecin en a eu connaissance	Déclaré par le médecin + rappel fait	27-Aug-2018	27-Aug-2018	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	004	Dr Quittet	04-02	14-avr-17	Patiente 04-02 : consentement non daté par la patiente	Déclaré par le médecin + rappel fait	20-Apr-2017	20-Apr-2017	Non-important	YES	Breaches in the informed consent or data privacy processes, ICF signed again on 18May2017
B1871047	004	Dr Quittet	04-02	22-mars-17	Patiente 04-02 : anémie du 10/03/17 non déclarée dans les 24h00 où le médecin en a eu connaissance	Déclaré par le médecin + rappel fait	20-Apr-2017	20-Apr-2017	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	004	Dr Quittet	04-02	09-juin-17	Patiente 04-02 : nausée du NK/06/17 non déclarée dans les 24h00 où le médecin en a eu connaissance	Déclaré par le médecin + rappel fait	26-Jun-2017	26-Jun-2017	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	004	Dr Quittet	04-02	13-mars-17	Patiente 04-02 : cytolyse hépatique du 19/3/17 non déclarée dans les 24h00 où le médecin en a eu connaissance	Déclaré par le médecin + rappel fait	26-Jun-2017	26-Jun-2017	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	004	Dr Quittet	04-02	07-sept-17	Patiente 04-02 : anémie du 21/08/17 non déclarée dans les 24h00 où le médecin en a eu connaissance	Déclaré par le médecin + rappel fait	27-Aug-2018	27-Aug-2018	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	004	Dr Quittet	04-02	10-sept-17	Patiente 04-02 : carence martiale du NK/03/17 non déclarée dans les 24h00 où le médecin en a eu connaissance	Déclaré par le médecin + rappel fait	27-Aug-2018	27-Aug-2018	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	004	Dr Quittet	04-02	06-juin-17	Patiente 04-02 : syndrome canalaire du nerf ulnaire du NK/01/18 non déclarée dans les 24h00 où le médecin en a eu connaissance	Déclaré par le médecin + rappel fait	27-Aug-2018	27-Aug-2018	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	004	Dr Quittet	04-02	06-juin-17	Patiente 04-02 : lombalgies basses du NK/NK/18 non déclarée dans les 24h00 où le médecin en a eu connaissance	Déclaré par le médecin + rappel fait	27-Aug-2018	27-Aug-2018	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	004	Dr Quittet	04-02	07-sept-17	Patient 04-02 : Anémie 27/06/17 à 12/07/18 non déclarée dans les 24h00 où le médecin en a eu connaissance	Déclaré par le médecin + rappel fait	30-Sep-2019	30-Sep-2019	Non-important	YES	Late Serious Adverse Event (SAE) Reporting

B1871047	004	Dr Quittet	04-03	24-août-18	Patient 04-03 : Diarrhée NK/03/18 à 4/04/19 grade 1 non déclarée dans les 24h00 où le médecin en a eu connaissance	Déclaré par le médecin + rappel fait	30-Sep-2019	30-Sep-2019	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	004	Dr Quittet	04-04	22-mai-19	Patient 04-04 : Aggravation de la sténose fémorale non déclarée dans les 24h00 où le médecin en a eu connaissance	Déclaré par le médecin + rappel fait	30-Sep-2019	30-Sep-2019	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	004	Dr Quittet	04-10	17-janv-22	Patient 04-10 : Anémie non déclarée dans les 24h00 où le médecin en a eu connaissance	Déclaré par le médecin + rappel fait	25-Mar-2022	25-Mar-2022	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	004	Dr Quittet	04-10	17-janv-22	Patient 04-10 : Maux de ventre non déclarés dans les 24h00 où le médecin en a eu connaissance	Déclaré par le médecin + rappel fait	25-Mar-2022	25-Mar-2022	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	004	Dr Quittet	04-10	17-janv-22	Patient 04-10 : Douleurs thoraciques passage aux urgences) non déclarées dans les 24h00 où le médecin en a eu connaissance	Déclaré par le médecin + rappel fait	25-Mar-2022	25-Mar-2022	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	004	Dr Quittet	04-10	17-janv-22	Patient 04-10 : Insuffisance cardiaque non déclarée dans les 24h00 où le médecin en a eu connaissance	Déclaré par le médecin + rappel fait	25-Mar-2022	25-Mar-2022	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	004	Dr Quittet	04-03	22-mars-22	Patient 04-03 : Blépharite EIG, transformation LMC 15/05/21 EIG, accident du travail, mauvaise compliance non déclarés dans les 24h où le centre en a eu connaissance	Déclaré le jour du monitoring par le Dr Quittet	27-Jun-2022	27-Jun-2022	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	004	Dr Quittet	04-04	21-mars-22	Patient 04-04 : EI Diarrhée, dyslipidémie non déclarés dans les 24h où le centre en a eu connaissance	Un rappel a été fait au médecin puis les déviations sont notées dans le mail post monitoring	27-Jun-2022	27-Jun-2022	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	004	Dr Quittet	04-08	21-mars-22	Patient 04-08 : Passage aux urgences EIG (raison inconnue), gastroentérite, névralgie EIG, intervention chirurgicale notée dans la CS du 10/02/20 raison inconnue non déclarés dans les 24h où le centre en a eu connaissance	Un rappel a été fait au médecin puis les déviations sont notées dans le mail post monitoring	27-Jun-2022	27-Jun-2022	Non-important	YES	Late Serious Adverse Event (SAE) Reporting

B1871047	004	Dr Quittet	04-09	21-mars-22	Patient 04-09 : Toxicité hépatique, fracture hanche gauche EIG, anémie non déclarés dans les 24h où le centre en a eu connaissance	Un rappel a été fait au médecin puis les déviations sont notées dans le mail post monitoring	27-Jun-2022	27-Jun-2022	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	004	Dr Quittet	04-09	21-nov-22	Patient 04-09 : Fatigue à l'effort, Essoufflement à l'effort, Thrombopénie non déclarés dans les 24h où le centre en a eu connaissance	Un rappel a été fait au médecin puis les déviations sont notées dans le mail post monitoring	11-Jul-2023	11-Jul-2023	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	004	Dr Quittet	04-05	27-févr-23	Patient 04-05 : 4 potentiels EIs détectés lors du monitoring du 27Fev2023 non reportés dans l'eCRF.	Email envoyé au PI le 28/02/2023 listant les EIs à valider et à enregistrer dans l'eCRF. 3 des 4 évènements ont été confirmés et reportés dans l'eCRF le 03/07/2023 par le PI.	11-Jul-2023	11-Jul-2023	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	004	Dr Quittet	04-10	27-févr-23	Patient 04-10 : 9 potentiels EIs détectés lors du monitoring du 27Fev2023 non reportés dans l'eCRF.	Email envoyé au PI le 28/02/2023 listant les EIs à valider et à enregistrer dans l'eCRF. 3 des 9 évènements ont été confirmés et reportés dans l'eCRF le 03/07/2023 par le PI.	11-Jul-2023	11-Jul-2023	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	004	Dr Quittet	04-01	03-juil-23	Patient 04-01 : Consentement v3.0 non signé par le patient	Email envoyé au PI le 06/07/2023 – Aucune action correctrice, patient sorti d'étude. Site was reminded, quality event was declared	21-Sep-2023	21-Sep-2023	Important	YES	Breaches in the informed consent or data privacy processes

B1871047	004	Dr Quittet	04-02	03-juil-23	Patient 04-02 : Consentement v3.0 non signé par le patient	Email envoyé au PI le 06/07/2023 – Aucune action correctrice, patient sorti d'étude. Site was reminded, quality event was declared	21-Sep-2023	21-Sep-2023	Important	YES	Breaches in the informed consent or data privacy processes
B1871047	004	Dr Quittet	04-03	03-juil-23	Patient 04-03 : Consentement v3.0 non signé par le patient	Email envoyé au PI le 06/07/2023 – Aucune action correctrice, patient sorti d'étude. Site was reminded, quality event was declared	21-Sep-2023	21-Sep-2023	Important	YES	Breaches in the informed consent or data privacy processes
B1871047	004	Dr Quittet	04-04	03-juil-23	Patient 04-04 : Consentement v3.0 non signé par le patient	Email envoyé au PI le 06/07/2023 – Aucune action correctrice, patient sorti d'étude. Site was reminded, quality event was declared	21-Sep-2023	21-Sep-2023	Important	YES	Breaches in the informed consent or data privacy processes
B1871047	004	Dr Quittet	04-05	03-juil-23	Patient 04-05 : Consentement v3.0 non signé par le patient	Email envoyé au PI le 06/07/2023 – Aucune action correctrice, patient sorti d'étude. Site was reminded, quality event was declared	21-Sep-2023	21-Sep-2023	Important	YES	Breaches in the informed consent or data privacy processes
B1871047	004	Dr Quittet	04-04	03-juil-23	Patient 04-04 : 1 EI « Hypertriglycéridémie » du 09Sep2020 non reporté dans l'eCRF dans les 24H après connaissance par le PI.	Rappel fait au PI pendant le monitoring + Email envoyé au PI le 06/07/2023.	21-Sep-2023	21-Sep-2023	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	004	Dr Quittet	04-08	03-juil-23	Patient 04-08 : 1 EI « Douleurs articulaires inflammatoires » du NK/NK/2022 non reporté dans l'eCRF dans les 24H après connaissance par le PI.	Rappel fait au PI pendant le monitoring + Email envoyé au PI le 06/07/2023.	21-Sep-2023	21-Sep-2023	Non-important	YES	Late Serious Adverse Event (SAE) Reporting

B1871047	005	Dr Anglaret/Santana	05-01	05-déc-16	Diarrhée NK/08/16 non déclaré dans les 24h où le centre en a eu connaissance	Rappel fait au centre	11-Dec-2017	11-Dec-2017	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	005	Dr Anglaret/Santana	05-01	14-nov-16	Les 1ers EI Surinfection bronchique 17/10/2016, Surinfection bronchique 17/10/2016 Dysurie NK/10/2016, Diarrhées grade 3 17/08/16 n'avaient pas été déclarés dans les 24h où le centre en a eu connaissance	Rappel fait au centre	17-Mar-2020	17-Mar-2020	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	005	Dr Anglaret/Santana	05-01	17-déc-19	Consentement V3 non signé car aucun médecin déclaré dans le centre.	Site was reminded, QE was declared	4-Jul-2023	4-Jul-2023	Important	YES	Breaches in the informed consent or data privacy processes
B1871047	006	Dr Benbrahim	06-01	20-janv-16	06-01 : la cytolyse hépatique n'a pas été déclarée à la PV dans les 24h où le médecin en a eu connaissance		6-Jun-2016	6-Jun-2016	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	008	Dr Voilat	08-01	13-juin-18	08-01 : Les douleurs osseuses n'ont pas été déclarées à la PV dans les 24h où le médecin en a eu connaissance	Rappel fait dans le mail post visite du 22/02/19	28-Feb-2019	28-Feb-2019	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	008	Dr Voilat	08-01	28-nov-16	08-01 : La diarrhée n'a pas été déclarée à la PV dans les 24h où le médecin en a eu connaissance	Rappel fait dans le mail post visite du 1/03/18	23-Apr-2018	23-Apr-2018	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	008	Dr Voilat	08-02	06-déc-17	08-02 : La constipation n'a pas été déclarée à la PV dans les 24h où le médecin en a eu connaissance	Rappel fait dans le mail post visite du 1/03/18	23-Apr-2018	23-Apr-2018	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	008	Dr Voilat	08-03	22-nov-17	08-03 : La diarrhée et la kératose actinique n'ont pas été déclarés à la PV dans les 24h où le médecin en a eu connaissance	Rappel fait dans le mail post visite du 1/03/18	23-Apr-2018	23-Apr-2018	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	008	Dr Voilat	08-03	07-juin-18	08-03 : L'eczéma n'a pas été déclaré à la PV dans les 24h où le médecin en a eu connaissance	Rappel fait dans le mail post visite du 22/02/19	28-Feb-2019	28-Feb-2019	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	008	Dr Voilat	08-03	06-févr-19	08-03 : Les nausées n'ont pas été déclarées à la PV dans les 24h où le médecin en a eu connaissance	Rappel fait dans le mail post visite du 22/02/19	28-Feb-2019	28-Feb-2019	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	008	Dr Voilat	08-04	31-déc-18	08-04 : Le fibrome n'a pas été déclaré à la PV dans les 24h où le médecin en a eu connaissance	Rappel fait dans le mail post visite du 22/02/19	28-Feb-2019	28-Feb-2019	Non-important	YES	Late Serious Adverse Event (SAE) Reporting

B1871047	008	Dr Voilat	08-04	08-nov-18	08-04 : Les troubles digestifs n'ont pas été déclarées à la PV dans les 24h où le médecin en a eu connaissance	Rappel fait dans le mail post visite du 22/02/19	28-Feb-2019	28-Feb-2019	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	009	Dr Cony Mahkoul / Parry	09-02	12-déc-16	Patient 09-02 : Lésions cutanées prurigineuses n'ont pas été déclarées dans les 24h00 où le centre en a eu connaissance	Rappel fait le 10/02/17 dans le mail post visite	17-Mar-2017	17-Mar-2017	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	009	Dr Cony Mahkoul / Parry	09-02	08-janv-18	Patient 09-02 : Les EI diminution de la libido, douleur poitrine, augmentation de la troppnine, OMI, constipation, migration d'une lithiase biliaire, gastroduodénite, infection pulmonaire n'ont pas été déclarées dans les 24h00 où le centre en a eu connaissance	Rappel fait le 11/01/18 dans le mail post visite	5-Feb-2017	5-Feb-2017	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	009	Dr Cony Mahkoul / Parry	09-02	29-oct-20	Patient 09-02 : Les EI chéilite, érythème phototoxique des mb inférieurs et supérieurs, eczema de l'épitrochloé, eczema du coude, douleurs des membres inférieurs, xérose cutanée, pneumothorax, HTA, douleur épaule droite, fourmillement paroi thoracique, dents cassées, atteinte neurologique main droite, compression ulnaire, léiomyome n'ont pas été déclarés dans les 24h00 où le centre en a eu connaissance	Rappel fait lors de la visite à la TRC et au Dr Cony-Makhoul ainsi que dans le mail post visite	25-Mar-2022	25-Mar-2022	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	009	Dr Cony Mahkoul / Parry	09-02	22-févr-21	Patient 09-02 : L'EI Eczema creux poplité cuisse pieds n'a pas été déclaré dans les 24h00 où le centre en a eu connaissance	Demande de le déclarer immédiatement dans le CRF et rappel fait le 24/02/21 dans le mail post visite	25-Mar-2022	25-Mar-2022	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	009	Dr Cony Mahkoul / Parry	09-03	08/01/18	Patient 09-03 : Les EI OMI, éruption du rachis, intolérance au sérétide, épanchement du genou droit, toux, insomnie n'ont pas été déclarées dans les 24h00 où le centre en a eu connaissance	Rappel fait le 11/01/18 dans le mail post visite	5-Feb-2017	5-Feb-2017	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	009	Dr Cony Mahkoul / Parry	09-04	17/04/19	Patient 09-04 : HTA, céphalées, éruption maculo-papuleuse non déclarés dans les 24h où l'investigateur en a eu connaissance	Rappel fait le 17/04/19 dans le mail post visite	20-Aug-2020	20-Aug-2020	Non-important	YES	Late Serious Adverse Event (SAE) Reporting

B1871047	009	Dr Cony Mahkoul / Parry	09-05	18/04/18	Patient 09-05 : Diarrhée, nausée, vomissement, augmentation de la PTH, kyste ovarien, rectorragie non déclarés dans les 24h où l'investigateur en a eu connaissance	Rappel fait le 22/04/18 dans le mail post visite	17-May-2018	17-May-2018	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	009	Dr Cony Mahkoul / Parry	09-05	20-avr-22	Paient 09-05 : Fatigue, tassement vertébral, anorexie, langue dépapillée, mycose buccale, ecchymose membre inférieur droit, plaie tibiale, mycose vaginale non déclarés dans les 24h où l'investigateur en a eu connaissance	Déclaration faite dans les 24h à la PV par P.POOS et demande de le déclarer immédiatement dans le CRF et rappel fait le 22/04/22 dans le mail post visite	27-Jun-2022	27-Jun-2022	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	009	Dr Cony Mahkoul / Parry	09-05	25-juil-23	Paient 09-05 : Glossodynie essentielle NK/04/2019 non déclarés dans les 24h où l'investigateur en a eu connaissance	Enregistré dans l'eCRF le 25/07/2023	7-Sep-2023	7-Sep-2023	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	009	Dr Cony Mahkoul / Parry	09-06	07-juin-22	Patient 09-06 : Douleurs testiculaires suite à vasectomie EI non déclarésdans les 24h où l'investigateur en a eu connaissance	Reporté le jour même par le centre après la demande de l'ARC	27-Jun-2022	27-Jun-2022	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	009	Dr Cony Mahkoul / Parry	09-07	07-juin-22	Patient 09-07 : Céphalées NK/NK/20 EI non déclaré dans les 24h où le centre en a eu connaissance	Reporté le jour même par le centre après la demande de l'ARC	27-Jun-2022	27-Jun-2022	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	009	Dr Cony Mahkoul / Parry	09-07	24/01/17	Protocol non-compliance, inclusion criteria 3 not fulfilled. Patient resistant or intolerant to prior TKI therapy for PC, PA or CB CML other than bosutinib.	Discussed with PI	17-May-2018	17-May-2018	Important	YES	Decision to classify this deviation as important/major during data review and to remove this patient from FAS
B1871047	009	Dr Cony Mahkoul / Parry	09-07	1/06/17 (ancienne case : date de la déviation	Patient 09-07 : crampes non déclarées dans les 24h où l'investigateur en a eu connaissance	Rappel fait le 17/04/19 dans le mail post visite	20-Aug-2020	20-Aug-2020	Non-important	YES	Late Serious Adverse Event (SAE) Reporting

B1871047	009	Dr Cony Mahkoul / Parry	09-08	08-juin-22	Patient 09-08 : Brûlures épigastriques NK/11/19 EI non déclaré dans les 24h où le centre en a eu connaissance	Reporté le 09/06/22 par le centre à la demande de l'ARC	27-Jun-2022	27-Jun-2022	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	009	Dr Cony Mahkoul / Parry	09-08	26/06/17	Patient 09-08 : EI diarrhée non déclarée dans les 24h où l'investigateur en a eu connaissance	Fait avant la visite	6-Dec-2018	6-Dec-2018	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	009	Dr Cony Mahkoul / Parry	09-08	8/11/18	Patient 09-08 : EI crépitant des 2 bases et œdèmes des membres inférieurs non déclarés dans les 24h où le centre en a eu connaissance	Rappel fait le 06/12/18 dans le mail post visite	6-Dec-2018	6-Dec-2018	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	009	Dr Cony Mahkoul / Parry	09-09	28/08/17, 9/10/17, 16/01/18, 16/01/18, 9/10/17, 25/04/18 (ancienne case : date de la déviation	Patient 09-09 : EI augmentation des transaminases, EIG abcès dentaire, EI grippe, EI : diminution du murmure vésiculaire, EI diarrhée, EI état dépressif non déclaré dans les 24h où le centre en a eu connaissance	Rappel fait le 12/11/19 dans le mail post visite	22-Nov-2019	22-Nov-2019	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	009	Dr Cony Mahkoul / Parry	09-10	21/12/17 ; 5/04/18 ; 25/03/18 (ancienne case : date de la déviation	Patient 09-10 : EI comédon inflammatoire, sténose de la veine de drainage (EIG), brûlure au niveau du doigt non déclarés dans les 24h où le centre en a eu connaissance	Rappel fait le 06/12/18 dans le mail post visite	6-Dec-2018	6-Dec-2018	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	009	Dr Cony Mahkoul / Parry	09-11	22-févr-21	Patient 09-11 : L'EI cataracte n'a pas été déclaré dans les 24h00 où le centre en a eu connaissance	Demande de le déclarer immédiatement dans le CRF et rappel fait le 24/02/21 dans le mail post visite	25-Mar-2022	25-Mar-2022	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	009	Dr Cony Mahkoul / Parry	09-12	22-févr-21	Patient 09-12 : L'EI vertiges n'a pas été déclaré dans les 24h00 où le centre en a eu connaissance	Demande de le déclarer immédiatement dans le CRF et rappel fait le 24/02/21 dans le mail post visite	25-Mar-2022	25-Mar-2022	Non-important	YES	Late Serious Adverse Event (SAE) Reporting

B1871047	009	Dr Cony Mahkoul / Parry	09-15	23-févr-21	Patient 09-15 : Les EI troubles urinaires, malaise vagal, troubles digestifs, douleurs épigastriques, carence martiale n'ont pas été déclarés dans les 24h00 où le centre en a eu connaissance	Demande de le déclarer immédiatement dans le CRF et rappel fait le 24/02/21 dans le mail post visite	25-Mar-2022	25-Mar-2022	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	009	Dr Cony Mahkoul / Parry	09-15	14-déc-21	Patient 09-15 : Les EI : douleurs épigastriques, colite, diminution de la tension, fatigue n'ont pas été déclarés dans les 24h00 où le centre en a eu connaissance	Demande de le déclarer immédiatement dans le CRF et rappel fait le 20/12/21 dans le mail post visite	25-Mar-2022	25-Mar-2022	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	009	Dr Cony Mahkoul / Parry	09-15	14-déc-21	Patient 09-15 : Passage aux urgences pour douleurs flancs non déclarés en EIG	Demande de le déclarer immédiatement dans le CRF et rappel fait le 20/12/21 dans le mail post visite	25-Mar-2022	25-Mar-2022	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	009	Dr Cony Mahkoul / Parry	09-16	30-mai-23	Patient 09-16 : EI#5a Surcharge athéromateuse au niveau carotidien non déclarés dans les 24h où le centre en a eu connaissance	Rappel fait au centre de la déclaration dans les 24H après en avoir connaissance	7-Sep-2023	7-Sep-2023	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	009	Dr Cony Mahkoul / Parry	09-17	14-déc-21	Patient 09-17- Les EI : oedèmes des membres inférieurs, brûlures mictionnelles, pollakiurie, gène de l'hypochondre gauche n'ont pas été déclarés dans les 24h00 où le centre en a eu connaissance	Demande de le déclarer immédiatement dans le CRF et rappel fait le 20/12/21 dans le mail post visite	25-Mar-2022	25-Mar-2022	Non-important	YES	Late Serious Adverse Event (SAE) Reporting

B1871047	009	Dr Cony Mahkoul / Parry	09-17	31-mai-23	Patient 09-17 : Potentiels EIs/EIGs non déclarés dans les 24H ou le centre en a eu connaissance : . Consultation du 18/07/2020 : Douleurs abdominales irradiants dans les reins . Consultation du 02/02/2021 : Asthénie, Constipation, Nausées, Déséquilibre du diabète, OMI bilatéraux fluctuants, Fuites urinaires . Consultation du 08/03/2021 : Majoration de l'Insuffisance Rénale Chronique (Bosulif diminué à 200mg/j) . Consultation du 29/4/2021 : Altération du sommeil, Baisse de l'appétit, Altération du transit (Alternance constipation/diarrhées) . Consultation du 25/11/2021 : Douleurs testiculaires	Envoi par email au centre le 27/06/2023 pour demande de report dans l'eCRF (si applicable). Rappel fait au centre de la déclaration dans les 24H après en avoir connaissance	7-Sep-2023	7-Sep-2023	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	009	Dr Cony Mahkoul / Parry	09-18	28/08/2017, 09/10/2017, 10/01/2018, 16/10/2018, 09/10/2017, 25/04/2018	EI augmentation de transaminases, EIG abcès dentaire, EI grippe, EI : diminution du murmure vésiculaire, EI diarhée, EI état dépressif non déclaré dans les 24 h où le centre en a eu connaissance	Rappel fait au centre de la déclaration dans les 24H après en avoir connaissance	22-Nov-2019	22-Nov-2019	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	009	Dr Cony Mahkoul / Parry	09-18	15/07/2019, 24/05/2019	Patient 09-18 : EI contipation et fatique non déclarés dans les 24h où le centre en a eu connaissance	Rappel fait au centre de la déclaration dans les 24H après en avoir connaissance	20-Aug-2020	20-Aug-2020	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	009	Dr Cony Mahkoul / Parry	09-19	15-déc-22	Patient 09-19 : 13 potentiels EI non déclarés dans les 24h où le centre en a eu connaissance	Rappel fait au centre de la déclaration dans les 24H après en avoir connaissance	7-Sep-2023	7-Sep-2023	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	009	Dr Cony Mahkoul / Parry	09-19	15-déc-22	Patient 09-19 : 4 potentiels EI non déclarés dans les 24h où le centre en a eu connaissance	Rappel fait au centre de la déclaration dans les 24H après en avoir connaissance	7-Sep-2023	7-Sep-2023	Non-important	YES	Late Serious Adverse Event (SAE) Reporting

B1871047	009	Dr Cony Mahkoul / Parry	09-20	13-déc-21	Patient 09-20 : EI diarhée et douleur bicep droit non déclarés dans les 24h où le centre en a eu connaissance	Rappel fait au centre de la déclaration dans les 24H après en avoir connaissance	25-Mar-2022	25-Mar-2022	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	009	Dr Cony Mahkoul / Parry	09-21	11-août-20	Patient 09-21 : Rhume non déclaré dans les 24h où le centre en a eu connaissance	Rappel fait à l'ARC du centre le 12/08/20 et le 19/08/20 dans le mail post visite	20-Aug-2020	20-Aug-2020	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	009	Dr Cony Mahkoul / Parry	09-21	10-févr-23	Patient 09-21 : EI#8a, 8b et 9c non déclarés dans les 24h où le centre en a eu connaissance	Rappel fait le 20/02/2023 lors de la visite	7-Sep-2023	7-Sep-2023	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	009	Dr Cony Mahkoul / Parry	09-22	Déclaré à la PV le 12/08/20 par P.POOS	Patient 09-22 : Carence en vitamine D, carence en folate et phlébite du membre inférieur gauche non déclaré dans les 24h où le centre en a eu connaissance	Rappel fait à l'ARC du centre le 12/08/20 et le 19/08/20 dans le mail post visite	20-Aug-2020	20-Aug-2020	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	009	Dr Cony Mahkoul / Parry	09-22	19-avr-22	Patient 09-22 : Anémie non déclaré dans les 24h où le centre en a eu connaissance	Déclaration faite dans les 24h après demande de l'ARC	27-Jun-2022	27-Jun-2022	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	009	Dr Cony Mahkoul / Parry	09-23	13-déc-21	Patient 09-23 : Douleurs thoraciques non déclarées en EIG (passage aux urgences)	Rappel fait à l'ARC que le passage aux urgences demande une déclaration en tant qu'EIG, Déclaré par l'ARC du centre le 13/12/21	25-Mar-2022	25-Mar-2022	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	009	Dr Cony Mahkoul / Parry	09-23	13-déc-21	Patient 09-23 : Les EI folliculite et éruption cuisses n'ont pas été déclarés dans les 24h où le centre en a eu connaissance	Déclaré par le centre le 13/12/21. Rappel fait pour la déclaration des EI	25-Mar-2022	25-Mar-2022	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	009	Dr Cony Mahkoul / Parry	09-02	14-déc-22	Patient 09-02 : formulaire de consentement v3 non signé par le patient et l'investigateur lors de la M36 du 16SEP2019.	None, identified once patient is out of study. Quality event declared	7-Sep-2023	7-Sep-2023	Important	YES	Breaches in the informed consent or data privacy processes
B1871047	009	Dr Cony Mahkoul / Parry	09-03	14-déc-22	Patient 09-03 : formulaire de consentement v3 non signé par le patient et l'investigateur lors de la M36 du 18NOV2019 (M33 non effectuée).	None, identified once patient is out of study. Quality event declared	7-Sep-2023	7-Sep-2023	Important	YES	Breaches in the informed consent or data privacy processes

B1871047	009	Dr Cony Mahkoul / Parry	09-04	14-déc-22	Patient 09-04 : formulaire de consentement v3 non signé par le patient et l'investigateur lors de la M36 du 24SEP2019.	None, identified once patient is out of study. Quality event declared	7-Sep-2023	7-Sep-2023	Important	YES	Breaches in the informed consent or data privacy processes
B1871047	010	Dr Rodon / Moldovan	10-01	06-sept-16	10-01: l'évènement indésirable « trouble digestif » n'a pas été déclaré à la PV dans les 24h où le médecin en a eu connaissance	Vu avec le Dr Rodon lors de la visite, rappel fait dans le mail post visite	20-Sep-2016	20-Sep-2016	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	010	Dr Rodon / Moldovan	10-01	02-mai-17	10-01 : La pose de prothèse EIG n'a pas été déclarée à la PV dans les 24hoù le médecin en a eu connaissance	Vu avec le Dr Rodon lors de la visite, rappel fait dans le mail post visite	23-Oct-2017	23-Oct-2017	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	010	Dr Rodon / Moldovan	10-01	28-nov-16	10-01 : La diarrhée de sep 2016 n'a pas été déclarée à la PV dans les 24h où le médecin en a eu connaissance	Vu avec le Dr Rodon lors de la visite, rappel fait dans le mail post visite	23-Oct-2017	23-Oct-2017	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	010	Dr Rodon / Moldovan	10-03	04-sept-16	10-03 : La cytolyse hépatique et l'apnée du sommeil n'ont pas été déclarés dans les 24h où le médecin en a eu connaissance	Vu avec le Dr Rodon lors de la visite, rappel fait dans le mail post visite	23-Oct-2017	23-Oct-2017	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	010	Dr Rodon / Moldovan	10-01	12-févr-18	10-01 : l'évènement indésirable « fatigue » et « augmentation de la TSH » n'ont pas été déclarés à la PV dans les 24h où le médecin en a eu connaissance	Vu avec le Dr Rodon lors de la visite, rappel fait dans le mail post visite	1-Oct-2019	1-Oct-2019	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	010	Dr Rodon / Moldovan	10-04	04-nov-20	Protocol non-compliance, inclusion criteria 3 not fulfilled. Patient resistant or intolerant to prior TKI therapy for PC, PA or CB CML other than bosutinib.	Discussed with PI	5-Feb-2021	5-Feb-2021	Important	YES	Decision to classify this deviation as important/major during data review and to remove this patient from FAS
B1871047	010	Dr Rodon / Moldovan	10-04	04-nov-20	10-04 : Mauvaise version du consentement signé	Vu avec le Dr Rodon et signalé dans le mail post visite. Mais le Dr Rodon ne reverra pas le patient avant son départ à la retraite. Paraphes faits le	5-Feb-2021	5-Feb-2021	Important	YES	Breaches in the informed consent or data privacy processes

						27/01/22 sur la version 2.1					
B1871047	011	Dr Rousselot	11-01	13-juin-19	11-01 : EIG aggravation de la sténose carotidienne NK/04/18 non déclaré dans les 24h où le Dr Rousselot en a eu connaissance	Signalé au centre dans le mail post visite du 15/06/19	5-Feb-2021	5-Feb-2021	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	011	Dr Rousselot	11-02	14-avr-16	11-02 : protocol inclusion criteria 5 not followed, no contraception for this female patient who is trying to be pregnant	Discussed with investigator who confirmed enrollment	27-Aug-2018	27-Aug-2018	YES	YES	Deviation classified as not important/minor during data review
B1871047	011	Dr Rousselot	11-07	UK-oct-18	11-07 : la chirurgie de la hernie inguinale (passage au bloc en ambulatoire) n'a pas été déclarée dans les 24h où le Dr Rousselot en a eu connaissance	Signalé au centre dans le mail post visite du 18/09/19	23-Dec-2019	23-Dec-2019	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	011	Dr Rousselot	11-12	04-avr-22	11-12 : L'EIG Récidive fistule anale n'a pas été déclaré dans les 24h où le centre en a eu connaissance	Déclaré par la TRC immédiatement et signalé au centre dans le mail post visite du 08/04/22	24-Jun-2022	24-Jun-2022	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	011	Dr Rousselot	11-13	15-févr-19	11-13 : L'EIG fissure anale n'a pas été déclaré dans les 24h où le centre en a eu connaissance	Signalé au centre dans le mail post visite du 18/02/19	28-Feb-2019	28-Feb-2019	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	011	Dr Rousselot	11-15	06-juil-18	11-15 : Visite d'inclusion effectuée la veille de la signature du consentement.		28-Feb-2019	28-Feb-2019	Important	YES	Breaches in the informed consent or data privacy processes
B1871047	011	Dr Rousselot	11-15	26-mai-23	11-15 : La pneumopathie du UK/09/19 au 11/10/19 (Hospitalisation du 03/10/19 au 07/10/19) n'a pas été déclaré dans les 24h où le centre en a eu connaissance	Rappel fait dans le mail post visite (EIG à déclarer à la PV)	6-Sep-2023	6-Sep-2023	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	011	Dr Rousselot	11-16	05-avr-22	11-16 : L'EIG Œdème angioneurologique 10/07/21 dans les 24h où le centre en a eu connaissance	Déclaré par la TRC immédiatement et signalé au centre	24-Jun-2022	24-Jun-2022	Non-important	YES	Late Serious Adverse Event (SAE) Reporting

						dans le mail post visite du 08/04/22					
B1871047	011	Dr Rousselot	11-17	19-oct-23	Protocol non-compliance, inclusion criteria 4 not fulfilled. Delai between enrollment and bosutinib initiation = 72 days	To remove this patient from FAS	15-Dec-2023	18-déc-23	Important	YES	Decision to classify this deviation as important/major during data review
B1871047	011	Dr Rousselot	11-17	02-nov-21	11-17 : Les EIG douleur du poignet et allergie au surimi n'ont pas été déclarés à la PV dans les 24h où le centre en a eu connaissance (car simple passage aux urgences)	Signalé au centre dans le mail post visite du 11/11/21	11-Jan-2022	11-Jan-2022	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	011	Dr Rousselot	11-23	14-févr-22	11-23 : L'EIG polypes (hospitalisation 6 et 7/01/21) n'a pas été déclaré dans les 24h où le centre en a eu connaissance	Rappel fait dans le mail post visite	25-Mar-2022	25-Mar-2022	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	012	Dr Coiteux	12-01	22-août-16	12001 : les évènements indésirables n'ont pas été déclarés à la PV dans les 24h où le médecin en a eu connaissance (voir ci-dessus AE)	Signalé dans le mail post visite du 26/08/16	14-Sep-2016	14-Sep-2016	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	012	Dr Coiteux	12-02	22-août-16	12002 : les évènements indésirables n'ont pas été déclarés à la PV dans les 24h où le médecin en a eu connaissance (voir ci-dessus AE)	Signalé dans le mail post visite du 26/08/16	14-Sep-2016	14-Sep-2016	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	012	Dr Coiteux	12-01	11-sept-18	12001 : L'EI diarrhée n'a pas été déclaré dans les 24h où le médecin en a eu connaissance	Signalé dans le mail post visite du 12/09/18	9-Nov-2018	9-Nov-2018	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	012	Dr Coiteux	12-02	09-nov-18	12002: Plusieurs Ei n'ont pas été déclarés dans les 24h où le médecin en a eu connaissance : Insuffisance rénale aigue 10/04/17 et diarrhée 3/06/16, etc	Signalé dans le mail post visite du 09/11/18	9-Nov-2018	9-Nov-2018	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	012	Dr Coiteux	12-02	16-nov-21	12002: Plusieurs Ei n'ont pas été déclarés dans les 24h où le médecin en a eu connaissance : décompensation cardiaque du 28/08/18, cataracte droite avec chirurgie du NK/NK/2016, bronchite NK/04/19, décompensation cardiaque NK/05/19, syndrome d'apnée du sommeil NK/NK/19	Signalé dans le mail post visite du 17/11/2021	11-Feb-2022	11-Feb-2022	Non-important	YES	Late Serious Adverse Event (SAE) Reporting

B1871047	012	Dr Coiteux	12-03	25-août-17	12003 : les évènements indésirables n'ont pas été déclarés à la PV dans les 24h où le médecin en a eu connaissance (diarrhée, hypotension, fatigue, hépatomégalie, tachycardie, dyspnée d'effort, syndrome inflammatoire)	Signalé dans le mail post visite du 29/08/17	25-Sep-2017	25-Sep-2017	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	012	Dr Coiteux	12-03	16-janv-20	12003 : les évènements indésirables n'ont pas été déclarés à la PV dans les 24h où le médecin en a eu connaissance : déficit en folate, hypercalcémie, oedèmes de membres inférieurs hyperkaliémie,	Signalé dans le mail post visite du 22/01/20	17-Mar-2020	17-Mar-2020	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	012	Dr Coiteux	12-04	08-nov-18	12004 : Les EI diarrhées du 14/09/18 et du 27/09/18 n'ont pas été déclarés dans les 24h où le médecin en a eu connaissance	Signalé dans le mail post visite du 09/11/18	9-Nov-2018	9-Nov-2018	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	012	Dr Coiteux	12-04	09-mai-22	12004 : L'EIG Traumatisme épaule droite avec désintertion du ligament du triceps du coude droit n'a pas été déclaré dans les 24h où le centre en a eu connaissance	Signalé dans le mail post visite du	27-Jun-2022	27-Jun-2022	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	012	Dr Coiteux	12-06	16-janv-20	12006 : L'EI cytolyse hépatique n'a pas été déclaré dans les 24h où le médecin en a eu connaissance	Signalé dans le mail post visite du 22/01/20	17-Mar-2020	17-Mar-2020	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	012	Dr Coiteux	12-06	16-janv-20	12006 : L'EIG Aggravation de la sténose fémorale n'a pas été déclaré dans les 24h où le médecin en a eu connaissance	Signalé dans le mail post visite du 22/01/20	17-Mar-2020	17-Mar-2020	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	012	Dr Coiteux	12-06	19-févr-21	12006 : L'EIG décompensation BPCO n'a pas été déclaré dans les 24h où le médecin en a eu connaissance	Un rappel est fait au médecin dans le mail post visite	17-Aug-2021	17-Aug-2021	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	012	Dr Coiteux	12-04	19-juin-23	12004 : Consentements v3.0 non signé par le patient. Le Dr Coiteux a confirmé en réponse à l'email du 25/04/2023, la non-obtention du consentement (oubli). Le patient a terminé l'étude.	Signalé dans le mail post visite du 28/07/23	21-Aug-2023	21-Aug-2023	Important	YES	Breaches in the informed consent or data privacy processes

B1871047	012	Dr Coiteux	12-06	19-juin-23	12006 : Consentements v3.0 non signé par le patient. Le Dr Coiteux a confirmé en réponse à l'email du 25/04/2023, la non-obtention du consentement (oubli). Le patient a terminé l'étude.	Signalé dans le mail post visite du 28/07/23	21-Aug-2023	21-Aug-2023	Important	YES	Breaches in the informed consent or data privacy processes
B1871047	013	Dr Etienne	13-07	08-déc-20	13-07 : EI : Manque d'efficacité, majoration de l'hypertension et majoration des myalgies non déclarés dans les 24h où le centre en a eu connaissance	Rappel effectué à l'ARC du centre ainsi que dans le mail post visite	5-Feb-2021	5-Feb-2021	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	013	Dr Etienne	13-07	04-févr-22	13-07 : EI : OMI et œdème des paupières non déclarés dans les 24h où le centre en a eu connaissance	Rappel fait dans le mail post visite	25-Mar-2022	25-Mar-2022	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	013	Dr Etienne	13-03	08-déc-20	13-03 : consentement V3.0 non signé par le patient.	Patient décédé	7-Jul-2023	7-Jul-2023	Important	YES	Breaches in the informed consent or data privacy processes
B1871047	013	Dr Etienne	13-06	08-déc-20	13-06 : consentement V3.0 non signé par le patient.	Rappel fait dans le mail post visite	7-Jul-2023	7-Jul-2023	Important	YES	Breaches in the informed consent or data privacy processes
B1871047	015	Dr Guerci / Roth Guepin	15-03	17-juil-18	15-03 : BPCO non déclarée dans les 24h où l'investigateur en a eu connaissance	Déclaré par l'ARC pendant la visite de monitoring	30-Sep-2019	30-Sep-2019	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	015	Dr Guerci / Roth Guepin	15-03	22-oct-18	15-03 : Diarrhée non déclarée dans les 24h où l'investigateur en a eu connaissance	Déclaré par l'ARC pendant la visite de monitoring	30-Sep-2019	30-Sep-2019	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	015	Dr Guerci / Roth Guepin	15-05	20-août-18	15-05 : Diarrhée non déclarée dans les 24h où l'investigateur en a eu connaissance	Déclaré par l'ARC pendant la visite de monitoring	30-Sep-2019	30-Sep-2019	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	015	Dr Guerci / Roth Guepin	15-05	18-févr-19	15-05 : Infections rhinopharyngées non déclarées dans les 24h où l'investigateur en a eu connaissance	Déclaré par l'ARC pendant la visite de monitoring	30-Sep-2019	30-Sep-2019	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	015	Dr Guerci / Roth Guepin	15-05	15-juil-19	15-05 : Eruption cutanée du torse non déclarée dans les 24h où l'investigateur en a eu connaissance	Déclaré par l'ARC pendant la visite de monitoring	30-Sep-2019	30-Sep-2019	Non-important	YES	Late Serious Adverse Event (SAE) Reporting

B1871047	015	Dr Guerci / Roth Guepin	15-02	03-oct-23	15-02 : 7 EI/EIG#02a, 02b, 03a, 03, 04a, 04b & 05a non déclarés dans les 24h après prise de connaissance par l'Investigateur.	EI/EIG#02a, 02b, 03a, 03, 04a, 04b & 05a confirmés et enregistrés dans l'eCRF par le centre.	23-Nov-2023	23-Nov-2023	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	015	Dr Guerci / Roth Guepin	15-05	03-oct-23	15-05 : 6 EI/EIG#02b, 03a, 04a, 04b, 05a, 05b & 06a non déclarés dans les 24h après prise de connaissance par l'Investigateur.	EI/EIG#02b, 03a, 04a, 04b, 05a, 05b & 06a confirmés et enregistrés dans l'eCRF par le centre.	23-Nov-2023	23-Nov-2023	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	015	Dr Guerci / Roth Guepin	15-08	03-oct-23	15-08 : 7 EI/EIG#02a, 02b, 03a, 03, 04a, 04b & 05a non déclarés dans les 24h après prise de connaissance par l'Investigateur.	EI/EIG#02a, 02b, 03a, 03, 04a, 04b & 05a confirmés et enregistrés dans l'eCRF par le centre.	23-Nov-2023	23-Nov-2023	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	015	Dr Guerci / Roth Guepin	15-03	10-oct-23	15-03 : 1 EI#02b non déclaré dans les 24h après prise de connaissance par l'Investigateur.	EI#02b confirmé et enregistré dans l'eCRF par le centre en post-visite.	23-Nov-2023	23-Nov-2023	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	015	Dr Guerci / Roth Guepin	15-06	10-oct-23	15-06 : 18 EI/EIG#01b, 02b, 03b, 04a, 04b, 05a, 05b, 06a, 06b, 07a, 07b, 08a, 08b, 09a, 09b, 10a, 10b & 11a non déclarés dans les 24h après prise de connaissance par l'Investigateur.	EI/EIG#01b, 02b, 03b, 04a, 04b, 05a, 05b, 06a, 06b, 07a, 07b, 08a, 08b, 09a, 09b, 10a, 10b & 11a confirmés et enregistrés dans l'eCRF par le centre en post-visite.	23-Nov-2023	23-Nov-2023	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	015	Dr Guerci / Roth Guepin	15-07	12-oct-23	15-07 : 11 EI/EIG#01b, 02a, 02b, 03a, 03b, 04a, 04b, 05a, 05b, 06a & 06b non déclarés dans les 24h après prise de connaissance par l'Investigateur.	EI/EIG#01b, 02a, 02b, 03a, 03b, 04a, 04b, 05a, 05b, 06a & 06b confirmés et enregistrés dans l'eCRF par le centre en post-visite.	23-Nov-2023	23-Nov-2023	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	016	Dr Ianotto / Dr Dalbies	16-01	21-sept-16	Patient 16-01 : réaction allergique et aggravation des tremblements non déclarés dans les 24h où le centre en a eu connaissance	Demande de déclaration immédiate faite (avec un rappel)	5-Feb-2021	5-Feb-2021	Non-important	YES	Late Serious Adverse Event (SAE) Reporting

B1871047	016	Dr Ianotto / Dr Dalbies	16-01	28/08/19	Patient 16-01 : Nausées, douleurs testiculaires, douleurs articulaires, vertiges, diarrhées, irritabilité, céphalées (sous bosulif), lésions cutanées, céphalées (sous posatinib), asthénie, sueur : EI non déclarés dans les 24h où le centre en a eu connaissance	Rappel au centre et dans le mail post visite	30-Sep-2019	30-Sep-2019	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	016	Dr Ianotto / Dr Dalbies	16-02	Relevé le 28/08/19 par l'ARC : non déclarés dans les 24h00 après la visite du patient	Patient 16-02 : Inflammation péri-inguinale, dénutrition, désunion cicatrice, anémie, HTA, douleurs épaule droite, cytolyse, carence vit D : EI non déclarés dans les 24h où le centre en a eu connaissance	Rappel au centre et dans le mail post visite	30-Sep-2019	30-Sep-2019	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	016	Dr Ianotto / Dr Dalbies	16-03	31-mai-22	Patient 16-03 : Décompensation cardiaque EIG, pneumopathie EIG, anémie du 13/09/16, anorexie, constipation, paraphlébite jambe gauche, anémie du 21/09/17, abcès oreille, douleurs d'artérite, OMI, diarrhée NK/01/18, hyponatrémie EIG, diarrhée chronique AEG : EI non déclarés dans les 24h où le centre en a eu connaissance	Rappel au centre et dans le mail post visite	27-Jun-2022	27-Jun-2022	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	016	Dr Ianotto / Dr Dalbies	16-04	15/01/18	Patient 16-04 : Prurit, insomnie, diarrhée, toux, dyspnée, couleurs articulaires, herpès, épisode infectieux, épanchement pleural, lithiase rénale, insuffisance cardiaque : EI non déclarés dans les 24h où le centre en a eu connaissance	Rappel au centre et dans le mail post visite	7-Feb-2018	7-Feb-2018	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	016	Dr Ianotto / Dr Dalbies	16-05	15/01/18	Patient 16-05 : douleurs abdominales, anorexie, perte de poids, dépression, lombalgies, constipation : EI non déclarés dans les 24h où le centre en a eu connaissance	Rappel au centre et dans le mail post visite	7-Feb-2018	7-Feb-2018	Non-important	YES	Late Serious Adverse Event (SAE) Reporting

B1871047	016	Dr Ianotto / Dr Dalbies	16-06	18/03/19	Patient 16-06 : Rhume, aérophagie, RGO, ballonnement, douleurs articulaires, mycoses, larmoiements, blépharite, varice membre inférieur droit : EI non déclarés dans les 24h où le centre en a eu connaissance	Rappel au centre et dans le mail post visite	26-Mar-2019	26-Mar-2019	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	016	Dr Ianotto / Dr Dalbies	16-07	18/03/19	Patient 16-07 : Constipation, miction impérieuse, prurit, croutes du cuir chevelu : EI non déclarés dans les 24h où le centre en a eu connaissance	Rappel au centre et dans le mail post visite	26-Mar-2019	26-Mar-2019	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	016	Dr Ianotto / Dr Dalbies	16-07	12/01/21	Patient 16-07 : épanchement pleural et insuffisance cardiaque non déclarés dans les 24h où le centre en a eu connaissance	Un rappel a été fait au centre les 12/01/21	5-Feb-2021	5-Feb-2021	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	016	Dr Ianotto / Dr Dalbies	16-08	12/01/21	Patient 16-08 : occlusion intestinale non déclarée en EIG mais en EI et rectorragie non déclarés dans les 24h où le centre en a eu connaissance	Un rappel a été fait au centre les 12/01/21	5-Feb-2021	5-Feb-2021	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	016	Dr Ianotto / Dr Dalbies	16-09	27/08/19	Patient 16-09 : Aigreurs : EI non déclarés dans les 24h où le centre en a eu connaissance	Rappel au centre et dans le mail post visite	30-Sep-2019	30-Sep-2019	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	016	Dr Ianotto / Dr Dalbies	16-10	12-janv-21	Patient 16-10 : Altération de l'état général (EIG), fatigue, irritation périanale, candidose des orteils, douleurs articulaires, douleurs musculaires, érésipèle, lésions cutanées. EI et EIG non déclarés dans les 24h où le centre en a eu connaissance	Vu avec l'ARC puis noté dans le mail post visite	5-Feb-2021	5-Feb-2021	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	016	Dr Ianotto / Dr Dalbies	16-10	03-avr-24	Patient 16-10: arret permanent pour intolérence d'après le PI dans l'eCRF, mais sans AE lié au bosutinib rapporté = discordance bosutinib treatment page mentions that bosutinib was stopped due to intolerance but no AE leading to bosutinib discontinuation can be found among AE forms. Discrepancy not raised durning data review nor during monitoring	None	03-avr-24	03-avr-24	YES	YES	Discrepancy not raised durning data review nor during monitoring

B1871047	016	Dr Ianotto / Dr Dalbies	16-06	24/11/20	Patient 16-06 Dyspnée, EI non déclaré dans les 24h où le centre en a eu connaissance.	Noté dans le mail post visite	03-juil-23	03-juil-23	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	016	Dr Ianotto / Dr Dalbies	16-06	17/09/19	Patient 16-06 Augmentation diurèse nocturne, EI non déclaré dans les 24h où le centre en a eu connaissance.	Noté dans le mail post visite	03-juil-23	03-juil-23	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	016	Dr Ianotto / Dr Dalbies	16-06	24/11/20	Patient 16-06 Epanchement Péricardite, EI non déclaré dans les 24h où le centre en a eu connaissance.	Noté dans le mail post visite	03-juil-23	03-juil-23	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	016	Dr Ianotto / Dr Dalbies	16-07	20/10/20	Patient 16-07 Douleur hanche, OMI, , EI non déclaré dans les 24h où le centre en a eu connaissance.	Noté dans le mail post visite	03-juil-23	03-juil-23	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	016	Dr Ianotto / Dr Dalbies	16-07	05/01/21	Patient 16-07 Toux grasse, EI non déclaré dans les 24h où le centre en a eu connaissance.	Noté dans le mail post visite	03-juil-23	03-juil-23	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	016	Dr Ianotto / Dr Dalbies	16-07	05/01/21	Patient 16-07 Acide urique augmenté, EI non déclaré dans les 24h où le centre en a eu connaissance.	Noté dans le mail post visite	03-juil-23	03-juil-23	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	016	Dr Ianotto / Dr Dalbies	16-07	06/04/21	Patient 16-07 Artériopathie des MI, EI non déclaré dans les 24h où le centre en a eu connaissance.	Noté dans le mail post visite	03-juil-23	03-juil-23	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	016	Dr Ianotto / Dr Dalbies	16-07	06/04/21	Patient 16-07 Occlusion du pontage fémoro-poplité droit (aggravation de l'artériopathie des MI), EI non déclaré dans les 24h où le centre en a eu connaissance.	Noté dans le mail post visite	03-juil-23	03-juil-23	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	017	Dr Gardembas	17-01	07-sept-19	Patient 17-01 : Diarrhée et œsophagite non déclarées dans les 24h00 où le médecin en a eu connaissance	Rappel fait dans le mail post visite du 3/12/19	23-Dec-2019	23-Dec-2019	Non-important	YES	Late Serious Adverse Event (SAE) Reporting

B1871047	022	Dr Adiko	22-01	20-sept-17	22-01 : EI « Thrombocytopénie » n'a pas été déclaré à la PV dans les 24h où le médecin en a eu connaissance	Rappel fait lors de la visite et dans le mail post visite	7-Feb-2018	7-Feb-2018	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	022	Dr Adiko	22-01	07-mars-18	22-01 : EI « bronchite », « anémie », « épigastralgies » et « constipation » n'ont pas été déclarés à la PV à la PV dans les 24h où le médecin en a eu connaissance	Rappel fait lors de la visite et dans le mail post visite	2-May-2019	2-May-2019	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	022	Dr Adiko	22-01	NK-janv-218	22-01 : EI « diarrhée » n'a pas été déclarée à la PV dans les 24h où le médecin en a eu connaissance	Rappel fait lors de la visite et dans le mail post visite	7-Feb-2018	7-Feb-2018	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	022	Dr Adiko	22-01	19-janv-23	22-01 : EI SUSPICION D'INFECTION FONGIQUE INVASIVE PULMONAIRE Non déclaré à la PV dans les 24h où le médecin en a eu connaissance	Porté à l'attention du Dr Adiko lors de la visite et dans le mail post visite	22-Jun-2023	22-Jun-2023	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	022	Dr Adiko	22-01	19-janv-23	22-01 : EI CHOC ANAPHYLACTIQUE Non déclaré à la PV dans les 24h où le médecin en a eu connaissance	Porté à l'attention du Dr Adiko lors de la visite et dans le mail post visite	22-Jun-2023	22-Jun-2023	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	022	Dr Adiko	22-01	19-janv-23	22-01 : EI NAUSEES Non déclaré à la PV dans les 24h où le médecin en a eu connaissance	Porté à l'attention du Dr Adiko lors de la visite et dans le mail post visite	22-Jun-2023	22-Jun-2023	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	022	Dr Adiko	22-01	19-janv-23	22-01 : EI ASTHENIE Non déclaré à la PV dans les 24h où le médecin en a eu connaissance	Porté à l'attention du Dr Adiko lors de la visite et dans le mail post visite	22-Jun-2023	22-Jun-2023	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	022	Dr Adiko	22-02	19-janv-23	22-02 : EI DYSLIPIDEMIE Non déclaré à la PV dans les 24h où le médecin en a eu connaissance	Porté à l'attention du Dr Adiko lors de la visite et dans le mail post visite	22-Jun-2023	22-Jun-2023	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	022	Dr Adiko	22-02	19-janv-23	22-02 : EI CHOLESTASE HEPATIQUE Non déclaré à la PV dans les 24h où le médecin en a eu connaissance	Porté à l'attention du Dr Adiko lors de la visite et dans le mail post visite	22-Jun-2023	22-Jun-2023	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	022	Dr Adiko	22-02	19-janv-23	22-02 : EI DIABETE TYPE II Non déclaré à la PV dans les 24h où le médecin en a eu connaissance	Porté à l'attention du Dr Adiko lors de	22-Jun-2023	22-Jun-2023	Non-important	YES	Late Serious Adverse Event (SAE) Reporting

						la visite et dans le mail post visite					
B1871047	022	Dr Adiko	22-02	19-janv-23	22-02 : EI LESIONS FOCALES LICHENOIDES NON SPECIFIQUES Non déclaré à la PV dans les 24h où le médecin en a eu connaissance	Porté à l'attention du Dr Adiko lors de la visite et dans le mail post visite	22-Jun-2023	22-Jun-2023	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	022	Dr Adiko	22-02	19-janv-23	22-02 : EI DOULEURS ARTICULAIRES Non déclaré à la PV dans les 24h où le médecin en a eu connaissance	Porté à l'attention du Dr Adiko lors de la visite et dans le mail post visite	22-Jun-2023	22-Jun-2023	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	023	Dr Martiniuc	23-01	07-janv-19	23-01 : EI plaie à la tête non déclarée dans les 24h où le site en a eu connaissance	Rappel fait dans le mail post visite du 18/04/20	2-May-2019	2-May-2019	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	024	Dr Réa	24-01	19-oct-23	24-01: eCRF non signé par le PI, celui-ci est parti et aucun successeur n'a été trouvé.		15-Dec-2023	18-déc-23	Important	YES	Decision to remove patient from FAS and SAF
B1871047	024	Dr Réa	24-02	19-oct-23	24-01: eCRF non signé par le PI, celui-ci est parti et aucun successeur n'a été trouvé.		15-Dec-2023	18-déc-23	Important	YES	Decision to remove patient from FAS and SAF
B1871047	024	Dr Réa	24-03	19-oct-23	24-01: eCRF non signé par le PI, celui-ci est parti et aucun successeur n'a été trouvé.		15-Dec-2023	18-déc-23	Important	YES	Decision to remove patient from FAS and SAF
B1871047	024	Dr Réa	24-04	19-oct-23	24-01: eCRF non signé par le PI, celui-ci est parti et aucun successeur n'a été trouvé.		15-Dec-2023	18-déc-23	Important	YES	Decision to remove patient from FAS and SAF
B1871047	024	Dr Réa	24-01	21-déc-17	Patient 24-01 : paresthésie non déclarée dans les 24h où le centre en a eu connaissance	Rappel fait dans le mail post visite du 31/12/2017	8-Jan-2017	8-Jan-2017	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	024	Dr Réa	24-01	15-nov-21	Patient 24-01 : EI non rapportés dans les 24h à la PV : fatigue 19/03/19, pic HTA 19/03/19, folliculite de l'aine NK/03/19, diarrhée NK/NK/19	Rappel fait dans le mail post visite du 18/11/2021	11-Jan-2022	11-Jan-2022	Non-important	YES	Late Serious Adverse Event (SAE) Reporting

B1871047	024	Dr Réa	24-03	21-déc-18	Patient 24-04 : EI non rapportés dans les 24h à la PV : les douleurs thoraciques NK/06/18, les dorsalgies et lombalgies NK/09/18, l'athérome 10/09/18, le lipome para-trapézoidien noté au 1/03/18, la dyspnée NK/06/18, la gastrite ulcérée NK/04/18, les douleurs abdominales NK/10/18 et une hernie ombilicale au 9/10/18	Rappel fait dans le mail post visite du 01/01/2019	15-Jan-2019	15-Jan-2019	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	024	Dr Réa	24-04	27-janv-22	Patient 24-04 : EI infection des voies aériennes, rhinopharyngite et grippe non déclarées dans les 24h où le centre en a eu connaissance	Rappel fait dans le mail post visite du 27/01/22	25-Mar-2022	25-Mar-2022	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	024	Dr Réa	24-02	15-nov-21	Patient 24-02 Délai de signature : Consentement V3.0 signé le 04/02/2022, Version 2.1 signée le 28/03/2017	Pas d'action correctrice possible.	3-Oct-2023	3-Oct-2023	Important	YES	Breaches in the informed consent or data privacy processes
B1871047	024	Dr Réa	24-03	15-nov-21	Patient 24-03 Délai de signature : Consentement V3.0 signé le 03/02/2023, Version 2.1 signée le 11/04/2017	Pas d'action correctrice possible.	3-Oct-2023	3-Oct-2023	Important	YES	Breaches in the informed consent or data privacy processes
B1871047	033	Dr Courby / Meunier	33-01	01-juil-20	33-01 : La constipation n'a pas été déclarée dans les 24h où le centre en a eu connaissance	Déclaré par l'ARC le 2/07/20. Noté dans le mail post visite du 5/07/20	21-Aug-2020	21-Aug-2020	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	033	Dr Courby / Meunier	33-01	27-févr-18	33-01 : La fracture du coccyx n'a pas été déclarée à la PV dans les 24h où le médecin en a eu connaissance	Déclaré à la PV par P.POOS le 25/04/19 et par l'ARC le 3/05/19. Rappel PV fait dans le mail post visite du 26/04/20	2-May-2019	2-May-2019	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	033	Dr Courby / Meunier	33-02	18-févr-18	33-02: l'évènement indésirable grave « sténose de l'artère sous- clavière pré-vertébrale » n'a pas été déclaré à la PV dans les 24h où le médecin en a eu connaissance	Déclaré par le centre le 20/02/18Rappel PV fait dans le mail post visite du 20/02/18	29-Mar-2018	29-Mar-2018	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	033	Dr Courby / Meunier	33-02	23-juin-17	33-02 : Les frissons et démangeaisons n'ont pas été déclarés à la PV dans les 24h où le médecin en a eu connaissance	Déclaré par l'ARC le 20/08/19. Rappel PV fait dans le mail pots visite du 26/04/20	2-May-2019	2-May-2019	Non-important	YES	Late Serious Adverse Event (SAE) Reporting

B1871047	033	Dr Courby / Meunier	33-05	01-juil-20	33-05 : les douleurs musculaires, la grande fatigabilité et la fragilité digestive n'ont pas été déclarés dans les 24h où le centre en a eu connaissance	Déclarés par l'ARC le 1/07/20. Noté dans le mail post visite du 5/07/20	21-Aug-2020	21-Aug-2020	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	033	Dr Courby / Meunier	33-06	26-oct-18	33-06 : L'anorexie avec agueusie, la dysgueusie, la mycose buccale, la sécheresse de la peau n'ont pas été déclarées à la PV dans les 24h où le médecin en a eu connaissance	Déclarés par P.POOS à la PV par mail le 24/ 04/19 et le 23-28/05/19 par l'ARC + Rappel PV fait dans le mail ptts visite du 26/04/20	2-May-2019	2-May-2019	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	033	Dr Courby / Meunier	33-07	31-oct-18	33-07 : Les évènements indésirables « diarrhée » et « douleurs abdominales » n'ont pas été déclarés à la PV dans les 24h où le médecin en a eu connaissance	Déclarés par l'ARC le 23/04/19. Rappel PV fait dans le mail post visite du 26/04/20	2-May-2019	2-May-2019	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	033	Dr Courby / Meunier	33-07	05-nov-21	33-07 : Les évènements indésirables « crise de goutte » et « augmentation de la tension » n'ont pas été déclarés à la PV dans les 24h où le médecin en a eu connaissance	Rappel PV fait dans le mail post visite du 08/11/21	11-Jan-2022	11-Jan-2022	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	033	Dr Courby / Meunier	33-02	06-mars-23	33-02 : Les événements indésirables suivants, démangeaison chevilles et tête, sensation de congestion gorge et nez, bronchite, OMI, sciatique n'ont pas été déclarés à la PV dans les 24h où le médecin en a eu connaissance	Rappel PV fait lors de la visite et dans le mail post visite du 11/04/2023	8-Jun-2023	8-Jun-2023	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	033	Dr Courby / Meunier	33-06	06-mars-23	33-06 : Les événements indésirables suivants, asthénie, syndrome dépressif, tremblements mains n'ont pas été déclarés à la PV dans les 24h où le médecin en a eu connaissance	Rappel PV fait lors de la visite et dans le mail post visite du 11/04/2023	8-Jun-2023	8-Jun-2023	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	033	Dr Courby / Meunier	33-08	07-mars-23	33-08 : L'événement indésirable suivant, douleur costale droite n'a pas été déclaré à la PV dans les 24h où le médecin en a eu connaissance	Rappel PV fait lors de la visite et dans le mail post visite du 11/04/2023	8-Jun-2023	8-Jun-2023	Non-important	YES	Late Serious Adverse Event (SAE) Reporting

B1871047	033	Dr Courby / Meunier	33-03	21-sept-23	Le consentement v3,0 n'a pas été signé par le patient	Patient is out of study, no action possible, quality event declared	8-Jun-2023	8-Jun-2023	Important	YES	Breaches in the informed consent or data privacy processes
B1871047	034	Dr Corm	34-01	15-juin-18	Patient 34-01 : Essoufflement à l'effort du 15/06/18 non déclarés dans les 24h00 où le médecin en a eu connaissance	Rappel fait à l'ARC + rappel fait dans le mail post visite du 16/0818	27-Aug-2018	27-Aug-2018	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	034	Dr Corm	34-01	07-sept-17	Patiente 34-01 : Essoufflement à l'effort et vertiges non déclarés dans les 24h00 où le médecin en a eu connaissance	Rappel fait à l'ARC + rappel fait dans le mail post visite du 16/0818	27-Aug-2018	27-Aug-2018	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	034	Dr Corm	34-01	29-nov-17	Patiente 34-01 : Eruption cutanée et troubles de la concentration non déclarés dans les 24h00 où le médecin en a eu connaissance	Rappel fait à l'ARC + rappel fait dans le mail post visite du 16/0818	27-Aug-2018	27-Aug-2018	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	034	Dr Corm	34-01	03-mars-21	Patient 34-01 : aggravation de l'angor : l'EIG hospitalisation pour pose de stent en 08/19 n'a pas été déclaré dans les 24h où le centre en a eu connaissance (Dr Corm). L'EI a bien été déclaré dans les temps	Rappel fait à l'ARC + rappel fait dans le mail post visite du 3/03/21	30-Apr-2021	30-Apr-2021	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	034	Dr Corm	34-02	03-mars-21	Patient 34-02 : asthénie du 16/12/19 non déclarée dans les 24h où le Dr Corm en a eu connaissance	Rappel fait à l'ARC + rappel fait dans le mail post visite du 3/03/21	30-Apr-2021	30-Apr-2021	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	036	Dr Costello	36-01	01/10/2019	Patient 36-01 : Diarrhée, douleur basithoraciques et de l'hypochondre, cytolyse hépatique non déclarés dans les 24h00 où le médecin en a eu connaissance	RRappel fait lors de la visite et dans le mail post visite	23/12/2019	23/12/2019	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	037	Dr Ivanov	36-01	10/04/2019	Patient 37-01 : Diarrhée, douleur musculaires non déclarés dans les 24h00 où le médecin en a eu connaissance	Rappel fait lors de la visite et dans le mail post visite	23/12/2019	23/12/2019	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	38-42-43-47-48- 49	Dr Tulure, Dr Remenieras, Dr Touati, Dr Girault, Dr Gourin, Dr Penot	38-01	23-janv-18	38-01 : la mycose du vagin et des plis inguinaux n'a pas été déclarée dans les 24h où le centre en a eu connaissance	Un rappel a été fait dans le mail post visite du 8/02/18	11-Mar-2018	11-Mar-2018	Non-important	YES	Late Serious Adverse Event (SAE) Reporting

B1871047	38-42-43-47-48- 49	Dr Tulure, Dr Remenieras, Dr Touati, Dr Girault, Dr Gourin, Dr Penot	38-01	23-janv-18	38-01: l'infection urinaire n'a pas été déclarée dans les 24h où le centre en a eu connaissance	Un rappel a été fait dans le mail post visite du 8/02/18	11-Mar-2018	11-Mar-2018	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	38-42-43-47-48- 49	Dr Tulure, Dr Remenieras, Dr Touati, Dr Girault, Dr Gourin, Dr Penot	38-01	23-févr-18	38-01 : la somnolence n'a pas été déclarée dans les 24h où le centre en a eu connaissance	Un rappel a été fait dans le mail post visite du 8/02/18	11-Mar-2018	11-Mar-2018	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	38-42-43-47-48- 49	Dr Tulure, Dr Remenieras, Dr Touati, Dr Girault, Dr Gourin, Dr Penot	38-02	09-sept-20	38-02 : La perte d'appétit, les céphalées et le déséquilibre n'ont pas été déclarés dans les 24h où le centre en a eu connaissance	Revu avec l'ARC du centre + indiqué dans le mail post visite	5-Feb-2021	5-Feb-2021	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	38-42-43-47-48- 49	Dr Tulure, Dr Remenieras, Dr Touati, Dr Girault, Dr Gourin, Dr Penot	42-01	14-févr-19	42-01 : L'épisode infectieux pulmonaire n'a pas été déclaré dans les 24h où le centre en a eu connaissance	Un rappel a été fait dans le mail post visite du 24/05/19	15-Jul-2019	15-Jul-2019	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	38-42-43-47-48- 49	Dr Tulure, Dr Remenieras, Dr Touati, Dr Girault, Dr Gourin, Dr Penot	42-01	14-févr-19	42-01 : Les douleurs des membres inférieurs n'ont pas été déclarés dans les 24h où le centre en a eu connaissance	Un rappel a été fait dans le mail post visite du 24/05/19	15-Jul-2019	15-Jul-2019	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	38-42-43-47-48- 49	Dr Tulure, Dr Remenieras, Dr Touati, Dr Girault, Dr Gourin, Dr Penot	42-01	08-juin-23	42-01: Les 4 EIs suivants n'ont pas été déclarés dans les 24h où le centre en a eu connaissance : - Cytolise Hépatique du 17/01/2018 au 28/02/2018 - Scoliose lombaire droite du 11/12/2018 en cours - Discarthrose L2-L5 du 11/12/2018 en cours - Altération de l'audition du 03/09/2019 en cours	Un rappel a été fait dans le mail post visite	27-Jun-2023	27-Jun-2023	Non-important	YES	Late Serious Adverse Event (SAE) Reporting

B1871047	38-42-43-47-48- 49	Dr Tulure, Dr Remenieras, Dr Touati, Dr Girault, Dr Gourin, Dr Penot	42-01	08-juin-23	42-01: Les EIs survenus lors du suivi à long terme n'ont pas été enregistrés dans l'eCRF / Aucune déclaration faites à la PV:- Consultation du 30Jan2020 (Troubles digestifs, douleurs flanc droit, nausées, altération de l'appétit)- Consultation du 11Mar2020 (Asthénie et Décollement du vitré (Ophtalmo))- Uvéite bilatérale – Hospitalisée du 25 au 26Mar2020 (opérée le 25/03/2020)- Uveïte antérieure - Urgence ophtalmo du 26May2020- Eruption annulaire centrifuge multiple des membres Inférieurs & de l'abdomen – Consultation d'urgence le 25Aug2020- Maladie de Lyme (Sérologie 02Sep2020)- Hyalite bilatérale, abolition des réflexes – Consultation du 10Sep2020- Douleurs articulaires chroniques – Consultation du 23Sep2020- Consultation du 16Mar2021 (Asthénie, Douleurs poly-articulaires et musculaires, troubles digestifs, douleurs abdominales)	Revu avec l'ARC du centre + indiqué dans le mail post visite	27-Jun-2023	27-Jun-2023	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	38-42-43-47-48- 49	Dr Tulure, Dr Remenieras, Dr Touati, Dr Girault, Dr Gourin, Dr Penot	42-02	07-juin-23	42-02: Les 2 EIs suivants n'ont pas été déclarés dans les 24h où le centre en a eu connaissance : - Infection gynécologique du 01/10/2019 au 15/09/2019 - Douleurs musculaires du NK/10/2020 au 16/03/2021	Un rappel a été fait dans le mail post visite	27-Jun-2023	27-Jun-2023	Non-important	YES	Late Serious Adverse Event (SAE) Reporting

B1871047	38-42-43-47-48- 49	Dr Tulure, Dr Remenieras, Dr Touati, Dr Girault, Dr Gourin, Dr Penot	42-02	07-juin-23	42-02: Les EIs survenus lors du suivi à long terme n'ont pas été enregistrés dans l'eCRF / Aucune déclaration faites à la PV: - Elévation discrète des IgG – Consultation du 17/12/2020 - Biopsie hépatique du 27/01/2021 (Lésions stéatohépatiques) - Quelques Œdèmes des Membres Inférieurs – Consultation du 16Mar2021 - Erythème faciale – Consultation du 16Mar021 - Transpiration profuse – Consultation du 28Jun2021 - Troubles érectiles - Consultation du 28Jun2021 - Baisse de moral – Consultation du 28Jun2021 - Dyspnée brutale (Céphalées + OMI) - Urgences (Déchocage) le 27Jan2022 - Pneumopathie fébrile avec OMI, prise de poids, hypokaliémie et poussée hypertensive (Hospitalisation le 29Jan2020) – Consultation du 01Mar2022.	Revu avec l'ARC du centre + indiqué dans le mail post visite	27-Jun-2023	27-Jun-2023	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	38-42-43-47-48- 49	Dr Tulure, Dr Remenieras, Dr Touati, Dr Girault, Dr Gourin, Dr Penot	43-01	10-oct-20	43-01 : Les céphalées, nausées,anxiété, vomissement, malaise n'ont pas été déclarés dans les 24h où le centre en eu connaissance	Revu avec l'ARC du centre + indiqué dans le mail post visite	5-Feb-2021	5-Feb-2021	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	38-42-43-47-48- 49	Dr Tulure, Dr Remenieras, Dr Touati, Dr Girault, Dr Gourin, Dr Penot	43-01	09-oct-20	43-01 : Le patient n'a pas signé la version 3 du consentement	Remise le 16Dec2019 mais refus de signature du patient, patient sortie à la demande du promoteur	5-Feb-2021	5-Feb-2021	Important	YES	Breaches in the informed consent or data privacy processes

B1871047	38-42-43-47-48- 49	Dr Tulure, Dr Remenieras, Dr Touati, Dr Girault, Dr Gourin, Dr Penot	43-01	07-juin-23	43-01: Les EIs survenus lors du suivi à long terme n'ont pas été enregistrés dans l'eCRF / Aucune déclaration faites à la PV: - Malaise – Consultation du 31Jul2019 - Toux en Juillet 2019 - Dyspnée d'effort en Juillet 2019 - Gêne respiratoire sévère / Insuffisance respiratoire (Piqûre Nucala) le 19/08/2019 - Surinfection pulmonaire (Arrêt temporaire Iclusig 4 jours) – Consultation du 22Sep2019 - Mycose buccale traitée par Fugizone - Consultation du 22Sep2019	Revu avec l'ARC du centre + indiqué dans le mail post visite	27-Jun-2023	27-Jun-2023	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	38-42-43-47-48- 49	Dr Tulure, Dr Remenieras, Dr Touati, Dr Girault, Dr Gourin, Dr Penot	43-02	10-oct-20	43-02 : L'asthénie n'a pas été déclarée dans les 24h où le centre en a eu connaissance	Revu avec l'ARC du centre + indiqué dans le mail post visite	5-Feb-2021	5-Feb-2021	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	38-42-43-47-48- 49	Dr Tulure, Dr Remenieras, Dr Touati, Dr Girault, Dr Gourin, Dr Penot	47-01	27-janv-22	47-01 : L'infection urinaire n'a pas été déclarée dans les 24h où le centre en a eu connaissance	Revu avec l'ARC du centre + signalé dans le mail post visite	25-Mar-2022	25-Mar-2022	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	38-42-43-47-48- 49	Dr Tulure, Dr Remenieras, Dr Touati, Dr Girault, Dr Gourin, Dr Penot	47-02	09-oct-20	47-02 : Le patient n'a pas signé la version 3 du consentement	Remise le 16Dec2019 mais refus de signature du patient, patient sortie à la demande du promoteur	5-Feb-2021	5-Feb-2021	Important	YES	Breaches in the informed consent or data privacy processes
B1871047	38-42-43-47-48- 49	Dr Tulure, Dr Remenieras, Dr Touati, Dr Girault, Dr Gourin, Dr Penot	47-03	09-oct-20	47-03 : Le patient n'a pas signé la version 3 du consentement	Remise le 16Dec2019 mais refus de signature du patient, patient sortie à la demande du promoteur	5-Feb-2021	5-Feb-2021	Important	YES	Breaches in the informed consent or data privacy processes

B1871047	38-42-43-47-48- 49	Dr Tulure, Dr Remenieras, Dr Touati, Dr Girault, Dr Gourin, Dr Penot	47-02	27-janv-22	47-02 : Les sueurs nocturnes n'ont pas été déclarées dans les 24h où le centre en a eu connaissance	Revu avec l'ARC du centre + signalé dans le mail post visite	25-Mar-2022	25-Mar-2022	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	38-42-43-47-48- 49	Dr Tulure, Dr Remenieras, Dr Touati, Dr Girault, Dr Gourin, Dr Penot	47-03	13-mai-19	47-03 : les troubles digestifs n'ont pas été déclarés dans les 24h où le centre en a eu connaissance	Un rappel a été fait dans le mail post visite du 24/05/19	15-Jul-2019	15-Jul-2019	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	38-42-43-47-48- 49	Dr Tulure, Dr Remenieras, Dr Touati, Dr Girault, Dr Gourin, Dr Penot	47-03	27-janv-22	47-03 : l'anxiété n'a pas été déclarée dans les 24h où le centre en a eu connaissance	Revu avec l'ARC du centre + signalé dans le mail post visite	25-Mar-2022	25-Mar-2022	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	38-42-43-47-48- 49	Dr Tulure, Dr Remenieras, Dr Touati, Dr Girault, Dr Gourin, Dr Penot	47-01	13-mai-19	47-03 : les troubles digestifs n'ont pas été déclarés dans les 24h où le centre en a eu connaissance	Un rappel a été fait dans le mail post visite du 24/05/19	15-Jul-2019	15-Jul-2019	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	38-42-43-47-48- 49	Dr Tulure, Dr Remenieras, Dr Touati, Dr Girault, Dr Gourin, Dr Penot	48-01	06-nov-18	48-01 : La douleur à la toux n'a pas été déclarée dans les 24h où le centre en a eu connaissance	Un rappel a été fait dans le mail post visite du 24/05/19	15-Jul-2019	15-Jul-2019	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	38-42-43-47-48- 49	Dr Tulure, Dr Remenieras, Dr Touati, Dr Girault, Dr Gourin, Dr Penot	48-01	09-oct-20	48-01 : Le patient n'a pas signé la version 3 du consentement	Remise le 16Dec2019 mais refus de signature du patient, patient sortie à la demande du promoteur	5-Feb-2021	5-Feb-2021	Important	YES	Breaches in the informed consent or data privacy processes
B1871047	38-42-43-47-48- 49	Dr Tulure, Dr Remenieras, Dr Touati, Dr Girault, Dr Gourin, Dr Penot	38-01	23-févr-23	38-01 : L'Asthénie et les Bouffées de Chaleur n'ont pas été déclarées dans les 24h où le centre en a eu connaissance	Un rappel a été fait à l'ARC avec report de l'EI le 23Fev2023.	7-Jun-2023	7-Jun-2023	Non-important	YES	Late Serious Adverse Event (SAE) Reporting

B1871047	38-42-43-47-48- 49	Dr Tulure, Dr Remenieras, Dr Touati, Dr Girault, Dr Gourin, Dr Penot	49-01	09-oct-20	49-01 : Le patient n'a pas signé la version 3 du consentement	Remise le 16Dec2019 mais refus de signature du patient, patient sortie à la demande du promoteur	5-Feb-2021	5-Feb-2021	Important	YES	Breaches in the informed consent or data privacy processes
B1871047	38-42-43-47-48- 49	Dr Tulure, Dr Remenieras, Dr Touati, Dr Girault, Dr Gourin, Dr Penot	49-01	30-oct-17	49-01: l'allergie au poignet n'a pas été déclarée dans les 24h où le centre en a eu connaissance	Un rappel a été fait dans le mail post visite du 8/02/18	11-Mar-2018	11-Mar-2018	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	38-42-43-47-48- 49	Dr Tulure, Dr Remenieras, Dr Touati, Dr Girault, Dr Gourin, Dr Penot	49-01	11-déc-17	49-01 : les nausées et la fatigue n'ont pas été déclarés dans les 24h où le centre en a eu connaissance	Un rappel a été fait dans le mail post visite du 8/02/18	11-Mar-2018	11-Mar-2018	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	38-42-43-47-48- 49	Dr Tulure, Dr Remenieras, Dr Touati, Dr Girault, Dr Gourin, Dr Penot	10-03	21-févr-23	10-03 : l'hépatomégalie stéatosique n'a pas été déclarée dans les 24h où le centre en a eu connaissance	Un rappel a été fait à l'ARC avec report de l'EI le 22Fev2023.	7-Jun-2023	7-Jun-2023	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	38-42-43-47-48- 49	Dr Tulure, Dr Remenieras, Dr Touati, Dr Girault, Dr Gourin, Dr Penot	38-01	20-juil-23	38-01 - Nouveaux EI#20a « Diarrhées NK/08/2018 -> 14/09/2018 » & EI#20b « Chute (Ecchymose au visage) NK/02/2018 -> 12/06/2018 »	Un rappel a été fait à l'ARC avec report des 2 EIs le 20/072023.	6-Sep-2023	6-Sep-2023	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	38-42-43-47-48- 49	Dr Tulure, Dr Remenieras, Dr Touati, Dr Girault, Dr Gourin, Dr Penot	38-01	20-juil-23	38-01 – 1 nouvel EI sur la période de suivi à Long Terme (18Jun2019 au 19Jan2021) détecté:	EIs détéctés le 20/072023 reporté uniquement dans le rapport de monitoring et le Deviation Log (Pas d'Envoi à la PV)	6-Sep-2023	6-Sep-2023	Non-important	YES	Late Serious Adverse Event (SAE) Reporting

B1871047	38-42-43-47-48- 49	Dr Tulure, Dr Remenieras, Dr Touati, Dr Girault, Dr Gourin, Dr Penot	38-01	14-mars-22	38-01 – Aucun EI survenu au-delà de 28 jours après l'arrêt de bosulif, soit sur la période de suivi à Long Terme n'est déclaré ni dans l'eCRF ni à la PV	Reviewed by CRA with site staff, project manager proposed to the site to provide a nurse to complete data entry for them if they don't have enough time, it was also suggested to amend the contract to add fees because long term follow-up visit fees are very low. Site refused and explained they don't want to share with Pfizer PV related to treatments prescribed alternatively to bosutilib. Quality event declared	14-mars-22	14-mars-22	Important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	38-42-43-47-48- 49	Dr Tulure, Dr Remenieras, Dr Touati, Dr Girault, Dr Gourin, Dr Penot	47-02	14-mars-22	47-02 – Aucun EI survenu au-delà de 28 jours après l'arrêt de bosulif, soit sur la période de suivi à Long Terme n'est déclaré ni dans l'eCRF ni à la PV	Reviewed by CRA with site staff, project manager proposed to the site to provide a nurse to complete data entry for them if they don't have enough time, it was also suggested to amend the contract to add fees because long term follow-up visit fees are very low. Site refused and explained they don't want to share	14-mars-22	14-mars-22	Important	YES	Late Serious Adverse Event (SAE) Reporting

						with Pfizer PV related to treatments prescribed alternatively to bosutilib. Quality event declared					
B1871047	38-42-43-47-48- 49	Dr Tulure, Dr Remenieras, Dr Touati, Dr Girault, Dr Gourin, Dr Penot	47-03	14-mars-22	47-03 – Aucun EI survenu au-delà de 28 jours après l'arrêt de bosulif, soit sur la période de suivi à Long Terme n'est déclaré ni dans l'eCRF ni à la PV	Reviewed by CRA with site staff, project manager proposed to the site to provide a nurse to complete data entry for them if they don't have enough time, it was also suggested to amend the contract to add fees because long term follow-up visit fees are very low. Site refused and explained they don't want to share with Pfizer PV related to treatments prescribed alternatively to bosutilib. Quality event declared	14-mars-22	14-mars-22	Important	YES	Late Serious Adverse Event (SAE) Reporting

B1871047	38-42-43-47-48- 49	Dr Tulure, Dr Remenieras, Dr Touati, Dr Girault, Dr Gourin, Dr Penot	48-01	14-mars-22	48-01 – Aucun EI survenu au-delà de 28 jours après l'arrêt de bosulif, soit sur la période de suivi à Long Terme n'est déclaré ni dans l'eCRF ni à la PV	Reviewed by CRA with site staff, project manager proposed to the site to provide a nurse to complete data entry for them if they don't have enough time, it was also suggested to amend the contract to add fees because long term follow-up visit fees are very low. Site refused and explained they don't want to share with Pfizer PV related to treatments prescribed alternatively to bosutilib. Quality event declared	14-mars-22	14-mars-22	Important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	38-42-43-47-48- 49	Dr Tulure, Dr Remenieras, Dr Touati, Dr Girault, Dr Gourin, Dr Penot	49-01	14-mars-22	49-01 – Aucun EI survenu au-delà de 28 jours après l'arrêt de bosulif, soit sur la période de suivi à Long Terme n'est déclaré ni dans l'eCRF ni à la PV	Reviewed by CRA with site staff, project manager proposed to the site to provide a nurse to complete data entry for them if they don't have enough time, it was also suggested to amend the contract to add fees because long term follow-up visit fees are very low. Site refused and explained they don't want to share	14-mars-22	14-mars-22	Important	YES	Late Serious Adverse Event (SAE) Reporting

						with Pfizer PV related to treatments prescribed alternatively to bosutilib. Quality event declared					
B1871047	039	Dr Fouillard / Abarah	09-01	16-nov-20	Les EI nausées, carence martiale et sécheresse de la peau n'ont pas été déclarées dans les 24h où le centre en a eu connaissance	Rappel fait à l'ARC puis dans le mail post visite	5-Feb-2021	5-Feb-2021	Non-important	YES	Late Serious Adverse Event (SAE) Reporting
B1871047	039	Dr Fouillard / Abarah	09-01	26-janv-22	Les EI angiodysplasie, brûlures gastriques, oedème des membres inférieurs, polypes intestinaux et EIG anémie ferriprive (hospitalisation du 19/02/21, du 19/05/21 et du 17/06/21) n'ont pas été déclarées dans les 24h où le centre en a eu connaissance	Rappel fait à l'ARC puis dans le mail post visite	25-Mar-2022	25-Mar-2022	Non-important	YES	Late Serious Adverse Event (SAE) Reporting

Appendix 7.3 Subjects Excluded from the Analysis

Table 80: Subjects Excluded from the Analyses

Patient No.	Safety Analysis Set (SAF)	Full Analysis Set (FAS)	Major deviation	Description of major deviation	Minor deviation
09-07	Yes	No	Yes	Inclusion criteria 3 not complied: Patient resistant or intolerant to prior TKI therapy for PC, PA or CB CML other than bosutinib	No
10-04	Yes	No	Yes	Inclusion criteria 3 not complied: Patient resistant or intolerant to prior TKI therapy for PC, PA or CB CML other than bosutinib	No
11-17	Yes	No	Yes	Excessive delay in initiating treatment	No
24-01	No	No	Yes	Center 24	No
24-02	No	No	Yes	Center 24	No
24-03	No	No	Yes	Center 24	No
24-04	No	No	Yes	Center 24	No

Appendix 7.4 Subjects Excluded from the Analyses

Appendix 7.4 Demographic Data

Non applicable

Appendix 7.5 Medication/Treatment Data

Table 81: Concomitant Drug Treatments - SAF (n=142)

ATC Name and Drug Name		Total N=142 n	Total N=142 n(%) patients
ALL		**1807**	**140 (98.6%)**
PROTON PUMP INHIBITORS	**ALL**	**77**	**61 (43%)**
	PANTOPRAZOLE	19	14 (9.9%)
	INEXIUM	12	12 (8.5%)
	ESOMEPRAZOLE	11	10 (7%)
	LANSOPRAZOLE	8	8 (5.6%)
	OMEPRAZOLE	8	8 (5.6%)
	EUPANTOL	5	3 (2.1%)
	INIPOMP	4	4 (2.8%)
	MOPRAL	3	3 (2.1%)
	PARIET	2	2 (1.4%)
	LANZOPRAZOL	1	1 (0.7%)
	OGASTORO	1	1 (0.7%)
	OMEPRAZOL	1	1 (0.7%)
	PROTON PUMP INHIBITORS	1	1 (0.7%)

ATC Name and Drug Name		Total N=142 n	n(%) patients
	RABEPRAZOLE	1	1 (0.7%)
PLATELET AGGREGATION INHIBITORS EXCL. HEPARIN	**ALL**	**73**	**58 (40.8%)**
	KARDEGIC	36	33 (23.2%)
	PLAVIX	8	8 (5.6%)
	ASPEGIC	6	6 (4.2%)
	ASPIRINE	5	4 (2.8%)
	CLOPIDOGREL	5	5 (3.5%)
	ACETYLSALICYLIC ACID	3	3 (2.1%)
	ASPIRINE PROTECT	3	3 (2.1%)
	BRILIQUE	3	3 (2.1%)
	ACETYLSALICYLATE LYSINE	2	2 (1.4%)
	EFFIENT	1	1 (0.7%)
	TICAGRELOR	1	1 (0.7%)
HMG COA REDUCTASE INHIBITORS	**ALL**	**57**	**49 (34.5%)**
	ATORVASTATINE	16	13 (9.2%)
	TAHOR	16	16 (11.3%)
	CRESTOR	10	10 (7%)
	PRAVASTATINE	5	5 (3.5%)
	FRACTAL	3	1 (0.7%)
	ROSUVASTATINE	3	2 (1.4%)
	SIMVASTATINE	2	2 (1.4%)
	FLUVASTATIN	1	1 (0.7%)

ATC Name and Drug Name		Total N=142 n	Total N=142 n(%) patients
	HMG COA REDUCTASE INHIBITORS	1	1 (0.7%)
SULFONAMIDES, PLAIN	**ALL**	**57**	**42 (29.6%)**
	LASILIX	32	26 (18.3%)
	FUROSEMIDE	19	14 (9.9%)
	LASIX	3	2 (1.4%)
	INDAPAMIDE	2	2 (1.4%)
	LASILIX SPECIAL	1	1 (0.7%)
GLUCOCORTICOIDS	**ALL**	**47**	**34 (23.9%)**
	SOLUPRED	13	8 (5.6%)
	PREDNISONE	8	6 (4.2%)
	CORTANCYL	7	5 (3.5%)
	PREDNISOLONE	5	5 (3.5%)
	BECOTIDE	3	3 (2.1%)
	BETAMETHASONE	2	2 (1.4%)
	CELESTENE	1	1 (0.7%)
	CORTISONE	1	1 (0.7%)
	GLUCOCORTICOIDS	1	1 (0.7%)
	HEXATRIONE	1	1 (0.7%)
	HYDROCORTISONE	1	1 (0.7%)
	METHYLPREDNISOLONE	1	1 (0.7%)
	PROLAIR	1	1 (0.7%)
	QVAR	1	1 (0.7%)

ATC Name and Drug Name		Total N=142 n	Total N=142 n(%) patients
	SOLUMEDROL	1	1 (0.7%)
ANILIDES	**ALL**	**44**	**38 (26.8%)**
	PARACETAMOL	26	22 (15.5%)
	DOLIPRANE	12	12 (8.5%)
	DAFALGAN	3	3 (2.1%)
	DAFALGAN CODEINE	1	1 (0.7%)
	FERVEX	1	1 (0.7%)
	PERFALGAN	1	1 (0.7%)
NATURAL OPIUM ALKALOIDS	**ALL**	**41**	**22 (15.5%)**
	OXYCODONE	8	8 (5.6%)
	OXYNORM	6	4 (2.8%)
	NATURAL OPIUM ALKALOIDS	5	5 (3.5%)
	SKENAN	5	2 (1.4%)
	ACTISKENAN	4	3 (2.1%)
	MORPHINE	4	3 (2.1%)
	OXYCONTIN	3	1 (0.7%)
	DAFALGAN CODEINE	2	2 (1.4%)
	KLIPAL	2	2 (1.4%)
	ANTARENE CODEINE	1	1 (0.7%)
	LAMALINE	1	1 (0.7%)
ANTIPROPULSIVES	**ALL**	**40**	**37 (26.1%)**
	IMODIUM	25	23 (16.2%)

ATC Name and Drug Name		Total N=142 n	Total N=142 n(%) patients
	LOPERAMIDE	14	14 (9.9%)
	ARESTAL	1	1 (0.7%)
BETA BLOCKING AGENTS, SELECTIVE	**ALL**	**39**	**36 (25.4%)**
	BISOPROLOL	22	21 (14.8%)
	ATENOLOL	4	4 (2.8%)
	CARDENSIEL	4	4 (2.8%)
	NEBIVOLOL	2	2 (1.4%)
	SECTRAL	2	2 (1.4%)
	TEMERIT	2	2 (1.4%)
	DETENSIEL	1	1 (0.7%)
	NEBILOX	1	1 (0.7%)
	TENORMINE	1	1 (0.7%)
DIHYDROPYRIDINE DERIVATIVES	**ALL**	**39**	**33 (23.2%)**
	AMLODIPINE	12	10 (7%)
	AMLOR	12	12 (8.5%)
	LOXEN	8	7 (4.9%)
	LERCAN	3	3 (2.1%)
	NIDREL	2	2 (1.4%)
	ADALATE	1	1 (0.7%)
	LERCANIDIPINE	1	1 (0.7%)
COMBINATIONS OF PENICILLINS, INCL. BETA-LACTAMASE INHIBITORS	**ALL**	**37**	**27 (19%)**
	AUGMENTIN	28	22 (15.5%)

ATC Name and Drug Name		Total N=142 n	Total N=142 n(%) patients
	TAZOCILLINE	9	9 (6.3%)
OTHER VIRAL VACCINES	**ALL**	**36**	**21 (14.8%)**
	OTHER VIRAL VACCINES	36	21 (14.8%)
ANGIOTENSIN II ANTAGONISTS, PLAIN	**ALL**	**35**	**31 (21.8%)**
	IRBESARTAN	9	6 (4.2%)
	CANDESARTAN	7	6 (4.2%)
	APROVEL	6	6 (4.2%)
	VALSARTAN	6	6 (4.2%)
	KENZEN	3	3 (2.1%)
	TAREG	2	2 (1.4%)
	ATACAND	1	1 (0.7%)
	MICARDIS	1	1 (0.7%)
THYROID HORMONES	**ALL**	**34**	**29 (20.4%)**
	LEVOTHYROX	29	26 (18.3%)
	EUTHYRAL	3	3 (2.1%)
	LEVOTHYROXINE	1	1 (0.7%)
	LEVOTHYROXINE SODIUM	1	1 (0.7%)
ALL OTHER THERAPEUTIC PRODUCTS	**ALL**	**33**	**27 (19%)**
	ALL OTHER THERAPEUTIC PRODUCTS	33	27 (19%)
ALPHA-ADRENORECEPTOR ANTAGONISTS	**ALL**	**31**	**17 (12%)**
	EUPRESSYL	7	4 (2.8%)
	TAMSULOSINE	4	3 (2.1%)

ATC Name and Drug Name		Total N=142 n	Total N=142 n(%) patients
	UROREC	4	4 (2.8%)
	MEDIATENSYL	3	2 (1.4%)
	XATRAL	3	3 (2.1%)
	ALFUZOSINE	2	2 (1.4%)
	URAPIDIL	2	2 (1.4%)
	ALPRESS	1	1 (0.7%)
	DOXAZOSINE	1	1 (0.7%)
	OMEXEL	1	1 (0.7%)
	OMIX	1	1 (0.7%)
	PRAZOSINE	1	1 (0.7%)
	SILODYX	1	1 (0.7%)
BENZODIAZEPINE DERIVATIVES	**ALL**	**27**	**21 (14.8%)**
	ALPRAZOLAM	7	6 (4.2%)
	XANAX	5	5 (3.5%)
	BROMAZEPAM	3	3 (2.1%)
	LEXOMIL	2	2 (1.4%)
	SERESTA	2	2 (1.4%)
	URBANYL	2	2 (1.4%)
	VALIUM	2	2 (1.4%)
	LORAZEPAM	1	1 (0.7%)
	NORDAZ	1	1 (0.7%)
	TEMESTA	1	1 (0.7%)

ATC Name and Drug Name		Total N=142 n	Total N=142 n(%) patients
	TRANXENE	1	1 (0.7%)
PENICILLINS WITH EXTENDED SPECTRUM	**ALL**	**27**	**20 (14.1%)**
	AMOXICILLINE	23	16 (11.3%)
	CLAMOXYL	4	4 (2.8%)
ACE INHIBITORS, PLAIN	**ALL**	**26**	**21 (14.8%)**
	RAMIPRIL	9	8 (5.6%)
	COVERSYL	6	6 (4.2%)
	PERINDOPRIL	6	6 (4.2%)
	TRIATEC	4	4 (2.8%)
	ACE INHIBITORS, PLAIN	1	1 (0.7%)
POTASSIUM	**ALL**	**25**	**20 (14.1%)**
	DIFFU K	19	15 (10.6%)
	POTASSIUM	2	2 (1.4%)
	DIFFU-K	1	1 (0.7%)
	KALEORID	1	1 (0.7%)
	NATI-K	1	1 (0.7%)
	PHOSPHORE	1	1 (0.7%)
PREPARATIONS INHIBITING URIC ACID PRODUCTION	**ALL**	**25**	**18 (12.7%)**
	ALLOPURINOL	20	15 (10.6%)
	ZYLORIC	4	3 (2.1%)
	ADENURIC	1	1 (0.7%)
OTHER OPIOIDS	**ALL**	**24**	**20 (14.1%)**

ATC Name and Drug Name		Total N=142 n	Total N=142 n(%) patients
	TRAMADOL	19	17 (12%)
	CONTRAMAL	3	3 (2.1%)
	IXPRIM	2	2 (1.4%)
OSMOTICALLY ACTING LAXATIVES	**ALL**	**22**	**15 (10.6%)**
	MOVICOL	7	7 (4.9%)
	MACROGOL	5	4 (2.8%)
	DUPHALAC	3	3 (2.1%)
	LACTULOSE	3	3 (2.1%)
	EDUCTYL	2	2 (1.4%)
	FORLAX	1	1 (0.7%)
	IMPORTAL	1	1 (0.7%)
BIGUANIDES	**ALL**	**21**	**20 (14.1%)**
	METFORMINE	16	16 (11.3%)
	GLUCOPHAGE	2	2 (1.4%)
	METFORMIN	1	1 (0.7%)
	METFORMIN EMBONATE	1	1 (0.7%)
	STAGID	1	1 (0.7%)
OTHER ANTIEPILEPTICS	**ALL**	**21**	**11 (7.7%)**
	LYRICA	5	4 (2.8%)
	GABAPENTINE	4	2 (1.4%)
	PREGABALIN	4	2 (1.4%)
	LACOSAMIDE	3	2 (1.4%)

ATC Name and Drug Name		Total N=142 n	Total N=142 n(%) patients
	KEPPRA	2	2 (1.4%)
	EPITOMAX	1	1 (0.7%)
	LAMICTAL	1	1 (0.7%)
	LEVETIRACETAM	1	1 (0.7%)
VITAMIN D AND ANALOGUES	**ALL**	**21**	**20 (14.1%)**
	UVEDOSE	11	11 (7.7%)
	ZYMAD	4	4 (2.8%)
	DEDROGYL	2	2 (1.4%)
	UN-ALFA	2	2 (1.4%)
	CHOLECALCIFEROL	1	1 (0.7%)
	COLECALCIFEROL	1	1 (0.7%)
OTHER ANTIHISTAMINES FOR SYSTEMIC USE	**ALL**	**20**	**15 (10.6%)**
	AERIUS	9	8 (5.6%)
	KESTIN	3	3 (2.1%)
	BILASTINE	2	1 (0.7%)
	ATARAX	1	1 (0.7%)
	DESLORATADINE	1	1 (0.7%)
	FEXOFENADINE	1	1 (0.7%)
	KESTINE	1	1 (0.7%)
	LORATADINE	1	1 (0.7%)
	TELFAST	1	1 (0.7%)
OTHER INTESTINAL ADSORBENTS	**ALL**	**20**	**20 (14.1%)**

ATC Name and Drug Name		Total N=142 n	Total N=142 n(%) patients
	SMECTA	17	17 (12%)
	DIOSMECTITE	3	3 (2.1%)
PROPIONIC ACID DERIVATIVES	**ALL**	**19**	**16 (11.3%)**
	IBUPROFENE	4	4 (2.8%)
	PROFENID	3	3 (2.1%)
	ADVIL	2	2 (1.4%)
	NAPROXENE	2	2 (1.4%)
	NUROFEN	2	1 (0.7%)
	APRANAX	1	1 (0.7%)
	BIPROFENID	1	1 (0.7%)
	CEBUTID	1	1 (0.7%)
	IBUPROFEN	1	1 (0.7%)
	KETOPROFEN	1	1 (0.7%)
	KETOPROFENE	1	1 (0.7%)
THIRD-GENERATION CEPHALOSPORINS	**ALL**	**19**	**15 (10.6%)**
	ROCEPHINE	11	10 (7%)
	OROKEN	3	3 (2.1%)
	CEFIXIME	2	2 (1.4%)
	FORTUM	2	2 (1.4%)
	ORELOX	1	1 (0.7%)
HEPARIN GROUP	**ALL**	**17**	**16 (11.3%)**
	LOVENOX	6	6 (4.2%)

ATC Name and Drug Name		Total N=142 n	Total N=142 n(%) patients
	CALCIPARINE	5	5 (3.5%)
	HEPARINE	2	2 (1.4%)
	INNOHEP	2	2 (1.4%)
	HEPARINE SODIQUE	1	1 (0.7%)
	TINZAPARIN	1	1 (0.7%)
OTHER ANTIDIARRHEALS	**ALL**	**17**	**16 (11.3%)**
	TIORFAN	15	14 (9.9%)
	OTHER ANTIDIARRHEALS	1	1 (0.7%)
	RACECADOTRIL	1	1 (0.7%)
OTHER BLOOD PRODUCTS	**ALL**	**17**	**9 (6.3%)**
	RED BLOOD CELLS	14	9 (6.3%)
	PLATELETS	3	1 (0.7%)
FLUOROQUINOLONES	**ALL**	**16**	**9 (6.3%)**
	OFLOXACINE	5	4 (2.8%)
	CIPROFLOXACINE	3	3 (2.1%)
	OFLOCET	3	2 (1.4%)
	CIFLOX	2	2 (1.4%)
	LEVOFLOXACINE	2	2 (1.4%)
	FLUOROQUINOLONES	1	1 (0.7%)
CORTICOSTEROIDS, POTENT (GROUP III)	**ALL**	**15**	**9 (6.3%)**
	DIPROSONE	8	6 (4.2%)
	BETAMETHASONE	2	2 (1.4%)

ATC Name and Drug Name		Total N=142 n	Total N=142 n(%) patients
	BETNEVAL	2	1 (0.7%)
	DIPROLENE	2	1 (0.7%)
	NERISONE	1	1 (0.7%)
OTHER DRUGS FOR FUNCTIONAL GASTROINTESTINAL DISORDERS	**ALL**	**15**	**13 (9.2%)**
	SPASFON	14	13 (9.2%)
	METEOSPASMYL	1	1 (0.7%)
PROPULSIVES	**ALL**	**15**	**13 (9.2%)**
	PRIMPERAN	6	6 (4.2%)
	METOCLOPRAMIDE	4	4 (2.8%)
	MOTILIUM	3	3 (2.1%)
	DOMPERIDONE	2	2 (1.4%)
DIRECT FACTOR XA INHIBITORS	**ALL**	**14**	**11 (7.7%)**
	XARELTO	8	7 (4.9%)
	ELIQUIS	6	5 (3.5%)
IRON BIVALENT, ORAL PREPARATIONS	**ALL**	**14**	**14 (9.9%)**
	TARDYFERON	8	8 (5.6%)
	FERROGRAD	3	3 (2.1%)
	FUMAFER	2	2 (1.4%)
	TIMOFEROL	1	1 (0.7%)
OTHER ANALGESICS AND ANTIPYRETICS	**ALL**	**14**	**13 (9.2%)**
	ACUPAN	12	11 (7.7%)
	NEFOPAM	2	2 (1.4%)

ATC Name and Drug Name		Total N=142 n	Total N=142 n(%) patients
OTHER ANTIANEMIC PREPARATIONS	**ALL**	**12**	**8 (5.6%)**
	ARANESP	3	3 (2.1%)
	BINOCRIT	2	1 (0.7%)
	ERYTHROPOIETIN	2	1 (0.7%)
	RETACRIT	2	1 (0.7%)
	EPORATIO	1	1 (0.7%)
	EPREX	1	1 (0.7%)
	NEORECORMON	1	1 (0.7%)
SELECTIVE BETA-2-ADRENORECEPTOR AGONISTS	**ALL**	**12**	**9 (6.3%)**
	BRICANYL	3	3 (2.1%)
	FORADIL	2	2 (1.4%)
	SALBUTAMOL	2	2 (1.4%)
	AIROMIR	1	1 (0.7%)
	EASYHALER	1	1 (0.7%)
	OXEOL	1	1 (0.7%)
	VENTILASTIN	1	1 (0.7%)
	VENTOLINE	1	1 (0.7%)
BENZODIAZEPINE RELATED DRUGS	**ALL**	**11**	**9 (6.3%)**
	IMOVANE	4	4 (2.8%)
	ZOPICLONE	3	3 (2.1%)
	STILNOX	2	2 (1.4%)
	ZOLPIDEM	2	2 (1.4%)

ATC Name and Drug Name		Total N=142 n	n(%) patients
IMIDAZOLE DERIVATIVES	**ALL**	**11**	**7 (4.9%)**
	FLAGYL	5	5 (3.5%)
	LOMEXIN	2	1 (0.7%)
	METRONIDAZOLE	2	2 (1.4%)
	MONAZOLE	1	1 (0.7%)
	PEVARYL	1	1 (0.7%)
INSULINS AND ANALOGUES FOR INJECTION, LONG-ACTING	**ALL**	**11**	**7 (4.9%)**
	LANTUS	6	5 (3.5%)
	LEVEMIR	3	3 (2.1%)
	INSULINE GLARGINE	2	2 (1.4%)
IRON, PARENTERAL PREPARATIONS	**ALL**	**11**	**9 (6.3%)**
	FERINJECT	5	5 (3.5%)
	VENOFER	3	3 (2.1%)
	FER	2	1 (0.7%)
	IRON, PARENTERAL PREPARATIONS	1	1 (0.7%)
OTHER DRUGS FOR PEPTIC ULCER AND GASTRO-OESOPHAGEAL REFLUX DISEASE (GORD)	**ALL**	**11**	**11 (7.7%)**
	GAVISCON	10	10 (7%)
	SODIUM ALGINATE	1	1 (0.7%)
OTHER EMOLLIENTS AND PROTECTIVES	**ALL**	**11**	**8 (5.6%)**
	OTHER EMOLLIENTS AND PROTECTIVES	7	6 (4.2%)
	DEXERYL	3	3 (2.1%)

ATC Name and Drug Name		Total N=142 n	n(%) patients
	XERIAL	1	1 (0.7%)
OTHER THERAPEUTIC PRODUCTS	**ALL**	**11**	**11 (7.7%)**
	OTHER THERAPEUTIC PRODUCTS	9	9 (6.3%)
	HOMEOPATHIC PREPARATION	2	2 (1.4%)
PREPARATIONS WITH NO EFFECT ON URIC ACID METABOLISM	**ALL**	**11**	**10 (7%)**
	COLCHIMAX	6	6 (4.2%)
	COLCHICINE	5	5 (3.5%)
SULFONAMIDES, UREA DERIVATIVES	**ALL**	**11**	**10 (7%)**
	DIAMICRON	7	6 (4.2%)
	GLICLAZIDE	3	3 (2.1%)
	GLIMEPIRIDE	1	1 (0.7%)
VITAMIN K ANTAGONISTS	**ALL**	**11**	**9 (6.3%)**
	PREVISCAN	7	6 (4.2%)
	COUMADINE	3	3 (2.1%)
	ACENOCOUMAROL	1	1 (0.7%)
ADRENERGICS IN COMBINATION WITH CORTICOSTEROIDS OR OTHER DRUGS, EXCL. ANTICHOLINERGICS	**ALL**	**10**	**10 (7%)**
	SERETIDE	5	5 (3.5%)
	INNOVAIR	3	3 (2.1%)
	SERETID	1	1 (0.7%)
	SYMBICORT	1	1 (0.7%)
DRUGS FOR TREATMENT OF HYPERKALEMIA AND HYPERPHOSPHATEMIA	**ALL**	**10**	**9 (6.3%)**

ATC Name and Drug Name		Total N=142 n	Total N=142 n(%) patients
	KAYEXALATE	8	8 (5.6%)
	RENAGEL	1	1 (0.7%)
	RESIKALI	1	1 (0.7%)
OTHER ANTIDEPRESSANTS	**ALL**	**10**	**10 (7%)**
	NORSET	3	3 (2.1%)
	OTHER ANTIDEPRESSANTS	2	2 (1.4%)
	ATHYMIL	1	1 (0.7%)
	CYMBALTA	1	1 (0.7%)
	DULOXETINE	1	1 (0.7%)
	MIANSERINE	1	1 (0.7%)
	VENLAFAXINE	1	1 (0.7%)
OTHER BLOOD GLUCOSE LOWERING DRUGS, EXCL. INSULINS	**ALL**	**10**	**7 (4.9%)**
	NOVONORM	5	3 (2.1%)
	DULAGLUTIDE	2	2 (1.4%)
	REPAGLINIDE	2	2 (1.4%)
	VICTOZA	1	1 (0.7%)
COMBINATIONS OF SULFONAMIDES AND TRIMETHOPRIM, INCL. DERIVATIVES	**ALL**	**9**	**8 (5.6%)**
	BACTRIM	7	6 (4.2%)
	COTRIMOXAZOLE	2	2 (1.4%)
ACE INHIBITORS AND DIURETICS	**ALL**	**8**	**7 (4.9%)**
	BIPRETERAX	4	4 (2.8%)
	PRETERAX	3	3 (2.1%)

ATC Name and Drug Name		Total N=142 n	Total N=142 n(%) patients
	CO-RENITEC	1	1 (0.7%)
ALDOSTERONE ANTAGONISTS	**ALL**	**8**	**7 (4.9%)**
	ALDACTONE	5	5 (3.5%)
	SPIRONOLACTONE	3	2 (1.4%)
ANGIOTENSIN II ANTAGONISTS AND DIURETICS	**ALL**	**8**	**5 (3.5%)**
	NISISCO	4	1 (0.7%)
	COAPROVEL	3	3 (2.1%)
	HYTACAND	1	1 (0.7%)
CORTICOSTEROIDS	**ALL**	**8**	**8 (5.6%)**
	BUDESONIDE	2	2 (1.4%)
	NASACORT	2	2 (1.4%)
	AVAMYS	1	1 (0.7%)
	DELIPROCT	1	1 (0.7%)
	NASONEX	1	1 (0.7%)
	RHINOCORT	1	1 (0.7%)
CORTICOSTEROIDS, VERY POTENT (GROUP IV)	**ALL**	**8**	**4 (2.8%)**
	CLARELUX	5	2 (1.4%)
	DERMOVAL	3	3 (2.1%)
DIPEPTIDYL PEPTIDASE 4 (DPP-4) INHIBITORS	**ALL**	**8**	**7 (4.9%)**
	JANUVIA	3	2 (1.4%)
	GALVUS	2	2 (1.4%)
	XELEVIA	2	2 (1.4%)

ATC Name and Drug Name		Total N=142 n	n(%) patients
	SITAGLIPTINE	1	1 (0.7%)
ANTICHOLINERGICS	**ALL**	**7**	**6 (4.2%)**
	ATROVENT	3	3 (2.1%)
	MYDRIATICUM	2	2 (1.4%)
	SPIRIVA	2	2 (1.4%)
FOLIC ACID AND DERIVATIVES	**ALL**	**7**	**6 (4.2%)**
	SPECIAFOLDINE	4	4 (2.8%)
	ACIDE FOLIQUE	3	2 (1.4%)
MACROLIDES	**ALL**	**7**	**6 (4.2%)**
	AZITROMYCINE	4	3 (2.1%)
	ERYTHROMYCINE	1	1 (0.7%)
	ROVAMYCINE	1	1 (0.7%)
	ROXITHROMYCINE	1	1 (0.7%)
PHENYLALKYLAMINE DERIVATIVES	**ALL**	**7**	**6 (4.2%)**
	ISOPTINE	3	3 (2.1%)
	VERAPAMIL	3	3 (2.1%)
	CARDIOPROTECT	1	1 (0.7%)
PHENYLPIPERIDINE DERIVATIVES	**ALL**	**7**	**5 (3.5%)**
	DUROGESIC	5	5 (3.5%)
	ABSTRAL	1	1 (0.7%)
	PECFENT	1	1 (0.7%)
PIPERAZINE DERIVATIVES	**ALL**	**7**	**6 (4.2%)**

ATC Name and Drug Name		Total N=142 n	n(%) patients
	CETIRIZINE	3	3 (2.1%)
	XYZALL	3	3 (2.1%)
	LEVOCETIRIZINE	1	1 (0.7%)
THIAZIDES, PLAIN	**ALL**	**7**	**7 (4.9%)**
	ESIDREX	6	6 (4.2%)
	HYDROCHLOROTHIAZIDE	1	1 (0.7%)
ANTIARRHYTHMICS, CLASS IC	**ALL**	**6**	**6 (4.2%)**
	FLECAINE	6	6 (4.2%)
IMIDAZOLE AND TRIAZOLE DERIVATIVES	**ALL**	**6**	**6 (4.2%)**
	KETODERM	2	2 (1.4%)
	AMYCOR	1	1 (0.7%)
	ECONAZOLE	1	1 (0.7%)
	FAZOL	1	1 (0.7%)
	FONX	1	1 (0.7%)
NON-SELECTIVE MONOAMINE REUPTAKE INHIBITORS	**ALL**	**6**	**6 (4.2%)**
	LAROXYL	4	4 (2.8%)
	ANAFRANIL	2	2 (1.4%)
OTHER LIPID MODIFYING AGENTS	**ALL**	**6**	**6 (4.2%)**
	EZETROL	4	4 (2.8%)
	EZETIMIBE	2	2 (1.4%)
SELECTIVE SEROTONIN REUPTAKE INHIBITORS	**ALL**	**6**	**6 (4.2%)**
	ESCITALOPRAM	2	2 (1.4%)

ATC Name and Drug Name		Total N=142 n	Total N=142 n(%) patients
	PAROXETINE	2	2 (1.4%)
	SEROPLEX	1	1 (0.7%)
	ZOLOFT	1	1 (0.7%)
SEROTONIN (5HT3) ANTAGONISTS	**ALL**	**6**	**6 (4.2%)**
	ONDANSETRON	3	3 (2.1%)
	ZOPHREN	2	2 (1.4%)
	SEROTONIN (5HT3) ANTAGONISTS	1	1 (0.7%)
ACE INHIBITORS AND CALCIUM CHANNEL BLOCKERS	**ALL**	**5**	**5 (3.5%)**
	COVERAM	3	3 (2.1%)
	LERCAPRESS	1	1 (0.7%)
	TARKA	1	1 (0.7%)
ANTIARRHYTHMICS, CLASS III	**ALL**	**5**	**5 (3.5%)**
	CORDARONE	3	3 (2.1%)
	AMIODARONE	2	2 (1.4%)
CORTICOSTEROIDS AND ANTIINFECTIVES IN COMBINATION	**ALL**	**5**	**4 (2.8%)**
	CHIBRO CADRON	2	1 (0.7%)
	TOBRADEX	2	2 (1.4%)
	STERDEX	1	1 (0.7%)
CORTICOSTEROIDS FOR SYSTEMIC USE	**ALL**	**5**	**4 (2.8%)**
	CORTICOSTEROID NOS	5	4 (2.8%)
DRUGS FOR URINARY FREQUENCY AND INCONTINENCE	**ALL**	**5**	**3 (2.1%)**
	TOVIAZ	2	1 (0.7%)

ATC Name and Drug Name		Total N=142 n	Total N=142 n(%) patients
	FESOTERODINE FUMARATE	1	1 (0.7%)
	TROSPIUM CHLORIDE	1	1 (0.7%)
	VESICARE	1	1 (0.7%)
FIBRATES	**ALL**	**5**	**4 (2.8%)**
	LIPANTHYL	3	3 (2.1%)
	FENOFIBRATE	2	2 (1.4%)
INFLUENZA VACCINES	**ALL**	**5**	**5 (3.5%)**
	INFLUENZA VACCINE	5	5 (3.5%)
OTHER ANTINEOPLASTIC AGENTS	**ALL**	**5**	**5 (3.5%)**
	HYDREA	5	5 (3.5%)
PROTEIN KINASE INHIBITORS	**ALL**	**5**	**3 (2.1%)**
	PONATINIB	3	1 (0.7%)
	NILOTINIB	1	1 (0.7%)
	TASIGNA	1	1 (0.7%)
UNSPECIFIED HERBAL AND TRADITIONAL MEDICINE	**ALL**	**5**	**5 (3.5%)**
	UNSPECIFIED HERBAL AND TRADITIONAL MEDICINE	2	2 (1.4%)
	PERMIXON	1	1 (0.7%)
	PIASCLEDINE	1	1 (0.7%)
	UNSPECIFIED HERBAL	1	1 (0.7%)
AMIDES	**ALL**	**4**	**4 (2.8%)**
	VERSATIS	2	2 (1.4%)
	CHIROCAINE	1	1 (0.7%)

ATC Name and Drug Name		Total N=142 n	n(%) patients
	EMLA	1	1 (0.7%)
ANGIOTENSIN II ANTAGONISTS AND CALCIUM CHANNEL BLOCKERS	**ALL**	**4**	**3 (2.1%)**
	EXFORGE	4	3 (2.1%)
ANTIDIARRHEAL MICROORGANISMS	**ALL**	**4**	**4 (2.8%)**
	ANTIDIARRHEAL MICROORGANISMS	2	2 (1.4%)
	PROBIOTICS NOS	1	1 (0.7%)
	ULTRA LEVURE	1	1 (0.7%)
ANTIINFECTIVES AND ANTISEPTICS FOR LOCAL ORAL TREATMENT	**ALL**	**4**	**4 (2.8%)**
	ELUDRIL	2	2 (1.4%)
	FUNGIZONE	1	1 (0.7%)
	LYSOPAINE	1	1 (0.7%)
ANTIINFLAMMATORY PREPARATIONS, NON-STEROIDS FOR TOPICAL USE	**ALL**	**4**	**4 (2.8%)**
	VOLTARENE	4	4 (2.8%)
BETA BLOCKING AGENTS, NON-SELECTIVE	**ALL**	**4**	**3 (2.1%)**
	SOTALOL	4	3 (2.1%)
DIPHENYLMETHANE DERIVATIVES	**ALL**	**4**	**4 (2.8%)**
	ATARAX	4	4 (2.8%)
HMG COA REDUCTASE INHIBITORS IN COMBINATION WITH OTHER LIPID MODIFYING AGENTS	**ALL**	**4**	**4 (2.8%)**
	EZETIMIBE W/SIMVASTATIN	2	2 (1.4%)
	INEGY	2	2 (1.4%)
IMIDAZOLINE RECEPTOR AGONISTS	**ALL**	**4**	**4 (2.8%)**

ATC Name and Drug Name		Total N=142 n	Total N=142 n(%) patients
	HYPERIUM	3	3 (2.1%)
	RILMENIDINE	1	1 (0.7%)
INSULINS AND ANALOGUES FOR INJECTION, FAST-ACTING	**ALL**	**4**	**4 (2.8%)**
	HUMALOG	2	2 (1.4%)
	NOVORAPID	2	2 (1.4%)
LOW-CEILING DIURETICS AND POTASSIUM-SPARING AGENTS	**ALL**	**4**	**4 (2.8%)**
	MODURETIC	2	2 (1.4%)
	ALDACTAZINE	1	1 (0.7%)
	ALTIZIDE W/SPIRONOLACTONE	1	1 (0.7%)
NUCLEOSIDES AND NUCLEOTIDES EXCL. REVERSE TRANSCRIPTASE INHIBITORS	**ALL**	**4**	**4 (2.8%)**
	VALACICLOVIR	2	2 (1.4%)
	ACICLOVIR	1	1 (0.7%)
	COPEGUS	1	1 (0.7%)
OTHER ANTIBIOTICS FOR TOPICAL USE	**ALL**	**4**	**3 (2.1%)**
	FUCIDINE	4	3 (2.1%)
OTHER GENERAL ANESTHETICS	**ALL**	**4**	**2 (1.4%)**
	KALINOX	2	1 (0.7%)
	KETAMINE	1	1 (0.7%)
	NITROUS OXIDE W/OXYGEN	1	1 (0.7%)
OTHER HORMONE ANTAGONISTS AND RELATED AGENTS	**ALL**	**4**	**1 (0.7%)**
	FIRMAGON	2	1 (0.7%)
	ZYTIGA	2	1 (0.7%)

ATC Name and Drug Name		Total N=142 n	Total N=142 n(%) patients
OTHER VASODILATORS USED IN CARDIAC DISEASES	**ALL**	**4**	**4 (2.8%)**
	IKOREL	2	2 (1.4%)
	ADANCOR	1	1 (0.7%)
	MOLSIDOMINE	1	1 (0.7%)
ANTIBIOTICS	**ALL**	**3**	**2 (1.4%)**
	AMBISOME	1	1 (0.7%)
	RIFADINE	1	1 (0.7%)
	RIFAMPICINE	1	1 (0.7%)
ANTIVERTIGO PREPARATIONS	**ALL**	**3**	**3 (2.1%)**
	BETASERC	2	2 (1.4%)
	TANGANIL	1	1 (0.7%)
CALCIUM	**ALL**	**3**	**3 (2.1%)**
	CACIT	1	1 (0.7%)
	CALCIDOSE	1	1 (0.7%)
	CALCIUM	1	1 (0.7%)
CHARCOAL PREPARATIONS	**ALL**	**3**	**3 (2.1%)**
	CARBOLEVURE	1	1 (0.7%)
	CARBOSYLANE	1	1 (0.7%)
	CHARCOAL PREPARATIONS	1	1 (0.7%)
COMBINATIONS OF ORAL BLOOD GLUCOSE LOWERING DRUGS	**ALL**	**3**	**3 (2.1%)**
	JANUMET	2	2 (1.4%)
	EUCREAS	1	1 (0.7%)

ATC Name and Drug Name		Total N=142 n	Total N=142 n(%) patients
CORTICOSTEROIDS, MODERATELY POTENT (GROUP II)	**ALL**	**3**	**3 (2.1%)**
	LOCOID	2	2 (1.4%)
	LOCAPRED	1	1 (0.7%)
DOPA AND DOPA DERIVATIVES	**ALL**	**3**	**2 (1.4%)**
	MODOPAR	2	2 (1.4%)
	LEVODOPA BENSERAZIDE	1	1 (0.7%)
ENEMAS	**ALL**	**3**	**3 (2.1%)**
	ENEMAS	2	2 (1.4%)
	MICROLAX	1	1 (0.7%)
MAGNESIUM	**ALL**	**3**	**3 (2.1%)**
	MAGNESIUM	3	3 (2.1%)
MUCOLYTICS	**ALL**	**3**	**3 (2.1%)**
	ACETYLCYSTEINE	1	1 (0.7%)
	BRONCHOKOD	1	1 (0.7%)
	SURBRONC	1	1 (0.7%)
NUCLEOSIDE AND NUCLEOTIDE REVERSE TRANSCRIPTASE INHIBITORS	**ALL**	**3**	**3 (2.1%)**
	ENTECAVIR	2	2 (1.4%)
	VIREAD	1	1 (0.7%)
ORGANIC NITRATES	**ALL**	**3**	**2 (1.4%)**
	ISOSORBIDE DINITRATE	1	1 (0.7%)
	NATISPRAY	1	1 (0.7%)
	TRINIPATCH	1	1 (0.7%)

ATC Name and Drug Name		Total N=142 n	Total N=142 n(%) patients
OTHER AMINOGLYCOSIDES	**ALL**	**3**	**3 (2.1%)**
	GENTAMICINE	2	2 (1.4%)
	AMIKLIN	1	1 (0.7%)
OTHER ANTIBACTERIALS	**ALL**	**3**	**3 (2.1%)**
	ZYVOXID	2	2 (1.4%)
	MONURIL	1	1 (0.7%)
OTHER ANTIEMETICS	**ALL**	**3**	**3 (2.1%)**
	VOGALENE	3	3 (2.1%)
OTHER DERMATOLOGICALS	**ALL**	**3**	**3 (2.1%)**
	OTHER DERMATOLOGICALS	3	3 (2.1%)
OTHER DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES, INHALANTS	**ALL**	**3**	**3 (2.1%)**
	OTHER DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES, INHALANTS	3	3 (2.1%)
SALICYLIC ACID AND DERIVATIVES	**ALL**	**3**	**3 (2.1%)**
	ASPIRINE	2	2 (1.4%)
	ASPEGIC	1	1 (0.7%)
SOFT PARAFFIN AND FAT PRODUCTS	**ALL**	**3**	**2 (1.4%)**
	EXCIPIAL	2	1 (0.7%)
	BIAFINE	1	1 (0.7%)
STREPTOGRAMINS	**ALL**	**3**	**3 (2.1%)**
	PYOSTACINE	3	3 (2.1%)
3-OXOANDROSTEN (4) DERIVATIVES	**ALL**	**2**	**2 (1.4%)**
	ANDROTARDYL	1	1 (0.7%)

ATC Name and Drug Name		Total N=142 n	n(%) patients
	TESTOSTERONE	1	1 (0.7%)
ACETIC ACID DERIVATIVES AND RELATED SUBSTANCES	**ALL**	**2**	**2 (1.4%)**
	DICLOFENAC	1	1 (0.7%)
	VOLTARENE	1	1 (0.7%)
ADRENERGIC AND DOPAMINERGIC AGENTS	**ALL**	**2**	**2 (1.4%)**
	ADRENALINE	2	2 (1.4%)
ALL OTHER NON-THERAPEUTIC PRODUCTS	**ALL**	**2**	**2 (1.4%)**
	ALL OTHER NON-THERAPEUTIC PRODUCTS	2	2 (1.4%)
AROMATASE INHIBITORS	**ALL**	**2**	**2 (1.4%)**
	ANASTROZOLE	1	1 (0.7%)
	ARIMIDEX	1	1 (0.7%)
BIOFLAVONOIDS	**ALL**	**2**	**2 (1.4%)**
	DAFLON	1	1 (0.7%)
	DIOSMINE	1	1 (0.7%)
CALCINEURIN INHIBITORS	**ALL**	**2**	**2 (1.4%)**
	ADVAGRAF	1	1 (0.7%)
	CICLOSPORINE	1	1 (0.7%)
CALCIUM, COMBINATIONS WITH VITAMIN D AND/OR OTHER DRUGS	**ALL**	**2**	**2 (1.4%)**
	CALCITE + D	1	1 (0.7%)
	OROCAL D3	1	1 (0.7%)
COXIBS	**ALL**	**2**	**2 (1.4%)**
	ARCOXIA	2	2 (1.4%)

ATC Name and Drug Name		Total N=142 n	Total N=142 n(%) patients
DIGITALIS GLYCOSIDES	**ALL**	**2**	**2 (1.4%)**
	HEMIGOXINE	2	2 (1.4%)
GONADOTROPIN RELEASING HORMONE ANALOGUES	**ALL**	**2**	**2 (1.4%)**
	DECAPEPTYL	2	2 (1.4%)
H2-RECEPTOR ANTAGONISTS	**ALL**	**2**	**2 (1.4%)**
	RANITIDINE	2	2 (1.4%)
INSULINS AND ANALOGUES	**ALL**	**2**	**2 (1.4%)**
	INSULINS AND ANALOGUES	2	2 (1.4%)
LEUKOTRIENE RECEPTOR ANTAGONISTS	**ALL**	**2**	**2 (1.4%)**
	MONTELUKAST	1	1 (0.7%)
	SINGULAIR	1	1 (0.7%)
MEDICAL GASES	**ALL**	**2**	**2 (1.4%)**
	OXYGEN	2	2 (1.4%)
MONOCLONAL ANTIBODIES	**ALL**	**2**	**2 (1.4%)**
	AVASTIN	1	1 (0.7%)
	MONOCLONAL ANTIBODIES	1	1 (0.7%)
NATURAL AND SEMISYNTHETIC ESTROGENS, PLAIN	**ALL**	**2**	**2 (1.4%)**
	ESTRADIOL	1	1 (0.7%)
	PROVAMES	1	1 (0.7%)
OTHER AGENTS AGAINST AMOEBIASIS AND OTHER PROTOZOAL DISEASES	**ALL**	**2**	**2 (1.4%)**
	ATOVAQUONE	1	1 (0.7%)
	WELLVONE	1	1 (0.7%)

ATC Name and Drug Name		Total N=142 n	Total N=142 n(%) patients
OTHER ANTIFUNGALS FOR TOPICAL USE	**ALL**	**2**	**2 (1.4%)**
	LAMISIL	1	1 (0.7%)
	MYCOSTER	1	1 (0.7%)
OTHER CARDIAC PREPARATIONS	**ALL**	**2**	**2 (1.4%)**
	STRIADYNE	1	1 (0.7%)
	VASTAREL	1	1 (0.7%)
OTHER CENTRALLY ACTING AGENTS	**ALL**	**2**	**2 (1.4%)**
	BACLOFEN	1	1 (0.7%)
	THIOCOLCHICOSIDE	1	1 (0.7%)
OTHER GYNECOLOGICALS	**ALL**	**2**	**1 (0.7%)**
	OTHER GYNECOLOGICALS	2	1 (0.7%)
PHENOTHIAZINE DERIVATIVES	**ALL**	**2**	**2 (1.4%)**
	THERALENE	1	1 (0.7%)
	TOPLEXIL	1	1 (0.7%)
PREGNEN (4) DERIVATIVES	**ALL**	**2**	**2 (1.4%)**
	ESTIMA	1	1 (0.7%)
	PROGESTERONE	1	1 (0.7%)
SOFTENERS, EMOLLIENTS	**ALL**	**2**	**1 (0.7%)**
	LANSOYL	1	1 (0.7%)
	PARAFFIN, LIQUID	1	1 (0.7%)
STOMATOLOGICAL PREPARATIONS	**ALL**	**2**	**2 (1.4%)**
	SODIUM BICARBONATE	2	2 (1.4%)

ATC Name and Drug Name		Total N=142 n	Total N=142 n(%) patients
SUBSTITUTED ALKYLAMINES	**ALL**	**2**	**2 (1.4%)**
	POLARAMINE	2	2 (1.4%)
SYNTHETIC ANTICHOLINERGICS, ESTERS WITH TERTIARY AMINO GROUP	**ALL**	**2**	**2 (1.4%)**
	DEBRIDAT	1	1 (0.7%)
	DUSPATALIN	1	1 (0.7%)
SYNTHETIC ESTROGENS, PLAIN	**ALL**	**2**	**1 (0.7%)**
	OESTROGEN	2	1 (0.7%)
TETRACYCLINES	**ALL**	**2**	**2 (1.4%)**
	DOXYCYCLINE	1	1 (0.7%)
	VIBRAMYCINE	1	1 (0.7%)
TRIAZOLE DERIVATIVES	**ALL**	**2**	**2 (1.4%)**
	FLUCONAZOLE	1	1 (0.7%)
	TRIFLUCAN	1	1 (0.7%)
ZINC PRODUCTS	**ALL**	**2**	**2 (1.4%)**
	MITOSYL	2	2 (1.4%)
ADRENERGICS IN COMBINATION WITH ANTICHOLINERGICS	**ALL**	**1**	**1 (0.7%)**
	ULTIBRO	1	1 (0.7%)
AGENTS FOR DERMATITIS, EXCLUDING CORTICOSTEROIDS	**ALL**	**1**	**1 (0.7%)**
	TACROLIMUS	1	1 (0.7%)
ANALGESICS	**ALL**	**1**	**1 (0.7%)**
	CYMBALTA	1	1 (0.7%)
ANTIBACTERIALS FOR SYSTEMIC USE	**ALL**	**1**	**1 (0.7%)**

ATC Name and Drug Name		Total N=142 n	Total N=142 n(%) patients
	D-MANNOSE	1	1 (0.7%)
ANTIINFLAMMATORY AGENTS, NON-STEROIDS	**ALL**	**1**	**1 (0.7%)**
	OCUFEN	1	1 (0.7%)
ANTINEOVASCULARISATION AGENTS	**ALL**	**1**	**1 (0.7%)**
	LUCENTIS	1	1 (0.7%)
ANTIPROPULSIVES; ANTIPROPULSIVES	**ALL**	**1**	**1 (0.7%)**
	IMODIUM; IMODIUM	1	1 (0.7%)
ANTIVIRALS	**ALL**	**1**	**1 (0.7%)**
	ZOVIRAX	1	1 (0.7%)
ANXIOLYTICS	**ALL**	**1**	**1 (0.7%)**
	DONORMYL	1	1 (0.7%)
BENZOTHIAZEPINE DERIVATIVES	**ALL**	**1**	**1 (0.7%)**
	BI TILDIEM	1	1 (0.7%)
BETA BLOCKING AGENTS	**ALL**	**1**	**1 (0.7%)**
	AZARGA	1	1 (0.7%)
BETA BLOCKING AGENTS, SELECTIVE, AND THIAZIDES	**ALL**	**1**	**1 (0.7%)**
	LODOZ	1	1 (0.7%)
BIGUANIDES AND AMIDINES	**ALL**	**1**	**1 (0.7%)**
	HEXOMEDINE	1	1 (0.7%)
BILE ACID SEQUESTRANTS	**ALL**	**1**	**1 (0.7%)**
	QUESTRAN	1	1 (0.7%)
BISPHOSPHONATES	**ALL**	**1**	**1 (0.7%)**

ATC Name and Drug Name		Total N=142 n	n(%) patients
	ACTONEL	1	1 (0.7%)
CARBAPENEMS	**ALL**	**1**	**1 (0.7%)**
	TIENAM	1	1 (0.7%)
CARBONIC ANHYDRASE INHIBITORS	**ALL**	**1**	**1 (0.7%)**
	DIAMOX	1	1 (0.7%)
CARBOXAMIDE DERIVATIVES	**ALL**	**1**	**1 (0.7%)**
	TRILEPTAL	1	1 (0.7%)
COMBINATIONS OF ANTIBACTERIALS	**ALL**	**1**	**1 (0.7%)**
	COMBINATIONS OF ANTIBACTERIALS	1	1 (0.7%)
CONTACT LAXATIVES	**ALL**	**1**	**1 (0.7%)**
	DULCOLAX	1	1 (0.7%)
CORTICOSTEROIDS FOR LOCAL ORAL TREATMENT	**ALL**	**1**	**1 (0.7%)**
	PREDNISOLONE	1	1 (0.7%)
CORTICOSTEROIDS, DERMATOLOGICAL PREPARATIONS	**ALL**	**1**	**1 (0.7%)**
	CORTICOSTEROID NOS	1	1 (0.7%)
DETOXIFYING AGENTS FOR ANTINEOPLASTIC TREATMENT	**ALL**	**1**	**1 (0.7%)**
	LEVOFOLINATE	1	1 (0.7%)
DRUGS USED IN HEREDITARY ANGIOEDEMA	**ALL**	**1**	**1 (0.7%)**
	BERINERT	1	1 (0.7%)
ELECTROLYTE SOLUTIONS	**ALL**	**1**	**1 (0.7%)**
	ELECTROLYTE SOLUTIONS	1	1 (0.7%)
ENZYME PREPARATIONS	**ALL**	**1**	**1 (0.7%)**

ATC Name and Drug Name		Total N=142 n	n(%) patients
	CREON	1	1 (0.7%)
FAT/CARBOHYDRATES/PROTEINS/MINERALS/VITAMINS, COMBINATIONS	**ALL**	**1**	**1 (0.7%)**
	FAT/CARBOHYDRATES/PROTEINS/MINERALS/VITAMINS, COMBINATIONS	1	1 (0.7%)
FATTY ACID DERIVATIVES	**ALL**	**1**	**1 (0.7%)**
	DEPAKOTE	1	1 (0.7%)
I.V. SOLUTIONS	**ALL**	**1**	**1 (0.7%)**
	SONDALIS HP	1	1 (0.7%)
INTERFERONS	**ALL**	**1**	**1 (0.7%)**
	PEGASYS	1	1 (0.7%)
IRON IN COMBINATION WITH FOLIC ACID	**ALL**	**1**	**1 (0.7%)**
	TARDYFERON B9	1	1 (0.7%)
MULTIVITAMINS, OTHER COMBINATIONS	**ALL**	**1**	**1 (0.7%)**
	MULTIVITAMINS, OTHER COMBINATIONS	1	1 (0.7%)
NEURAMINIDASE INHIBITORS	**ALL**	**1**	**1 (0.7%)**
	TAMIFLU	1	1 (0.7%)
OPIOID ANESTHETICS	**ALL**	**1**	**1 (0.7%)**
	SUFENTANIL	1	1 (0.7%)
OPIUM ALKALOIDS AND DERIVATIVES	**ALL**	**1**	**1 (0.7%)**
	TUSSIDANE	1	1 (0.7%)
OTHER AGENTS AGAINST LEISHMANIASIS AND TRYPANOSOMIASIS	**ALL**	**1**	**1 (0.7%)**
	PENTACARINAT	1	1 (0.7%)

ATC Name and Drug Name		Total N=142 n	Total N=142 n(%) patients
OTHER ANTIHYPERTENSIVES	**ALL**	**1**	**1 (0.7%)**
	BOSENTAN	1	1 (0.7%)
OTHER ANTIINFECTIVES	**ALL**	**1**	**1 (0.7%)**
	FLUCONAZOLE	1	1 (0.7%)
OTHER ANTIINFLAMMATORY AND ANTIRHEUMATIC AGENTS, NON-STEROIDS	**ALL**	**1**	**1 (0.7%)**
	NABUCOX	1	1 (0.7%)
OTHER ANTIMYCOTICS FOR SYSTEMIC USE	**ALL**	**1**	**1 (0.7%)**
	CANCIDAS	1	1 (0.7%)
OTHER ANTIPSYCHOTICS	**ALL**	**1**	**1 (0.7%)**
	RISPERIDONE	1	1 (0.7%)
OTHER ANTITHROMBOTIC AGENTS	**ALL**	**1**	**1 (0.7%)**
	ARIXTRA	1	1 (0.7%)
OTHER ANXIOLYTICS	**ALL**	**1**	**1 (0.7%)**
	STRESAM	1	1 (0.7%)
OTHER IMMUNOSUPPRESSANTS	**ALL**	**1**	**1 (0.7%)**
	METHOTREXATE	1	1 (0.7%)
OTHER MINERAL PRODUCTS	**ALL**	**1**	**1 (0.7%)**
	PHOSPHONEUROS	1	1 (0.7%)
OTHER OPHTHALMOLOGICALS	**ALL**	**1**	**1 (0.7%)**
	VISMED	1	1 (0.7%)
OTHER PLAIN VITAMIN PREPARATIONS	**ALL**	**1**	**1 (0.7%)**
	VITAMINE	1	1 (0.7%)

ATC Name and Drug Name		Total N=142 n	Total N=142 n(%) patients
OTHER PSYCHOSTIMULANTS AND NOOTROPICS	**ALL**	**1**	**1 (0.7%)**
	NEUROTIN	1	1 (0.7%)
PERIPHERAL OPIOID RECEPTOR ANTAGONISTS	**ALL**	**1**	**1 (0.7%)**
	PERIPHERAL OPIOID RECEPTOR ANTAGONISTS	1	1 (0.7%)
PNEUMOCOCCAL VACCINES	**ALL**	**1**	**1 (0.7%)**
	PNEUMOCOCCAL VACCINE	1	1 (0.7%)
PROGESTOGENS	**ALL**	**1**	**1 (0.7%)**
	DESOGESTREL	1	1 (0.7%)
PROGESTOGENS AND ESTROGENS, FIXED COMBINATIONS	**ALL**	**1**	**1 (0.7%)**
	MERCILON	1	1 (0.7%)
PROSTAGLANDINS	**ALL**	**1**	**1 (0.7%)**
	PROSTINE	1	1 (0.7%)
PROTEIN SUPPLEMENTS	**ALL**	**1**	**1 (0.7%)**
	FORTIMEL	1	1 (0.7%)
PYRIMIDINE ANALOGUES	**ALL**	**1**	**1 (0.7%)**
	EFUDIX	1	1 (0.7%)
SECOND-GENERATION CEPHALOSPORINS	**ALL**	**1**	**1 (0.7%)**
	CEFUROXIME	1	1 (0.7%)
SOLUTIONS FOR PARENTERAL NUTRITION	**ALL**	**1**	**1 (0.7%)**
	RENUTRYL	1	1 (0.7%)
SULFUR-CONTAINING IMIDAZOLE DERIVATIVES	**ALL**	**1**	**1 (0.7%)**
	THYROZOL	1	1 (0.7%)

ATC Name and Drug Name		Total N=142 n	Total N=142 n(%) patients
SYMPATHOMIMETICS, COMBINATIONS EXCL. CORTICOSTEROIDS	**ALL**	**1**	**1 (0.7%)**
	RHINOFLUIMUCIL	1	1 (0.7%)
VITAMIN B12 (CYANOCOBALAMIN AND ANALOGUES)	**ALL**	**1**	**1 (0.7%)**
	VITAMIN B12	1	1 (0.7%)
VITAMIN K	**ALL**	**1**	**1 (0.7%)**
	VITAMINE K	1	1 (0.7%)
VITAMINS, OTHER COMBINATIONS	**ALL**	**1**	**1 (0.7%)**
	VITAMINS, OTHER COMBINATIONS	1	1 (0.7%)

Table 15.4.1 Concomitant Drug Treatments - SAF (n=142)

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Appendix 7.6 Endpoint Data

Appendix 7.7 Adverse Events: Measures taken to prevent AE

Table 82: Measures taken to prevent AE - SAF (n=142)

Patient No.	Date of initiation of bosutinib treatment	SOC name	PT name	CTCAE grade	Date of occurrence	Is the event serious?	Status	Date of recovery	Is it reasonably possible that the event may be related to the study medication?	Is it reasonably possible that the event may be related to a concomitant drug?	Name of the drug (1)	Action taken (1)	Name of the drug (2)	Action taken (2)
01-01	24/02/2016	Gastrointestinal disorders	Vomiting	Grade 3	NK/03/2016	Yes	Recovery	07/03/2016	No	No	BOSULIF	Not applicable		.
		General disorders and administration site conditions	General physical health deterioration	Grade 3	06/03/2016	Yes	Recovery	19/04/2016	No	No	BOSULIF	Not applicable		.
		Renal and urinary disorders	Pollakiuria	Grade 1	04/04/2016	No	Recovery	05/04/2016	No	No	BOSULIF	Not applicable		.
		Gastrointestinal disorders	Oral discomfort	Grade 1	06/10/2016	No	Recovery	UK/10/2016	No	No		Not applicable		.
		Metabolism and nutrition disorders	Gout	Grade 2	08/03/2016	No	Recovery	21/03/2016	No	No	BOSULIF	Not applicable		.
		Skin and subcutaneous tissue disorders	Purpura	Grade 2	21/03/2016	No	Recovery	22/03/2016	No	No	BOSULIF	Not applicable		.
		Infections and infestations	Infection	Grade 2	22/03/2016	No	Recovery	29/03/2016	No	No	BOSULIF	Not applicable		.
		Gastrointestinal disorders	Diarrhoea	Grade 2	12/03/2016	No	Recovery	15/03/2016	No	Yes	BOSULIF	Not applicable		.
		Gastrointestinal disorders	Mouth haemorrhage	Grade 1	23/03/2016	No	Recovery	23/03/2016	No	No		Not applicable		Not applicable
		Gastrointestinal disorders	Rectal haemorrhage	Grade 3	06/03/2016	Yes	Recovery	15/04/2016	No	No		Not applicable		Not applicable

Patient No.	Date of initiation of bosutinib treatment	SOC name	PT name	CTCAE grade	Date of occurrence	Is the event serious?	Status	Date of recovery	Is it reasonably possible that the event may be related to the study medication?	Is it reasonably possible that the event may be related to a concomitant drug?	Name of the drug (1)	Action taken (1)	Name of the drug (2)	Action taken (2)
		Renal and urinary disorders	Renal impairment	Grade 3	07/03/2016	No	Recovery	29/03/2016	No	No		Not applicable		Not applicable
		Blood and lymphatic system disorders	Anaemia	Grade 4	06/03/2016	Yes	Subject not recovered		No	No		Not applicable		Not applicable
		Gastrointestinal disorders	Abdominal pain upper	Grade 2	05/04/2016	No	Subject not recovered		No	No		Not applicable		Not applicable
		Respiratory, thoracic and mediastinal disorders	Epistaxis	Grade 2	20/03/2016	No	Recovery	23/03/2016	No	No		Not applicable		Not applicable
		Blood and lymphatic system disorders	Pancytopenia	Grade 3	21/03/2016	Yes	Recovery	18/04/2016	No	No		Not applicable		Not applicable
		Respiratory, thoracic and mediastinal disorders	Acute pulmonary oedema	Grade 3	01/04/2016	Yes	Recovery	01/04/2016	No	No		Not applicable		Not applicable
		Cardiac disorders	Cardiac failure	Grade 2	17/11/2016	Yes	Subject not recovered		No	No	BOSULIF	Not applicable		.
		Skin and subcutaneous tissue disorders	Skin necrosis	Grade 2	11/04/2016	No	Subject not recovered		No	No		Not applicable		Not applicable
		Respiratory, thoracic and mediastinal disorders	Pleural effusion	Grade 2	05/04/2016	Yes	Recovery	19/04/2016	No	No		Not applicable		Not applicable
		Nervous system disorders	Balance disorder	Grade 1	06/12/2016	No	Recovery	NK/12/2016	No	No	BOSULIF	Not applicable		.
		Vascular disorders	Peripheral arterial occlusive disease	Grade 2	26/02/2016	Yes	Recovery	15/05/2016	No	No	BOSULIF	Not applicable		.
		Skin and subcutaneous tissue disorders	Skin ulcer	Grade 3	NK/09/2016	Yes	Subject not recovered		No	No	BOSULIF	Not applicable		.
		Gastrointestinal disorders	Aphthous stomatitis	Grade 2	04/04/2016	No	Recovery	15/04/2016	No	No	BOSULIF	Not applicable		.

Patient No.	Date of initiation of bosutinib treatment	SOC name	PT name	CTCAE grade	Date of occurrence	Is the event serious?	Status	Date of recovery	Is it reasonably possible that the event may be related to the study medication?	Is it reasonably possible that the event may be related to a concomitant drug?	Name of the drug (1)	Action taken (1)	Name of the drug (2)	Action taken (2)
		Endocrine disorders	Hypothyroidism	Grade 2	24/10/2016	No	Subject not recovered		No	No	BOSULIF	Not applicable		.
		Injury, poisoning and procedural complications	Overdose	Grade 2	14/12/2016	No	Recovery	NK/12/2016	No	Yes	BOSULIF	Not applicable	OXYNORM	Dose reduction
		Musculoskeletal and connective tissue disorders	Back pain	Grade 3	05/09/2016	Yes	Recovery in progress		No	No	BOSULIF	Not applicable		.
		Nervous system disorders	Neuralgia	Grade 2	30/10/2016	No	Subject not recovered		No	No	BOSULIF	Not applicable		.
		Infections and infestations	Infection	Grade 2	05/09/2016	Yes	Recovery	23/09/2016	No	No	BOSULIF	Not applicable		.
		Infections and infestations	Sepsis	Grade 5	10/01/2017	Yes	Subject not recovered		No	No	BOSULIF	Not applicable		.
		Infections and infestations	Candida infection	Grade 2	08/04/2016	No	Recovery	UK/04/2016	No	No	BOSULIF	Not applicable		.
		Psychiatric disorders	Depressed mood	Grade 2	NK/01/2017	No	Subject not recovered		No	No	BOSULIF	Not applicable		.
		Gastrointestinal disorders	Gastrointestinal disorder	Grade 2	05/09/2016	Yes	Recovery	23/09/2016	No	No	BOSULIF	Not applicable		.
		Infections and infestations	Bronchitis	Grade 2	17/11/2016	Yes	Recovery	24/11/2016	No	No	BOSULIF	Not applicable		.
		Respiratory, thoracic and mediastinal disorders	Cough	Grade 1	NK/10/2016	No	Recovery	NK/10/2016	No	No	BOSULIF	Not applicable		.
		Metabolism and nutrition disorders	Decreased appetite	Grade 1	NK/10/2016	No	Subject not recovered		No	No	BOSULIF	Not applicable		.
		Gastrointestinal disorders	Dry mouth	Grade 1	NK/10/2016	No	Recovery	NK/10/2016	No	No	BOSULIF	Not applicable		.
		Respiratory, thoracic and mediastinal disorders	Dyspnoea	Grade 1	NK/10/2016	No	Recovery	NK/11/2016	No	No	BOSULIF	Not applicable		.

Patient No.	Date of initiation of bosutinib treatment	SOC name	PT name	CTCAE grade	Date of occurrence	Is the event serious?	Status	Date of recovery	Is it reasonably possible that the event may be related to the study medication?	Is it reasonably possible that the event may be related to a concomitant drug?	Name of the drug (1)	Action taken (1)	Name of the drug (2)	Action taken (2)
		Skin and subcutaneous tissue disorders	Skin ulcer	Grade 3	14/12/2016	Yes	Subject not recovered		No	No	BOSULIF	Not applicable		.
01-02	08/09/2017	Gastrointestinal disorders	Diarrhoea	Grade 1	NK/09/2017	No	Recovery	28/11/2017	Yes	No		No dose modification		.
		Infections and infestations	Pneumonia	Grade 2	NK/11/2018	No	Recovery	NK/11/2018	No	No	BOSUTINIB	No dose modification		.
		Gastrointestinal disorders	Constipation	Grade 1	NK/11/2017	No	Recovery	09/01/2018	No	No	BOSULIF	No dose modification		.
		Gastrointestinal disorders	Diarrhoea	Grade 1	NK/06/2018	No	Recovery	05/09/2018	Yes	No	BOSULIF	No dose modification		.
		Infections and infestations	Infection	Grade 1	NK/01/2019	No	Recovery	NK/01/2019	No	No	BOSULIF	No dose modification		.
		Renal and urinary disorders	Renal failure	Grade 1	14/11/2017	No	Subject not recovered		No	Yes	BOSULIF	No dose modification	EXFORGE	Withdrawal (temporary or permanent, or deferred administration)
		Injury, poisoning and procedural complications	Tendon rupture	Grade 2	NK/08/2019	Yes	Recovery	16/08/2019	No	No	BOSULIF	No dose modification		.
		Renal and urinary disorders	Haematuria	Grade 2	UK/12/2019	No	Recovery	08/01/2020	No	No	BOSULIF	No dose modification		.
		Respiratory, thoracic and mediastinal disorders	Dyspnoea	Grade 1	UK/10/2020	No	Subject not recovered		No	No	BOSULIF	No dose modification		.

Patient No.	Date of initiation of bosutinib treatment	SOC name	PT name	CTCAE grade	Date of occurrence	Is the event serious?	Status	Date of recovery	Is it reasonably possible that the event may be related to the study medication?	Is it reasonably possible that the event may be related to a concomitant drug?	Name of the drug (1)	Action taken (1)	Name of the drug (2)	Action taken (2)
01-03	14/12/2017	Respiratory, thoracic and mediastinal disorders	Haemoptysis	Grade 2	29/11/2018	No	Subject not recovered		No	No	BOSULIF	No dose modification		.
		General disorders and administration site conditions	Asthenia	Grade 1	20/12/2018	No	Subject not recovered		No	No	BOSULIF	No dose modification		.
		Metabolism and nutrition disorders	Diabetes mellitus inadequate control	Grade 2	22/11/2018	No	Recovery	20/12/2018	No	No	BOSULIF	No dose modification		.
		Cardiac disorders	Extrasystoles	Grade 1	13/09/2019	No	Subject not recovered		No	No	BOSULIF	No dose modification		.
		Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Gastrointestinal stromal tumour	Grade 3	16/10/2020	Yes	Recovery	UK/07/2021	No	No	BOSULIF	No dose modification		.
01-04	07/03/2018	Nervous system disorders	Dizziness	Grade 1	21/03/2018	No	Recovery	17/04/2018	Yes	No	BOSULIF	Dose reduction		.
		Gastrointestinal disorders	Vomiting	Grade 1	21/03/2018	No	Recovery	05/04/2018	Yes	No	BOSULIF	Dose reduction		.
		Respiratory, thoracic and mediastinal disorders	Pleural effusion	Grade 3	02/07/2018	Yes	Recovery	23/08/2018	Yes	No	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.
		Nervous system disorders	Transient ischaemic attack	Grade 1	05/06/2018	Yes	Recovery	NK/06/2018	No	No	BOSULIF	No dose modification		.
		Metabolism and nutrition disorders	Hypokalaemia	Grade 3	11/07/2018	No	Recovery	12/07/2018	No	No	BOSULIF	No dose modification		.

Patient No.	Date of initiation of bosutinib treatment	SOC name	PT name	CTCAE grade	Date of occurrence	Is the event serious?	Status	Date of recovery	Is it reasonably possible that the event may be related to the study medication?	Is it reasonably possible that the event may be related to a concomitant drug?	Name of the drug (1)	Action taken (1)	Name of the drug (2)	Action taken (2)
		Metabolism and nutrition disorders	Vitamin D deficiency	Grade 2	NK/07/2018	No	Recovery	NK/07/2018	No	No	BOSULIF	No dose modification		.
		Psychiatric disorders	Depression	Grade 2	05/07/2018	No	Recovery	NK/07/2018	No	No	BOSULIF	No dose modification		.
		Vascular disorders	Hypertension	Grade 2	21/03/2018	No	Recovery	29/03/2018	Yes	No	BOSULIF	Dose reduction		.
		Musculoskeletal and connective tissue disorders	Arthralgia	Grade 1	05/04/2018	No	Recovery	17/04/2018	Yes	No	BOSULIF	No dose modification		.
		General disorders and administration site conditions	Fatigue	Grade 1	17/04/2018	No	Recovery	29/05/2018	No	No	BOSULIF	No dose modification		.
		Gastrointestinal disorders	Nausea	Grade 1	07/03/2018	No	Recovery	21/03/2018	Yes	No	BOSULIF	No dose modification		.
		Respiratory, thoracic and mediastinal disorders	Dyspnoea	Grade 1	17/04/2018	No	Recovery	29/05/2018	Yes	No	BOSULIF	No dose modification		.
		Nervous system disorders	Headache	Grade 1	27/05/2018	No	Recovery	NK/06/2018	No	No	BOSULIF	No dose modification		.
		Metabolism and nutrition disorders	Folate deficiency	Grade 2	NK/07/2018	No	Recovery	NK/07/2018	No	No	BOSULIF	Not applicable		.
		Respiratory, thoracic and mediastinal disorders	Pleural fibrosis	Grade 1	23/08/2018	No	Recovery	NK/08/2018	No	No	BOSULIF	Not applicable		.
		Infections and infestations	Diverticulitis	Grade 2	17/06/2019	No	Recovery	NK/06/2019	No	No	BOSULIF	Not applicable		.
		Metabolism and nutrition disorders	Hypokalaemia	Grade 1	09/07/2018	No	Recovery with sequellae	10/07/2018	No	No	BOSULIF	Not applicable		.
		General disorders and administration site conditions	Chest pain	Grade 1	12/09/2019	No	Recovery	NK/NK/2020	No	No	BOSULIF	Not applicable		.

Patient No.	Date of initiation of bosutinib treatment	SOC name	PT name	CTCAE grade	Date of occurrence	Is the event serious?	Status	Date of recovery	Is it reasonably possible that the event may be related to the study medication?	Is it reasonably possible that the event may be related to a concomitant drug?	Name of the drug (1)	Action taken (1)	Name of the drug (2)	Action taken (2)
		Musculoskeletal and connective tissue disorders	Osteoporosis	Grade 1	NK/09/2019	No	Subject not recovered		No	No	BOSULIF	Not applicable		.
		Respiratory, thoracic and mediastinal disorders	Pulmonary pain	Grade 1	NK/10/2020	No	Recovery	NK/10/2020	No	No	BOSULIF	Not applicable		.
01-05	15/01/2019	Infections and infestations	Infection	Grade 1	NK/04/2019	No	Recovery	NK/04/2019	No	No	BOSULIF	No dose modification		.
		Nervous system disorders	Hypoaesthesia	Grade 1	NK/04/2019	No	Recovery	12/07/2019	Yes	No	BOSULIF	No dose modification		.
		Eye disorders	Retinal haemorrhage	Grade 2	NK/NK/2019	No	Recovery	NK/NK/2020	No	No	BOSUTINIB	No dose modification		.
		Blood and lymphatic system disorders	Iron deficiency anaemia	Grade 3	NK/10/2019	No	Recovery	04/12/2019	No	No	BOSUTINIB	No dose modification		.
		Respiratory, thoracic and mediastinal disorders	Dyspnoea	Grade 2	NK/10/2020	No	Recovery	19/10/2020	No	No	BOSULIF	No dose modification		.
		General disorders and administration site conditions	Oedema peripheral	Grade 1	26/01/2021	No	Recovery	08/03/2021	No	No	BOSULIF	No dose modification		.
		Musculoskeletal and connective tissue disorders	Arthralgia	Grade 1	13/01/2020	No	Recovery	20/04/2020	No	No	BOSULIF	No dose modification		.
		Investigations	Electrocardiogram ST segment depression	Grade 1	14/01/2021	No	Unknown		No	No	BOSULIF	No dose modification		.
		Gastrointestinal disorders	Rectal haemorrhage	Grade 1	UK/03/2021	No	Recovery	NK/NK/2021	No	No	BOSULIF	No dose modification		.
		Gastrointestinal disorders	Hiatus hernia	Grade 1	UK/06/2021	No	Subject not recovered		No	No	BOSULIF	No dose modification		.

Patient No.	Date of initiation of bosutinib treatment	SOC name	PT name	CTCAE grade	Date of occurrence	Is the event serious?	Status	Date of recovery	Is it reasonably possible that the event may be related to the study medication?	Is it reasonably possible that the event may be related to a concomitant drug?	Name of the drug (1)	Action taken (1)	Name of the drug (2)	Action taken (2)
01-06	16/01/2019	General disorders and administration site conditions	Asthenia	Grade 1	16/09/2019	No	Recovery	NK/10/2019	No	No	BOSULIF	Not applicable		.
		General disorders and administration site conditions	Asthenia	Grade 1	22/04/2020	No	Recovery	NK/06/2020	No	No	BOSULIF	Not applicable		.
		Gastrointestinal disorders	Abdominal pain upper	Grade 1	26/02/2019	No	Recovery	29/06/2020	Yes	No	BOSULIF	No dose modification		.
		Skin and subcutaneous tissue disorders	Skin reaction	Grade 1	NK/03/2019	No	Recovery	25/03/2019	No	No	BOSULIF	No dose modification		.
		Hepatobiliary disorders	Hepatocellular injury	Grade 3	02/03/2019	No	Recovery	23/03/2019	Yes	No	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.
		General disorders and administration site conditions	Asthenia	Grade 1	08/04/2019	No	Recovery	NK/05/2019	No	No	BOSULIF	Not applicable		.
		Musculoskeletal and connective tissue disorders	Myalgia	Grade 1	06/05/2019	No	Recovery	NK/04/2021	No	No	BOSULIF	Not applicable		.
		Skin and subcutaneous tissue disorders	Alopecia	Grade 1	03/06/2019	No	Recovery	NK/08/2019	No	No	BOSULIF	Not applicable		.
		Respiratory, thoracic and mediastinal disorders	Dyspnoea exertional	Grade 1	01/07/2019	No	Subject not recovered		No	No	BOSULIF	Not applicable		.
		Vascular disorders	Hypertensive crisis	Grade 1	05/08/2019	No	Recovery	NK/10/2019	No	No	BOSULIF	Not applicable		.
		Endocrine disorders	Hypothyroidism	Grade 2	NK/10/2020	Yes	Subject not recovered		No	No	BOSULIF	Not applicable		.

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		Musculoskeletal and connective tissue disorders	Neck pain	Grade 1	23/09/2020	No	Recovery	NK/12/2020	No	No	BOSULIF	Not applicable		.
		Musculoskeletal and connective tissue disorders	Arthralgia	Grade 1	17/03/2021	No	Subject not recovered		No	No	BOSULIF	Not applicable		.
		Investigations	Blood thyroid stimulating hormone decreased	Grade 1	16/11/2019	No	Recovery	12/12/2020	No	No	BOSULIF	Not applicable		.
		Respiratory, thoracic and mediastinal disorders	Dysphonia	Grade 1	NK/10/2020	No	Recovery	NK/12/2020	No	No	BOSULIF	Not applicable		.
02-01	24/10/2015	Gastrointestinal disorders	Diarrhoea	Grade 1	NK/08/2016	No	Recovery	NK/NK/2018	Yes	No	BOSULIF	No dose modification		.
		Respiratory, thoracic and mediastinal disorders	Dysphonia	Grade 1	NK/NK/2018	No	Recovery	NK/NK/2018	No	No	BOSULIF	No dose modification		.
		Investigations	Weight decreased	Grade 2	NK/02/2018	No	Subject not recovered		Yes	No	BOSULIF	Dose reduction		.
		Gastrointestinal disorders	Nausea	Grade 2	NK/02/2018	No	Recovery	17/12/2018	Yes	No	BOSULIF	Dose reduction		.
02-02	28/10/2015	Infections and infestations	Erysipelas	Grade 2	NK/10/2017	Yes	Recovery	NK/10/2017	No	No	BOSULIF	No dose modification		.
		Gastrointestinal disorders	Tooth disorder	Grade 2	NK/NK/2017	Yes	Recovery	22/06/2017	No	No	BOSULIF	No dose modification		.
		Gastrointestinal disorders	Diarrhoea	Grade 2	NK/NK/2016	No	Recovery	24/05/2016	Yes	No	BOSULIF	No dose modification		.

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02-04	30/10/2015	Gastrointestinal disorders	Nausea	Grade 1	NK/11/2015	No	Recovery	NK/11/2015	Yes	No		No dose modification		.
		Blood and lymphatic system disorders	Iron deficiency anaemia	Grade 2	04/10/2016	No	Recovery	01/03/2017	No	No	BOSULIF	Dose reduction		.
		Gastrointestinal disorders	Diarrhoea	Grade 1	14/12/2016	No	Recovery	16/01/2017	Yes	No	BOSULIF	No dose modification		.
		Gastrointestinal disorders	Diarrhoea	Grade 1	NK/NK/2018	No	Recovery	22/01/2019	Yes	No	BOSULIF	No dose modification		.
		Metabolism and nutrition disorders	Iron deficiency	Grade 1	20/12/2018	No	Subject not recovered		No	No	BOSULIF	No dose modification		.
		Metabolism and nutrition disorders	Hypokalaemia	Grade 4	20/12/2018	No	Recovery	NK/01/2019	No	Yes	BOSULIF	No dose modification	KAYEXALATE	Withdrawal (temporary or permanent, or deferred administration)
02-05	26/07/2016	Gastrointestinal disorders	Diarrhoea	Grade 1	26/07/2016	No	Recovery	NK/08/2016	Yes	No	BOSULIF	No dose modification		.
		Renal and urinary disorders	Renal failure	Grade 3	03/10/2016	Yes	Subject not recovered		No	No	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.
		General disorders and administration site conditions	Oedema	Grade 2	08/06/2017	No	Recovery	20/02/2019	No	Yes	GLIVEC	No dose modification	BOSULIF	Not applicable

Patient No.	Date of initiation of bosutinib treatment	SOC name	PT name	CTCAE grade	Date of occurrence	Is the event serious?	Status	Date of recovery	Is it reasonably possible that the event may be related to the study medication?	Is it reasonably possible that the event may be related to a concomitant drug?	Name of the drug (1)	Action taken (1)	Name of the drug (2)	Action taken (2)
		Metabolism and nutrition disorders	Hyperkalaemia	Grade 2	NK/06/2017	No	Recovery	14/06/2017	No	Yes	GLIVEC	No dose modification	TARKA	Withdrawal (temporary or permanent, or deferred administration)
		Endocrine disorders	Hyperparathyroidism	Grade 2	NK/01/2018	No	Subject not recovered		No	No	BOSULIF	Not applicable	GLIVEC	No dose modification
		Infections and infestations	Localised infection	Grade 1	NK/07/2018	No	Recovery	NK/07/2018	No	No	BOSULIF	Not applicable	GLIVEC	No dose modification
		Musculoskeletal and connective tissue disorders	Muscle spasms	Grade 1	NK/10/2018	No	Recovery	NK/01/2019	No	No	BOSULIF	Not applicable	GLIVEC	No dose modification
02-06	05/07/2017	Metabolism and nutrition disorders	Iron deficiency	Grade 1	06/10/2017	No	Recovery	23/11/2017	No	No	BOSULIF	No dose modification		.
		Hepatobiliary disorders	Cholecystitis acute	Grade 3	27/09/2018	Yes	Recovery	06/11/2018	No	No	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.
		Gastrointestinal disorders	Diarrhoea	Grade 2	04/10/2018	No	Recovery	NK/11/2018	No	Yes	BOSULIF	No dose modification	AUGMENTIN	No dose modification
		Cardiac disorders	Extrasystoles	Grade 2	NK/10/2018	No	Recovery	29/04/2019	No	No	BOSULIFI	No dose modification		.
		Gastrointestinal disorders	Diarrhoea	Grade 1	NK/09/2019	No	Recovery	12/09/2019	Yes	No	BOSULIF	No dose modification		.

Patient No.	Date of initiation of bosutinib treatment	SOC name	PT name	CTCAE grade	Date of occurrence	Is the event serious?	Status	Date of recovery	Is it reasonably possible that the event may be related to the study medication?	Is it reasonably possible that the event may be related to a concomitant drug?	Name of the drug (1)	Action taken (1)	Name of the drug (2)	Action taken (2)
02-07	17/10/2018	Gastrointestinal disorders	Diarrhoea	Grade 1	20/10/2018	No	Recovery	03/05/2019	Yes	No	BOSULIF	No dose modification		.
		Endocrine disorders	Hyperthyroidism	Grade 1	08/07/2019	No	Recovery	14/10/2019	No	No	BOSULIF	No dose modification		.
02-08	26/06/2019	Endocrine disorders	Hyperthyroidism	Grade 1	05/11/2019	No	Recovery	06/02/2020	No	No	BOSUIF	No dose modification		.
		Investigations	Weight increased	Grade 2	22/06/2020	No	Subject not recovered		No	No	BOSULIF	No dose modification		.
		Cardiac disorders	Tachycardia	Grade 1	NK/12/2020	No	Recovery	10/03/2021	No	No	BOSULIF	No dose modification		.
		Endocrine disorders	Hyperparathyroidism secondary	Grade 2	29/03/2021	No	Subject not recovered		No	No	BOSULIF	No dose modification		.
		Renal and urinary disorders	Renal failure	Grade 1	23/06/2021	No	Subject not recovered		Yes	No	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.
		Musculoskeletal and connective tissue disorders	Musculoskeletal pain	Grade 2	NK/06/2021	No	Recovery	NK/07/2021	No	No	BOSULIF	No dose modification		.
02-09	03/10/2019	Gastrointestinal disorders	Aphthous stomatitis	Grade 1	NK/NK/2021	No	Recovery	09/02/2022	No	No	BOSULIF	No dose modification		.

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03-01	19/05/2016	Skin and subcutaneous tissue disorders	Urticaria	Grade 1	17/06/2016	No	Recovery	29/08/2016	Yes	No	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)	BOSULIF	Dose reduction
		Gastrointestinal disorders	Diarrhoea	Grade 1	NK/05/2016	No	Recovery	15/06/2016	Yes	No	BOSULIF	No dose modification		.
		Gastrointestinal disorders	Vomiting	Grade 1	NK/05/2016	No	Recovery	NK/05/2016	Yes	No		No dose modification		.
		Gastrointestinal disorders	Nausea	Grade 1	NK/06/2016	No	Subject not recovered		Yes	No	BOSULIF	No dose modification		.
		Injury, poisoning and procedural complications	Intentional product misuse	.	NK/NK/2018	No	Recovery	01/09/2018	No	No	BOSULIF	Not applicable		.
		Infections and infestations	Bronchitis	Grade 2	NK/10/2018	Yes	Recovery	NK/12/2018	No	No	BOSULIF	No dose modification		.
		Infections and infestations	Tooth infection	Grade 1	NK/03/2019	No	Recovery	NK/04/2019	No	No	BOSULIF	No dose modification		.
03-02	09/12/2019	Gastrointestinal disorders	Diarrhoea	Grade 2	NK/12/2019	No	Recovery	NK/05/2020	Yes	No	BOSUTINIB	Withdrawal (temporary or permanent, or deferred administration)		.

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		Gastrointestinal disorders	Abdominal pain	Grade 2	NK/12/2019	No	Recovery	NK/05/2020	Yes	No	BOSUTINIB	Withdrawal (temporary or permanent, or deferred administration)		.
		Immune system disorders	Hypersensitivity	Grade 2	NK/04/2020	No	Recovery	NK/05/2020	Yes	No	BOSUTINIB	Withdrawal (temporary or permanent, or deferred administration)		.
		Blood and lymphatic system disorders	Iron deficiency anaemia	Grade 1	17/05/2021	No	Recovery	12/12/2022	No	Yes	SPRYCEL	No dose modification		.
04-01	09/11/2016	Gastrointestinal disorders	Diarrhoea	Grade 3	06/12/2017	No	Recovery	10/01/2018	Yes	No	BOSULIF	Dose reduction		.
		Gastrointestinal disorders	Diarrhoea	Grade 1	NK/11/2016	No	Recovery	NK/05/2017	Yes	No	BOSULIF	No dose modification		.
		Gastrointestinal disorders	Nausea	Grade 2	06/11/2017	No	Recovery	10/01/2018	Yes	No	BOSULIF	Dose reduction		.
		Gastrointestinal disorders	Vomiting	Grade 2	06/11/2017	No	Recovery	10/01/2018	Yes	No	BOSULIF	Dose reduction		.
		Gastrointestinal disorders	Diarrhoea	Grade 1	06/11/2017	No	Recovery	10/01/2018	Yes	No	BOSULIF	Dose reduction		.
04-02	16/12/2016	Blood and lymphatic system disorders	Anaemia	Grade 3	10/03/2017	No	Recovery	30/03/2017	Yes	No	BOSULIF	No dose modification		.

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		Blood and lymphatic system disorders	Anaemia	Grade 3	15/05/2017	Yes	Recovery	27/06/2017	Yes	No	TRANSFUSION	No dose modification		.
		Hepatobiliary disorders	Hepatocellular injury	Grade 1	10/03/2017	No	Recovery	16/05/2017	No	Yes	BOSULIF	Dose reduction		.
		Gastrointestinal disorders	Nausea	Grade 1	NK/06/2017	No	Recovery	07/09/2017	Yes	No	BOSULIF	No dose modification		.
		Blood and lymphatic system disorders	Anaemia	Grade 3	21/08/2017	No	Recovery	07/09/2017	No	No	BOSULIF	No dose modification		.
		Metabolism and nutrition disorders	Iron deficiency	Grade 3	NK/03/2017	No	Recovery	28/05/2018	No	No	BOSULIF	No dose modification		.
		Nervous system disorders	Ulnar tunnel syndrome	Grade 3	NK/01/2018	Yes	Recovery	21/06/2018	No	No	BOSULIF	No dose modification		.
		Musculoskeletal and connective tissue disorders	Back pain	Grade 1	NK/NK/2018	No	Subject not recovered		No	No	BOSULIF	No dose modification		.
		Ear and labyrinth disorders	Vertigo	Grade 2	17/10/2018	Yes	Recovery	NK/10/2018	No	No	BOSULIF	No dose modification		.
		Blood and lymphatic system disorders	Anaemia	Grade 3	27/06/2017	No	Recovery	12/07/2017	No	No	BOSULIF	No dose modification		.
		Metabolism and nutrition disorders	Iron deficiency	Grade 2	08/08/2019	No	Subject not recovered		No	No	BOSULIF	No dose modification		.
04-03	22/03/2018	Gastrointestinal disorders	Dysphagia	Grade 1	28/04/2018	Yes	Recovery	29/04/2018	No	Yes	BOSULIF	No dose modification	ALFUZOLINE	No dose modification
		Eye disorders	Blepharitis	Grade 1	01/07/2019	Yes	Recovery	NK/08/2019	No	No	BOSULIF	No dose modification		.

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		Gastrointestinal disorders	Diarrhoea	Grade 1	NK/03/2018	No	Recovery	04/04/2019	Yes	No	BOSULIF	Dose reduction		.
		General disorders and administration site conditions	Treatment noncompliance	Grade 3	NK/NK/2019	No	Recovery	18/04/2021	No	No	BOSULIF	Not applicable		.
		Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Chronic myeloid leukaemia	Grade 3	15/05/2021	Yes	Subject not recovered		No	No	BOSULIF	Dose increase		.
		Injury, poisoning and procedural complications	Accident at work	Grade 2	NK/NK/2021	No	Recovery	NK/NK/2021	No	No	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.
04-04	30/01/2019	Vascular disorders	Hypertension	Grade 2	03/09/2020	No	Recovery in progress		Yes	No	BOSUTINIB	Dose reduction	LOXEN 50 MG LP	.
		Nervous system disorders	Carotid artery stenosis	Grade 3	NK/NK/2019	Yes	Recovery	28/02/2019	No	Yes	BOSULIF	No dose modification	TASIGNA	Not applicable
		Vascular disorders	Peripheral artery stenosis	Grade 3	NK/NK/2019	Yes	Recovery	NK/06/2019	No	Yes	BOSULIF	No dose modification	TASIGNA	Not applicable
		Cardiac disorders	Coronary artery stenosis	Grade 3	29/03/2021	Yes	Recovery	NK/09/2021	No	Yes	BOSULIF	No dose modification	TASIGNA	Not applicable
		Nervous system disorders	Carotid artery stenosis	Grade 3	29/03/2021	Yes	Recovery	NK/09/2021	No	Yes	BOSULIF	No dose modification	TASIGNA	Not applicable
		Metabolism and nutrition disorders	Hypertriglyceridaemia	Grade 1	09/12/2020	No	Recovery	NK/NK/2021	No	Yes	LOXEN	No dose modification	BOSULIF	No dose modification

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04-05	08/07/2019	Cardiac disorders	Coronary artery insufficiency	Grade 3	14/02/2020	Yes	Recovery	15/04/2020	No	No	BOSUTINIB	No dose modification		.
		Renal and urinary disorders	Haematuria	Grade 1	NK/01/2022	No	Recovery	14/02/2022	No	Yes	BRILIQUE	Withdrawal (temporary or permanent, or deferred administration)		.
		Psychiatric disorders	Anxiety	Grade 1	NK/01/2022	No	Recovery	14/02/2022	No	No	BOSULIF	No dose modification		.
		Musculoskeletal and connective tissue disorders	Osteoarthritis	Grade 3	01/09/2021	No	Recovery	NK/09/2021	No	No	BOSULIF	No dose modification		.
04-06	06/09/2019	Congenital, familial and genetic disorders	Gene mutation	Grade 1	30/04/2020	Yes	Recovery	29/06/2021	No	No	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)	PONATINIB	No dose modification
04-07	09/09/2019	Ear and labyrinth disorders	Vertigo	Grade 2	01/04/2021	No	Recovery	08/04/2021	No	No	BOSULIF	No dose modification		.
		Infections and infestations	Corona virus infection	Grade 2	23/12/2021	No	Recovery	27/12/2021	No	No	BOSULIF	No dose modification		.
04-08	19/09/2019	Gastrointestinal disorders	Diarrhoea	Grade 2	26/02/2020	No	Recovery	30/03/2021	Yes	Yes	BOSUTINIB DIMINUTION DOSE A 200 MG	Dose reduction	AUCUNE	Not applicable

Patient No.	Date of initiation of bosutinib treatment	SOC name	PT name	CTCAE grade	Date of occurrence	Is the event serious?	Status	Date of recovery	Is it reasonably possible that the event may be related to the study medication?	Is it reasonably possible that the event may be related to a concomitant drug?	Name of the drug (1)	Action taken (1)	Name of the drug (2)	Action taken (2)
		Infections and infestations	Gastroenteritis	Grade 1	NK/03/2021	No	Recovery	NK/03/2021	No	No	BOSUTINIB	No dose modification		.
		Nervous system disorders	Cervicobrachial syndrome	Grade 3	23/12/2021	Yes	Recovery	30/12/2021	No	No	BOSULIF	Dose reduction		.
		Musculoskeletal and connective tissue disorders	Arthritis	Grade 2	NK/11/2022	No	Subject not recovered		No	No	BOSULIF	No dose modification		.
04-09	10/10/2019	General disorders and administration site conditions	Fatigue	Grade 1	NK/10/2019	No	Recovery	NK/11/2019	Yes	No	BOSUTINIB	No dose modification		.
		Respiratory, thoracic and mediastinal disorders	Dyspnoea	Grade 1	NK/10/2019	No	Recovery	NK/11/2019	Yes	No	BOSUTINIB	No dose modification		.
		Hepatobiliary disorders	Hepatotoxicity	Grade 3	23/01/2021	No	Recovery	26/11/2021	No	Yes	BOSULIF	Not applicable	PONATINIB	No dose modification
		Blood and lymphatic system disorders	Anaemia	Grade 3	30/03/2021	Yes	Recovery	09/06/2021	No	Yes	BOSULIF	Not applicable	PONATINIB	No dose modification
		Blood and lymphatic system disorders	Thrombocytopenia	Grade 3	29/09/2020	No	Recovery	23/11/2021	No	Yes	BOSULIF	Not applicable	PONATINIB	No dose modification
		Injury, poisoning and procedural complications	Hip fracture	.	NK/NK/2021	Yes	Recovery	NK/NK/2021	No	No	BOSULIF	Not applicable	PONATINIB	No dose modification
04-10	20/11/2019	Skin and subcutaneous tissue disorders	Rash pruritic	Grade 2	31/05/2020	No	Subject not recovered		No	No	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.

Patient No.	Date of initiation of bosutinib treatment	SOC name	PT name	CTCAE grade	Date of occurrence	Is the event serious?	Status	Date of recovery	Is it reasonably possible that the event may be related to the study medication?	Is it reasonably possible that the event may be related to a concomitant drug?	Name of the drug (1)	Action taken (1)	Name of the drug (2)	Action taken (2)
		Blood and lymphatic system disorders	Anaemia	Grade 2	23/01/2020	No	Recovery in progress		Yes	Yes	BOSULIF	Dose reduction	INEXIUM	No dose modification
		Gastrointestinal disorders	Abdominal pain upper	Grade 2	NK/12/2019	No	Recovery	24/02/2020	Yes	No	BOSULIF	No dose modification		.
		General disorders and administration site conditions	Chest pain	Grade 3	NK/04/2021	Yes	Recovery	01/06/2021	No	No	BOSULIF	No dose modification		.
		Cardiac disorders	Cardiac failure	Grade 2	NK/06/2021	No	Subject not recovered		No	No	BOSULIF	No dose modification		.
		Nervous system disorders	Tremor	Grade 1	28/09/2021	No	Recovery	03/11/2021	No	No	BOSULIF	No dose modification		.
		General disorders and administration site conditions	Oedema	Grade 3	15/11/2021	Yes	Recovery	14/12/2021	No	No	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.
		Renal and urinary disorders	Acute kidney injury	Grade 3	01/12/2021	Yes	Recovery	14/12/2021	No	No	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.
		General disorders and administration site conditions	Chest pain	Grade 3	01/12/2021	Yes	Recovery	12/01/2022	No	No	BOSULIF	No dose modification		.

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05-01	05/08/2016	Gastrointestinal disorders	Diarrhoea	Grade 3	17/08/2016	No	Recovery	23/08/2016	Yes	No	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		Dose reduction
		Infections and infestations	Bronchitis	Grade 2	16/10/2016	Yes	Recovery	27/10/2016	No	No		No dose modification		.
		Nervous system disorders	Somnolence	Grade 2	16/10/2016	Yes	Recovery	17/10/2016	No	Yes		No dose modification		.
		Renal and urinary disorders	Dysuria	Grade 2	NK/10/2016	Yes	Recovery	14/11/2016	No	Yes		No dose modification		.
		Musculoskeletal and connective tissue disorders	Arthritis	Grade 2	NK/04/2017	No	Recovery	20/07/2017	No	No	BOSULIF	No dose modification		.
		Musculoskeletal and connective tissue disorders	Back disorder	Grade 2	07/09/2017	No	Recovery	19/10/2017	No	No		No dose modification		.
		Nervous system disorders	Trigeminal neuralgia	Grade 2	07/08/2017	Yes	Recovery	08/08/2017	No	No		No dose modification		.
		Gastrointestinal disorders	Diarrhoea	Grade 1	NK/08/2016	No	Recovery	NK/11/2016	Yes	No	BOSULIF	No dose modification		.
		Musculoskeletal and connective tissue disorders	Muscle spasms	Grade 1	UK/11/2018	No	Recovery in progress		Yes	No	BOSULIF	No dose modification		.

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06-01	16/12/2015	Hepatobiliary disorders	Hepatocellular injury	Grade 3	19/01/2016	No	Recovery	23/06/2016	Yes	No	BOSULIF	Dose reduction	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)
		Vascular disorders	Hypertensive crisis	Grade 3	21/11/2017	No	Subject not recovered		Yes	No	BOSULIF	No dose modification		.
		Renal and urinary disorders	Renal failure	Grade 1	NK/01/2018	No	Recovery	08/03/2018	No	Yes	BOSULIF	No dose modification	VALSARTAN	No dose modification
		Renal and urinary disorders	Renal failure	Grade 1	11/04/2019	No	Subject not recovered		No	Yes	EXFORGE	Withdrawal (temporary or permanent, or deferred administration)	BOSULIF	Dose reduction
		Metabolism and nutrition disorders	Hypertriglyceridaemia	Grade 1	03/08/2018	No	Unknown		Yes	No	BOSULIF	No dose modification		.
08-01	24/10/2016	Gastrointestinal disorders	Diarrhoea	Grade 1	NK/04/2017	No	Recovery	09/08/2017	Yes	No	BOSUTINIB	No dose modification		.
		Metabolism and nutrition disorders	Iron deficiency	Grade 2	24/04/2018	No	Recovery	30/11/2018	No	No		No dose modification		.
		Musculoskeletal and connective tissue disorders	Bone pain	Grade 1	13/06/2018	No	Recovery	27/08/2018	No	No		No dose modification		.
		Musculoskeletal and connective tissue disorders	Neck pain	Grade 1	UK/04/2019	No	Recovery	11/12/2019	No	No		No dose modification		.

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08-02	05/07/2017	Hepatobiliary disorders	Hepatocellular injury	Grade 3	13/09/2017	No	Recovery	31/01/2018	Yes	No	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.
		Gastrointestinal disorders	Vomiting	Grade 2	NK/12/2017	No	Recovery	31/01/2018	Yes	No	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.
		Hepatobiliary disorders	Hepatic pain	Grade 2	NK/12/2017	No	Recovery	31/01/2018	Yes	No	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.
		Gastrointestinal disorders	Constipation	Grade 1	NK/10/2017	No	Recovery	23/10/2017	No	No	BOSULIF	No dose modification		.
		Skin and subcutaneous tissue disorders	Rash pruritic	Grade 1	07/02/2018	No	Recovery	12/09/2018	No	Yes		No dose modification		.
		Musculoskeletal and connective tissue disorders	Pain in extremity	Grade 2	13/10/2018	Yes	Recovery	17/10/2018	No	No	AUCUNE	No dose modification		.
		Cardiac disorders	Atrial fibrillation	Grade 2	14/10/2018	Yes	Recovery	17/10/2018	No	No		No dose modification		.

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		Cardiac disorders	Atrial fibrillation	Grade 2	10/10/2019	Yes	Recovery	11/10/2019	No	No		Not applicable		.
		General disorders and administration site conditions	Chills	Grade 1	12/08/2018	No	Recovery	12/08/2018	No	No	BOSULIF	No dose modification		.
		Musculoskeletal and connective tissue disorders	Arthritis	Grade 2	11/02/2018	Yes	Recovery	19/02/2018	No	No	BOSULIF	No dose modification		.
		Respiratory, thoracic and mediastinal disorders	Oropharyngeal pain	Grade 1	NK/02/2018	No	Recovery	NK/02/2018	No	No	BOSULIF	No dose modification		.
		Respiratory, thoracic and mediastinal disorders	Cough	Grade 1	NK/02/2018	No	Recovery	NK/02/2018	No	No	BOSULIF	No dose modification		.
		Cardiac disorders	Atrial fibrillation	Grade 1	NK/04/2018	No	Subject not recovered		No	No	BOSULIF	No dose modification		.
		Musculoskeletal and connective tissue disorders	Chondrocalcinosis	Grade 2	14/10/2018	Yes	Recovery	19/10/2018	No	No	BOSULIF	No dose modification		.
		Gastrointestinal disorders	Nausea	Grade 1	27/10/2018	No	Recovery	09/01/2019	No	Yes	TASIGNA	No dose modification		.
		General disorders and administration site conditions	Asthenia	Grade 1	NK/04/2018	No	Recovery	09/01/2019	No	Yes	TASIGNA	No dose modification		.
		Metabolism and nutrition disorders	Vitamin D deficiency	Grade 2	03/01/2019	No	Recovery	UK/UK/2019	No	No	BOSULIF	No dose modification		.
		Respiratory, thoracic and mediastinal disorders	Dyspnoea exertional	Grade 1	16/04/2019	No	Subject not recovered		No	No	BOSULIF	No dose modification		.
		Gastrointestinal disorders	Dyspepsia	Grade 1	NK/10/2018	No	Recovery	16/04/2019	No	No	BOSULIF	No dose modification		.
		Metabolism and nutrition disorders	Hypertriglyceridaemia	Grade 1	19/04/2019	No	Subject not recovered		No	No	BOSULIF	No dose modification		.

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		Vascular disorders	Hypertension	Grade 2	28/06/2019	No	Subject not recovered		No	No	BOSULIF	No dose modification		.
		Respiratory, thoracic and mediastinal disorders	Orthopnoea	Grade 1	18/07/2019	No	Recovery	NK/07/2019	No	No	BOSULIF	No dose modification		.
		Immune system disorders	Hypersensitivity	Grade 1	23/07/2019	No	Recovery	NK/08/2019	No	Yes	BOSULIF	No dose modification	COVERAM, ATORVASTATINE ET FLEICAINE	Withdrawal (temporary or permanent, or deferred administration)
		Respiratory, thoracic and mediastinal disorders	Cough	Grade 1	NK/07/2019	No	Recovery	31/07/2019	No	No	BOSULIF	No dose modification		.
		General disorders and administration site conditions	Chest pain	Grade 2	03/12/2019	Yes	Recovery	03/12/2019	No	No	BOSULIF	No dose modification		.
		Renal and urinary disorders	Oliguria	Grade 1	NK/11/2019	No	Recovery	NK/12/2019	No	No	BOSULIF	No dose modification		.
		Gastrointestinal disorders	Nausea	Grade 1	14/02/2018	No	Recovery	14/02/2018	No	Yes	BOSULIF	No dose modification	ACTISKENAN	Withdrawal (temporary or permanent, or deferred administration)

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		Gastrointestinal disorders	Vomiting	Grade 1	14/02/2018	No	Recovery	14/02/2018	No	Yes	BOSULIF	No dose modification	ACTISKENAN	Withdrawal (temporary or permanent, or deferred administration)
		Vascular disorders	Phlebitis	Grade 1	15/02/2018	No	Recovery	15/02/2018	No	No	BOSULIF	No dose modification		.
		Gastrointestinal disorders	Functional gastrointestinal disorder	Grade 1	01/07/2020	No	Subject not recovered		No	No	BOSULIF	Not applicable		.
		Gastrointestinal disorders	Constipation	Grade 1	09/02/2018	No	Recovery	NK/02/2018	No	No	BOSULIF	Not applicable		.
		Respiratory, thoracic and mediastinal disorders	Asthma	Grade 1	NK/07/2019	No	Subject not recovered		No	No	BOSULIF	Not applicable		.
08-03	23/08/2017	Gastrointestinal disorders	Diarrhoea	Grade 1	NK/08/2017	No	Recovery	06/02/2019	Yes	No	BOSULIF	No dose modification		.
		Skin and subcutaneous tissue disorders	Actinic keratosis	Grade 2	22/11/2017	No	Recovery	28/02/2018	No	No	BOSUTINIB	No dose modification		.
		Gastrointestinal disorders	Nausea	Grade 1	NK/NK/2019	No	Recovery	20/11/2019	Yes	No		No dose modification		.
		Skin and subcutaneous tissue disorders	Eczema	Grade 2	07/06/2018	No	Recovery	NK/06/2018	No	No		No dose modification		.

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08-04	13/10/2018	Hepatobiliary disorders	Hepatocellular injury	Grade 4	08/12/2018	Yes	Recovery	04/02/2019	Yes	No	BOSUTINIB	Withdrawal (temporary or permanent, or deferred administration)		.
		Gastrointestinal disorders	Gastrointestinal disorder	Grade 2	NK/10/2018	No	Recovery	02/01/2019	Yes	No	BOSUTINIB	No dose modification		.
		Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Uterine leiomyoma	Grade 1	31/12/2018	Yes	Recovery	30/10/2019	No	No	BOSUTINIB	No dose modification		.
		Nervous system disorders	Dizziness	Grade 2	NK/NK/2019	No	Recovery	08/04/2019	No	No		No dose modification		.
		General disorders and administration site conditions	Asthenia	Grade 2	NK/NK/2019	No	Recovery	08/04/2019	Yes	No		No dose modification		.
		Gastrointestinal disorders	Abdominal pain upper	Grade 1	10/12/2018	No	Recovery	NK/12/2018	Yes	No	BOSULIF	Not applicable		.
		Vascular disorders	Pallor	Grade 1	05/03/2019	No	Recovery	08/04/2019	No	No	BOSULIF	Not applicable		.
09-01	04/05/2016	Gastrointestinal disorders	Abdominal distension	Grade 1	04/05/2016	No	Recovery	09/08/2016	Yes	No	BOSULIF	Dose reduction		.
		Musculoskeletal and connective tissue disorders	Rotator cuff syndrome	Grade 2	NK/05/2017	No	Recovery	01/06/2017	No	No	BOSULIF	No dose modification		.
		Musculoskeletal and connective tissue disorders	Intervertebral disc protrusion	Grade 2	NK/05/2018	No	Subject not recovered		No	No	BOSULIF	No dose modification		.

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		Vascular disorders	Pallor	Grade 1	04/05/2016	No	Recovery	09/08/2016	Yes	No	BOSULIF	Dose reduction		.
09-02	08/09/2016	Nervous system disorders	Headache	Grade 3	08/09/2016	No	Recovery	09/09/2016	Yes	No	BOSULIF	No dose modification		.
		Gastrointestinal disorders	Diarrhoea	Grade 1	09/09/2016	No	Recovery	13/03/2017	Yes	No	BOSULIF	No dose modification		.
		Skin and subcutaneous tissue disorders	Stasis dermatitis	Grade 1	12/12/2016	No	Recovery	13/03/2017	No	No	BOSULIF	No dose modification		.
		Hepatobiliary disorders	Cholecystitis chronic	Grade 3	31/01/2017	Yes	Recovery	24/03/2017	No	No	BOSULIF	No dose modification		.
		Skin and subcutaneous tissue disorders	Eczema	Grade 2	13/03/2017	No	Recovery	25/01/2018	No	Yes	BOSULIF	No dose modification	NICORANDIL	Withdrawal (temporary or permanent, or deferred administration)
		Respiratory, thoracic and mediastinal disorders	Pleurisy	Grade 3	24/06/2017	Yes	Recovery	26/09/2017	No	No	BOSUTINIB	No dose modification		.
		General disorders and administration site conditions	Chest pain	Grade 1	NK/01/2017	No	Recovery	NK/01/2017	No	No	BOSULIF	No dose modification		.
		Investigations	Troponin increased	Grade 1	24/01/2017	No	Recovery	NK/NK/2017	Yes	No	BOSULIF	No dose modification		.
		Psychiatric disorders	Libido decreased	Grade 2	NK/01/2017	No	Recovery	19/03/2018	Yes	No	BOSULIF	No dose modification		.

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		General disorders and administration site conditions	Oedema peripheral	Grade 1	19/06/2017	No	Recovery	04/09/2017	Yes	No	BOSULIF	No dose modification		.
		Gastrointestinal disorders	Gastritis	Grade 2	NK/09/2017	No	Recovery	12/12/2017	No	No	BOSULIF	No dose modification		.
		Hepatobiliary disorders	Cholelithiasis	Grade 2	26/09/2017	No	Recovery	NK/10/2017	No	No	BOSULIF	No dose modification		.
		Gastrointestinal disorders	Constipation	Grade 2	NK/09/2017	No	Recovery	NK/11/2017	No	No	BOSULIF	No dose modification		.
		Infections and infestations	Pneumonia	Grade 2	13/09/2017	No	Recovery	20/10/2017	No	No	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.
		Nervous system disorders	Carpal tunnel syndrome	Grade 3	NK/NK/2018	No	Recovery	24/09/2018	No	No	BOSULIF	No dose modification		.
		Gastrointestinal disorders	Diarrhoea	Grade 1	20/03/2018	No	Recovery	24/09/2018	Yes	No	BOSULIF	No dose modification		.
		Cardiac disorders	Arrhythmia	Grade 1	19/03/2018	No	Recovery	19/04/2019	No	No	BOSULIF	No dose modification		.
		Respiratory, thoracic and mediastinal disorders	Pleural effusion	Grade 1	11/04/2018	No	Recovery	24/03/2019	Yes	No	BOSULIF	No dose modification		.
		Respiratory, thoracic and mediastinal disorders	Pleural effusion	Grade 2	25/03/2019	Yes	Recovery	26/09/2019	Yes	No	BOSULIF	No dose modification		.

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		Cardiac disorders	Cardiac failure	Grade 1	05/03/2019	No	Recovery	04/07/2019	No	No	BOSULF	No dose modification		.
		Skin and subcutaneous tissue disorders	Prurigo	Grade 2	ND/03/2019	No	Recovery	23/09/2019	No	No	BOSULIF	No dose modification		.
		Musculoskeletal and connective tissue disorders	Neck pain	Grade 3	09/09/2016	No	Recovery	09/09/2016	Yes	No	BOSULIF	No dose modification		.
		Musculoskeletal and connective tissue disorders	Musculoskeletal pain	Grade 3	08/09/2016	No	Recovery	09/09/2016	Yes	No	BOSULIF	No dose modification		.
		Skin and subcutaneous tissue disorders	Eczema	Grade 2	24/07/2017	No	Recovery	25/01/2018	No	No	BOSULIF	No dose modification		.
		Gastrointestinal disorders	Cheilitis	Grade 1	ND/04/2017	No	Recovery	27/04/2017	No	No	BOSULIF	No dose modification		.
		Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Leiomyoma	Grade 2	16/11/2017	No	Recovery	16/11/2017	No	No	BOSULIF	No dose modification		.
		Nervous system disorders	Nerve compression	Grade 3	NK/02/2018	No	Recovery	09/02/2018	No	No	BOSULIF	No dose modification		.
		Nervous system disorders	Nervous system disorder	Grade 1	08/10/2018	No	Recovery	25/03/2019	No	No	BOSULIF	No dose modification		.
		Musculoskeletal and connective tissue disorders	Musculoskeletal pain	Grade 2	11/07/2019	No	Recovery in progress		No	No	BOSULIF	No dose modification		.
		Injury, poisoning and procedural complications	Tooth fracture	Grade 1	NK/09/2019	No	Recovery	NK/09/2019	No	No	BOSULIF	Not applicable		.
		Nervous system disorders	Paraesthesia	Grade 1	NK/09/2019	No	Recovery in progress		No	No	BOSULIF	Not applicable		.

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		Skin and subcutaneous tissue disorders	Eczema	Grade 1	24/09/2018	No	Recovery	17/12/2018	No	No	BOSULIF	No dose modification		.
		Skin and subcutaneous tissue disorders	Dry skin	Grade 1	24/06/2019	No	Recovery in progress		No	No	BOSULIF	No dose modification		.
09-03	17/10/2016	Gastrointestinal disorders	Haemorrhoidal haemorrhage	Grade 1	18/10/2016	No	Recovery	16/01/2017	No	No		No dose modification		.
		Respiratory, thoracic and mediastinal disorders	Productive cough	Grade 2	NK/05/2017	No	Recovery	26/02/2018	No	No	BOSULIF	No dose modification		.
		Skin and subcutaneous tissue disorders	Rash	Grade 1	NK/10/2017	No	Recovery	27/05/2019	No	No	BOSULIF	No dose modification		.
		Musculoskeletal and connective tissue disorders	Joint effusion	Grade 2	NK/10/2017	No	Recovery	NK/10/2017	No	No	BOSULIF	No dose modification		.
		Psychiatric disorders	Insomnia	Grade 3	23/10/2017	No	Recovery	27/02/2018	No	No	BOSULIF	No dose modification		.
		General disorders and administration site conditions	Oedema peripheral	Grade 1	16/01/2017	No	Recovery	29/10/2018	No	No	BOSULIF	No dose modification		.
		Investigations	Blood creatinine increased	Grade 2	23/04/2018	No	Recovery	25/06/2018	No	No	BOSULIF	No dose modification		.
		Musculoskeletal and connective tissue disorders	Arthralgia	Grade 1	NK/01/2018	No	Recovery	27/05/2019	No	No	BOSULIF	No dose modification		.
		Injury, poisoning and procedural complications	Fall	Grade 2	NK/07/2018	No	Recovery	NK/07/2018	No	No	BOSUKIF	No dose modification		.
		Infections and infestations	Anal abscess	Grade 1	NK/02/2019	No	Recovery	06/05/2019	No	No	BOSULIF	No dose modification		.

Patient No.	Date of initiation of bosutinib treatment	SOC name	PT name	CTCAE grade	Date of occurrence	Is the event serious?	Status	Date of recovery	Is it reasonably possible that the event may be related to the study medication?	Is it reasonably possible that the event may be related to a concomitant drug?	Name of the drug (1)	Action taken (1)	Name of the drug (2)	Action taken (2)
09-04	10/10/2016	Skin and subcutaneous tissue disorders	Rash maculo-papular	Grade 2	15/01/2017	No	Recovery	26/01/2017	Yes	Yes	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)	VALSARTAN	No dose modification
		Hepatobiliary disorders	Hepatocellular injury	Grade 2	15/01/2017	No	Recovery	10/03/2017	Yes	Yes	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)	VALSARTAN	No dose modification
		Vascular disorders	Hypertension	Grade 2	22/11/2016	No	Recovery	NK/NK/2017	Yes	No	BOSULIF	No dose modification		.
		Nervous system disorders	Headache	Grade 2	15/01/2017	No	Recovery	26/01/2017	Yes	No	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.
		Musculoskeletal and connective tissue disorders	Arthralgia	Grade 1	NK/06/2017	No	Recovery in progress		No	Yes	BOSULIF	Not applicable	SPRYCEL	No dose modification
		Musculoskeletal and connective tissue disorders	Myalgia	Grade 2	NK/06/2017	No	Recovery in progress		No	Yes	BOSULIF	Not applicable	SPRYCEL	No dose modification
		Endocrine disorders	Haemorrhagic thyroid cyst	Grade 1	NK/07/2018	No	Recovery	NK/08/2018	No	No	BOSULIF	Not applicable		.

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		Musculoskeletal and connective tissue disorders	Pain in extremity	Grade 1	NK/06/2019	No	Recovery in progress		No	No	BOSULIF	Not applicable		.
		General disorders and administration site conditions	Fatigue	Grade 1	NK/11/2018	No	Recovery	11/06/2019	No	No	SPRYCELL	No dose modification	BOSULIF	Not applicable
		Psychiatric disorders	Insomnia	Grade 1	NK/NK/2019	No	Subject not recovered		No	No	SPRYCELL	No dose modification		.
		Investigations	Blood pressure decreased	Grade 1	27/08/2019	No	Subject not recovered		No	Yes	NISIS	No dose modification		.
09-05	01/01/2017	Infections and infestations	Upper respiratory tract infection	Grade 2	15/01/2017	No	Recovery	NK/01/2017	No	No	BOSULIF	No dose modification		.
		General disorders and administration site conditions	Malaise	Grade 2	15/03/2017	No	Recovery	15/03/2017	No	No	BOSULIF	No dose modification		.
		General disorders and administration site conditions	Ill-defined disorder	Grade 1	26/04/2017	No	Subject not recovered		No	No	BOSULIF	Dose reduction		.
		General disorders and administration site conditions	Malaise	Grade 2	03/05/2017	No	Recovery	04/05/2017	No	No	BOSULIF	No dose modification		.
		Skin and subcutaneous tissue disorders	Ecchymosis	Grade 1	26/02/2018	No	Recovery	29/04/2019	No	No	BOSULIF	No dose modification		.
		Injury, poisoning and procedural complications	Fall	Grade 3	13/03/2018	Yes	Recovery	25/11/2019	No	No	BOSULIF	No dose modification		.
		Reproductive system and breast disorders	Ovarian cyst	Grade 1	22/01/2018	No	Subject not recovered		No	No	BOSULIF	No dose modification		.
		Investigations	Blood parathyroid hormone increased	Grade 1	NK/NK/2018	No	Recovery	NK/NK/2018	No	No	BOSULIF	No dose modification		.

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		Gastrointestinal disorders	Rectal haemorrhage	Grade 1	22/03/2017	No	Recovery	22/03/2017	No	No	BOSULIF	No dose modification		.
		Gastrointestinal disorders	Nausea	Grade 1	18/01/2017	No	Recovery	18/01/2017	No	Yes	BOSULIF	No dose modification	CLAMOXYL	Withdrawal (temporary or permanent, or deferred administration)
		Gastrointestinal disorders	Vomiting	Grade 1	18/01/2017	No	Recovery	18/01/2017	No	Yes	BOSULIF	No dose modification	CLAMOXYL	Withdrawal (temporary or permanent, or deferred administration)
		Gastrointestinal disorders	Diarrhoea	Grade 2	17/01/2017	No	Recovery	18/01/2018	No	Yes	CLAMOXYL	Withdrawal (temporary or permanent, or deferred administration)	BOSULIF	No dose modification
		Gastrointestinal disorders	Oral lichen planus	Grade 1	NK/09/2018	No	Recovery	NK/02/2019	No	No	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.

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		Infections and infestations	Urinary tract infection	Grade 2	24/12/2018	No	Recovery	03/01/2019	No	No	BOSULIF	No dose modification		.
		Vascular disorders	Hypertension	Grade 2	21/01/2019	No	Recovery	13/09/2019	No	No	BOSULIF	No dose modification		.
		Investigations	Cardiac murmur	Grade 1	21/01/2019	No	Recovery	13/09/2019	No	No	BOSULIF	No dose modification		.
		Injury, poisoning and procedural complications	Animal bite	Grade 3	19/09/2019	No	Recovery	25/09/2019	No	No	BOSULIF	No dose modification		.
		Infections and infestations	Oral fungal infection	Grade 2	NK/02/2019	No	Recovery	NK/02/2019	No	No	BOSULIF	No dose modification		.
		Injury, poisoning and procedural complications	Spinal compression fracture	Grade 1	13/03/2018	No	Subject not recovered		No	No	BOSULIF	No dose modification		.
		Metabolism and nutrition disorders	Decreased appetite	Grade 1	26/04/2017	No	Recovery	13/12/2019	Yes	No	BOSULIF	No dose modification		.
		Infections and infestations	Vulvovaginal mycotic infection	Grade 1	NK/09/2018	No	Recovery	29/11/2018	No	No	BOSULIF	No dose modification		.
		Gastrointestinal disorders	Glossodynia	Grade 2	NK/04/2019	No	Subject not recovered		No	No	BOSULIF	No dose modification		.
09-06	06/01/2017	Gastrointestinal disorders	Constipation	Grade 1	21/06/2017	No	Recovery	25/09/2017	Yes	No	BOSULIF	No dose modification		.
		Gastrointestinal disorders	Constipation	Grade 1	NK/01/2017	No	Recovery	NK/01/2017	Yes	No	BOSULIF	No dose modification		.
		Gastrointestinal disorders	Abdominal pain	Grade 1	NK/04/2017	No	Recovery	09/01/2018	Yes	No	BOSULIF	No dose modification		.

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		Infections and infestations	Influenza	Grade 2	14/01/2019	No	Recovery	21/01/2019	No	No	BOSULIF	No dose modification		.
		Reproductive system and breast disorders	Erectile dysfunction	Grade 1	NK/NK/2019	No	Subject not recovered		No	No	BOSULIF	No dose modification		.
		Gastrointestinal disorders	Nausea	Grade 1	NK/05/2019	No	Recovery	27/01/2020	No	No	BOSULIF	No dose modification		.
		Gastrointestinal disorders	Abdominal pain	Grade 1	NK/12/2019	No	Recovery	NK/12/2019	No	No	BOSULIF	No dose modification		.
		Surgical and medical procedures	Vasectomy	Grade 2	07/02/2017	No	Recovery	NK/02/2017	No	No	BOSULIF	No dose modification		.
09-07	26/01/2017	Investigations	Transaminases increased	Grade 3	29/05/2017	No	Recovery	29/06/2017	Yes	Yes	BOSUTINIB	Dose reduction	PARACETAMOL	No dose modification
		General disorders and administration site conditions	Chills	Grade 1	09/02/2017	No	Recovery	09/02/2017	Yes	No	BOSULIF	No dose modification		.
		Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Melanocytic naevus	Grade 1	09/05/2018	No	Recovery	25/01/2019	No	No	BOSULIF	No dose modification		.
		Respiratory, thoracic and mediastinal disorders	Rhinorrhoea	Grade 1	22/11/2018	No	Recovery	14/02/2019	No	No	BOSULIF	No dose modification		.
		Skin and subcutaneous tissue disorders	Actinic keratosis	Grade 2	21/APR/17	No	Recovery	25/01/2019	No	No	BOSULIF	No dose modification		.
		Musculoskeletal and connective tissue disorders	Muscle spasms	Grade 2	NK/05/2017	No	Recovery	01/06/2017	No	No	BOSULIF	No dose modification		.
		General disorders and administration site conditions	Pyrexia	Grade 1	NK/03/2019	No	Recovery	NK/03/2019	No	No	BOSULIF	No dose modification		.

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		Gastrointestinal disorders	Diarrhoea	Grade 1	NK/09/2019	No	Recovery	14/05/2020	Yes	No	BOSULIF	No dose modification		.
		Gastrointestinal disorders	Abdominal pain upper	Grade 1	NK/09/2019	No	Recovery	14/05/2020	Yes	No	BOSULIF	No dose modification		.
		Nervous system disorders	Headache	Grade 2	NK/NK/2020	No	Subject not recovered		No	No	BOSULIF	No dose modification		.
09-08	15/03/2017	Gastrointestinal disorders	Diarrhoea	Grade 1	29/03/2017	No	Recovery	NK/04/2017	Yes	No	BOSULIF	Dose reduction		.
		Respiratory, thoracic and mediastinal disorders	Rales	Grade 1	08/11/2018	No	Recovery	20/07/2020	No	No	BOSULIF	No dose modification		.
		General disorders and administration site conditions	Oedema peripheral	Grade 1	08/11/2018	No	Recovery	20/07/2020	No	No	BOSULIF	No dose modification		.
		Gastrointestinal disorders	Dyspepsia	Grade 2	NK/11/2019	No	Recovery	20/07/2020	No	No	BOSULIF	No dose modification		.
09-09	16/05/2017	Investigations	Transaminases increased	Grade 1	28/08/2017	No	Recovery	09/10/2017	No	No	BOSULIF	No dose modification		.
		Infections and infestations	Tooth abscess	Grade 3	14/09/2017	Yes	Recovery	16/01/2018	No	No	BOSULIF	No dose modification		.
		Infections and infestations	Influenza	Grade 2	NK/12/2017	No	Recovery	16/01/2018	No	No	BOSULIF	No dose modification		.
		Gastrointestinal disorders	Diarrhoea	Grade 1	NK/09/2017	No	Recovery	09/10/2017	No	Yes	BOSULIF	No dose modification	AUGMENTIN	No dose modification
		Investigations	Breath sounds abnormal	Grade 1	16/01/2018	No	Subject not recovered		No	No	BOSULIF	No dose modification		.

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		Psychiatric disorders	Depression	Grade 1	NK/04/2018	No	Recovery in progress		No	No	BOSULIF	No dose modification		.
09-10	21/09/2017	Gastrointestinal disorders	Diarrhoea	Grade 2	20/10/2017	No	Recovery	08/02/2018	Yes	No	BOSULIF	Dose reduction		.
		Gastrointestinal disorders	Nausea	Grade 2	05/12/2017	No	Recovery	30/04/2018	Yes	No	BOSULIF	Dose reduction		.
		Skin and subcutaneous tissue disorders	Dermatitis bullous	Grade 1	27/10/2017	No	Recovery with sequellae	22/12/2017	No	No	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.
		Vascular disorders	Haemorrhage	Grade 4	03/05/2018	Yes	Recovery	05/05/2018	No	No	BOSULIF	No dose modification		.
		General disorders and administration site conditions	General physical health deterioration	Grade 2	07/06/2018	No	Subject not recovered		No	No	BOSULIF	Not applicable		.
		Infections and infestations	Bronchitis	Grade 1	19/05/2018	No	Recovery	30/06/2018	No	No	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.

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		Gastrointestinal disorders	Vomiting	Grade 2	04/06/2018	No	Recovery	05/06/2018	Yes	No	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.
		General disorders and administration site conditions	Therapeutic response decreased	Grade 2	03/04/2018	No	Subject not recovered		No	No	BOSULIF	Dose increase		.
		Gastrointestinal disorders	Diarrhoea	Grade 1	09/02/2018	No	Recovery	10/08/2018	Yes	Yes	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)	LEVOFLOXACINE	No dose modification
		Skin and subcutaneous tissue disorders	Acne	Grade 1	21/12/2017	No	Recovery	NK/04/2018	No	No	BOSULIF	No dose modification		.
		Injury, poisoning and procedural complications	Arteriovenous fistula occlusion	Grade 3	15/02/2018	No	Recovery	28/02/2018	No	No	BOSULIF	No dose modification		.
		Injury, poisoning and procedural complications	Thermal burn	Grade 1	25/03/2018	No	Recovery	NK/NK/2018	No	No	BOSULIF	No dose modification		.
		General disorders and administration site conditions	General physical health deterioration	Grade 5	01/02/2018	Yes	Subject not recovered		No	No	BOSULIF	No dose modification		.
		General disorders and administration site conditions	Malaise	Grade 3	07/02/2019	Yes	Recovery	07/02/2019	No	No	BOSULIF	Not applicable		.

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		Gastrointestinal disorders	Constipation	Grade 2	NK/07/2018	No	Recovery	10/08/2018	No	No	BOSULIF	Not applicable		.
		Psychiatric disorders	Depression	Grade 2	NK/08/2018	No	Subject not recovered		No	No	BOSULIF	Not applicable		.
		Injury, poisoning and procedural complications	Wound	Grade 2	30/10/2018	No	Subject not recovered		No	No	BOSULIF	Not applicable		.
		Metabolism and nutrition disorders	Malnutrition	Grade 4	22/09/2017	Yes	Subject not recovered		Yes	No	BOSULIF	No dose modification		.
		Infections and infestations	Staphylococcal infection	Grade 3	05/02/2019	Yes	Subject not recovered		No	No	BOSULIF	Not applicable		.
		Metabolism and nutrition disorders	Malnutrition	Grade 2	26/02/2019	No	Recovery	01/03/2019	No	No	BOSULIF	Not applicable		.
		Infections and infestations	Oral fungal infection	Grade 2	NK/02/2019	No	Unknown		No	No	BOSULIF	Not applicable		.
		Blood and lymphatic system disorders	Pancytopenia	Grade 4	21/02/2019	Yes	Subject not recovered		No	Yes	BOSULIF	Not applicable	HYDREA	Dose reduction
		General disorders and administration site conditions	Malaise	Grade 4	26/02/2019	Yes	Subject not recovered		No	No	BOSULIF	Not applicable		.
		Skin and subcutaneous tissue disorders	Dermatitis bullous	Grade 2	01/02/2018	No	Recovery	NK/NK/2018	No	No	BOSULIF	No dose modification		.
		Metabolism and nutrition disorders	Folate deficiency	Grade 3	15/02/2019	Yes	Recovery in progress		No	No	BOSULIF	Not applicable		.
		Blood and lymphatic system disorders	Anaemia	Grade 2	03/05/2018	No	Recovery	NK/NK/2018	No	No	BOSULIF	Not applicable		.
09-11	04/09/2018	Investigations	Pulse absent	Grade 1	25/02/2019	No	Subject not recovered		No	No	BOSULIF	No dose modification		.

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		Eye disorders	Cataract	Grade 2	NK/NK/2019	No	Recovery	NK/03/2019	No	No	BOSULIF	No dose modification		.
		Gastrointestinal disorders	Abdominal pain upper	Grade 2	21/06/2021	No	Recovery	14/10/2021	Yes	Yes	BOSULIF	Dose reduction	FLUVASTATIN E	No dose modification
		Gastrointestinal disorders	Diarrhoea	Grade 1	21/06/2021	No	Recovery in progress		Yes	No	BOSULIF	No dose modification		.
09-12	25/09/2018	Respiratory, thoracic and mediastinal disorders	Cough	Grade 2	NK/11/2018	No	Subject not recovered		Yes	No	BOSULIF	No dose modification		.
		Gastrointestinal disorders	Nausea	Grade 2	NK/09/2018	No	Recovery	NK/06/2019	Yes	No	BOSULIF	No dose modification		.
		Investigations	Weight decreased	Grade 1	NK/09/2018	No	Subject not recovered		Yes	No	BOSULIF	No dose modification		.
		Gastrointestinal disorders	Abdominal pain upper	Grade 2	NK/09/2018	No	Subject not recovered		Yes	No	BOSULIF	No dose modification		.
		Nervous system disorders	Memory impairment	Grade 1	NK/12/2018	No	Recovery	24/06/2019	No	No	BOSULIF	No dose modification		.
		Musculoskeletal and connective tissue disorders	Arthritis	Grade 1	NK/12/2018	No	Subject not recovered		No	No	BOSULIF	No dose modification		.
		Gastrointestinal disorders	Intestinal obstruction	Grade 2	NK/NK/2019	No	Recovery	05/11/2019	No	No	BOSEVAL	No dose modification		.
		Infections and infestations	Conjunctivitis	Grade 1	NK/NK/2019	No	Recovery	NK/NK/2020	No	No	BOSEVAL	No dose modification		.
		General disorders and administration site conditions	Asthenia	Grade 2	05/11/2019	No	Subject not recovered		Yes	No	BOSULIF	No dose modification		.

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		Gastrointestinal disorders	Aphthous stomatitis	Grade 1	07/04/2020	No	Subject not recovered		No	No	BOSULIF	No dose modification		.
		Infections and infestations	Rhinitis	Grade 2	NK/NK/2020	No	Recovery	08/12/2020	No	No	BOSULIF	No dose modification		.
		Infections and infestations	Gingivitis	Grade 1	NK/NK/2020	No	Recovery	08/12/2020	No	Yes	SPIRAMYCINE METRONIDAZOLE	Withdrawal (temporary or permanent, or deferred administration)		.
		Nervous system disorders	Dizziness	Grade 1	18/12/2018	No	Subject not recovered		No	No	BOSULIF	No dose modification		.
		Gastrointestinal disorders	Diarrhoea	Grade 2	NK/12/2020	No	Recovery	12/10/2021	Yes	No	BOSULIF	Dose reduction		.
		Gastrointestinal disorders	Abdominal pain	Grade 2	NK/12/2020	No	Recovery	12/10/2021	Yes	No	BOSULIF	Dose reduction		.
		Vascular disorders	Hot flush	Grade 1	NK/03/2021	No	Subject not recovered		No	No	BOSULIF	No dose modification		.
		Gastrointestinal disorders	Rectal haemorrhage	Grade 1	NK/07/2021	No	Recovery	NK/07/2021	No	No	BOSULIF	No dose modification		.
		Gastrointestinal disorders	Abdominal pain lower	Grade 1	NK/03/2021	No	Subject not recovered		No	No	BOSULIF	No dose modification		.
		Metabolism and nutrition disorders	Decreased appetite	Grade 1	NK/03/2021	No	Subject not recovered		No	No	BOSULIF	No dose modification		.

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09-14	12/11/2018	Gastrointestinal disorders	Diarrhoea	Grade 1	NK/11/2018	No	Recovery	03/03/2020	Yes	No	BOSULIF	No dose modification		.
		Infections and infestations	Gastroenteritis	Grade 2	22/01/2019	No	Recovery	24/01/2019	No	No	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.
		Infections and infestations	Rhinitis	Grade 2	NK/08/2019	No	Recovery	02/09/2019	No	No	BOSULIF	No dose modification		.
		General disorders and administration site conditions	Fatigue	Grade 1	25/11/2019	No	Recovery	02/03/2020	No	No	BOSULIF	No dose modification		.
		Musculoskeletal and connective tissue disorders	Pain in extremity	Grade 1	NK/09/2020	No	Recovery	NK/NK/2020	No	No	SPRYCEL	No dose modification		.
		Hepatobiliary disorders	Hepatic steatosis	Grade 1	30/01/2020	No	Subject not recovered		No	No	BOSULIF	No dose modification		.
		Metabolism and nutrition disorders	Hypertriglyceridaemia	Grade 1	14/04/2020	No	Recovery	17/10/2020	No	No	BOSULIF	Not applicable	DASATINIB	No dose modification
		Hepatobiliary disorders	Hepatocellular injury	Grade 2	02/03/2020	No	Recovery	08/06/2020	No	Yes	BOSULIF	Not applicable	DASATINIB	No dose modification
		Social circumstances	Miscarriage of partner	.	UK/08/2020	Yes	Recovery	UK/08/2020	No	No	BOSULIF	Not applicable	DASATINIB	No dose modification
		Social circumstances	Pregnancy of partner	.	UK/09/2020	Yes	Recovery	UK/06/2021	No	No	BOSULIF	Not applicable	DASATINIB	No dose modification

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		Hepatobiliary disorders	Hepatocellular injury	Grade 2	30/09/2021	No	Subject not recovered		No	Yes	BOSULIF	Not applicable	DASATINIB	No dose modification
		General disorders and administration site conditions	Ill-defined disorder	.	14/09/2020	No	Subject not recovered		No	Yes	BOSULIF	Not applicable	DASATINIB	No dose modification
09-15	04/02/2019	Gastrointestinal disorders	Diarrhoea	Grade 1	NK/02/2019	No	Recovery	18/11/2019	Yes	No	BOSULIF	No dose modification		.
		Infections and infestations	Cystitis	Grade 2	01/05/2019	No	Recovery	06/06/2019	No	No	BOSULIF	No dose modification		.
		Gastrointestinal disorders	Abdominal pain	Grade 3	29/06/2019	Yes	Recovery	04/07/2019	Yes	No	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.
		General disorders and administration site conditions	Asthenia	Grade 1	05/06/2019	No	Recovery	15/06/2019	Yes	No	BOSULIF	No dose modification		.
		Musculoskeletal and connective tissue disorders	Joint ankylosis	Grade 1	NK/07/2019	No	Recovery	25/11/2019	No	No	BOSULIF	No dose modification		.
		General disorders and administration site conditions	Chest pain	Grade 2	NK/12/2019	No	Recovery	09/03/2020	No	No	BOSULIF	No dose modification		.
		Reproductive system and breast disorders	Vulvovaginal burning sensation	Grade 2	NK/02/2020	No	Recovery	09/03/2020	No	No	BOSULIF	No dose modification		.
		Gastrointestinal disorders	Abdominal pain upper	Grade 1	NK/02/2020	No	Recovery	NK/02/2020	No	Yes	METRONIDAZOLE	No dose modification	BOSULIF	No dose modification

Patient No.	Date of initiation of bosutinib treatment	SOC name	PT name	CTCAE grade	Date of occurrence	Is the event serious?	Status	Date of recovery	Is it reasonably possible that the event may be related to the study medication?	Is it reasonably possible that the event may be related to a concomitant drug?	Name of the drug (1)	Action taken (1)	Name of the drug (2)	Action taken (2)
		Gastrointestinal disorders	Gastrointestinal disorder	Grade 1	10/02/2020	No	Recovery	17/02/2020	No	Yes	TARDYFERON	Withdrawal (temporary or permanent, or deferred administration)	BOSULIF	No dose modification
		Gastrointestinal disorders	Eosinophilic colitis	Grade 2	27/08/2020	No	Recovery	NK/NK/2021	Yes	No	BOSULIF	No dose modification		.
		Nervous system disorders	Presyncope	Grade 1	03/07/2019	No	Recovery	03/07/2019	No	Yes	BOSULIF	No dose modification	ACUPAN	No dose modification
		Gastrointestinal disorders	Diarrhoea	Grade 2	13/03/2020	No	Subject not recovered		Yes	No	BOSULIF	Dose reduction		.
		Cardiac disorders	Palpitations	Grade 1	13/03/2020	No	Recovery	18/05/2020	Yes	No	BOSULIF	Dose reduction		.
		Skin and subcutaneous tissue disorders	Eczema	Grade 1	NK/03/2020	No	Recovery	01/12/2020	No	No	BOSULIF	No dose modification		.
		Respiratory, thoracic and mediastinal disorders	Cough	Grade 1	NK/03/2020	No	Recovery	NK/03/2020	No	No	BOSULIF	No dose modification		.
		Psychiatric disorders	Morose	Grade 1	NK/11/2020	No	Recovery	22/02/2021	No	No	BOSULIF	No dose modification		.
		General disorders and administration site conditions	Asthenia	Grade 1	NK/11/2020	No	Recovery	22/02/2021	No	No	BOSULIF	No dose modification		.
		Infections and infestations	Corona virus infection	Grade 2	04/01/2021	No	Recovery	12/02/2021	No	No	BOSULIF	No dose modification		.

Patient No.	Date of initiation of bosutinib treatment	SOC name	PT name	CTCAE grade	Date of occurrence	Is the event serious?	Status	Date of recovery	Is it reasonably possible that the event may be related to the study medication?	Is it reasonably possible that the event may be related to a concomitant drug?	Name of the drug (1)	Action taken (1)	Name of the drug (2)	Action taken (2)
		Respiratory, thoracic and mediastinal disorders	Vocal cord polyp	Grade 2	NK/06/2020	Yes	Recovery	26/08/2021	No	No	BOSULIF	No dose modification		.
		Ear and labyrinth disorders	Ear discomfort	Grade 1	NK/02/2021	No	Recovery	18/10/2021	No	No	BOSULIF	No dose modification		.
		Renal and urinary disorders	Pollakiuria	Grade 2	NK/02/2019	No	Recovery	NK/05/2019	No	No	BOSULIF	No dose modification		.
		Hepatobiliary disorders	Hepatocellular injury	Grade 3	17/02/2022	No	Recovery	28/02/2022	Yes	No	BOSULIF	Dose reduction		.
		Gastrointestinal disorders	Gastrointestinal disorder	Grade 2	NK/06/2020	No	Recovery in progress		Yes	No	BOSULIF	No dose modification		.
		Metabolism and nutrition disorders	Iron deficiency	Grade 2	NK/12/2019	No	Recovery in progress		No	No	BOSULIF	No dose modification		.
09-16	19/03/2019	Gastrointestinal disorders	Nausea	Grade 2	NK/03/2019	No	Recovery	27/02/2020	Yes	No	BOSULIF	No dose modification		.
		Gastrointestinal disorders	Diarrhoea	Grade 1	NK/03/2019	No	Recovery	13/05/2019	Yes	No	BOSULIF	No dose modification		.
		Gastrointestinal disorders	Abdominal pain upper	Grade 2	19/03/2019	No	Recovery	11/09/2019	Yes	No	BOSULIF	No dose modification		.
		Gastrointestinal disorders	Gastrooesophageal reflux disease	Grade 2	NK/06/2019	No	Recovery	11/09/2019	Yes	No	BOSULIF	No dose modification		.
		Gastrointestinal disorders	Constipation	Grade 2	NK/10/2019	No	Recovery	27/02/2020	No	No	BOSULIF	No dose modification		.
		Musculoskeletal and connective tissue disorders	Myalgia	Grade 1	NK/10/2019	No	Recovery	27/02/2020	Yes	No	BOSULIF	No dose modification		.

Patient No.	Date of initiation of bosutinib treatment	SOC name	PT name	CTCAE grade	Date of occurrence	Is the event serious?	Status	Date of recovery	Is it reasonably possible that the event may be related to the study medication?	Is it reasonably possible that the event may be related to a concomitant drug?	Name of the drug (1)	Action taken (1)	Name of the drug (2)	Action taken (2)
		Infections and infestations	Laryngitis	Grade 2	NK/11/2019	No	Recovery	NK/11/2019	No	No	BOSULIF	No dose modification		.
		General disorders and administration site conditions	Drug ineffective	Grade 1	28/01/2020	No	Recovery	28/01/2020	Yes	No	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.
		Nervous system disorders	Carotid arteriosclerosis	Grade 1	09/03/2020	No	Subject not recovered		No	No		.		.
		Infections and infestations	Tooth abscess	Grade 2	NK/05/2020	No	Recovery	02/06/2020	No	No	BOSEVAL	Not applicable		.
		Musculoskeletal and connective tissue disorders	Myalgia	Grade 1	NK/09/2021	No	Subject not recovered		No	No	ICLUSIG	No dose modification		.
		Skin and subcutaneous tissue disorders	Dry skin	Grade 1	NK/09/2021	No	Subject not recovered		No	No	ICLUSIG	No dose modification		.
09-17	01/04/2019	Renal and urinary disorders	Urinary retention	Grade 3	17/07/2020	Yes	Recovery	11/08/2020	No	No	BOSULIF	No dose modification		.
		General disorders and administration site conditions	Oedema peripheral	Grade 2	18/07/2020	No	Recovery	NK/07/2020	No	No	BOSULIF	No dose modification		.
		Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Prostate cancer	Grade 3	03/09/2020	No	Subject not recovered		No	No	BOSULIF	No dose modification		.
		Renal and urinary disorders	Dysuria	Grade 1	03/07/2020	No	Recovery	NK/07/2020	No	No	BOSULIF	No dose modification		.

Patient No.	Date of initiation of bosutinib treatment	SOC name	PT name	CTCAE grade	Date of occurrence	Is the event serious?	Status	Date of recovery	Is it reasonably possible that the event may be related to the study medication?	Is it reasonably possible that the event may be related to a concomitant drug?	Name of the drug (1)	Action taken (1)	Name of the drug (2)	Action taken (2)
		Infections and infestations	Urinary tract infection	Grade 4	02/08/2021	Yes	Recovery	17/08/2021	No	No	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.
		Renal and urinary disorders	Pollakiuria	Grade 2	NK/NK/2020	No	Recovery	26/05/2021	No	No	BOSULIF	No dose modification		.
		Gastrointestinal disorders	Abdominal discomfort	Grade 1	NK/12/2020	No	Recovery	08/03/2021	No	No	BOSULIF	No dose modification		.
		Infections and infestations	Urinary tract infection	Grade 2	31/08/2020	No	Recovery	05/09/2020	No	No	BOSULIF	No dose modification		.
		Injury, poisoning and procedural complications	Toxicity to various agents	Grade 1	ND/01/2021	No	Recovery in progress		No	Yes	BOSEVAL	No dose modification	FIRMAGON ABIRATERONE	No dose modification
		Renal and urinary disorders	Chronic kidney disease	Grade 1	08/03/2021	No	Subject not recovered		No	No	BOSULIF	Dose reduction		.
09-18	15/05/2019	Gastrointestinal disorders	Constipation	Grade 2	NK/NK/2019	No	Recovery	10/03/2021	Yes	No	BOSULIF	No dose modification		.
		General disorders and administration site conditions	Fatigue	Grade 1	NK/05/2019	No	Recovery	14/10/2019	Yes	No	BOSULIF	No dose modification		.
		Gastrointestinal disorders	Diarrhoea	Grade 1	NK/NK/2020	No	Recovery	NK/NK/2020	No	No	BOSULIF	No dose modification		.
		Gastrointestinal disorders	Abdominal pain upper	Grade 1	NK/12/2019	No	Recovery	27/04/2020	No	No	BOSULIF	No dose modification		.

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		Skin and subcutaneous tissue disorders	Rash pruritic	Grade 2	01/11/2021	No	Recovery with sequellae	15/03/2022	No	No	BOSEVAL	No dose modification		.
		Nervous system disorders	Dizziness	Grade 1	16/11/2020	No	Recovery	19/03/2021	No	No	BOSULIF	No dose modification		.
		General disorders and administration site conditions	Influenza like illness	Grade 1	NK/NK/2020	No	Recovery	NK/NK/2020	No	No	BOSULIF	No dose modification		.
		Infections and infestations	Corona virus infection	Grade 1	NK/NK/2022	No	Recovery	NK/NK/2022	No	No	BOSULIF	No dose modification		.
09-19	23/05/2019	Gastrointestinal disorders	Diarrhoea	Grade 2	NK/05/2019	No	Recovery	05/08/2019	Yes	No	BOSULIF	No dose modification		.
		Metabolism and nutrition disorders	Decreased appetite	Grade 1	NK/05/2019	No	Recovery	05/08/2019	Yes	No	BOSULIF	No dose modification		.
		Musculoskeletal and connective tissue disorders	Spinal pain	Grade 2	20/01/2020	No	Recovery	27/02/2020	No	No	BOSULIF	No dose modification		.
		Respiratory, thoracic and mediastinal disorders	Lung disorder	Grade 4	21/03/2020	Yes	Recovery	27/04/2020	No	No	BOSULIF	No dose modification		.
		Gastrointestinal disorders	Constipation	Grade 2	NK/05/2020	No	Subject not recovered		No	Yes	VIDAZA	No dose modification	PONATINIB	No dose modification
		Gastrointestinal disorders	Nausea	Grade 2	19/06/2020	No	Recovery	20/07/2020	No	Yes	VIDAZA	No dose modification	PONATINIB	No dose modification
		Nervous system disorders	Migraine	Grade 1	17/07/2020	No	Recovery	25/08/2020	No	No		.		.
		Vascular disorders	Intermittent claudication	Grade 2	25/08/2020	No	Subject not recovered		No	No		.		.
		General disorders and administration site conditions	Asthenia	Grade 2	17/11/2020	No	Subject not recovered		No	No		.		.

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		Psychiatric disorders	Anxiety	Grade 2	04/03/2021	No	Subject not recovered		No	No	BOSULIF	Not applicable		.
		Injury, poisoning and procedural complications	Limb injury	Grade 1	20/07/2020	No	Recovery	17/11/2020	No	No	BOSULIF	Not applicable		.
		General disorders and administration site conditions	Drug ineffective	Grade 1	26/03/2020	No	Subject not recovered		Yes	No	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.
		General disorders and administration site conditions	Asthenia	Grade 2	01/03/2020	No	Recovery in progress		No	No	BOSULIF	No dose modification		.
		Blood and lymphatic system disorders	Agranulocytosis	Grade 2	17/07/2020	No	Recovery	UK/07/2020	No	Yes	PONATINIB	Dose reduction	VIDAZA	Withdrawal (temporary or permanent, or deferred administration)
		Nervous system disorders	Neuropathy peripheral	Grade 2	21/09/2020	No	Subject not recovered		No	No	BOSULIF	Not applicable		.
		Vascular disorders	Hypertension	Grade 3	28/02/2021	Yes	Recovery in progress		No	Yes	PONATINIB	Withdrawal (temporary or permanent, or deferred administration)		.

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		Renal and urinary disorders	Renal artery stenosis	Grade 2	01/04/2021	Yes	Recovery	15/09/2021	No	No	BOSULIF	Not applicable		.
		Vascular disorders	Hot flush	Grade 1	28/02/2021	No	Recovery	UK/03/2021	No	No		.	BOSULIF	Not applicable
		Skin and subcutaneous tissue disorders	Dermatitis exfoliative	Grade 1	28/02/2021	No	Recovery	UK/03/2021	No	No		.	BOSULIF	Not applicable
		Gastrointestinal disorders	Vomiting	Grade 2	03/04/2021	No	Recovery	30/04/2021	No	Yes	BOSULIF	Not applicable	IMATINIB	Withdrawal (temporary or permanent, or deferred administration)
		Renal and urinary disorders	Renal failure	Grade 3	12/04/2021	Yes	Recovery	30/04/2021	No	No	BOSULIF	Not applicable	IEC	Withdrawal (temporary or permanent, or deferred administration)
		General disorders and administration site conditions	Drug intolerance	Grade 2	01/05/2021	No	Recovery	UK/UK/2022	No	Yes	DASATINIB	Dose reduction	BOSULIF	Not applicable
		Reproductive system and breast disorders	Gynaecomastia	Grade 2	UK/08/2021	No	Recovery in progress		No	No	BOSULIF	Not applicable		.

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		Blood and lymphatic system disorders	Neutropenia	Grade 2	30/08/2021	No	Recovery	UK/10/2021	No	Yes	BOSULIF	Not applicable	VIDAZA	Withdrawal (temporary or permanent, or deferred administration)
		Blood and lymphatic system disorders	Anaemia	Grade 1	15/09/2021	No	Recovery	22/09/2021	No	No	BOSULIF	Not applicable		.
		Respiratory, thoracic and mediastinal disorders	Pulmonary embolism	Grade 2	06/01/2022	Yes	Recovery	UK/02/2022	No	No	BOSULIF	Not applicable		.
		General disorders and administration site conditions	Chest pain	Grade 2	07/01/2022	Yes	Recovery	NK/01/2022	No	No	BOSULIF	Not applicable		.
		Metabolism and nutrition disorders	Hyperkalaemia	Grade 3	17/11/2021	No	Recovery	13/12/2021	No	Yes	BOSULIF	Not applicable	COVERSYL	Withdrawal (temporary or permanent, or deferred administration)
		Renal and urinary disorders	Renal failure	Grade 2	25/10/2021	No	Recovery	18/11/2021	No	Yes	BOSULIF	Not applicable	COVERSYL	Withdrawal (temporary or permanent, or deferred administration)

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		Gastrointestinal disorders	Diarrhoea	Grade 2	09/03/2022	No	Recovery	04/04/2022	No	Yes	BOSULIF	Not applicable	DUPHALAC	Withdrawal (temporary or permanent, or deferred administration)
		Musculoskeletal and connective tissue disorders	Spinal pain	Grade 2	21/09/2020	No	Recovery in progress		No	No	BOSULIF	Not applicable		.
		Musculoskeletal and connective tissue disorders	Intervertebral disc disorder	Grade 2	21/09/2020	No	Recovery in progress		No	No		.		.
		Blood and lymphatic system disorders	Anaemia	Grade 2	19/03/2020	No	Recovery	27/07/2020	No	No	BOSULIF	No dose modification		.
		Gastrointestinal disorders	Constipation	Grade 2	UK/03/2020	No	Recovery	NK/04/2020	No	Yes	BOSULIF	No dose modification	TRAITEMENTS MORPHINIQUES	Withdrawal (temporary or permanent, or deferred administration)
		Metabolism and nutrition disorders	Hypocalcaemia	Grade 3	NK/03/2020	Yes	Recovery	NK/03/2020	No	No	BOSULIF	No dose modification		.
		General disorders and administration site conditions	Chest pain	Grade 2	NK/02/2021	No	Recovery	NK/02/2021	No	No	BOSULIF	Not applicable		.
09-20	08/08/2019	Musculoskeletal and connective tissue disorders	Arthritis	Grade 2	NK/11/2019	No	Recovery	NK/01/2020	No	No	BOSULIF	No dose modification		.
		Gastrointestinal disorders	Faeces soft	Grade 1	NK/02/2020	No	Recovery	04/05/2020	Yes	No	BOSULIF	No dose modification		.

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		Skin and subcutaneous tissue disorders	Dermatitis contact	Grade 1	04/05/2020	No	Recovery	25/07/2020	No	No	BOSULIF	No dose modification		.
		Hepatobiliary disorders	Cholelithiasis	Grade 3	25/07/2020	Yes	Recovery	29/07/2020	No	No	BOSULIF	No dose modification		.
		Congenital, familial and genetic disorders	Dilatation intrahepatic duct congenital	Grade 1	28/10/2020	No	Subject not recovered		No	No	BOSULIF	No dose modification		.
		Musculoskeletal and connective tissue disorders	Myalgia	Grade 3	06/03/2021	Yes	Recovery	07/05/2021	No	No	BOSULIF	No dose modification		.
		Musculoskeletal and connective tissue disorders	Tendonitis	Grade 1	09/11/2021	No	Recovery	09/02/2022	No	No	BOSULIF	No dose modification		.
		Renal and urinary disorders	Renal failure	Grade 2	12/05/2022	No	Recovery in progress		Yes	No	BOSULIF	Dose reduction		.
09-21	19/11/2019	Gastrointestinal disorders	Diarrhoea	Grade 1	NK/11/2019	No	Recovery	NK/NK/2019	Yes	No	BOSULIF	Dose reduction		.
		Gastrointestinal disorders	Abdominal pain	Grade 1	NK/11/2019	No	Recovery	17/02/2020	Yes	No	BOSULIF	Dose reduction		.
		Hepatobiliary disorders	Hepatocellular injury	Grade 1	17/02/2020	No	Recovery	23/11/2020	Yes	No	BOSULIF	No dose modification		.
		Infections and infestations	Nasopharyngitis	Grade 1	NK/02/2020	No	Recovery	NK/02/2020	No	No	BOSULIF	No dose modification		.
		Infections and infestations	Vaginal infection	Grade 2	05/06/2020	No	Recovery	18/11/2020	No	No	BOSULIF	No dose modification		.
		Reproductive system and breast disorders	Vulvovaginal burning sensation	Grade 1	NK/02/2020	No	Recovery	17/02/2020	No	No	BOSULIF	No dose modification		.

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		Gastrointestinal disorders	Aphthous stomatitis	Grade 1	NK/02/2020	No	Recovery	17/02/2020	No	No	BOSULIF	No dose modification		.
		Reproductive system and breast disorders	Genital burning sensation	Grade 2	18/11/2020	No	Recovery	23/11/2020	No	No	BOSULIF	No dose modification		.
		Injury, poisoning and procedural complications	Maternal exposure during pregnancy	Grade 3	03/06/2021	No	Recovery	22/02/2022	No	No	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.
		Gastrointestinal disorders	Diarrhoea	Grade 2	22/02/2022	No	Recovery	NK/04/2022	Yes	No	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.
		Psychiatric disorders	Depression	Grade 2	ND/04/2022	No	Subject not recovered		No	No	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.
		General disorders and administration site conditions	Treatment noncompliance	Grade 1	NK/NK/2020	No	Recovery with sequellae	NK/04/2022	Yes	No	BOSULIF	Not applicable		.
		General disorders and administration site conditions	Treatment noncompliance	Grade 1	11/07/2022	No	Subject not recovered		No	Yes	BOSUTINIB	Not applicable	IMATINIB	No dose modification

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		Infections and infestations	Corona virus infection	Grade 1	NK/04/2022	No	Recovery	NK/04/2022	No	No	BOSULIF	No dose modification		.
09-22	13/11/2019	Investigations	Lipase increased	Grade 2	09/12/2019	No	Recovery	26/02/2020	Yes	No	BOSULIF	Dose reduction		.
		Musculoskeletal and connective tissue disorders	Chondrocalcinosis	Grade 3	NK/12/2019	Yes	Recovery	17/02/2020	No	No	BOSULIF	No dose modification		.
		Vascular disorders	Phlebitis	Grade 2	10/01/2020	Yes	Recovery	ND/04/2020	No	No	BOSULIF	No dose modification		.
		Investigations	Coronavirus test positive	Grade 2	07/12/2020	No	Recovery	NK/12/2020	No	No	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.
		Gastrointestinal disorders	Diarrhoea	Grade 1	NK/08/2020	No	Recovery	03/06/2021	Yes	No	BOSULIF	No dose modification		.
		Metabolism and nutrition disorders	Fluid retention	Grade 2	11/03/2021	No	Recovery	NK/03/2021	Yes	No	BOSULIF	Dose reduction		.
		Musculoskeletal and connective tissue disorders	Arthralgia	Grade 2	NK/12/2020	No	Recovery	08/11/2021	No	No	BOSULIF	No dose modification		.
		Gastrointestinal disorders	Chronic gastritis	Grade 1	K	No	Recovery	K	No	No	BOSULIF	No dose modification		.
		Gastrointestinal disorders	Rectal polyp	Grade 2	K	No	Recovery	18/02/2022	No	No	BOSULIF	No dose modification		.

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		Blood and lymphatic system disorders	Anaemia	Grade 1	20/01/2021	No	Recovery	19/08/2021	No	No	BOSULIF	No dose modification		.
		Metabolism and nutrition disorders	Vitamin D deficiency	Grade 2	NK/01/2020	No	Recovery	NK/NK/2020	No	No	BOSULIF	No dose modification		.
		Metabolism and nutrition disorders	Folate deficiency	Grade 2	NK/01/2020	No	Recovery	NK/NK/2020	No	No	BOSULIF	No dose modification		.
09-23	19/12/2019	Skin and subcutaneous tissue disorders	Dry skin	Grade 1	23/03/2020	No	Recovery	22/06/2020	No	No	BOSULIF	No dose modification		.
		Infections and infestations	Folliculitis	Grade 1	05/10/2020	No	Recovery	NK/10/2020	No	No	BOSULIF	No dose modification		.
		Gastrointestinal disorders	Diarrhoea	Grade 1	NK/06/2020	No	Recovery	11/01/2021	Yes	No	BOSULIF	No dose modification		.
		Skin and subcutaneous tissue disorders	Ecchymosis	Grade 1	NK/06/2020	No	Recovery	05/10/2020	No	No	BOSULIF	No dose modification		.
		Hepatobiliary disorders	Hepatocellular injury	Grade 2	29/04/2020	No	Recovery	02/11/2020	Yes	No	BOSULIF	No dose modification		.
		General disorders and administration site conditions	Chest pain	Grade 2	13/10/2020	Yes	Recovery	15/10/2020	No	No	BOSULIF	No dose modification		.
		Skin and subcutaneous tissue disorders	Rash	Grade 2	20/11/2020	No	Subject not recovered		Yes	No	BOSULIF	No dose modification		.
		Skin and subcutaneous tissue disorders	Rash	Grade 2	16/01/2020	No	Recovery	NK/01/2020	No	No	BOSEVAL	No dose modification		.

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10-01	17/03/2016	Gastrointestinal disorders	Gastrointestinal disorder	Grade 2	NK/03/2016	No	Recovery	NK/03/2016	No	No	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.
		Gastrointestinal disorders	Diarrhoea	Grade 2	NK/09/2016	No	Recovery	02/05/2017	Yes	No		Dose reduction		.
		Musculoskeletal and connective tissue disorders	Osteoarthritis	Grade 2	NK/NK/2017	Yes	Recovery	NK/NK/2017	No	No	BOSULIF	No dose modification		.
		Blood and lymphatic system disorders	Anaemia	Grade 2	NK/NK/2017	No	Recovery	NK/NK/2017	No	No	BOSULIF	No dose modification		.
		General disorders and administration site conditions	Fatigue	Grade 1	12/04/2018	No	Recovery	01/08/2018	No	No	BOSULIF	No dose modification		.
		Investigations	Blood thyroid stimulating hormone increased	Grade 1	NK/04/2018	No	Unknown		No	No	BOSULIF	No dose modification		.
		Gastrointestinal disorders	Diarrhoea	Grade 1	NK/NK/2019	No	Recovery	06/03/2019	Yes	No	BOSULIF	No dose modification		.
10-02	20/04/2016	Gastrointestinal disorders	Diarrhoea	Grade 2	20/04/2016	No	Recovery	26/04/2016	Yes	No		Withdrawal (temporary or permanent, or deferred administration)		.

Patient No.	Date of initiation of bosutinib treatment	SOC name	PT name	CTCAE grade	Date of occurrence	Is the event serious?	Status	Date of recovery	Is it reasonably possible that the event may be related to the study medication?	Is it reasonably possible that the event may be related to a concomitant drug?	Name of the drug (1)	Action taken (1)	Name of the drug (2)	Action taken (2)
		General disorders and administration site conditions	Pain	Grade 1	22/08/2018	No	Recovery	22/11/2018	No	No		Not applicable		.
10-03	31/08/2016	Infections and infestations	Sepsis	Grade 3	03/09/2016	Yes	Recovery	13/09/2016	No	No	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.
		Hepatobiliary disorders	Hepatocellular injury	Grade 3	04/09/2016	No	Recovery	09/09/2016	Yes	No	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.
		Respiratory, thoracic and mediastinal disorders	Sleep apnoea syndrome	Grade 2	NK/09/2016	No	Subject not recovered		No	No	BOSULIF	No dose modification		.
		Injury, poisoning and procedural complications	Arthropod bite	Grade 2	NK/08/2018	No	Recovery	NK/08/2018	No	No	BOSULIF	Not applicable		.
		Surgical and medical procedures	Thyroidectomy	Grade 3	10/12/2017	Yes	Recovery	13/12/2017	No	No	BOSULIF	No dose modification		.
		Eye disorders	Eyelid oedema	Grade 2	26/11/2017	No	Recovery	28/11/2017	No	No	BOSULIF	No dose modification		.
		Hepatobiliary disorders	Hepatomegaly	Grade 1	NK/11/2016	No	Unknown		No	No	BOSULIF	Not applicable		.

Patient No.	Date of initiation of bosutinib treatment	SOC name	PT name	CTCAE grade	Date of occurrence	Is the event serious?	Status	Date of recovery	Is it reasonably possible that the event may be related to the study medication?	Is it reasonably possible that the event may be related to a concomitant drug?	Name of the drug (1)	Action taken (1)	Name of the drug (2)	Action taken (2)
10-04	07/11/2019	Hepatobiliary disorders	Hepatitis	Grade 3	02/12/2019	No	Recovery	13/01/2020	Yes	No		Withdrawal (temporary or permanent, or deferred administration)		.
		Respiratory, thoracic and mediastinal disorders	Dyspnoea exertional	Grade 1	14/01/2021	No	Recovery	08/04/2021	No	Yes	GLIVEC	No dose modification		.
		Eye disorders	Periorbital oedema	Grade 1	14/01/2021	No	Recovery	08/04/2021	No	Yes	GLIVEC	No dose modification		.
		Skin and subcutaneous tissue disorders	Skin lesion	Grade 1	14/01/2021	No	Recovery	08/04/2021	No	Yes	GLIVEC	No dose modification		.
		General disorders and administration site conditions	Asthenia	Grade 1	06/05/2020	No	Subject not recovered		No	Yes	GLIVEC	No dose modification	SPRYCEL	No dose modification
		Ear and labyrinth disorders	Hypoacusis	Grade 3	06/09/2021	Yes	Recovery	16/09/2021	No	No		Not applicable		.
		Skin and subcutaneous tissue disorders	Purpura	Grade 1	21/10/2021	No	Recovery	27/01/2022	No	Yes	GLIVEC	No dose modification		.
		Respiratory, thoracic and mediastinal disorders	Pleural effusion	Grade 3	06/06/2020	Yes	Recovery	27/06/2020	No	Yes	SPRYCEL	Withdrawal (temporary or permanent, or deferred administration)		.
		Blood and lymphatic system disorders	Anaemia	Grade 1	19/01/2021	No	Subject not recovered		No	Yes	SPRYCEL	No dose modification		.

Patient No.	Date of initiation of bosutinib treatment	SOC name	PT name	CTCAE grade	Date of occurrence	Is the event serious?	Status	Date of recovery	Is it reasonably possible that the event may be related to the study medication?	Is it reasonably possible that the event may be related to a concomitant drug?	Name of the drug (1)	Action taken (1)	Name of the drug (2)	Action taken (2)
		Eye disorders	Retinal vein occlusion	Grade 3	15/07/2021	Yes	Recovery	01/02/2022	No	No	GLIVEC	No dose modification		.
		Vascular disorders	Hypertension	Grade 3	19/06/2020	No	Recovery	20/06/2020	No	No	GLIVEC	No dose modification		.
11-01	21/03/2016	Hepatobiliary disorders	Hepatocellular injury	Grade 2	02/05/2016	No	Recovery	24/06/2016	Yes	No	BOSULIF	Dose reduction	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)
		Infections and infestations	Laryngitis	Grade 1	15/12/2016	No	Recovery	12/01/2017	No	No		No dose modification		.
		Eye disorders	Uveitis	Grade 1	31/08/2017	No	Recovery	31/10/2017	No	No		No dose modification		.
		Respiratory, thoracic and mediastinal disorders	Epistaxis	Grade 1	08/11/2017	No	Recovery	05/04/2018	No	Yes		No dose modification	KARDEGIC	No dose modification
		Infections and infestations	Paronychia	Grade 3	28/03/2018	No	Recovery	29/05/2018	No	No		No dose modification		.
		Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Benign pancreatic neoplasm	Grade 2	08/03/2018	No	Subject not recovered		No	No		No dose modification		.
		Metabolism and nutrition disorders	Dyslipidaemia	Grade 1	29/05/2018	No	Subject not recovered		No	No	BOSUTINIB	No dose modification		.
		General disorders and administration site conditions	Chest pain	Grade 1	29/05/2018	No	Recovery	16/11/2018	No	No	BOSUTINIB	No dose modification		.

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		Nervous system disorders	Carotid artery stenosis	Grade 4	05/03/2018	Yes	Recovery	10/01/2019	No	No	BOSUTINIB	No dose modification		.
		Infections and infestations	Herpes ophthalmic	Grade 3	NK/07/2018	No	Recovery	05/04/2019	No	No	BOSUTINIB	No dose modification		.
		Musculoskeletal and connective tissue disorders	Tendonitis	Grade 1	NK/10/2018	No	Subject not recovered		No	No	BOSUTINIB	No dose modification		.
		Nervous system disorders	Hypoaesthesia	Grade 1	29/01/2019	No	Recovery	NK/02/2019	No	No	BOSUTINIB	No dose modification		.
		Vascular disorders	Hypertension	Grade 3	29/01/2019	No	Recovery	29/01/2019	No	No	BOSUTINIB	No dose modification		.
		Renal and urinary disorders	Renal cyst	Grade 1	05/04/2018	No	Subject not recovered		No	No	BOSULIF	No dose modification		.
11-02	14/04/2016	Gastrointestinal disorders	Flatulence	Grade 1	01/06/2016	No	Recovery	30/06/2016	Yes	No	BOSUTINIB	No dose modification		.
		Gastrointestinal disorders	Diarrhoea	Grade 1	01/06/2016	No	Recovery	NK/05/2017	Yes	No	BOSUTINIB	Dose reduction		.
		Injury, poisoning and procedural complications	Maternal exposure during pregnancy	.	15/05/2017	No	Recovery	21/01/2018	No	No	BOSUTINIB	Withdrawal (temporary or permanent, or deferred administration)		.
		Gastrointestinal disorders	Gastrooesophageal reflux disease	Grade 2	NK/02/2018	No	Subject not recovered		Yes	No	BOSUTINIB	No dose modification		.

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		Pregnancy, puerperium and perinatal conditions	Complication of pregnancy	Grade 3	29/11/2017	Yes	Recovery	04/12/2017	No	No		Not applicable		.
		Gastrointestinal disorders	Abdominal pain upper	Grade 2	29/11/2017	No	Recovery	04/12/2017	No	No		Not applicable		.
		Respiratory, thoracic and mediastinal disorders	Oropharyngeal pain	Grade 1	NK/10/2017	No	Recovery	NK/11/2017	No	No		Not applicable		.
		Nervous system disorders	Dizziness	Grade 1	NK/07/2017	No	Recovery	NK/11/2017	No	No		Not applicable		.
		Gastrointestinal disorders	Diarrhoea	Grade 1	NK/04/2018	No	Subject not recovered		Yes	No	BOSUTINIB	No dose modification		.
		Skin and subcutaneous tissue disorders	Night sweats	Grade 2	NK/12/2018	No	Recovery	04/04/2019	No	No		No dose modification		.
11-03	18/04/2016	Gastrointestinal disorders	Diarrhoea	Grade 1	NK/06/2016	No	Recovery	01/03/2017	Yes	No	BOSULIF@, BOSUTINUB	No dose modification		.
		Respiratory, thoracic and mediastinal disorders	Sleep apnoea syndrome	Grade 2	01/04/2017	No	Subject not recovered		No	No	BOSULIF	No dose modification		.
		General disorders and administration site conditions	Reduced drug effect	Grade 1	30/06/2017	No	Unknown		Yes	No	BOSUTINIB	Withdrawal (temporary or permanent, or deferred administration)		.
		Eye disorders	Eye swelling	Grade 1	NK/07/2017	No	Recovery	10/08/2017	No	No		Not applicable		.
		Metabolism and nutrition disorders	Dyslipidaemia	Grade 2	26/10/2017	No	Subject not recovered		No	Yes	BOSULIF	Not applicable	NILOTINIB	No dose modification

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		Investigations	Blood glucose abnormal	Grade 1	UK/07/2017	No	Subject not recovered		No	Yes	BOSULIF	Not applicable	NILOTINIB	No dose modification
11-04	02/09/2016	Gastrointestinal disorders	Abdominal pain upper	Grade 1	NK/10/2016	No	Recovery	26/01/2017	Yes	No	BOSUTINIB	Dose reduction		.
		Musculoskeletal and connective tissue disorders	Myalgia	Grade 2	NK/09/2016	No	Recovery	02/02/2017	Yes	No	BOSUTINIB	Dose reduction		.
		Infections and infestations	Sinusitis	Grade 2	15/12/2016	No	Recovery	04/01/2017	No	No		No dose modification		.
		Metabolism and nutrition disorders	Diabetes mellitus	Grade 2	07/03/2017	No	Subject not recovered		No	No	BOSUTINIB	No dose modification		.
		Musculoskeletal and connective tissue disorders	Myalgia	Grade 1	03/02/2017	No	Recovery	31/08/2017	Yes	No	BOSUTINIB	No dose modification		.
		Gastrointestinal disorders	Diarrhoea	Grade 2	01/08/2017	No	Recovery	30/08/2017	No	Yes	BOSUTINIB	No dose modification	METFORMINE	Withdrawal (temporary or permanent, or deferred administration)
		Gastrointestinal disorders	Tooth disorder	Grade 2	NK/09/2017	No	Recovery	NK/09/2017	No	No	BOSUTINIB	No dose modification		.
11-05	09/02/2017	Infections and infestations	Bronchitis	Grade 2	02/01/2018	No	Recovery	07/01/2018	No	No	BOSUTINIB	No dose modification		.
		Musculoskeletal and connective tissue disorders	Intervertebral disc disorder	Grade 2	01/12/2018	No	Subject not recovered		No	No	BOSUTINIB	No dose modification		.

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		Musculoskeletal and connective tissue disorders	Spinal osteoarthritis	Grade 2	14/12/2018	No	Subject not recovered		No	No	BOSUTINIB	No dose modification		.
		Infections and infestations	Gastroenteritis	Grade 1	13/10/2019	No	Recovery	15/10/2019	No	No	BOSULIF	No dose modification		.
		Infections and infestations	Nasopharyngitis	Grade 1	02/12/2019	No	Recovery	07/12/2019	No	No	BOSULIF	No dose modification		.
11-06	17/03/2017	Hepatobiliary disorders	Hepatitis	Grade 3	17/05/2017	No	Recovery	31/07/2017	Yes	No	BOSUTINIB	Withdrawal (temporary or permanent, or deferred administration)		.
		Investigations	Blood thyroid stimulating hormone increased	Grade 1	23/03/2017	No	Recovery	NK/NK/2017	No	No	BOSUTINIB	No dose modification		.
		Musculoskeletal and connective tissue disorders	Back pain	Grade 2	03/01/2018	No	Recovery	01/02/2018	No	No	BOSUTINIB	No dose modification		.
		General disorders and administration site conditions	Face oedema	Grade 1	13/04/2017	No	Recovery	15/06/2017	No	No	BOSUTINIB	No dose modification		.
		Infections and infestations	Bronchitis	Grade 2	28/04/2018	No	Recovery	NK/05/2018	No	No	BOSUTINIB	No dose modification		.

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		Hepatobiliary disorders	Cholelithiasis obstructive	Grade 3	NK/11/2018	Yes	Recovery	10/12/2018	No	No	BOSUTINIB	Withdrawal (temporary or permanent, or deferred administration)		.
		Musculoskeletal and connective tissue disorders	Osteoarthritis	Grade 2	02/04/2019	No	Recovery	NK/11/2019	No	No	BOSUTINIB	No dose modification		.
		Skin and subcutaneous tissue disorders	Onychoclasis	Grade 1	NK/09/2019	No	Recovery	NK/11/2019	No	No	BOSUTINIB	No dose modification		.
11-07	29/03/2017	Gastrointestinal disorders	Diarrhoea	Grade 2	13/04/2017	No	Recovery	16/06/2017	Yes	No		Dose reduction		.
		Musculoskeletal and connective tissue disorders	Musculoskeletal pain	Grade 2	19/04/2017	No	Recovery	21/09/2017	Yes	No	BOSUTINIB	Dose reduction		.
		Injury, poisoning and procedural complications	Fall	Grade 2	14/12/2017	No	Recovery	14/12/2017	No	No	BOSUTINIB	No dose modification		.
		Skin and subcutaneous tissue disorders	Pruritus	Grade 1	NK/03/2017	No	Recovery	NK/05/2017	No	No	BOSUTINIB	No dose modification		.
		Gastrointestinal disorders	Dysphagia	Grade 1	NK/03/2017	No	Recovery	NK/05/2017	No	No	BOSUTINIB	No dose modification		.
		Gastrointestinal disorders	Inguinal hernia	Grade 2	01/09/2018	Yes	Recovery	08/10/2018	No	No	BOSUTINIB	No dose modification		.
		Skin and subcutaneous tissue disorders	Actinic keratosis	Grade 1	01/08/2018	No	Recovery	04/04/2019	No	No	BOSUTINIB	No dose modification		.

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		Skin and subcutaneous tissue disorders	Erythema	Grade 1	15/09/2017	No	Recovery	04/04/2019	Yes	No	BOSUTINIB	No dose modification		.
		Renal and urinary disorders	Chronic kidney disease	Grade 2	20/09/2018	No	Subject not recovered		No	No	BOSUTINIB	No dose modification		.
		Musculoskeletal and connective tissue disorders	Arthralgia	Grade 1	01/09/2019	No	Subject not recovered		No	No	BOSUTINIB	No dose modification		.
		Musculoskeletal and connective tissue disorders	Muscle spasms	Grade 2	08/01/2020	No	Recovery	12/01/2020	No	No	BOSUTINIB	No dose modification		.
11-08	24/03/2017	Gastrointestinal disorders	Diarrhoea	Grade 1	16/04/2017	No	Recovery	20/04/2017	Yes	No	BOSULIF®, BOSUTINIB	No dose modification		.
		Gastrointestinal disorders	Diarrhoea	Grade 2	01/05/2017	No	Recovery	14/05/2017	Yes	No	BOSULIF®, BOSUTINIB	No dose modification		.
		Gastrointestinal disorders	Abdominal pain	Grade 1	NK/12/2017	No	Recovery	NK/06/2018	Yes	No	BOSUTINIB	No dose modification		.
		Gastrointestinal disorders	Diarrhoea	Grade 2	NK/06/2018	No	Recovery	14/01/2019	Yes	No	BOSUTINIB	Dose reduction		.
		Infections and infestations	Bronchitis	Grade 2	18/06/2018	No	Recovery	NK/12/2018	No	No	BOSUTINIB	No dose modification		.
		Gastrointestinal disorders	Diarrhoea	Grade 1	01/09/2017	No	Subject not recovered		Yes	No	BOSUTINIB	No dose modification		.
		Gastrointestinal disorders	Diarrhoea	Grade 2	09/12/2019	No	Recovery	13/12/2019	Yes	No	BOSUTINIB	No dose modification		.
11-09	03/06/2017	Musculoskeletal and connective tissue disorders	Osteoarthritis	Grade 3	09/12/2019	Yes	Recovery	19/12/2019	No	No	BOSULIF	No dose modification		.

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		Blood and lymphatic system disorders	Anaemia	Grade 3	09/12/2019	No	Recovery	10/12/2019	No	No	BOSULIF	No dose modification		.
		Gastrointestinal disorders	Diarrhoea	Grade 1	15/06/2017	No	Recovery	10/07/2017	Yes	No	BOSULIF®, BOSUTINIB	No dose modification		.
		Gastrointestinal disorders	Diarrhoea	Grade 1	01/09/2017	No	Recovery in progress		Yes	No	BOSUTINIB	No dose modification		.
		Gastrointestinal disorders	Flatulence	Grade 1	01/09/2017	No	Recovery in progress		Yes	No	BOSUTINIB	No dose modification		.
		Infections and infestations	Gastroenteritis	Grade 3	15/02/2019	No	Recovery	20/02/2019	No	No	BOSUTINIB	No dose modification		.
		Musculoskeletal and connective tissue disorders	Osteoarthritis	Grade 3	NK/11/2018	No	Subject not recovered		No	No	BOSUTINIB	No dose modification		.
		Respiratory, thoracic and mediastinal disorders	Chronic obstructive pulmonary disease	Grade 2	17/04/2020	No	Subject not recovered		No	No	BOSULIF	No dose modification		.
		Renal and urinary disorders	Chronic kidney disease	Grade 2	21/03/2019	No	Subject not recovered		No	No	BOSULITF	No dose modification		.
11-10	01/09/2017	Gastrointestinal disorders	Diarrhoea	Grade 2	08/09/2017	No	Recovery	NK/10/2019	Yes	No	BOSUTINIB	No dose modification		.
		Musculoskeletal and connective tissue disorders	Arthralgia	Grade 2	22/09/2017	No	Recovery	05/04/2018	Yes	No	BOSUTINIB	No dose modification		.
		Infections and infestations	Influenza	Grade 2	12/10/2017	No	Recovery	19/10/2017	No	No	BOSUTINIB	No dose modification		.
		Nervous system disorders	Headache	Grade 1	22/09/2017	No	Recovery	21/12/2017	No	No	BOSUTINIB	No dose modification		.

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		Respiratory, thoracic and mediastinal disorders	Dyspnoea exertional	Grade 1	05/04/2018	No	Recovery	04/10/2018	No	No	BOSUTINIB	No dose modification		.
		Respiratory, thoracic and mediastinal disorders	Rhinorrhoea	Grade 1	26/10/2017	No	Recovery	NK/10/2017	No	No	BOSUTINIB	No dose modification		.
		General disorders and administration site conditions	Asthenia	Grade 1	04/10/2018	No	Recovery	04/04/2019	No	No	BOSUTINIB	No dose modification		.
		Musculoskeletal and connective tissue disorders	Tendon pain	Grade 2	NK/06/2019	No	Recovery	26/03/2020	Yes	No	BOSUTINIB	No dose modification		.
		Eye disorders	Photopsia	Grade 1	NK/10/2017	No	Recovery	21/12/2017	No	No	BOSUTINIB	No dose modification		.
		Infections and infestations	Herpes simplex	Grade 2	12/10/2020	No	Recovery in progress		No	No	BOSUTINIB	No dose modification		.
		Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Lipoma	Grade 1	04/10/2018	No	Recovery	04/04/2019	No	No	BOSUTINIB	No dose modification		.
		Gastrointestinal disorders	Diarrhoea	Grade 1	NK/10/2020	No	Recovery in progress		Yes	No	BOSUTINIB	Dose reduction		.
11-11	23/11/2017	Hepatobiliary disorders	Hepatocellular injury	Grade 3	14/02/2018	Yes	Recovery	30/07/2018	Yes	No	BOSUTINIB	Withdrawal (temporary or permanent, or deferred administration)		.
		Infections and infestations	Bronchitis	Grade 1	NK/03/2018	No	Recovery	NK/03/2018	No	No	BOSUTINIB	No dose modification		.

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		Respiratory, thoracic and mediastinal disorders	Asthma	Grade 1	NK/07/2019	No	Recovery	NK/07/2019	No	No	DASATINIB	No dose modification		.
		Gastrointestinal disorders	Diarrhoea	Grade 1	NK/10/2018	No	Recovery	31/01/2019	No	Yes	BOSULIF	Not applicable	DASATINIB	No dose modification
		Respiratory, thoracic and mediastinal disorders	Asthma	Grade 2	NK/02/2019	No	Recovery	NK/NK/2019	No	No	BOSULIF	Not applicable		.
11-12	07/03/2018	Injury, poisoning and procedural complications	Post procedural complication	Grade 3	12/09/2018	Yes	Subject not recovered		No	No	BOSUTINIB	Withdrawal (temporary or permanent, or deferred administration)		.
		Musculoskeletal and connective tissue disorders	Back pain	Grade 2	18/06/2020	No	Recovery	21/01/2021	No	No	DASATINIB	No dose modification		.
		Gastrointestinal disorders	Anal fistula	Grade 3	13/12/2018	Yes	Recovery	20/10/2020	No	No	DASATINIB	No dose modification		.
		Vascular disorders	Hot flush	Grade 1	NK/11/2018	No	Recovery	13/12/2018	No	Yes	DASATINIB	Dose reduction		.
11-13	22/04/2018	Gastrointestinal disorders	Diarrhoea	Grade 1	NK/05/2018	No	Recovery	01/10/2018	Yes	No	BOSUTINIB	Withdrawal (temporary or permanent, or deferred administration)		.

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		Gastrointestinal disorders	Haemorrhoids	Grade 2	20/06/2018	No	Recovery	24/06/2018	Yes	No	BOSUTINIB	Withdrawal (temporary or permanent, or deferred administration)		.
		Gastrointestinal disorders	Anal fissure	Grade 2	NK/08/2018	Yes	Recovery	31/08/2018	No	No	BOSUTINIB	Withdrawal (temporary or permanent, or deferred administration)		.
		Infections and infestations	Erysipelas	Grade 2	15/04/2019	No	Recovery	22/04/2019	No	No	BOSUTINIB	No dose modification		.
		General disorders and administration site conditions	Asthenia	Grade 1	NK/NK/2019	No	Subject not recovered		No	No	BOSUTINIB	No dose modification		.
		Skin and subcutaneous tissue disorders	Dry skin	Grade 1	NK/11/2019	No	Subject not recovered		No	No	BOSUTINIB	No dose modification		.
		Infections and infestations	Corona virus infection	Grade 1	04/03/2021	No	Recovery	11/03/2021	No	No		Not applicable		.
		Skin and subcutaneous tissue disorders	Actinic keratosis	Grade 1	NK/01/2021	No	Recovery	NK/NK/2021	No	No		No dose modification		.
		Skin and subcutaneous tissue disorders	Intertrigo	Grade 1	02/07/2020	No	Recovery	NK/NK/2021	No	No		No dose modification		.

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		Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Acrochordon	Grade 2	UK/UK/2020	No	Recovery	UK/UK/2020	No	No	BOSULIF	No dose modification		.
		Infections and infestations	Folliculitis	Grade 1	02/07/2020	No	Recovery	NK/NK/2020	No	No	BOSULIF	No dose modification		.
11-15	09/07/2018	Nervous system disorders	Neuropathy peripheral	Grade 1	NK/01/2019	No	Subject not recovered		No	No	BOSUTINIB	No dose modification		.
		Infections and infestations	Bronchitis	Grade 2	18/09/2019	No	Recovery	23/09/2019	No	No	BOSULIF	Not applicable		.
		Respiratory, thoracic and mediastinal disorders	Lung disorder	Grade 3	UK/09/2019	Yes	Recovery	11/10/2019	No	No	BOSULIF	Not applicable		.
11-16	06/07/2018	General disorders and administration site conditions	Asthenia	Grade 1	06/07/2018	No	Recovery	17/01/2019	Yes	No	BOSUTINIB	No dose modification		.
		Gastrointestinal disorders	Abdominal distension	Grade 1	NK/07/2018	No	Recovery	NK/08/2018	Yes	No	BOSUTINIB	No dose modification		.
		Gastrointestinal disorders	Diarrhoea	Grade 1	21/08/2018	No	Recovery	21/08/2018	Yes	No	BOSUTINIB	No dose modification		.
		Eye disorders	Conjunctival haemorrhage	Grade 1	22/08/2018	No	Recovery	NK/08/2018	No	No	BOSUTINIB	No dose modification		.
		Infections and infestations	Nasopharyngitis	Grade 2	28/09/2018	No	Recovery	03/10/2018	No	No	BOSUTINIB	No dose modification		.
		Respiratory, thoracic and mediastinal disorders	Dyspnoea exertional	Grade 1	18/10/2018	No	Recovery	17/01/2019	No	No	BOSUTINIB	No dose modification		.
		Vascular disorders	Hypertension	Grade 1	22/08/2018	No	Recovery	22/08/2018	No	No	BOSUTINIB	No dose modification		.

Patient No.	Date of initiation of bosutinib treatment	SOC name	PT name	CTCAE grade	Date of occurrence	Is the event serious?	Status	Date of recovery	Is it reasonably possible that the event may be related to the study medication?	Is it reasonably possible that the event may be related to a concomitant drug?	Name of the drug (1)	Action taken (1)	Name of the drug (2)	Action taken (2)
		Infections and infestations	Urinary tract infection	Grade 2	NK/01/2019	No	Recovery	NK/01/2019	No	No	BOSUTINIB	No dose modification		.
		General disorders and administration site conditions	Pyrexia	Grade 2	20/07/2019	Yes	Recovery	26/07/2019	Yes	No	BOSUTINIB	No dose modification		.
		General disorders and administration site conditions	Asthenia	Grade 3	NK/NK/2019	Yes	Recovery	19/08/2019	Yes	No		Withdrawal (temporary or permanent, or deferred administration)		.
		Infections and infestations	Pneumonia	Grade 3	09/08/2019	Yes	Recovery	21/08/2019	Yes	No	BOSUTINIB	No dose modification		.
		Respiratory, thoracic and mediastinal disorders	Pleural effusion	Grade 2	19/07/2019	Yes	Recovery	UK/11/2019	Yes	No	BOSUTINIB	Withdrawal (temporary or permanent, or deferred administration)		.
		Cardiac disorders	Pericardial effusion	Grade 2	20/07/2019	Yes	Recovery	NK/11/2019	Yes	No	BOSUTINIB	Withdrawal (temporary or permanent, or deferred administration)		.
		General disorders and administration site conditions	Chest pain	Grade 1	19/07/2019	No	Recovery	26/07/2019	No	No	BOSUTINIB	No dose modification		.

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		Renal and urinary disorders	Chronic kidney disease	Grade 3	18/09/2018	Yes	Subject not recovered		No	No		No dose modification		.
		Infections and infestations	Gastroenteritis	Grade 1	NK/07/2019	No	Recovery	20/07/2019	No	No		No dose modification		.
		Gastrointestinal disorders	Diarrhoea	Grade 1	NK/07/2019	No	Recovery	NK/08/2019	No	No		No dose modification		.
		Gastrointestinal disorders	Abdominal pain upper	Grade 1	08/08/2019	No	Recovery	08/08/2019	No	No		No dose modification		.
		Blood and lymphatic system disorders	Anaemia	Grade 2	NK/07/2019	No	Recovery	NK/08/2019	No	No		Not applicable		.
		Metabolism and nutrition disorders	Vitamin D deficiency	Grade 2	NK/07/2019	No	Recovery	NK/08/2019	No	No		Not applicable		.
		Nervous system disorders	Dizziness	Grade 1	08/08/2019	No	Recovery	08/08/2019	No	No		Not applicable		.
		Skin and subcutaneous tissue disorders	Hyperhidrosis	Grade 1	08/08/2019	No	Recovery	08/08/2019	No	No		Not applicable		.
		Respiratory, thoracic and mediastinal disorders	Dyspnoea	Grade 2	NK/07/2019	Yes	Recovery in progress		Yes	No	BOSUTINIB	Withdrawal (temporary or permanent, or deferred administration)		.
		General disorders and administration site conditions	Asthenia	Grade 1	NK/12/2019	No	Recovery	05/03/2020	Yes	No	BOSUTINIB	No dose modification		.

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		Skin and subcutaneous tissue disorders	Angioedema	Grade 3	10/07/2020	Yes	Recovery	11/07/2020	No	Yes	TRIATEC	Withdrawal (temporary or permanent, or deferred administration)		.
		Gastrointestinal disorders	Abdominal rigidity	Grade 2	03/07/2020	No	Recovery	NK/07/2020	No	Yes	BOSUTINIB	No dose modification		.
		Gastrointestinal disorders	Gastrointestinal disorder	Grade 1	NK/12/2019	No	Recovery	NK/03/2020	Yes	No	BOSUTINIB	No dose modification		.
		Infections and infestations	Cystitis	Grade 2	19/09/2019	No	Recovery	NK/09/2019	No	No	TRAITEMENT EN MONODOSE	No dose modification		.
		Gastrointestinal disorders	Abdominal distension	Grade 1	NK/07/2019	No	Recovery	NK/08/2019	Yes	No	BOSUTINIB	No dose modification		.
		Psychiatric disorders	Anxiety	Grade 2	31/07/2019	No	Recovery	NK/08/2019	No	No		.		.
		Metabolism and nutrition disorders	Decreased appetite	Grade 2	NK/08/2019	No	Recovery	NK/11/2019	No	No		.		.
11-17	15/12/2018	General disorders and administration site conditions	Asthenia	Grade 2	10/01/2019	No	Recovery	16/05/2019	Yes	No	BOSUTINIB	No dose modification		.
		Gastrointestinal disorders	Constipation	Grade 1	10/01/2019	No	Recovery	16/05/2019	No	No	BOSUTINIB	No dose modification		.
		Musculoskeletal and connective tissue disorders	Arthralgia	Grade 1	10/01/2019	No	Recovery	NK/07/2020	Yes	No	BOSUTINIB	No dose modification		.

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		Respiratory, thoracic and mediastinal disorders	Dyspnoea exertional	Grade 1	10/01/2019	No	Recovery	16/05/2019	Yes	No	BOSUTINIB	No dose modification		.
		Psychiatric disorders	Insomnia	Grade 1	10/01/2019	No	Recovery	16/05/2019	No	No	BOSUTINIB	No dose modification		.
		Skin and subcutaneous tissue disorders	Psoriasis	Grade 1	10/01/2019	No	Recovery	16/05/2019	Yes	No	BOSUTINIB	No dose modification		.
		Immune system disorders	Food allergy	Grade 2	28/03/2019	Yes	Recovery	30/03/2019	No	No	BOSUTINIB	No dose modification		.
		Gastrointestinal disorders	Gastrointestinal motility disorder	Grade 1	16/05/2019	No	Recovery	21/11/2019	No	No	BOSUTINIB	No dose modification		.
		Musculoskeletal and connective tissue disorders	Arthralgia	Grade 2	NK/01/2020	Yes	Recovery	27/02/2020	No	No	BOSUTINIB	No dose modification		.
		General disorders and administration site conditions	Asthenia	Grade 2	UK/12/2019	No	Recovery	30/04/2020	Yes	No	BOSUTINIB	Dose reduction		.
		Skin and subcutaneous tissue disorders	Eczema	Grade 1	UK/12/2018	No	Recovery	30/04/2020	Yes	No	BOSUTINIB	Dose reduction		.
		Musculoskeletal and connective tissue disorders	Arthralgia	Grade 2	NK/07/2020	No	Subject not recovered		Yes	No	BOSUTINIB	Withdrawal (temporary or permanent, or deferred administration)		.

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		Respiratory, thoracic and mediastinal disorders	Dyspnoea exertional	Grade 1	NK/10/2020	No	Recovery	NK/11/2020	No	Yes	BOSULIF	Not applicable	DASATINIB	Withdrawal (temporary or permanent, or deferred administration)
		Respiratory, thoracic and mediastinal disorders	Dyspnoea exertional	Grade 1	NK/11/2021	No	Subject not recovered		No	No	BOSULIF	No dose modification		.
		Musculoskeletal and connective tissue disorders	Pain in extremity	Grade 1	NK/11/2021	No	Subject not recovered		No	No	BOSULIF	No dose modification		.
		Respiratory, thoracic and mediastinal disorders	Pleural effusion	Grade 2	05/11/2020	No	Recovery	NK/11/2020	No	Yes	BOSULIF	Not applicable	DASATINIB	Withdrawal (temporary or permanent, or deferred administration)
		Respiratory, thoracic and mediastinal disorders	Cough	Grade 1	NK/10/2020	No	Recovery	NK/11/2020	No	Yes	BOSULIF	Not applicable	DASATINIB	Withdrawal (temporary or permanent, or deferred administration)

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		General disorders and administration site conditions	Oedema	Grade 1	NK/02/2021	No	Recovery	NK/03/2021	No	Yes	BOSULIF	No dose modification	BIPRETERAX	Withdrawal (temporary or permanent, or deferred administration)
11-18	12/11/2018	Gastrointestinal disorders	Diarrhoea	Grade 1	04/12/2018	No	Recovery	04/12/2018	Yes	No	BOSUTINIB	No dose modification		.
		Gastrointestinal disorders	Diarrhoea	Grade 2	16/01/2019	No	Subject not recovered		Yes	No	BOSUTINIB	No dose modification		.
		Eye disorders	Eyelid ptosis	Grade 1	K	No	Recovery	15/01/2019	No	No	BOSUTINIB	Withdrawal (temporary or permanent, or deferred administration)		.
		Infections and infestations	Bronchitis	Grade 2	NK/12/2018	No	Recovery	NK/12/2018	No	No	BOSUTINIB	No dose modification		.
		Skin and subcutaneous tissue disorders	Urticaria	Grade 2	08/04/2019	No	Recovery	03/05/2019	No	No	BOSUTINIB	No dose modification		.
		Infections and infestations	Laryngitis	Grade 1	08/04/2019	No	Recovery	NK/05/2019	No	No	BOSUTINIB	No dose modification		.
		Musculoskeletal and connective tissue disorders	Flank pain	Grade 1	NK/10/2019	No	Recovery	30/10/2019	No	No	BOSUTINIB	No dose modification		.
		Skin and subcutaneous tissue disorders	Nail pigmentation	Grade 2	NK/03/2019	No	Recovery in progress		Yes	No	BOSULIF	No dose modification		.

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		Infections and infestations	Urinary tract infection	Grade 2	26/10/2020	No	Recovery	17/11/2020	No	No	BOFULIF	No dose modification		.
		Musculoskeletal and connective tissue disorders	Periarthritis	Grade 1	28/04/2020	No	Recovery in progress		No	No		Not applicable		.
		Respiratory, thoracic and mediastinal disorders	Sleep apnoea syndrome	Grade 1	21/06/2019	No	Recovery in progress		No	No	BOSULIF	No dose modification		.
		Musculoskeletal and connective tissue disorders	Spinal osteoarthritis	Grade 2	NK/04/2020	No	Recovery	NK/NK/2020	No	No	BOSULIF	No dose modification		.
		Skin and subcutaneous tissue disorders	Dry skin	Grade 1	NK/11/2019	No	Recovery	NK/NK/2020	No	No	BOSULIF	No dose modification		.
		Infections and infestations	Folliculitis	Grade 1	26/12/2019	No	Recovery	NK/NK/2020	No	No	BOSULIF	No dose modification		.
		Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Seborrhoeic keratosis	Grade 2	09/12/2021	No	Recovery in progress		No	No	BOSULIF	No dose modification		.
		Vascular disorders	Varicose vein	Grade 1	09/12/2021	No	Subject not recovered		No	No	BOSULIF	No dose modification		.
		Gastrointestinal disorders	Oral mucosa erosion	Grade 1	10/12/2020	No	Recovery	NK/12/2020	No	No	BOSULIF	No dose modification		.
		Eye disorders	Eyelid disorder	Grade 1	26/12/2019	No	Recovery	NK/NK/2020	No	No	BOSULIF	No dose modification		.
		Gastrointestinal disorders	Abdominal pain lower	Grade 2	NK/NK/2021	No	Recovery	NK/05/2021	No	No	BOSULIF	No dose modification		.
		Nervous system disorders	Headache	Grade 1	NK/04/2020	No	Recovery	NK/NK/2020	No	No	BOSULIF	No dose modification		.

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11-19	08/11/2018	Gastrointestinal disorders	Abdominal pain upper	Grade 1	08/11/2018	No	Recovery	NK/12/2019	Yes	No	BOSUTINIB	No dose modification		.
		General disorders and administration site conditions	Influenza like illness	Grade 2	23/02/2019	No	Recovery	24/02/2019	No	No	BOSUTINIB	No dose modification		.
		General disorders and administration site conditions	Asthenia	Grade 1	24/02/2019	No	Recovery	NK/03/2019	No	No	BOSUTINIB	No dose modification		.
		Musculoskeletal and connective tissue disorders	Myalgia	Grade 1	14/04/2020	No	Recovery	NK/NK/2020	No	No	BOSUTINIB	No dose modification		.
11-20	20/05/2019	Gastrointestinal disorders	Nausea	Grade 2	30/05/2019	No	Recovery	15/06/2019	Yes	No	BOSUTINIB	No dose modification		.
		Gastrointestinal disorders	Vomiting	Grade 1	02/06/2019	No	Recovery	24/06/2019	Yes	No	BOSUTINIB	No dose modification		.
		Gastrointestinal disorders	Diarrhoea	Grade 3	02/06/2019	No	Recovery	08/06/2019	Yes	No	BOSUTINIB	No dose modification		.
		Gastrointestinal disorders	Dyspepsia	Grade 1	NK/09/2019	No	Recovery	18/06/2020	Yes	No	BOSUTINIB	Dose reduction		.
		Gastrointestinal disorders	Abdominal pain upper	Grade 1	NK/09/2019	No	Recovery	18/06/2020	Yes	No	BOSUTINIB	Dose reduction		.
		General disorders and administration site conditions	Asthenia	Grade 1	24/06/2019	No	Recovery	04/07/2019	No	No	BOSUTINIB	No dose modification		.
		Gastrointestinal disorders	Abdominal pain	Grade 2	20/02/2020	No	Recovery	28/02/2020	Yes	No	BOSUTINIB	No dose modification		.
		Gastrointestinal disorders	Abdominal pain	Grade 2	07/03/2020	No	Recovery	27/03/2020	Yes	No	BOSUTINIB	Dose reduction		.

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		Nervous system disorders	Anosmia	Grade 2	27/02/2020	No	Recovery	10/03/2020	No	No	BOSUTINIB	No dose modification		.
		Skin and subcutaneous tissue disorders	Pityriasis	Grade 1	12/04/2020	No	Recovery	10/05/2020	No	No	BOSUTINIB	No dose modification		.
		Infections and infestations	Corona virus infection	Grade 1	NK/02/2020	No	Recovery	NK/03/2020	No	No	BOSUTINIB	No dose modification		.
		Gastrointestinal disorders	Abdominal pain upper	Grade 1	02/12/2021	No	Recovery	09/06/2022	No	No	BOSULIF	No dose modification		.
		Skin and subcutaneous tissue disorders	Alopecia	Grade 1	NK/NK/2021	No	Recovery	09/06/2022	No	No	BOSULIF	No dose modification		.
11-21	06/07/2019	Hepatobiliary disorders	Hepatocellular injury	Grade 1	19/08/2019	No	Recovery	11/09/2019	Yes	No	BOSUTINIB	Dose reduction		.
		Gastrointestinal disorders	Diarrhoea	Grade 1	18/08/2019	No	Recovery	03/10/2019	Yes	No	BOSUTINIB	Dose reduction		.
		Gastrointestinal disorders	Nausea	Grade 1	06/07/2019	No	Recovery	09/07/2019	Yes	No	BOSUTINIB	No dose modification		.
		Skin and subcutaneous tissue disorders	Rash	Grade 1	06/08/2019	No	Recovery	03/10/2019	Yes	No	BOSUTINIB	Dose reduction		.
		Musculoskeletal and connective tissue disorders	Musculoskeletal pain	Grade 1	NK/12/2019	No	Subject not recovered		No	No	BOSUTINIB	No dose modification		.
		Respiratory, thoracic and mediastinal disorders	Sleep apnoea syndrome	Grade 1	NK/12/2019	No	Recovery	11/06/2022	No	No	BOSUTINIB	No dose modification		.
		Gastrointestinal disorders	Abdominal hernia	Grade 1	30/01/2020	No	Subject not recovered		No	No	BOSUTINIB	Dose reduction		.

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		Musculoskeletal and connective tissue disorders	Musculoskeletal pain	Grade 2	NK/NK/2020	No	Subject not recovered		No	No	BOSUTINIB	No dose modification		.
		Hepatobiliary disorders	Cholelithiasis	Grade 2	03/11/2020	No	Subject not recovered		No	No	BOSUTINIB	No dose modification		.
		Gastrointestinal disorders	Gastric ulcer	Grade 2	NK/02/2020	No	Subject not recovered		No	No	BOSUTINIB	Dose increase		.
		Musculoskeletal and connective tissue disorders	Muscle spasms	Grade 1	NK/04/2020	No	Recovery	NK/04/2020	Yes	No	BOSUTINIB	Dose reduction		.
		Infections and infestations	Skin infection	Grade 1	06/11/2021	No	Recovery	18/11/2021	No	No	BOSUTINIB	No dose modification		.
		Respiratory, thoracic and mediastinal disorders	Dyspnoea	Grade 1	21/03/2022	No	Recovery in progress		No	No	BOSUTINIB	No dose modification		.
		Gastrointestinal disorders	Gastrointestinal disorder	Grade 2	NK/12/2020	No	Recovery	NK/05/2021	Yes	No	BOSULIF	No dose modification		.
		Musculoskeletal and connective tissue disorders	Back pain	Grade 1	NK/06/2020	No	Recovery in progress		No	No	BOSULIF	Not applicable		.
		Nervous system disorders	Axonal neuropathy	Grade 3	NK/07/2022	Yes	Subject not recovered		Yes	No	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.
		Renal and urinary disorders	Renal artery stenosis	Grade 2	01/09/2022	No	Subject not recovered		No	No	BOSULIF	No dose modification		.

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		Renal and urinary disorders	Renal cyst	Grade 1	01/09/2022	No	Subject not recovered		No	No	BOSULIF	No dose modification		.
		Infections and infestations	Diverticulitis	Grade 1	01/09/2022	No	Subject not recovered		No	No	BOSULIF	No dose modification		.
		Hepatobiliary disorders	Hepatic steatosis	Grade 1	03/11/2020	No	Subject not recovered		No	No	BOSULIF	No dose modification		.
		Reproductive system and breast disorders	Benign prostatic hyperplasia	Grade 1	03/11/2020	No	Subject not recovered		No	No	BOSULIF	No dose modification		.
11-22	10/11/2019	Gastrointestinal disorders	Diarrhoea	Grade 1	14/11/2019	No	Recovery	NK/NK/2020	Yes	No	BOSULIF	No dose modification		.
		Infections and infestations	Pharyngitis	Grade 1	29/11/2019	No	Recovery	NK/12/2019	No	No	BOSULIF	No dose modification		.
		Respiratory, thoracic and mediastinal disorders	Dyspnoea	Grade 2	13/06/2020	Yes	Recovery	NK/09/2020	No	No	BOSULIF	No dose modification		.
		Respiratory, thoracic and mediastinal disorders	Pleural effusion	Grade 2	13/07/2020	No	Recovery	14/10/2020	Yes	No	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.
		Respiratory, thoracic and mediastinal disorders	Pleural effusion	Grade 2	15/01/2021	No	Recovery	04/02/2021	Yes	No	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.

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		Musculoskeletal and connective tissue disorders	Osteoarthritis	Grade 4	27/02/2021	Yes	Recovery	NK/02/2021	No	No	NILOTINIB	No dose modification		.
		Gastrointestinal disorders	Diarrhoea	Grade 2	05/11/2020	No	Recovery	04/02/2021	Yes	No	BOSUTINIB	No dose modification		.
		Endocrine disorders	Basedow's disease	Grade 2	20/11/2021	No	Subject not recovered		No	No	NILOTINIB	No dose modification	BOSULIF	Not applicable
		Cardiac disorders	Atrial fibrillation	Grade 2	02/12/2021	No	Subject not recovered		No	No	NILOTINIB	No dose modification	BOSULIF	Not applicable
		Infections and infestations	Corona virus infection	Grade 1	NK/01/2022	No	Recovery	31/01/2022	No	No	NILOTINIB	No dose modification		.
		Respiratory, thoracic and mediastinal disorders	Lung disorder	Grade 2	15/01/2022	No	Recovery	NK/02/2022	No	No	NILOTINIB	No dose modification		.
		Metabolism and nutrition disorders	Dehydration	Grade 3	26/04/2022	No	Recovery	15/05/2022	No	No	NILOTINIB	No dose modification		.
		Renal and urinary disorders	Acute kidney injury	Grade 3	26/04/2022	No	Recovery	15/05/2022	No	Yes	NILOTINIB	No dose modification	BISOPROLOL	Withdrawal (temporary or permanent, or deferred administration)
		Respiratory, thoracic and mediastinal disorders	Pleural effusion	Grade 2	01/05/2022	No	Subject not recovered		No	Yes	NILOTINIB	No dose modification		.
		Renal and urinary disorders	Chronic kidney disease	Grade 3	UK/06/2022	No	Subject not recovered		No	Yes	BOSULIF	Not applicable	NILOTINIB	No dose modification

Patient No.	Date of initiation of bosutinib treatment	SOC name	PT name	CTCAE grade	Date of occurrence	Is the event serious?	Status	Date of recovery	Is it reasonably possible that the event may be related to the study medication?	Is it reasonably possible that the event may be related to a concomitant drug?	Name of the drug (1)	Action taken (1)	Name of the drug (2)	Action taken (2)
		Gastrointestinal disorders	Diarrhoea	Grade 3	05/10/2022	No	Recovery	10/10/2022	No	Yes	BOSULIF	Not applicable	NILOTINIB	No dose modification
		Nervous system disorders	Carotid artery stenosis	Grade 2	04/03/2021	No	Subject not recovered		No	Yes	BOSUTINIB	Not applicable	NILOTINIB	No dose modification
		Metabolism and nutrition disorders	Dyslipidaemia	Grade 2	NK/05/2021	No	Subject not recovered		No	Yes	BOSUTINIB	Not applicable	NILOTINIB	No dose modification
11-23	09/12/2019	Hepatobiliary disorders	Hepatocellular injury	Grade 3	23/01/2020	No	Recovery	03/02/2020	Yes	No	BOSUTINIB	Dose reduction	BOSUTINIB	Withdrawal (temporary or permanent, or deferred administration)
		General disorders and administration site conditions	Fatigue	Grade 1	NK/NK/2020	No	Recovery	10/01/2020	No	No	BOSUTINIB	No dose modification		.
		Hepatobiliary disorders	Hepatocellular injury	Grade 2	12/03/2020	No	Recovery	16/04/2020	Yes	No	BOSUTINIB	Dose reduction	BOSUTINIB	Withdrawal (temporary or permanent, or deferred administration)
		Skin and subcutaneous tissue disorders	Rash	Grade 1	NK/06/2020	No	Recovery	NK/06/2020	No	No	BOSUTIF	No dose modification		.
		Infections and infestations	Fungal infection	Grade 1	NK/01/2021	No	Recovery	NK/NK/2021	No	No	BOSUTINIB	Not applicable		.
		Cardiac disorders	Atrial fibrillation	Grade 2	NK/NK/2020	No	Recovery	NK/01/2021	No	No	BOSUTUNIB	Not applicable		.

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		Vascular disorders	Arteriosclerosis	Grade 2	14/06/2021	No	Subject not recovered		No	No	BOSUTINIB	Not applicable		.
		General disorders and administration site conditions	Polyp	Grade 3	11/09/2021	Yes	Recovery	06/01/2022	No	No	BOSUTINIB	Not applicable		.
		Vascular disorders	Hypotension	Grade 1	NK/12/2020	No	Recovery	NK/12/2020	No	Yes	BOSUTINIB	Not applicable	PERINDOPRIL	Dose reduction
		General disorders and administration site conditions	Fatigue	Grade 1	16/04/2021	No	Recovery	NK/NK/2021	No	No	BOSUTINIB	Not applicable		.
		Skin and subcutaneous tissue disorders	Dry skin	Grade 1	10/01/2022	No	Recovery	12/04/2022	No	No	BOSUTINIB	Not applicable		.
11-24	29/12/2019	Gastrointestinal disorders	Diarrhoea	Grade 1	NK/01/2020	No	Recovery	23/04/2020	Yes	No	BOSUTINIB	No dose modification		.
		Gastrointestinal disorders	Salivary hypersecretion	Grade 1	NK/01/2020	No	Recovery	15/03/2020	No	No	BOSUTINIB	No dose modification		.
		Hepatobiliary disorders	Hepatocellular injury	Grade 2	06/04/2020	No	Recovery	28/04/2020	Yes	No	BOSUTINIB	Dose reduction		.
		Nervous system disorders	Sciatica	Grade 2	NK/01/2022	No	Subject not recovered		No	No	BOSULIF	Not applicable	NILOTINIB	No dose modification
		General disorders and administration site conditions	Hernia	Grade 1	NK/01/2022	No	Subject not recovered		No	No	BOSULIF	Not applicable	NILOTINIB	No dose modification
		Gastrointestinal disorders	Abdominal pain	Grade 1	NK/10/2021	No	Recovery	NK/10/2021	No	No	NILOTINIB	No dose modification		.
		Musculoskeletal and connective tissue disorders	Intervertebral disc protrusion	Grade 1	NK/01/2021	No	Recovery in progress		No	No	NILOTINIB	No dose modification		.

Patient No.	Date of initiation of bosutinib treatment	SOC name	PT name	CTCAE grade	Date of occurrence	Is the event serious?	Status	Date of recovery	Is it reasonably possible that the event may be related to the study medication?	Is it reasonably possible that the event may be related to a concomitant drug?	Name of the drug (1)	Action taken (1)	Name of the drug (2)	Action taken (2)
		Gastrointestinal disorders	Constipation	Grade 1	NK/11/2020	No	Recovery	18/03/2021	No	No	NILOTINIB	No dose modification		.
		Musculoskeletal and connective tissue disorders	Myalgia	Grade 1	NK/08/2020	No	Recovery	NK/NK/2020	Yes	No	NILOTINIB	No dose modification		.
11-25	16/12/2019	Gastrointestinal disorders	Diarrhoea	Grade 2	26/12/2019	No	Recovery	17/01/2020	Yes	No	BOSUTINIB	Dose reduction		.
		Musculoskeletal and connective tissue disorders	Osteoarthritis	Grade 2	26/12/2019	No	Subject not recovered		No	No	BOSUTINIB	No dose modification		.
		Eye disorders	Cystoid macular oedema	Grade 2	01/06/2020	No	Subject not recovered		No	No	BOSUTINIB	No dose modification		.
		Skin and subcutaneous tissue disorders	Pruritus	Grade 2	NK/06/2020	No	Recovery	NK/NK/2021	Yes	No	BOSUTINIB	No dose modification		.
		Nervous system disorders	Headache	Grade 1	04/03/2021	No	Recovery	NK/04/2021	No	No	BOSUTINIB	No dose modification		.
		Gastrointestinal disorders	Diarrhoea	Grade 1	NK/09/2021	No	Recovery	NK/07/2022	Yes	No	BOSUTINIB	Withdrawal (temporary or permanent, or deferred administration)		.
		Nervous system disorders	Memory impairment	Grade 1	NK/12/2020	No	Recovery in progress		No	No	BOSUTINIB	No dose modification		.
		Psychiatric disorders	Sleep disorder	Grade 1	NK/12/2020	No	Recovery in progress		No	No	BOSUTINIB	No dose modification		.

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		Nervous system disorders	Dizziness	Grade 1	NK/12/2020	No	Recovery	NK/NK/2021	No	No	BOSUTINIB	No dose modification		.
		General disorders and administration site conditions	Chest pain	Grade 1	K	No	Recovery in progress		No	No	BOSUTINIB	No dose modification		.
		Gastrointestinal disorders	Diarrhoea	Grade 1	NK/04/2021	No	Recovery	NK/04/2021	Yes	No	BOSUTINIB	No dose modification		.
		Musculoskeletal and connective tissue disorders	Pain in extremity	Grade 1	NK/09/2021	No	Recovery	31/03/2022	No	No	BOSUTINIB	No dose modification		.
		Infections and infestations	Nasopharyngitis	Grade 2	25/03/2022	No	Recovery	01/04/2022	No	No	BOSUTINIB	No dose modification		.
		Nervous system disorders	Sciatica	Grade 2	02/03/2021	No	Recovery	NK/03/2021	No	No	BOSUTINIB	No dose modification		.
		General disorders and administration site conditions	Drug intolerance	Grade 1	NK/10/2021	No	Recovery	NK/10/2021	No	Yes	BOSULIF	No dose modification	DIAMOX	Withdrawal (temporary or permanent, or deferred administration)
		General disorders and administration site conditions	Asthenia	Grade 1	NK/NK/2022	No	Subject not recovered		No	No	BOSULIF	No dose modification		.
		General disorders and administration site conditions	Pain	Grade 2	UK/06/2020	No	Recovery	10/08/2022	No	No	BOSULIF	No dose modification		.
		Infections and infestations	Corona virus infection	Grade 2	24/06/2022	No	Recovery	01/07/2022	No	No	BOSULIF	No dose modification		.

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		Psychiatric disorders	Depression	Grade 1	NK/NK/2020	No	Subject not recovered		No	No	BOSULIF	No dose modification		.
		Gastrointestinal disorders	Hiatus hernia	Grade 2	NK/NK/2022	No	Recovery in progress		No	No	BOSUTINIB	Not applicable	DASATINIB	No dose modification
		Cardiac disorders	Pericardial effusion	Grade 2	NK/02/2023	No	Subject not recovered		No	Yes	BOSUTINIB	Not applicable	DASATINIB	Withdrawal (temporary or permanent, or deferred administration)
		Infections and infestations	Influenza	Grade 2	14/02/2023	No	Recovery in progress		No	No	BOSUTINIB	Not applicable	DASATINIB	No dose modification
		General disorders and administration site conditions	Oedema peripheral	Grade 1	07/03/2023	No	Subject not recovered		No	No	BOSUTINIB	Not applicable	DASATINIB	No dose modification
		Cardiac disorders	Cardiomegaly	Grade 1	06/03/2023	No	Subject not recovered		No	No	BOSULIF	Not applicable	DASATINIB	No dose modification
		Respiratory, thoracic and mediastinal disorders	Dyspnoea	Grade 1	06/03/2023	No	Subject not recovered		No	No	BOSULIF	Not applicable	DASATINIB	No dose modification
		Gastrointestinal disorders	Diarrhoea	Grade 1	17/01/2020	No	Recovery	UK/UK/2020	Yes	No	BOSULIF	No dose modification		.
12-01	31/05/2016	Nervous system disorders	Headache	Grade 2	02/06/2016	No	Recovery	13/12/2016	Yes	No		No dose modification		.
		Infections and infestations	Bronchitis	Grade 2	13/12/2016	No	Recovery	18/12/2016	No	No	BOSULIF®, BOSUTINIB	No dose modification		.

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		Endocrine disorders	Thyroid mass	Grade 1	04/11/2016	No	Subject not recovered		No	No	BOSULIF®, BOSUTINIB	No dose modification			.
		Gastrointestinal disorders	Diarrhoea	Grade 1	11/04/2017	No	Recovery	08/08/2017	No	No	BOSULIF	No dose modification			.
		Reproductive system and breast disorders	Benign prostatic hyperplasia	Grade 1	NK/NK/2017	No	Subject not recovered		No	No	BOSULIF	No dose modification			.
		Vascular disorders	Arteriosclerosis	Grade 2	29/03/2018	No	Subject not recovered		Yes	No	BOSULIF	Dose reduction			.
		Metabolism and nutrition disorders	Dyslipidaemia	Grade 2	NK/03/2017	No	Recovery	31/08/2017	Yes	No	BOSULIF	No dose modification			.
		Metabolism and nutrition disorders	Vitamin D deficiency	Grade 2	NK/08/2017	No	Recovery	29/03/2018	No	No	BOSULIF	No dose modification			.
		Renal and urinary disorders	Renal failure	Grade 2	NK/03/2017	No	Subject not recovered		Yes	No	BOSULIF	No dose modification			.
		Musculoskeletal and connective tissue disorders	Back pain	Grade 1	NK/02/2018	No	Recovery	NK/02/2018	No	No	BOSULIF	Not applicable			.
		Respiratory, thoracic and mediastinal disorders	Asthma	Grade 2	NK/06/2018	No	Recovery	30/10/2018	No	No	BOSULIF	Not applicable			.
12-02	03/06/2016	Metabolism and nutrition disorders	Decreased appetite	Grade 3	03/06/2016	No	Recovery	12/09/2016	Yes	No	BOSULIF®, BOSUTINIB	Withdrawal (temporary or permanent, or deferred administration)			.

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		General disorders and administration site conditions	Fatigue	Grade 2	03/06/2016	No	Recovery	12/09/2016	Yes	No	BOSULIF®, BOSUTINIB	Withdrawal (temporary or permanent, or deferred administration)		.
		General disorders and administration site conditions	Hyperthermia	Grade 1	03/06/2016	No	Recovery	13/07/2016	Yes	No		No dose modification		.
		Nervous system disorders	Headache	Grade 1	03/06/2016	No	Recovery	13/07/2016	Yes	No		No dose modification		.
		Respiratory, thoracic and mediastinal disorders	Dysphonia	Grade 1	13/07/2016	No	Recovery	03/08/2016	No	No		Not applicable		.
		Renal and urinary disorders	Acute kidney injury	Grade 2	05/06/2016	Yes	Recovery	06/06/2016	No	No	BOSULIF®, BOSUTINIB	No dose modification		.
		Gastrointestinal disorders	Diarrhoea	Grade 2	03/06/2016	No	Recovery	12/09/2016	Yes	No	BOSULIF®, BOSUTINIB	Withdrawal (temporary or permanent, or deferred administration)		.
		Gastrointestinal disorders	Nausea	Grade 2	03/06/2016	No	Recovery	12/09/2016	Yes	No	BOSULIF®, BOSUTINIB	Withdrawal (temporary or permanent, or deferred administration)		.

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		Infections and infestations	Bronchitis	Grade 2	11/10/2016	No	Recovery with sequellae	NK/12/2016	No	No	SPRYCEL	Dose reduction	BOSULIF	Not applicable
		Infections and infestations	Bronchitis	Grade 2	NK/12/2016	No	Recovery	03/01/2017	No	No		Not applicable		.
		Cardiac disorders	Cardiac failure	Grade 2	14/12/2016	Yes	Recovery with sequellae	03/01/2017	No	No		Not applicable		.
		Cardiac disorders	Cardiac failure	Grade 2	12/02/2017	Yes	Recovery with sequellae	21/02/2017	No	No		Not applicable		.
		Respiratory, thoracic and mediastinal disorders	Pleural effusion	Grade 2	13/04/2017	Yes	Recovery with sequellae	13/04/2017	No	Yes	SPRYCEL	Withdrawal (temporary or permanent, or deferred administration)		.
		Infections and infestations	Otitis media acute	Grade 2	01/04/2017	No	Recovery	NK/04/2017	No	No		Not applicable		.
		Renal and urinary disorders	Acute kidney injury	Grade 2	10/04/2017	Yes	Recovery	14/04/2017	No	Yes	CANDESARTAN	Withdrawal (temporary or permanent, or deferred administration)		.
		Cardiac disorders	Palpitations	Grade 1	23/08/2017	No	Recovery	23/08/2017	No	No		Not applicable		.
		Respiratory, thoracic and mediastinal disorders	Dyspnoea	Grade 1	23/08/2017	No	Recovery	23/08/2017	No	No		Not applicable		.
		Cardiac disorders	Cardiac failure	Grade 2	29/03/2018	Yes	Recovery	30/03/2018	No	No		Not applicable		.

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		General disorders and administration site conditions	Oedema peripheral	Grade 1	15/03/2018	No	Recovery	20/07/2018	No	No		Not applicable		.
		Respiratory, thoracic and mediastinal disorders	Dyspnoea	Grade 1	NK/NK/2018	No	Recovery	20/07/2018	No	No		Not applicable		.
		Ear and labyrinth disorders	Deafness unilateral	Grade 2	NK/NK/2017	No	Subject not recovered		No	No		Not applicable		.
		Infections and infestations	Onychomycosis	Grade 1	NK/04/2017	No	Recovery	NK/04/2017	No	No		Not applicable		.
		Metabolism and nutrition disorders	Vitamin D deficiency	Grade 1	10/04/2017	No	Recovery	14/04/2017	No	No		Not applicable		.
		Musculoskeletal and connective tissue disorders	Back pain	Grade 1	26/07/2017	No	Recovery	02/10/2017	No	No		Not applicable		.
		Ear and labyrinth disorders	Vestibular disorder	Grade 2	12/04/2017	No	Subject not recovered		No	No		Not applicable		.
		General disorders and administration site conditions	Fatigue	Grade 1	01/10/2016	No	Recovery	30/10/2016	No	Yes		Not applicable		.
		Metabolism and nutrition disorders	Decreased appetite	Grade 1	26/10/2016	No	Recovery	03/01/2017	No	Yes		Not applicable		.
		General disorders and administration site conditions	Oedema peripheral	Grade 1	23/08/2017	No	Recovery	02/10/2017	No	No		Not applicable		.
		General disorders and administration site conditions	Asthenia	Grade 1	NK/03/2018	No	Subject not recovered		No	No	BOSULIF	Not applicable		.
		Infections and infestations	Herpes zoster	Grade 1	NK/NK/2018	No	Subject not recovered		No	No	BOSULIF	Not applicable		.
		Metabolism and nutrition disorders	Gout	Grade 2	NK/NK/2018	No	Recovery	NK/NK/2018	No	No	BOSULIF	Not applicable		.

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		Cardiac disorders	Cardiac failure	Grade 3	28/08/2018	Yes	Recovery	14/09/2018	No	No	BOSULIF	Not applicable		.
		Infections and infestations	Ear infection	Grade 2	NK/07/2017	No	Recovery	NK/07/2017	No	No	BOSULIF	Not applicable		.
		Infections and infestations	Onychomycosis	Grade 1	08/10/2018	No	Recovery	05/11/2018	No	No	BOSULIF	Not applicable		.
		Nervous system disorders	Cognitive disorder	Grade 2	NK/11/2018	No	Subject not recovered		No	No	BOSULIF	Not applicable		.
		Respiratory, thoracic and mediastinal disorders	Chronic obstructive pulmonary disease	Grade 2	NK/NK/2018	No	Subject not recovered		No	No	BOSULIF	Not applicable		.
		Reproductive system and breast disorders	Prostatitis	Grade 2	18/02/2019	No	Recovery	11/03/2019	No	No	BOSULIF	Not applicable		.
		Renal and urinary disorders	Polyuria	Grade 2	NK/02/2019	No	Subject not recovered		No	No	BOSULIF	Not applicable		.
		Eye disorders	Cataract	Grade 2	NK/NK/2016	Yes	Recovery	20/12/2016	No	No	BOSULIF	Not applicable		.
		Nervous system disorders	Areflexia	Grade 1	10/04/2017	No	Subject not recovered		No	No	BOSULIF	Not applicable		.
		Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Prostatic adenoma	Grade 2	NK/NK/2019	No	Subject not recovered		No	No	BOSULIF	Not applicable		.
		Infections and infestations	Bronchitis	Grade 3	NK/04/2019	Yes	Recovery	NK/06/2019	No	No	BOSULIF	Not applicable		.
		Cardiac disorders	Cardiac failure	Grade 2	NK/05/2019	Yes	Recovery	NK/06/2019	No	No	BOSULIF	Not applicable		.
		Respiratory, thoracic and mediastinal disorders	Sleep apnoea syndrome	Grade 3	NK/NK/2019	Yes	Subject not recovered		No	No	BOSULIF	Not applicable		.
		Gastrointestinal disorders	Vomiting	Grade 2	03/06/2016	No	Recovery	27/07/2016	Yes	No	BOSULIF	No dose modification		.
		General disorders and administration site conditions	Asthenia	Grade 1	NK/03/2017	No	Recovery	NK/03/2017	No	No	BOSULIF	Not applicable		.

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12-03	30/06/2016	Gastrointestinal disorders	Diarrhoea	Grade 2	NK/07/2016	No	Recovery	06/07/2017	Yes	No	BOSULIF®, BOSUTINIB	Withdrawal (temporary or permanent, or deferred administration)		.
		General disorders and administration site conditions	Fatigue	Grade 2	NK/07/2016	No	Recovery	30/08/2017	Yes	No	BOSULIF®, BOSUTINIB	Dose reduction		.
		Vascular disorders	Hypotension	Grade 1	NK/08/2016	No	Recovery	22/02/2017	Yes	No	BOSULIF	Dose reduction		.
		General disorders and administration site conditions	Inflammation	Grade 2	24/08/2016	No	Recovery	30/08/2017	Yes	No	BOSULIF®, BOSUTINIB	Dose reduction		.
		Hepatobiliary disorders	Hepatomegaly	Grade 2	26/10/2016	No	Subject not recovered		No	No	BOSULIF	No dose modification		.
		Respiratory, thoracic and mediastinal disorders	Dyspnoea exertional	Grade 1	NK/NK/2017	No	Recovery	21/06/2017	No	No	BOSULIF	No dose modification		.
		Cardiac disorders	Tachycardia	Grade 1	22/02/2017	No	Recovery	21/06/2017	No	No		No dose modification		.
		Hepatobiliary disorders	Hepatic fibrosis	Grade 2	29/05/2017	No	Subject not recovered		No	No	BOSULIF	No dose modification		.
		Investigations	Weight decreased	Grade 2	22/02/2017	No	Recovery	16/06/2018	Yes	No	BOSULIF®, BOSUTINIB	No dose modification		.
		General disorders and administration site conditions	Oedema peripheral	Grade 1	29/05/2017	No	Recovery	21/06/2017	No	No	BOSULIF	No dose modification		.

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		Metabolism and nutrition disorders	Folate deficiency	Grade 1	21/07/2017	No	Unknown		No	No	BOSULIF	No dose modification		.
		Metabolism and nutrition disorders	Hypercalcaemia	Grade 1	06/07/2017	No	Recovery	30/08/2017	No	No		.	BOSULIF	Not applicable
		Metabolism and nutrition disorders	Hyperkalaemia	Grade 1	06/07/2017	No	Recovery	07/07/2017	No	No	BOSULIF	Not applicable		.
		General disorders and administration site conditions	Asthenia	Grade 2	06/12/2017	No	Recovery	22/10/2018	No	Yes	BOSULIF	Not applicable	SPRYCEL	No dose modification
		Reproductive system and breast disorders	Gynaecomastia	Grade 1	31/08/2017	No	Subject not recovered		No	No	BOSULIF	Not applicable	SPRYCEL	No dose modification
		Respiratory, thoracic and mediastinal disorders	Pleural effusion	Grade 3	23/10/2018	Yes	Recovery	21/11/2018	No	Yes	BOSULIF	Not applicable	SPRYCEL	Withdrawal (temporary or permanent, or deferred administration)
		Respiratory, thoracic and mediastinal disorders	Acute respiratory failure	Grade 2	09/11/2018	Yes	Recovery	19/02/2019	No	No	BOSULIF	Not applicable	SPRYCEL	No dose modification
		Respiratory, thoracic and mediastinal disorders	Pulmonary arterial hypertension	Grade 3	NK/11/2018	Yes	Recovery	19/02/2019	No	No	BOSULIF	Not applicable	SPRYCEL	No dose modification
		Respiratory, thoracic and mediastinal disorders	Hypoventilation	Grade 2	NK/NK/2019	Yes	Subject not recovered		No	No	BOSULIF	Not applicable	IMATINIB	No dose modification
		Respiratory, thoracic and mediastinal disorders	Sleep apnoea syndrome	Grade 2	NK/NK/2019	Yes	Subject not recovered		No	No	BOSULIF	Not applicable	IMATINIB	No dose modification

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		Infections and infestations	Infection	Grade 2	NK/10/2018	No	Recovery	NK/11/2018	No	No	BOSULIF	Not applicable	SPRYCEL	No dose modification
12-04	13/09/2018	Gastrointestinal disorders	Diarrhoea	Grade 2	14/09/2018	No	Recovery	16/09/2018	Yes	No	BOSULIF®, BOSUTINIB	Withdrawal (temporary or permanent, or deferred administration)		.
		Gastrointestinal disorders	Diarrhoea	Grade 2	27/09/2018	No	Recovery	15/10/2018	Yes	No	BOSULIF®, BOSUTINIB	Dose reduction	BOSUTINIB	Withdrawal (temporary or permanent, or deferred administration)
		Hepatobiliary disorders	Hepatocellular injury	Grade 3	09/10/2018	No	Recovery	30/04/2019	Yes	No	BOSULIF®, BOSUTINIB	Withdrawal (temporary or permanent, or deferred administration)		.
		Vascular disorders	Hypertensive crisis	Grade 1	30/04/2019	No	Recovery	30/04/2019	No	No	BOSULIF	Not applicable		.
		Musculoskeletal and connective tissue disorders	Myalgia	Grade 1	NK/05/2019	No	Recovery	NK/NK/2019	No	Yes	BOSULIF	Not applicable	IMATINIB	No dose modification
		Gastrointestinal disorders	Gastrointestinal disorder	Grade 1	NK/06/2019	No	Recovery	23/02/2021	No	Yes	BOSULIF	Not applicable	IMATINIB	No dose modification

Patient No.	Date of initiation of bosutinib treatment	SOC name	PT name	CTCAE grade	Date of occurrence	Is the event serious?	Status	Date of recovery	Is it reasonably possible that the event may be related to the study medication?	Is it reasonably possible that the event may be related to a concomitant drug?	Name of the drug (1)	Action taken (1)	Name of the drug (2)	Action taken (2)
		Musculoskeletal and connective tissue disorders	Muscle spasms	Grade 1	NK/06/2019	No	Recovery	23/02/2021	No	Yes	BOSULIF	Not applicable	IMATINIB	No dose modification
		Injury, poisoning and procedural complications	Limb injury	Grade 3	NK/NK/2020	Yes	Recovery	14/04/2020	No	No	BOSULIF	Not applicable	IMATINIB	No dose modification
		Infections and infestations	Upper respiratory tract infection	Grade 2	NK/06/2020	No	Recovery	NK/07/2020	No	No	BOSULIF	Not applicable	IMATINIB	No dose modification
		Blood and lymphatic system disorders	Anaemia	Grade 1	NK/NK/2019	No	Subject not recovered		No	Yes	BOSULIF	Not applicable	IMATINIB	No dose modification
		Gastrointestinal disorders	Tooth disorder	Grade 2	NK/NK/2019	No	Recovery	NK/NK/2020	No	No	BOSULIF	Not applicable	IMATINIB	No dose modification
		Skin and subcutaneous tissue disorders	Intertrigo	Grade 2	NK/08/2021	No	Recovery	NK/10/2021	No	Yes	BOSULIF	Not applicable	IMATINIB	No dose modification
		Skin and subcutaneous tissue disorders	Dry skin	Grade 1	NK/08/2021	No	Recovery	NK/10/2021	No	Yes	BOSULIF	Not applicable	IMATINIB	No dose modification
		Gastrointestinal disorders	Nausea	Grade 1	NK/08/2021	No	Subject not recovered		No	Yes	BOSULIF	Not applicable	IMATINIB	No dose modification
		Gastrointestinal disorders	Vomiting	Grade 1	NK/08/2021	No	Subject not recovered		No	Yes	BOSUMIF	Not applicable	IMATINIB	No dose modification
		General disorders and administration site conditions	Asthenia	Grade 1	NK/10/2020	No	Recovery	23/02/2021	No	Yes	BOSULIF	Not applicable	IMATINIB	No dose modification
		Gastrointestinal disorders	Diarrhoea	Grade 1	NK/10/2020	No	Recovery	23/02/2021	No	Yes	BOSULIF	Not applicable	IMATINIB	No dose modification
12-05	14/11/2018	Gastrointestinal disorders	Abdominal pain	Grade 2	NK/11/2018	No	Recovery in progress		Yes	No	BOSULIF	Dose reduction		.

Patient No.	Date of initiation of bosutinib treatment	SOC name	PT name	CTCAE grade	Date of occurrence	Is the event serious?	Status	Date of recovery	Is it reasonably possible that the event may be related to the study medication?	Is it reasonably possible that the event may be related to a concomitant drug?	Name of the drug (1)	Action taken (1)	Name of the drug (2)	Action taken (2)
		Gastrointestinal disorders	Nausea	Grade 2	NK/11/2018	No	Recovery	13/02/2019	Yes	No	BOSULIF	No dose modification		.
		Gastrointestinal disorders	Diarrhoea	Grade 2	NK/11/2018	No	Recovery in progress		Yes	No	BOSULIF	Dose reduction		.
		Infections and infestations	Cystitis	Grade 2	NK/02/2019	No	Recovery	03/06/2019	No	No	BOSULIF	No dose modification		.
		Skin and subcutaneous tissue disorders	Alopecia	Grade 1	NK/12/2019	No	Recovery	30/09/2020	No	No	BOSULIF	No dose modification		.
		Infections and infestations	Influenza	Grade 1	17/03/2020	No	Recovery	NK/NK/2020	No	No	BOSULIF	No dose modification		.
		Metabolism and nutrition disorders	Iron deficiency	Grade 2	30/09/2020	No	Subject not recovered		No	No	BOSULIF	No dose modification		.
		General disorders and administration site conditions	Fatigue	Grade 1	17/12/2019	No	Recovery	27/05/2020	Yes	No	BOSULIF	No dose modification		.
12-06	02/04/2019	Hepatobiliary disorders	Hepatocellular injury	Grade 2	20/05/2019	No	Recovery	11/06/2019	Yes	No	BOSULIF	Dose reduction	BOSUTINIB	Withdrawal (temporary or permanent, or deferred administration)
		Vascular disorders	Peripheral artery stenosis	Grade 3	02/09/2019	Yes	Recovery	29/11/2019	No	No	BOSULIF	No dose modification		.
		Respiratory, thoracic and mediastinal disorders	Chronic obstructive pulmonary disease	Grade 3	24/01/2020	Yes	Recovery	30/01/2020	No	No	BOSULIF	No dose modification		.

Patient No.	Date of initiation of bosutinib treatment	SOC name	PT name	CTCAE grade	Date of occurrence	Is the event serious?	Status	Date of recovery	Is it reasonably possible that the event may be related to the study medication?	Is it reasonably possible that the event may be related to a concomitant drug?	Name of the drug (1)	Action taken (1)	Name of the drug (2)	Action taken (2)
		Musculoskeletal and connective tissue disorders	Muscle spasms	Grade 1	NK/NK/2020	No	Recovery	10/08/2021	No	Yes	BOSULIF	No dose modification	ATORVASTATINE	Dose reduction
		Musculoskeletal and connective tissue disorders	Tendon pain	Grade 1	NK/NK/2020	No	Recovery	10/08/2021	No	Yes	BOSULIF	No dose modification	ATORVASTATINE	Dose reduction
		Infections and infestations	Nasopharyngitis	Grade 2	20/01/2020	No	Recovery	25/01/2020	No	No	BOSULIF	No dose modification		.
		Blood and lymphatic system disorders	Lymphopenia	Grade 1	10/08/2021	No	Recovery	01/02/2022	Yes	No	BOSULIF	No dose modification		.
		Ear and labyrinth disorders	Tinnitus	Grade 2	NK/NK/2022	No	Subject not recovered		No	No	BOSULIF	No dose modification		.
13-01	26/03/2016	Blood and lymphatic system disorders	Anaemia	Grade 3	13/04/2016	Yes	Recovery	13/07/2016	Yes	No		No dose modification		.
		General disorders and administration site conditions	Pyrexia	Grade 2	13/04/2016	No	Recovery	17/04/2016	No	No		No dose modification		.
		Psychiatric disorders	Paranoia	Grade 3	19/04/2016	No	Recovery	25/05/2016	No	Yes		No dose modification		.
		Injury, poisoning and procedural complications	Head injury	Grade 1	21/04/2016	No	Recovery	21/04/2016	No	No		No dose modification		.
		Infections and infestations	Urinary tract infection	Grade 2	26/04/2016	No	Recovery	25/05/2016	No	No		No dose modification		.
		Gastrointestinal disorders	Constipation	Grade 2	22/05/2016	No	Recovery	22/05/2016	No	No		No dose modification		.
		Skin and subcutaneous tissue disorders	Rash	Grade 1	11/05/2016	No	Recovery	24/05/2016	No	No		No dose modification		.

Patient No.	Date of initiation of bosutinib treatment	SOC name	PT name	CTCAE grade	Date of occurrence	Is the event serious?	Status	Date of recovery	Is it reasonably possible that the event may be related to the study medication?	Is it reasonably possible that the event may be related to a concomitant drug?	Name of the drug (1)	Action taken (1)	Name of the drug (2)	Action taken (2)
		General disorders and administration site conditions	Oedema peripheral	Grade 1	13/04/2016	No	Recovery	NK/NK/2016	No	No		No dose modification		.
		Psychiatric disorders	Insomnia	Grade 1	14/04/2016	No	Recovery	18/06/2016	No	No		No dose modification		.
		Metabolism and nutrition disorders	Hypokalaemia	Grade 1	15/04/2016	No	Recovery	22/04/2016	Yes	No		No dose modification		.
		General disorders and administration site conditions	General physical health deterioration	Grade 5	26/07/2016	Yes	Subject not recovered		No	No		Withdrawal (temporary or permanent, or deferred administration)		.
13-02	09/05/2016	Renal and urinary disorders	Renal colic	Grade 1	12/04/2017	No	Recovery	19/04/2017	No	No	TRAITEMENT SYMPTOMATIQUE INCONNU	No dose modification		.
13-03	12/12/2016	Gastrointestinal disorders	Nausea	Grade 2	13/12/2016	No	Recovery	02/03/2017	Yes	No		No dose modification		.
		Renal and urinary disorders	Acute kidney injury	Grade 2	23/02/2017	No	Recovery	17/03/2017	Yes	No	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.
		Cardiac disorders	Cardiac failure	Grade 3	24/01/2017	Yes	Recovery	22/03/2017	No	No	BOSULIF	No dose modification		.

Patient No.	Date of initiation of bosutinib treatment	SOC name	PT name	CTCAE grade	Date of occurrence	Is the event serious?	Status	Date of recovery	Is it reasonably possible that the event may be related to the study medication?	Is it reasonably possible that the event may be related to a concomitant drug?	Name of the drug (1)	Action taken (1)	Name of the drug (2)	Action taken (2)
		Metabolism and nutrition disorders	Decreased appetite	Grade 2	NK/12/2016	No	Recovery	02/03/2017	Yes	No	BOSULIF	No dose modification		.
		Cardiac disorders	Arrhythmia supraventricular	Grade 2	NK/03/2017	Yes	Recovery	22/03/2017	No	No	BOSULIF	Not applicable		.
		Respiratory, thoracic and mediastinal disorders	Dyspnoea	Grade 2	NK/04/2017	No	Subject not recovered		No	Yes	BOSULIF	Not applicable	SPRYCEL	No dose modification
		General disorders and administration site conditions	Asthenia	Grade 2	NK/04/2017	No	Recovery	NK/NK/2017	No	Yes	BOSULIF	Not applicable	SPRYCEL	No dose modification
		Investigations	Liver function test abnormal	Grade 2	NK/03/2017	No	Recovery	22/01/2018	No	Yes	BOSULIF	Not applicable	SPRYCEL	No dose modification
		Musculoskeletal and connective tissue disorders	Arthralgia	Grade 1	NK/03/2017	No	Unknown		No	No	BOSULIF	Not applicable	SPRYCEL	No dose modification
		Endocrine disorders	Hypothyroidism	Grade 2	26/07/2017	No	Recovery	22/01/2018	No	No	BOSULIF	Not applicable	SPRYCEL	No dose modification
		Cardiac disorders	Cardiac failure	Grade 2	NK/NK/2018	No	Recovery	07/05/2018	No	Yes	BOSULIF	Not applicable	LEVOTHYROX	Dose reduction
		Metabolism and nutrition disorders	Gout	Grade 2	NK/NK/2018	No	Recovery	NK/NK/2018	No	No	BOSULIF	Not applicable		.
		Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Monoclonal gammopathy	Grade 1	NK/03/2017	No	Recovery	NK/03/2017	No	No	BOSULIF	No dose modification		.
		Renal and urinary disorders	Renal failure	Grade 3	23/04/2019	Yes	Recovery	26/06/2019	No	No	BOSULIF	Not applicable		.
		Musculoskeletal and connective tissue disorders	Arthritis	Grade 3	NK/08/2019	Yes	Recovery	NK/09/2019	No	Yes	BOSULIF	Not applicable	DIURETIQUES	Dose reduction

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		Reproductive system and breast disorders	Gynaecomastia	Grade 2	NK/NK/2020	No	Subject not recovered		No	No	BOSULIF	Not applicable		.
		Investigations	Weight decreased	Grade 2	NK/NK/2017	No	Recovery	02/03/2017	No	No	BOSULIF	Not applicable	SPRYCEL	Not applicable
		Investigations	Weight increased	Grade 3	12/06/2017	No	Recovery	07/05/2018	No	No	BOSULIF	Not applicable	SPRYCEL	Not applicable
		Skin and subcutaneous tissue disorders	Dermatitis	Grade 1	NK/11/2017	No	Recovery	NK/01/2018	No	No	BOSULIF	Not applicable		.
		Renal and urinary disorders	Renal failure	Grade 2	17/03/2017	No	Subject not recovered		No	No	BOSULIF	Not applicable		.
13-04	15/03/2018	Infections and infestations	Bronchitis	Grade 2	19/04/2018	No	Recovery	25/04/2018	No	No		No dose modification		.
		General disorders and administration site conditions	Asthenia	Grade 2	15/03/2018	No	Recovery	27/08/2018	Yes	No	BOSULIF	Dose reduction		.
		Renal and urinary disorders	Pollakiuria	Grade 1	13/03/2018	No	Recovery	27/08/2018	Yes	No		No dose modification		.
		Musculoskeletal and connective tissue disorders	Osteoarthritis	Grade 3	17/09/2018	Yes	Recovery	04/12/2018	No	No	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.
		Vascular disorders	Arterial occlusive disease	Grade 3	20/09/2018	Yes	Subject not recovered		No	No	BOSULIF	No dose modification		.
		Blood and lymphatic system disorders	Anaemia	Grade 2	05/06/2019	No	Recovery	16/12/2019	No	No	BOSULIF	No dose modification		.

Patient No.	Date of initiation of bosutinib treatment	SOC name	PT name	CTCAE grade	Date of occurrence	Is the event serious?	Status	Date of recovery	Is it reasonably possible that the event may be related to the study medication?	Is it reasonably possible that the event may be related to a concomitant drug?	Name of the drug (1)	Action taken (1)	Name of the drug (2)	Action taken (2)
		Infections and infestations	Localised infection	Grade 2	NK/09/2019	No	Recovery	16/12/2019	No	No	BOSULIF	No dose modification		.
		Skin and subcutaneous tissue disorders	Vascular skin disorder	Grade 3	04/02/2019	No	Subject not recovered		No	No	BOSULIF	No dose modification		.
		General disorders and administration site conditions	Condition aggravated	Grade 5	02/02/2020	Yes	Subject not recovered		No	No		Unknown		.
13-05	07/02/2018	Gastrointestinal disorders	Constipation	Grade 1	27/08/2018	No	Recovery	09/12/2018	No	No	BOSUTINIB	No dose modification		.
		Gastrointestinal disorders	Dry mouth	Grade 2	27/05/2019	No	Subject not recovered		Yes	No	BOSUTINIB	Dose reduction		.
13-06	12/04/2018	Renal and urinary disorders	Renal failure	Grade 3	20/06/2018	Yes	Recovery	03/07/2018	Yes	No	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.
		Cardiac disorders	Cardiac failure	Grade 3	20/06/2018	Yes	Recovery	03/07/2018	Yes	No	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.
		Infections and infestations	Sepsis	Grade 3	20/06/2018	No	Recovery	26/06/2018	No	No	BOSUTINIB	No dose modification		.
		Gastrointestinal disorders	Melaena	Grade 2	08/06/2018	No	Recovery	12/06/2018	Yes	No	BOSULIF	No dose modification		.

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		Vascular disorders	Hypotension	Grade 2	NK/10/2018	Yes	Recovery	NK/11/2018	No	No	BOSULIF	Not applicable		.
		Investigations	Weight decreased	Grade 2	NK/10/2018	No	Subject not recovered		No	No	BOSULIF	Not applicable		.
		Skin and subcutaneous tissue disorders	Dermatitis bullous	Grade 1	NK/10/2018	No	Recovery	26/11/2018	No	No	BOSULIF	Not applicable		.
		Vascular disorders	Hypotension	Grade 2	NK/04/2019	No	Recovery	NK/04/2019	No	Yes	BOSULIF	Not applicable	ESIDREX	Withdrawal (temporary or permanent, or deferred administration)
		Skin and subcutaneous tissue disorders	Eczema	Grade 1	NK/04/2019	No	Recovery	NK/01/2020	No	Yes	BOSULIF	Not applicable	ELIQUIS	No dose modification
		General disorders and administration site conditions	Therapeutic response decreased	Grade 2	21/01/2019	No	Recovery	25/09/2019	No	No	BOSULIF	Not applicable		.
		General disorders and administration site conditions	Oedema peripheral	Grade 2	NK/04/2019	No	Recovery	NK/09/2019	No	No	BOSULIF	Not applicable		.
		Skin and subcutaneous tissue disorders	Pruritus	Grade 2	NK/09/2019	No	Recovery	NK/01/2020	No	Yes	BOSULIF	Not applicable	GLIVEC	Withdrawal (temporary or permanent, or deferred administration)
		Musculoskeletal and connective tissue disorders	Arthralgia	Grade 3	NK/01/2020	Yes	Recovery	04/08/2020	No	No	BOSULIF	Not applicable		.

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		Blood and lymphatic system disorders	Anaemia	Grade 3	09/06/2020	No	Recovery	09/06/2020	No	No	BOSULIF	Not applicable		.
		Musculoskeletal and connective tissue disorders	Arthralgia	Grade 1	NK/10/2020	No	Recovery	NK/01/2021	No	No	BOSULIF	Not applicable		.
		General disorders and administration site conditions	Therapeutic response decreased	Grade 2	04/08/2020	No	Subject not recovered		No	No	BOSULIF	Not applicable		.
13-07	02/05/2019	General disorders and administration site conditions	Asthenia	Grade 1	04/05/2019	No	Subject not recovered		Yes	No	BOSUTINIB	No dose modification		.
		Skin and subcutaneous tissue disorders	Pruritus	Grade 1	04/05/2019	No	Recovery	NK/05/2019	Yes	No	BOSUTINIB	No dose modification		.
		Ear and labyrinth disorders	Vertigo	Grade 2	NK/02/2020	No	Subject not recovered		Yes	No	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.
		Gastrointestinal disorders	Diarrhoea	Grade 3	NK/10/2020	No	Recovery	21/12/2020	No	No	BOSULIF	Not applicable		.
		General disorders and administration site conditions	Drug ineffective	Grade 2	01/08/2019	No	Recovery	16/01/2020	Yes	No	BOSULIF	Dose increase		.
		Vascular disorders	Hypertension	Grade 2	22/10/2019	No	Recovery	22/10/2020	No	No	BOSULIF	No dose modification		.
		Musculoskeletal and connective tissue disorders	Myalgia	Grade 2	22/10/2019	No	Recovery	16/01/2020	No	No	BOSULIF	No dose modification		.

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		Respiratory, thoracic and mediastinal disorders	Dyspnoea	Grade 2	UK/12/2020	No	Subject not recovered		Yes	No	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.
		Respiratory, thoracic and mediastinal disorders	Sleep apnoea syndrome	Grade 1	02/02/2021	No	Subject not recovered		No	No	BOSULIF	No dose modification		.
		Musculoskeletal and connective tissue disorders	Arthralgia	Grade 3	NK/NK/2021	Yes	Recovery	15/12/2021	No	No	BOSULIF	No dose modification		.
		General disorders and administration site conditions	Oedema peripheral	Grade 1	NK/06/2020	No	Recovery	NK/08/2021	No	No	BOSULIF	Not applicable		.
		Eye disorders	Eyelid oedema	Grade 1	29/06/2021	No	Recovery	NK/08/2021	Yes	No	BOSULIF	No dose modification		.
		Psychiatric disorders	Anxiety	Grade 2	UK/UK/2020	No	Subject not recovered		No	No	BOSULIF	No dose modification		.
15-01	04/04/2016			.		.	.		.	.		.		.
15-02	23/05/2016	Gastrointestinal disorders	Diarrhoea	Grade 2	24/05/2016	No	Recovery	27/06/2016	Yes	No	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.
		Surgical and medical procedures	Angioplasty	Grade 3	07/11/2016	Yes	Recovery	05/04/2017	No	No	BOSULIF	Not applicable	SPRYCEL	No dose modification

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		Skin and subcutaneous tissue disorders	Eczema	Grade 1	NK/01/2017	No	Recovery	11/04/2017	No	No	BOSULIF	Not applicable	SPRYCEL	Unknown
		Injury, poisoning and procedural complications	Ankle fracture	Grade 2	NK/01/2017	No	Recovery	11/04/2017	No	No	BOSULIF	Not applicable	SPRYCEL	No dose modification
		Gastrointestinal disorders	Gastric ulcer	Grade 2	02/06/2017	Yes	Recovery	30/08/2017	No	No	BOSULIF	Not applicable	SPRYCEL	No dose modification
		Gastrointestinal disorders	Hiatus hernia	Grade 1	02/06/2017	Yes	Recovery	30/08/2017	No	No	BOSULIF	Not applicable	SPRYCEL	No dose modification
		Gastrointestinal disorders	Oesophagitis	Grade 1	02/06/2017	Yes	Recovery	30/08/2017	No	No	BOSULIF	Not applicable	SPRYCEL	No dose modification
		Gastrointestinal disorders	Erosive duodenitis	Grade 1	02/06/2017	Yes	Recovery	30/08/2017	No	No	BOSULIF	Not applicable	SPRYCEL	No dose modification
15-03	12/04/2017	Respiratory, thoracic and mediastinal disorders	Chronic obstructive pulmonary disease	Grade 1	09/07/2018	No	Recovery	29/05/2019	No	No	BOSULIF	No dose modification		.
		Gastrointestinal disorders	Diarrhoea	Grade 1	26/07/2018	No	Subject not recovered		Yes	No	BOSULIF	No dose modification		.
		Infections and infestations	Urinary tract infection	Grade 1	K	No	Unknown		No	No		.		.
		Respiratory, thoracic and mediastinal disorders	Hypoxia	Grade 1	UN/01/2020	No	Unknown		No	No		.		.
15-05	14/05/2018	Investigations	Intestinal transit time increased	Grade 2	NK/05/2018	No	Recovery	20/08/2018	Yes	No	BOSULIF	No dose modification		.
		Infections and infestations	Nasopharyngitis	Grade 2	NK/12/2018	No	Recovery	NK/NK/2019	No	No	BOSULIF	No dose modification		.

Patient No.	Date of initiation of bosutinib treatment	SOC name	PT name	CTCAE grade	Date of occurrence	Is the event serious?	Status	Date of recovery	Is it reasonably possible that the event may be related to the study medication?	Is it reasonably possible that the event may be related to a concomitant drug?	Name of the drug (1)	Action taken (1)	Name of the drug (2)	Action taken (2)
		Respiratory, thoracic and mediastinal disorders	Pleural effusion	Grade 1	08/04/2021	No	Recovery in progress		Yes	No	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.
		Infections and infestations	Infection	Grade 1	01/06/2018	No	Recovery	NK/06/2018	No	No	BOSULIF	No dose modification		.
		Musculoskeletal and connective tissue disorders	Back pain	Grade 1	NK/05/2018	No	Recovery	07/12/2018	No	No	BOSULIF	No dose modification		.
		Vascular disorders	Hot flush	Grade 1	NK/05/2018	No	Recovery	11/06/2018	No	No	BOSULIF	No dose modification		.
		Metabolism and nutrition disorders	Decreased appetite	Grade 1	NK/05/2018	No	Recovery	11/06/2018	No	No	BOSULIF	No dose modification		.
		Gastrointestinal disorders	Diarrhoea	Grade 1	NK/09/2018	No	Recovery	07/12/2018	Yes	No	BOSULIF	No dose modification		.
		Gastrointestinal disorders	Abdominal pain	Grade 1	NK/12/2018	No	Recovery	07/12/2018	Yes	No	BOSULIF	No dose modification		.
15-06	14/01/2019	Skin and subcutaneous tissue disorders	Rash	Grade 1	15/07/2019	No	Recovery	30/09/2019	Yes	No	BOSULIF	No dose modification		.
		Gastrointestinal disorders	Diarrhoea	Grade 1	NK/01/2019	No	Recovery	28/01/2019	Yes	No	BOSULIF	No dose modification		.

Patient No.	Date of initiation of bosutinib treatment	SOC name	PT name	CTCAE grade	Date of occurrence	Is the event serious?	Status	Date of recovery	Is it reasonably possible that the event may be related to the study medication?	Is it reasonably possible that the event may be related to a concomitant drug?	Name of the drug (1)	Action taken (1)	Name of the drug (2)	Action taken (2)
		Cardiac disorders	Pericarditis	Grade 3	12/09/2019	Yes	Recovery	19/09/2019	Yes	No	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.
		Ear and labyrinth disorders	Tinnitus	Grade 1	NK/04/2019	No	Recovery	17/07/2019	Yes	No	BOSULIF	No dose modification		.
		Cardiac disorders	Pericarditis	Grade 1	29/11/2019	Yes	Recovery	13/01/2020	Yes	No	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.
		Psychiatric disorders	Insomnia	Grade 1	NK/04/2019	No	Recovery	17/07/2019	Yes	No	BOSULIF	No dose modification		.
		General disorders and administration site conditions	Asthenia	Grade 1	NK/03/2019	No	Recovery	17/07/2019	Yes	No	BOSULIF	No dose modification		.
		General disorders and administration site conditions	Influenza like illness	Grade 1	NK/03/2019	No	Recovery	18/03/2019	No	No	BOSULIF	No dose modification		.
		Investigations	Lipase increased	Grade 1	15/03/2019	No	Recovery	16/04/2019	Yes	No	BOSULIF	No dose modification		.
		General disorders and administration site conditions	Chest pain	Grade 1	NK/01/2020	No	Recovery	24/03/2020	No	Yes	BOSULIF	Not applicable	IMATINIB	No dose modification
		Respiratory, thoracic and mediastinal disorders	Cough	Grade 1	NK/01/2020	No	Recovery	NK/01/2020	No	Yes	BOSULIF	Not applicable	IMATINIB	No dose modification

Patient No.	Date of initiation of bosutinib treatment	SOC name	PT name	CTCAE grade	Date of occurrence	Is the event serious?	Status	Date of recovery	Is it reasonably possible that the event may be related to the study medication?	Is it reasonably possible that the event may be related to a concomitant drug?	Name of the drug (1)	Action taken (1)	Name of the drug (2)	Action taken (2)
		Musculoskeletal and connective tissue disorders	Myalgia	Grade 1	04/02/2020	No	Recovery	24/03/2020	No	Yes	BOSULIF	Not applicable	IMATINIB	No dose modification
		Musculoskeletal and connective tissue disorders	Muscle spasms	Grade 1	NK/02/2020	No	Recovery	24/03/2020	No	Yes	BOSULIF	Not applicable	IMATINIB	No dose modification
		Eye disorders	Eyelid oedema	Grade 1	18/02/2020	No	Recovery	03/03/2020	No	Yes	BOSULIF	Not applicable	IMATINIB	No dose modification
		Investigations	Blood creatinine increased	Grade 1	18/02/2020	No	Recovery	23/06/2020	No	Yes	BOSULIF	Not applicable	IMATINIB	No dose modification
		Nervous system disorders	Headache	Grade 1	23/03/2020	No	Recovery	14/05/2020	No	Yes	BOSULIF	Not applicable	IMATINIB	No dose modification
		Respiratory, thoracic and mediastinal disorders	Dyspnoea	Grade 1	08/04/2020	No	Recovery	20/04/2020	No	Yes	BOSULIF	Not applicable	IMATINIB	No dose modification
		Gastrointestinal disorders	Abdominal pain upper	Grade 2	08/04/2020	No	Recovery	20/04/2020	No	Yes	BOSULIF	Not applicable	IMATINIB	No dose modification
		Eye disorders	Conjunctival haemorrhage	Grade 1	20/04/2020	No	Recovery	14/05/2020	No	Yes	BOSULIF	Not applicable	IMATINIB	No dose modification
		Infections and infestations	Corona virus infection	Grade 1	16/12/2021	No	Recovery	NK/12/2021	No	No	BOSULIF	Not applicable	IMATINIB	No dose modification
		Musculoskeletal and connective tissue disorders	Osteoarthritis	Grade 2	11/01/2021	Yes	Recovery	NK/02/2021	No	No	BOSULIF	Not applicable	IMATINIB	No dose modification

Patient No.	Date of initiation of bosutinib treatment	SOC name	PT name	CTCAE grade	Date of occurrence	Is the event serious?	Status	Date of recovery	Is it reasonably possible that the event may be related to the study medication?	Is it reasonably possible that the event may be related to a concomitant drug?	Name of the drug (1)	Action taken (1)	Name of the drug (2)	Action taken (2)
15-07	30/04/2019	Respiratory, thoracic and mediastinal disorders	Pleural effusion	Grade 2	07/07/2020	No	Recovery	27/01/2021	Yes	No	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)	IMATINIB	No dose modification
		Respiratory, thoracic and mediastinal disorders	Dysphonia	Grade 1	13/06/2019	No	Recovery	NK/07/2019	No	No	BOSULIF	No dose modification		.
		Gastrointestinal disorders	Diarrhoea	Grade 1	19/05/2019	No	Recovery	19/05/2019	No	No	BOSULIF	No dose modification		.
		Investigations	Weight increased	Grade 1	30/04/2019	No	Recovery	23/07/2019	No	No	BOSULIF	No dose modification		.
		Blood and lymphatic system disorders	Anaemia	Grade 1	28/05/2019	No	Recovery	27/06/2019	Yes	No	BOSULIF	No dose modification		.
		Musculoskeletal and connective tissue disorders	Muscle spasms	Grade 1	07/05/2019	No	Recovery	21/05/2019	No	No	BOSULIF	No dose modification		.
		Infections and infestations	Abdominal abscess	Grade 3	03/10/2019	Yes	Recovery with sequellae	18/10/2019	No	No	BOSULIF	No dose modification		.
		Infections and infestations	Abdominal abscess	Grade 2	NK/07/2020	No	Recovery in progress		No	No	BOSULIF	Not applicable	IMATINIB	No dose modification
		Investigations	Blood creatinine increased	Grade 2	28/05/2019	No	Recovery	02/03/2023	Yes	Yes	BOSULIF	Not applicable	IMATINIB	No dose modification
		Investigations	Blood urea increased	Grade 1	28/05/2019	No	Recovery	26/10/2021	Yes	No	BOSULIF	Not applicable	IMATINIB	No dose modification

Patient No.	Date of initiation of bosutinib treatment	SOC name	PT name	CTCAE grade	Date of occurrence	Is the event serious?	Status	Date of recovery	Is it reasonably possible that the event may be related to the study medication?	Is it reasonably possible that the event may be related to a concomitant drug?	Name of the drug (1)	Action taken (1)	Name of the drug (2)	Action taken (2)
		Musculoskeletal and connective tissue disorders	Muscle spasms	Grade 1	04/05/2021	No	Recovery	03/08/2021	Yes	No	BOSULIF	Not applicable	IMATINIB	No dose modification
		Vascular disorders	Hypertension	Grade 2	04/05/2021	No	Recovery	04/05/2021	No	No	BOSULIF	Not applicable	IMATINIB	No dose modification
15-08	06/11/2019	General disorders and administration site conditions	Generalised oedema	Grade 2	05/07/2021	Yes	Recovery	10/08/2021	Yes	No	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)	BOSULIF	Dose reduction
		Respiratory, thoracic and mediastinal disorders	Pleural effusion	Grade 2	05/07/2021	Yes	Subject not recovered		Yes	No	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.
		General disorders and administration site conditions	Asthenia	Grade 1	NK/05/2021	No	Recovery	09/11/2021	Yes	No	BOSULIF	No dose modification		.
		Skin and subcutaneous tissue disorders	Skin lesion	Grade 1	NK/05/2021	No	Recovery	10/08/2021	No	No	BOSULIF	No dose modification		.
		Metabolism and nutrition disorders	Iron deficiency	Grade 1	NK/05/2021	No	Recovery	09/11/2021	No	No	BOSULIF	No dose modification		.
		Investigations	Breath sounds abnormal	Grade 1	10/08/2021	No	Recovery	29/03/2022	No	No	BOSULIF	No dose modification		.
		Metabolism and nutrition disorders	Decreased appetite	Grade 1	29/03/2022	No	Subject not recovered		No	Yes	BOSULIF	Not applicable	IMATINIB	No dose modification

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		Respiratory, thoracic and mediastinal disorders	Dyspnoea	Grade 1	29/03/2022	No	Subject not recovered		No	No	BOSULIF	Not applicable		.
		Metabolism and nutrition disorders	Hypokalaemia	Grade 2	17/11/2022	No	Subject not recovered		No	No	BOSULIF	Not applicable	IMATINIB	No dose modification
16-01	21/03/2016	Injury, poisoning and procedural complications	Scratch	Grade 1	17/05/2016	No	Recovery	23/08/2016	Yes	No	BOSUTINIB	No dose modification		.
		Gastrointestinal disorders	Vomiting	Grade 1	22/03/2016	No	Recovery	NK/04/2016	Yes	No		No dose modification		.
		Gastrointestinal disorders	Diarrhoea	Grade 1	22/03/2016	No	Recovery	23/08/2016	Yes	No		Dose reduction		.
		Gastrointestinal disorders	Eructation	Grade 1	22/03/2016	No	Recovery	23/08/2016	Yes	No		No dose modification		.
		Gastrointestinal disorders	Abdominal pain	Grade 1	NK/08/2016	No	Recovery	16/12/2016	Yes	No		Dose reduction		.
		General disorders and administration site conditions	Asthenia	Grade 1	NK/08/2016	No	Recovery	16/12/2016	Yes	No		Dose reduction		.
		Nervous system disorders	Dizziness	Grade 1	NK/08/2016	No	Recovery	09/03/2018	Yes	No		Dose reduction		.
		Nervous system disorders	Tremor	Grade 2	NK/08/2016	Yes	Recovery	26/02/2019	No	No	BOSUTINIB	No dose modification		.
		Immune system disorders	Hypersensitivity	Grade 1	04/05/2016	No	Recovery	23/08/2016	No	No	BOSUTINIB	No dose modification		.

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		Skin and subcutaneous tissue disorders	Pruritus	Grade 2	16/12/2016	No	Recovery	11/05/2018	Yes	No		Withdrawal (temporary or permanent, or deferred administration)		.
		Cardiac disorders	Arrhythmia	Grade 1	NK/05/2017	No	Recovery	01/12/2017	No	No	BOSULIF	No dose modification		.
		Musculoskeletal and connective tissue disorders	Musculoskeletal chest pain	Grade 1	NK/05/2017	No	Recovery	01/12/2017	No	No	BOSUTINIB	No dose modification		.
		General disorders and administration site conditions	Reduced drug effect	Grade 1	19/05/2017	No	Recovery	12/10/2017	Yes	No	AUGMENTATION DE DOSE	Dose increase		.
		General disorders and administration site conditions	Pain	Grade 3	NK/03/2018	Yes	Recovery	21/03/2018	No	Yes		Dose reduction		.
		General disorders and administration site conditions	Reduced drug effect	Grade 3	09/03/2018	No	Recovery	11/05/2018	Yes	No		Withdrawal (temporary or permanent, or deferred administration)		.
		Gastrointestinal disorders	Nausea	Grade 2	16/12/2016	No	Recovery	19/05/2017	Yes	No		No dose modification		.
		Reproductive system and breast disorders	Testicular pain	Grade 1	10/12/2016	No	Recovery	19/05/2017	No	No		No dose modification		.
		Musculoskeletal and connective tissue disorders	Arthralgia	Grade 1	NK/03/2017	No	Recovery	19/05/2017	Yes	No		No dose modification		.

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		Nervous system disorders	Dizziness	Grade 1	NK/05/2017	No	Recovery	10/08/2017	No	Yes		No dose modification		.
		Gastrointestinal disorders	Diarrhoea	Grade 2	NK/05/2017	No	Recovery	01/12/2017	Yes	No		Dose reduction		.
		Psychiatric disorders	Irritability	Grade 1	01/12/2017	No	Recovery	09/03/2018	No	No		No dose modification		.
		Nervous system disorders	Headache	Grade 2	NK/02/2018	No	Recovery	09/03/2018	Yes	No	BOSUTINIB	Withdrawal (temporary or permanent, or deferred administration)		.
		Skin and subcutaneous tissue disorders	Skin lesion	Grade 1	09/03/2018	No	Recovery	11/05/2018	No	No	BOSUTINIB	No dose modification		.
		Nervous system disorders	Headache	Grade 2	NK/03/2018	No	Recovery	NK/03/2018	No	Yes	ICLUSIG	Dose reduction		.
		General disorders and administration site conditions	Asthenia	Grade 1	NK/03/2018	No	Recovery	NK/03/2018	Yes	Yes	ICLUSIG	Dose reduction		.
		Skin and subcutaneous tissue disorders	Hyperhidrosis	Grade 1	NK/03/2018	No	Recovery	NK/03/2018	No	Yes	ICLUSIG	Dose reduction		.
		Gastrointestinal disorders	Constipation	Grade 1	23/08/2016	No	Recovery	16/12/2016	Yes	No		No dose modification		.
		Renal and urinary disorders	Urinary tract disorder	Grade 1	NK/05/2018	No	Subject not recovered		No	No	BOSULIF	Not applicable	PONATINIB	No dose modification

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		Vascular disorders	Arteriosclerosis	Grade 1	NK/05/2018	No	Subject not recovered		No	No	BOSULIF	Not applicable	PONATINIB	Dose increase
		Cardiac disorders	Bradycardia	Grade 1	NK/10/2018	No	Recovery	NK/01/2019	No	No	BOSULIF	Not applicable	PONATINIB	No dose modification
		Gastrointestinal disorders	Constipation	Grade 1	NK/01/2019	No	Recovery	05/04/2019	No	Yes	PONATINIB	No dose modification		.
		Musculoskeletal and connective tissue disorders	Muscle spasms	Grade 1	NK/01/2019	No	Recovery	05/04/2019	No	Yes	PONATINIB	No dose modification		.
		Musculoskeletal and connective tissue disorders	Arthralgia	Grade 1	NK/01/2019	No	Recovery	05/04/2019	No	Yes	PONATINIB	No dose modification		.
		Skin and subcutaneous tissue disorders	Pruritus	Grade 1	NK/01/2019	No	Recovery	05/04/2019	No	Yes	PONATINIB	No dose modification		.
		Vascular disorders	Hypertension	Grade 2	NK/01/2019	No	Recovery	05/04/2019	No	Yes	PONATINIB	No dose modification		.
		Musculoskeletal and connective tissue disorders	Musculoskeletal pain	Grade 1	NK/03/2018	No	Subject not recovered		No	Yes	PONATINIB	No dose modification		.
16-02	03/06/2016	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Neoplasm progression	Grade 1	03/10/2017	No	Recovery	04/09/2018	Yes	No	BOSULIF	Dose increase		.
		Vascular disorders	Haematoma	Grade 1	06/03/2019	No	Recovery	NK/04/2019	No	No	BOSULIF	No dose modification		.
		Injury, poisoning and procedural complications	Hip fracture	Grade 3	NK/04/2019	Yes	Recovery in progress		No	No		No dose modification		.

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		Hepatobiliary disorders	Jaundice cholestatic	Grade 2	14/05/2019	No	Recovery in progress		Yes	No	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.
		Infections and infestations	Urinary tract infection	Grade 2	21/05/2019	No	Recovery	NK/06/2019	No	No	BOSULIF	No dose modification		.
		General disorders and administration site conditions	Inflammation	Grade 1	20/03/2018	No	Recovery	12/06/2018	No	No	BOSULIF	No dose modification		.
		Metabolism and nutrition disorders	Malnutrition	Grade 2	12/06/2018	No	Subject not recovered		No	No	BOSULIF	No dose modification		.
		Vascular disorders	Haematoma	Grade 1	NK/05/2019	No	Recovery in progress		No	No		No dose modification		.
		Blood and lymphatic system disorders	Anaemia	Grade 2	02/05/2019	No	Recovery	06/05/2019	No	No	BOSULIF	No dose modification		.
		Vascular disorders	Hypertension	Grade 3	02/05/2019	No	Subject not recovered		No	No		No dose modification		.
		Musculoskeletal and connective tissue disorders	Arthralgia	Grade 2	07/05/2019	No	Subject not recovered		No	No		No dose modification		.
		Metabolism and nutrition disorders	Vitamin D deficiency	Grade 2	16/05/2019	No	Subject not recovered		No	No		No dose modification		.

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16-03	24/07/2016	Respiratory, thoracic and mediastinal disorders	Lung disorder	Grade 4	NK/06/2018	Yes	Subject not recovered		Yes	No	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.
		Gastrointestinal disorders	Constipation	Grade 2	NK/NK/2016	No	Subject not recovered		No	Yes	DUROGESIC	No dose modification		.
		General disorders and administration site conditions	Multiviceral failure	Grade 5	30/10/2018	Yes	Subject not recovered		No	No	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.
		Infections and infestations	Urinary tract infection bacterial	Grade 2	UK/10/2018	No	Recovery in progress		No	No	BOSULIF	No dose modification		.
		Cardiac disorders	Cardiac failure	Grade 3	13/09/2016	Yes	Recovery	26/09/2016	No	No	BOSUTINIB	No dose modification		.
		Respiratory, thoracic and mediastinal disorders	Lung disorder	Grade 2	13/09/2016	No	Recovery	26/09/2016	No	No	BOSUTINIB	No dose modification		.
		Blood and lymphatic system disorders	Anaemia	Grade 2	13/09/2016	No	Recovery	26/09/2016	No	No	BOSUTINIB	No dose modification		.
		Metabolism and nutrition disorders	Decreased appetite	Grade 2	13/09/2016	No	Recovery	26/09/2016	No	No	BOSUTINIB	No dose modification		.
		Metabolism and nutrition disorders	Hyponatraemia	Grade 3	10/11/2016	Yes	Recovery	16/11/2016	Yes	No	BOSUTINIB	No dose modification		.

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		Gastrointestinal disorders	Diarrhoea	Grade 2	10/11/2016	No	Recovery	16/11/2016	Yes	No	BOSUTINIB	No dose modification		.
		Vascular disorders	Phlebitis	Grade 2	NK/02/2017	No	Recovery	NK/12/2017	No	No	BOSUTINIB	No dose modification		.
		Blood and lymphatic system disorders	Anaemia	Grade 2	21/09/2017	No	Recovery	NK/NK/2017	No	No	BOSUTINIB	No dose modification		.
		Infections and infestations	Ear infection	Grade 2	NK/10/2017	No	Recovery	31/10/2017	No	No	BOSUTINIB	No dose modification		.
		Vascular disorders	Arteritis	Grade 2	NK/12/2017	No	Recovery in progress		No	No	BOSUTINIB	No dose modification		.
		General disorders and administration site conditions	Oedema peripheral	Grade 1	24/04/2018	No	Recovery	NK/04/2018	No	No	BOSUTINIB	No dose modification		.
		General disorders and administration site conditions	General physical health deterioration	Grade 1	27/10/2016	No	Recovery	NK/11/2016	No	No	BOSUTINIB	No dose modification		.
16-04	06/10/2016	Cardiac disorders	Myocardial infarction	Grade 4	19/08/2017	Yes	Recovery	23/08/2017	No	No		No dose modification		.
		Infections and infestations	Bronchitis	Grade 2	10/09/2017	Yes	Recovery	07/12/2017	No	No	BOSUTINIB	No dose modification		.
		Respiratory, thoracic and mediastinal disorders	Pleural effusion	Grade 2	15/11/2017	No	Recovery	NK/11/2017	Yes	No	BOSUTINIB	Withdrawal (temporary or permanent, or deferred administration)		.

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		Renal and urinary disorders	Renal failure	Grade 3	30/12/2017	Yes	Recovery in progress		Yes	No	BOSUTINIB	Withdrawal (temporary or permanent, or deferred administration)		.
		Skin and subcutaneous tissue disorders	Pruritus	Grade 1	27/04/2017	No	Recovery	21/09/2017	No	No		No dose modification		.
		Gastrointestinal disorders	Diarrhoea	Grade 1	NK/03/2017	No	Recovery	21/09/2017	Yes	No		No dose modification		.
		Psychiatric disorders	Insomnia	Grade 1	NK/10/2016	No	Recovery	05/10/2017	No	No		No dose modification		.
		Respiratory, thoracic and mediastinal disorders	Cough	Grade 2	NK/10/2016	No	Recovery	UK/12/2016	No	No	BOSUTINIB	Withdrawal (temporary or permanent, or deferred administration)		.
		Respiratory, thoracic and mediastinal disorders	Dyspnoea	Grade 3	06/10/2016	No	Recovery	22/02/2018	No	No	BOSUTINIB	Withdrawal (temporary or permanent, or deferred administration)		.
		Musculoskeletal and connective tissue disorders	Arthralgia	Grade 1	06/10/2016	No	Recovery	NK/12/2016	No	No		No dose modification		.

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		Infections and infestations	Herpes simplex	Grade 1	26/10/2016	No	Recovery	NK/12/2016	No	No		No dose modification		.
		Infections and infestations	Infection	Grade 2	26/10/2016	No	Recovery	02/11/2016	No	No	BOSULIF	No dose modification		.
		Respiratory, thoracic and mediastinal disorders	Pleural effusion	Grade 2	10/09/2017	No	Recovery	NK/09/2017	Yes	No	BOSULIF	No dose modification		.
		Renal and urinary disorders	Nephrolithiasis	Grade 1	NK/08/2017	No	Recovery	31/05/2018	No	No		Not applicable		.
		Cardiac disorders	Cardiac failure	Grade 3	30/12/2017	Yes	Recovery	05/01/2018	Yes	No	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.
		Injury, poisoning and procedural complications	Omissions of a medication dose	Grade 1	NK/05/2017	No	Recovery	22/06/2017	Yes	No		No dose modification		.
		Injury, poisoning and procedural complications	Omissions of a medication dose	Grade 1	NK/11/2017	No	Recovery	07/12/2017	Yes	No		No dose modification		.
		General disorders and administration site conditions	Asthenia	Grade 3	02/11/2017	No	Recovery	22/02/2018	Yes	No	BOSUTINIB	Withdrawal (temporary or permanent, or deferred administration)		.

Patient No.	Date of initiation of bosutinib treatment	SOC name	PT name	CTCAE grade	Date of occurrence	Is the event serious?	Status	Date of recovery	Is it reasonably possible that the event may be related to the study medication?	Is it reasonably possible that the event may be related to a concomitant drug?	Name of the drug (1)	Action taken (1)	Name of the drug (2)	Action taken (2)
		General disorders and administration site conditions	General physical health deterioration	Grade 2	31/05/2018	No	Recovery	06/09/2018	Yes	No	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.
		Gastrointestinal disorders	Faecaloma	Grade 2	NK/NK/2019	No	Recovery	NK/NK/2019	No	No		Not applicable		.
		Skin and subcutaneous tissue disorders	Dry skin	Grade 1	NK/09/2018	No	Recovery	06/12/2018	No	Yes	GLIVEC	No dose modification		.
		Musculoskeletal and connective tissue disorders	Back pain	Grade 2	NK/NK/2019	No	Subject not recovered		No	No		Not applicable		.
		General disorders and administration site conditions	Oedema peripheral	Grade 1	NK/03/2019	No	Subject not recovered		No	Yes	GLIVEC	No dose modification		.
		General disorders and administration site conditions	Asthenia	Grade 1	NK/06/2019	No	Subject not recovered		No	Yes	GLIVEC	No dose modification		.
		Respiratory, thoracic and mediastinal disorders	Dyspnoea exertional	Grade 1	NK/06/2019	No	Subject not recovered		No	Yes	GLIVEC	No dose modification		.
		Eye disorders	Eyelid oedema	Grade 1	NK/09/2019	No	Subject not recovered		No	Yes	GLIVEC	No dose modification		.
16-05	12/12/2016	Gastrointestinal disorders	Diarrhoea	Grade 2	NK/02/2017	No	Recovery	20/02/2017	Yes	No	BOSUTINIB	Dose reduction		.

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		Gastrointestinal disorders	Abdominal pain	Grade 3	NK/01/2017	No	Recovery	12/02/2018	Yes	No	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.
		Investigations	Weight decreased	Grade 2	20/02/2017	No	Recovery	12/02/2018	Yes	Yes		Dose reduction		.
		Psychiatric disorders	Depression	Grade 2	20/02/2017	No	Recovery	18/12/2017	Yes	No		No dose modification		.
		Gastrointestinal disorders	Constipation	Grade 3	20/02/2017	No	Subject not recovered		No	Yes	DUROGESIC	Dose reduction	ICLUSIG	No dose modification
		General disorders and administration site conditions	Pain	Grade 3	07/06/2017	No	Recovery	12/02/2018	Yes	No	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.
		Metabolism and nutrition disorders	Decreased appetite	Grade 2	20/02/2017	No	Recovery	12/02/2018	Yes	No	BOSUTINIB	No dose modification		.
		Musculoskeletal and connective tissue disorders	Groin pain	Grade 1	NK/05/2018	No	Recovery	NK/NK/2018	No	No	BOSULIF	Not applicable		.
		Musculoskeletal and connective tissue disorders	Tendonitis	Grade 1	NK/05/2018	No	Recovery	NK/NK/2018	No	No	BOSULIF	Not applicable		.
		Gastrointestinal disorders	Toothache	Grade 2	NK/01/2019	No	Recovery	NK/01/2019	No	No		Not applicable		.

Patient No.	Date of initiation of bosutinib treatment	SOC name	PT name	CTCAE grade	Date of occurrence	Is the event serious?	Status	Date of recovery	Is it reasonably possible that the event may be related to the study medication?	Is it reasonably possible that the event may be related to a concomitant drug?	Name of the drug (1)	Action taken (1)	Name of the drug (2)	Action taken (2)
		Musculoskeletal and connective tissue disorders	Back pain	Grade 2	NK/11/2019	No	Subject not recovered		No	Yes	ICLUSIG	No dose modification		.
16-06	27/11/2017	Gastrointestinal disorders	Constipation	Grade 2	19/02/2018	No	Subject not recovered		No	No	BOSUTINIB	No dose modification		.
		Infections and infestations	Nasopharyngitis	Grade 2	NK/12/2017	No	Recovery	NK/12/2017	No	No		No dose modification		.
		Gastrointestinal disorders	Aerophagia	Grade 1	NK/01/2018	No	Recovery	NK/01/2018	No	No		No dose modification		.
		Gastrointestinal disorders	Gastrooesophageal reflux disease	Grade 1	NK/02/2018	No	Recovery	NK/04/2018	No	No		No dose modification		.
		Gastrointestinal disorders	Abdominal distension	Grade 1	NK/02/2018	No	Recovery	NK/04/2018	No	No		No dose modification		.
		Musculoskeletal and connective tissue disorders	Arthralgia	Grade 1	NK/02/2018	No	Recovery	17/03/2020	Yes	No	BOSUTINIB	No dose modification		.
		Infections and infestations	Fungal infection	Grade 2	NK/02/2018	No	Subject not recovered		No	No	BOSUTINIB	No dose modification		.
		Eye disorders	Lacrimation increased	Grade 1	NK/09/2018	No	Recovery	NK/11/2018	No	No		No dose modification		.
		Eye disorders	Blepharitis	Grade 1	NK/09/2018	No	Recovery	NK/11/2018	No	No		No dose modification		.
		Vascular disorders	Varicose vein	Grade 1	12/02/2019	No	Subject not recovered		No	No		No dose modification		.
		Renal and urinary disorders	Nocturia	Grade 1	17/09/2019	No	Subject not recovered		Yes	No		No dose modification		.

Patient No.	Date of initiation of bosutinib treatment	SOC name	PT name	CTCAE grade	Date of occurrence	Is the event serious?	Status	Date of recovery	Is it reasonably possible that the event may be related to the study medication?	Is it reasonably possible that the event may be related to a concomitant drug?	Name of the drug (1)	Action taken (1)	Name of the drug (2)	Action taken (2)
		General disorders and administration site conditions	Therapeutic response decreased	Grade 2	30/12/2019	No	Recovery	02/06/2020	Yes	No	BOSULIF	Dose increase		.
		Respiratory, thoracic and mediastinal disorders	Dyspnoea	Grade 1	24/11/2020	No	Subject not recovered		Yes	No	BOSULIF	No dose modification		.
		Cardiac disorders	Pericarditis	Grade 1	NK/NK/2020	No	Subject not recovered		Yes	No	BOSULIF	No dose modification		.
		Nervous system disorders	Sensory disturbance	Grade 1	NK/NK/2020	No	Recovery	NK/NK/2020	No	No	BOSULIF	No dose modification		.
		General disorders and administration site conditions	Gait disturbance	Grade 1	29/09/2020	No	Recovery	NK/NK/2020	No	No	BOSULIF	No dose modification		.
16-07	04/04/2018	Injury, poisoning and procedural complications	Omissions of a medication dose	Grade 1	NK/NK/2018	No	Recovery	NK/NK/2018	No	No		Not applicable		.
		Gastrointestinal disorders	Constipation	Grade 2	26/06/2018	No	Subject not recovered		No	Yes		No dose modification		.
		Renal and urinary disorders	Micturition urgency	Grade 2	20/12/2018	No	Recovery in progress		No	No		No dose modification		.
		Skin and subcutaneous tissue disorders	Scab	Grade 1	08/01/2019	No	Recovery	15/10/2019	Yes	No		No dose modification		.
		Skin and subcutaneous tissue disorders	Pruritus	Grade 1	08/01/2019	No	Recovery	15/10/2019	Yes	No		No dose modification		.
		Respiratory, thoracic and mediastinal disorders	Pleural effusion	Grade 3	21/05/2019	Yes	Recovery	08/07/2019	Yes	No	BOSULIF	No dose modification		.

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		General disorders and administration site conditions	Therapeutic response decreased	Grade 2	05/11/2019	No	Recovery	07/01/2020	Yes	No	BOSULIF	Dose increase		.
		Respiratory, thoracic and mediastinal disorders	Dyspnoea	Grade 2	NK/02/2020	No	Subject not recovered		Yes	No	BOSULIF	No dose modification		.
		Musculoskeletal and connective tissue disorders	Muscle spasms	Grade 1	07/07/2020	No	Recovery	20/10/2020	Yes	No		Not applicable		.
		Blood and lymphatic system disorders	Thrombocytosis	Grade 2	07/07/2020	No	Subject not recovered		No	No		No dose modification		.
		Cardiac disorders	Cardiac failure	Grade 3	NK/04/2019	Yes	Recovery	12/04/2019	Yes	No	BOSULIF	No dose modification		.
		Musculoskeletal and connective tissue disorders	Arthralgia	Grade 2	20/10/2020	No	Subject not recovered		No	No		No dose modification		.
		General disorders and administration site conditions	Oedema peripheral	Grade 1	20/10/2020	No	Subject not recovered		Yes	No		No dose modification		.
		Respiratory, thoracic and mediastinal disorders	Productive cough	Grade 1	05/01/2021	No	Subject not recovered		No	No		No dose modification		.
		Vascular disorders	Arterial disorder	Grade 2	NK/04/2021	No	Subject not recovered		No	No		No dose modification		.
		Investigations	Blood uric acid increased	Grade 2	07/07/2020	No	Recovery	21/09/2021	No	No		.		.
		Injury, poisoning and procedural complications	Vascular graft occlusion	Grade 3	06/04/2021	Yes	Subject not recovered		No	No	BOSULIF	No dose modification		.
16-08	30/01/2019	Blood and lymphatic system disorders	Anaemia	Grade 3	01/03/2019	No	Recovery	21/03/2019	No	Yes	BOSULIF	No dose modification		.

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		Respiratory, thoracic and mediastinal disorders	Respiratory distress	Grade 4	20/03/2019	Yes	Recovery	23/04/2019	No	No	BOSULIF	No dose modification		.
		Gastrointestinal disorders	Intestinal obstruction	Grade 3	20/03/2019	Yes	Recovery	29/03/2019	Yes	No	BOSULIF	No dose modification		.
		General disorders and administration site conditions	Drug ineffective	Grade 2	30/07/2019	No	Subject not recovered		Yes	No	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.
		Gastrointestinal disorders	Rectal haemorrhage	Grade 1	25/02/2019	No	Recovery	25/02/2019	No	No		No dose modification		.
		Infections and infestations	Pneumonia	Grade 5	18/06/2021	Yes	Subject not recovered		Yes	No		No dose modification		.
		Gastrointestinal disorders	Constipation	Grade 2	19/04/2019	No	Subject not recovered		Yes	No	BOSULIF	No dose modification		.
		Gastrointestinal disorders	Eructation	Grade 1	29/10/2019	No	Recovery	29/10/2019	No	No	BOSULIF	No dose modification		.
		Cardiac disorders	Palpitations	Grade 1	22/12/2019	No	Recovery	22/12/2019	No	No	BOSULIF	Not applicable		.
		Infections and infestations	Influenza	Grade 3	15/02/2020	Yes	Recovery	22/02/2020	No	No	BOSULIF	Not applicable		.
		Respiratory, thoracic and mediastinal disorders	Dyspnoea	Grade 2	10/02/2020	Yes	Recovery with sequellae	16/10/2020	No	Yes	BOSULIF	Not applicable	PONATINIB	No dose modification
		General disorders and administration site conditions	Chest pain	Grade 2	10/02/2020	Yes	Recovery with sequellae	NK/08/2020	No	Yes	BOSULIF	Not applicable	PONATINIB	No dose modification

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		Renal and urinary disorders	Prerenal failure	Grade 3	15/02/2020	Yes	Subject not recovered		No	No	BOSULIF	Not applicable	PONATINIB	No dose modification
		Infections and infestations	Urinary tract infection	Grade 2	15/02/2020	Yes	Recovery	17/02/2022	No	No	BOSULIF	Not applicable		.
		Respiratory, thoracic and mediastinal disorders	Dyspnoea	Grade 2	27/03/2020	No	Subject not recovered		No	Yes	BOSULIF	Not applicable	PONATINIB	No dose modification
		Vascular disorders	Pallor	Grade 1	NK/03/2020	No	Subject not recovered		No	Yes	BOSULIF	Not applicable	PONATINIB	No dose modification
		Musculoskeletal and connective tissue disorders	Pain in extremity	Grade 2	NK/03/2020	No	Recovery	NK/NK/2020	No	Yes	BOSULIF	Not applicable	PONATINIB	Dose reduction
		Skin and subcutaneous tissue disorders	Rash pruritic	Grade 1	NK/03/2020	No	Recovery	NK/NK/2020	No	Yes	BOSULIF	Not applicable	PONATINIB	No dose modification
		General disorders and administration site conditions	Chest discomfort	Grade 1	25/08/2020	No	Recovery	27/06/2021	No	Yes	BOSULIF	Not applicable	PONATINIB	No dose modification
		Skin and subcutaneous tissue disorders	Hyperhidrosis	Grade 1	25/08/2020	No	Recovery	NK/NK/2020	No	Yes	BOSULIF	Not applicable	PONATINIB	No dose modification
		Infections and infestations	Folliculitis	Grade 1	25/08/2020	No	Recovery	NK/NK/2020	No	Yes	BOSULIF	Not applicable	PONATINIB	No dose modification
		Skin and subcutaneous tissue disorders	Erythema	Grade 1	25/08/2020	No	Recovery	NK/NK/2020	No	Yes	BOSULIF	Not applicable	PONATINIB	No dose modification
		Respiratory, thoracic and mediastinal disorders	Chronic obstructive pulmonary disease	Grade 2	16/10/2020	Yes	Subject not recovered		No	No	BOSULIF	Not applicable	PONATINIB	No dose modification
		Musculoskeletal and connective tissue disorders	Limb discomfort	Grade 1	25/11/2020	No	Recovery	NK/NK/2020	No	No	BOSULIF	Not applicable	PONATINIB	No dose modification

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		General disorders and administration site conditions	Drug ineffective	Grade 1	25/11/2020	No	Subject not recovered		No	Yes	BOSULIF	Not applicable	PONATINIB	Withdrawal (temporary or permanent, or deferred administration)
		Cardiac disorders	Cardiac failure	Grade 3	NK/02/2021	Yes	Recovery with sequellae	22/03/2021	No	Yes	BOSULIF	Not applicable	PONATINIB	No dose modification
		Cardiac disorders	Cardiac failure	Grade 3	NK/03/2021	Yes	Recovery with sequellae	14/04/2021	No	Yes	BOSULIF	Not applicable	PONATINIB	Withdrawal (temporary or permanent, or deferred administration)
		General disorders and administration site conditions	Malaise	Grade 3	22/05/2021	Yes	Recovery	28/05/2021	No	No	BOSULIF	Not applicable	PONATINIB	Not applicable
		Metabolism and nutrition disorders	Hyperkalaemia	Grade 2	NK/05/2021	No	Subject not recovered		No	No	BOSULIF	Not applicable	PONATINIB	Not applicable
		Blood and lymphatic system disorders	Anaemia	Grade 2	NK/05/2021	No	Subject not recovered		No	No	BOSULIF	Not applicable	PONATINIB	Not applicable
16-09	02/05/2019	Gastrointestinal disorders	Dyspepsia	Grade 1	13/06/2019	No	Recovery	11/07/2019	Yes	No	BOSULIF	No dose modification		.
		Nervous system disorders	Petit mal epilepsy	Grade 3	11/09/2019	No	Recovery	NK/10/2019	No	No	BOSUTINIB	No dose modification		.
		Gastrointestinal disorders	Diarrhoea	Grade 1	NK/10/2019	No	Recovery	NK/10/2019	Yes	No	BOSUTINIB	No dose modification		.

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		Infections and infestations	Nasopharyngitis	Grade 1	03/02/2020	No	Recovery	NK/02/2020	No	No		No dose modification		.
		Skin and subcutaneous tissue disorders	Dry skin	Grade 2	13/12/2021	No	Subject not recovered		Yes	No	BOSULIF	No dose modification		.
		Vascular disorders	Hypertension	Grade 2	NK/10/2021	No	Recovery	12/05/2022	Yes	No	BOSULIF	No dose modification		.
16-10	17/10/2019	Gastrointestinal disorders	Abdominal pain	Grade 2	NK/01/2020	No	Subject not recovered		Yes	Yes	BOSULIF	Dose reduction	NILOTINIB	No dose modification
		Gastrointestinal disorders	Diarrhoea	Grade 2	NK/01/2020	No	Subject not recovered		Yes	Yes	BOSULIF	Dose reduction	NILOTINIB	No dose modification
		Gastrointestinal disorders	Gastrooesophageal reflux disease	Grade 2	NK/01/2020	No	Recovery	NK/03/2020	Yes	No	BOSULIF	No dose modification		.
		Nervous system disorders	Headache	Grade 2	NK/01/2020	No	Subject not recovered		Yes	Yes	BOSULIF	No dose modification	NILOTINIB	No dose modification
		Skin and subcutaneous tissue disorders	Pruritus	Grade 1	NK/01/2020	No	Subject not recovered		Yes	No	BOSULIF	No dose modification		.
		Psychiatric disorders	Nervousness	Grade 1	NK/01/2020	No	Recovery	NK/05/2020	No	No	BOSULIF	No dose modification		.
		Infections and infestations	Erysipelas	Grade 2	08/03/2020	No	Recovery	27/03/2020	Yes	No	BOSUTINIB	No dose modification		.
		Musculoskeletal and connective tissue disorders	Back pain	Grade 2	24/02/2020	No	Subject not recovered		No	No		No dose modification		.
		Infections and infestations	Erysipelas	Grade 2	16/07/2020	No	Recovery	NK/07/2020	Yes	No		No dose modification		.

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		Injury, poisoning and procedural complications	Omissions of a medication dose	Grade 1	NK/NK/2020	No	Recovery	NK/NK/2020	Yes	No		No dose modification		.
		General disorders and administration site conditions	General physical health deterioration	Grade 3	09/03/2020	Yes	Recovery	13/03/2020	No	No		No dose modification		.
		Infections and infestations	Candida infection	Grade 2	09/03/2020	No	Recovery	NK/NK/2020	No	No		No dose modification		.
		Gastrointestinal disorders	Anorectal discomfort	Grade 1	28/10/2019	No	Recovery	NK/11/2019	No	No	BOSULIF	No dose modification		.
		Musculoskeletal and connective tissue disorders	Arthralgia	Grade 2	20/04/2020	No	Subject not recovered		Yes	Yes	BOSULIF	Dose reduction	NILOTINIB	No dose modification
		Musculoskeletal and connective tissue disorders	Myalgia	Grade 1	NK/10/2020	No	Subject not recovered		Yes	No	BOSULIF	No dose modification		.
		General disorders and administration site conditions	Fatigue	Grade 1	20/10/2020	No	Subject not recovered		Yes	Yes	BOSULIF	No dose modification	NILOTINIB	No dose modification
		Infections and infestations	Erysipelas	Grade 2	24/09/2020	No	Recovery	03/10/2020	No	No		No dose modification		.
		Skin and subcutaneous tissue disorders	Skin lesion	Grade 1	NK/01/2020	No	Recovery	13/04/2021	Yes	No	BOSULIF	No dose modification		.
		Infections and infestations	Corona virus infection	Grade 1	NK/12/2021	No	Recovery	25/01/2022	No	No	BOSULIF	Not applicable	TASIGNA	No dose modification
		General disorders and administration site conditions	Chest pain	Grade 1	25/01/2022	No	Subject not recovered		No	Yes	TASIGNA	No dose modification	BOSULIF	Not applicable
		Eye disorders	Dry eye	Grade 1	NK/01/2022	No	Recovery	25/01/2022	No	Yes	BOSUTINIB	Not applicable	NILOTINIB	No dose modification

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17-01	18/12/2018	Gastrointestinal disorders	Oesophagitis	Grade 2	28/01/2019	No	Recovery	06/06/2019	No	No	BOSULIF	No dose modification		.
		Gastrointestinal disorders	Diarrhoea	Grade 1	NK/12/2018	No	Recovery	07/05/2019	Yes	No	BOSULIF	No dose modification		.
		Hepatobiliary disorders	Hepatocellular injury	Grade 3	11/10/2019	No	Recovery	14/12/2019	Yes	No	BOSULIF	Dose reduction		.
22-01	24/08/2017	Blood and lymphatic system disorders	Thrombocytopenia	Grade 4	20/09/2017	Yes	Recovery	08/03/2018	Yes	No	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		Dose reduction
		Infections and infestations	Bronchitis	Grade 2	25/02/2018	No	Recovery	NK/03/2018	No	No	BOSUTINIB	No dose modification		.
		Blood and lymphatic system disorders	Anaemia	Grade 2	02/03/2018	No	Recovery	08/03/2018	No	No	BOSUTINIB	No dose modification		.
		Gastrointestinal disorders	Abdominal pain upper	Grade 2	25/02/2018	No	Recovery	NK/02/2018	No	No	BOSUTINIB	No dose modification		.
		Gastrointestinal disorders	Constipation	Grade 2	07/03/2018	No	Recovery in progress		No	No		No dose modification		.
		Infections and infestations	Pneumonia fungal	Grade 4	UK/05/2018	Yes	Recovery with sequellae	01/06/2018	No	Yes	BIG	No dose modification		.

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		Immune system disorders	Anaphylactic shock	Grade 4	06/06/2018	Yes	Recovery	08/06/2018	No	Yes	SAL	Withdrawal (temporary or permanent, or deferred administration)		.
		Gastrointestinal disorders	Nausea	Grade 2	01/06/2018	Yes	Recovery	09/07/2018	No	Yes	BIG+FB2S	No dose modification	ALLOGREFFE	No dose modification
22-02	24/11/2017	Gastrointestinal disorders	Diarrhoea	Grade 2	NK/12/2017	No	Recovery	NK/01/2018	Yes	No		Withdrawal (temporary or permanent, or deferred administration)		.
		General disorders and administration site conditions	Asthenia	Grade 1	06/07/2018	No	Recovery in progress		No	Yes	AMLODIPINE	Withdrawal (temporary or permanent, or deferred administration)		.
		Metabolism and nutrition disorders	Dyslipidaemia	Grade 2	06/07/2018	No	Recovery in progress		No	Yes	TASIGNA	No dose modification		.
		Hepatobiliary disorders	Cholestasis	Grade 2	06/07/2018	No	Recovery in progress		No	Yes	TASIGNA	No dose modification		.
		Metabolism and nutrition disorders	Type 2 diabetes mellitus	Grade 2	06/07/2018	No	Recovery in progress		No	Yes	TASIGNA	No dose modification		.

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		Skin and subcutaneous tissue disorders	Lichenoid keratosis	Grade 2	06/01/2019	No	Recovery	22/01/2020	No	Yes	METFORMINE	Withdrawal (temporary or permanent, or deferred administration)		.
		Musculoskeletal and connective tissue disorders	Arthralgia	Grade 1	23/04/2019	No	Recovery	02/11/2020	No	Yes	CRESTOR	No dose modification		.
23-01	07/07/2016	Musculoskeletal and connective tissue disorders	Osteoarthritis	Grade 2	01/12/2016	No	Subject not recovered		No	No	BOSULIF	No dose modification		.
		Metabolism and nutrition disorders	Diabetes mellitus	Grade 2	04/09/2019	.	Subject not recovered		No	Yes	BOSULIF	No dose modification		.
		Nervous system disorders	Sciatica	Grade 2	10/01/2017	No	Recovery	18/10/2017	No	No		No dose modification		.
		Vascular disorders	Hypertension	Grade 2	NK/10/2017	No	Subject not recovered		No	No		No dose modification		.
		Musculoskeletal and connective tissue disorders	Osteoarthritis	Grade 2	NK/09/2018	No	Recovery	09/10/2018	No	No	BOSULIF	No dose modification		.
		General disorders and administration site conditions	Drug intolerance	Grade 2	NK/09/2018	No	Recovery	09/10/2018	No	Yes	BOSULIF	No dose modification	IXPRIM	Unknown
		Hepatobiliary disorders	Cholecystitis	Grade 3	08/11/2018	Yes	Recovery	26/11/2018	No	No	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.

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		General disorders and administration site conditions	Ulcer	Grade 2	19/11/2018	No	Recovery	26/11/2018	No	No	BOSULIF	No dose modification		.
		Injury, poisoning and procedural complications	Wound	Grade 1	11/11/2018	No	Recovery	05/03/2019	No	No	BOSUTINIB	No dose modification		.
		Nervous system disorders	Dizziness	Grade 1	NK/09/2018	No	Recovery	NK/09/2018	No	No	BOSULIF	No dose modification		.
		General disorders and administration site conditions	General physical health deterioration	.	07/08/2019	.	Recovery	13/09/2019	No	No	BOSULIF	No dose modification		.
		Infections and infestations	Pyelonephritis	Grade 3	11/07/2019	Yes	Recovery	22/07/2019	No	No	BOSUTINIB	No dose modification		.
		General disorders and administration site conditions	Pyrexia	Grade 3	27/07/2019	Yes	Recovery	13/09/2019	No	No	BOSUTINIB	No dose modification		.
		Musculoskeletal and connective tissue disorders	Chondrocalcinosis	Grade 2	NK/08/2019	No	Recovery	13/09/2019	No	No	BOSULIF	No dose modification		.
		Nervous system disorders	Coma	Grade 2	19/08/2019	Yes	Recovery	19/08/2019	No	No	BOSULIF	No dose modification		.
		Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Meningioma	Grade 1	19/08/2019	No	Subject not recovered		No	No	BOSULIF	No dose modification		.
		Infections and infestations	Pneumonia aspiration	Grade 3	19/08/2019	Yes	Recovery	26/08/2019	No	No	BOSULIF	No dose modification		.
		Gastrointestinal disorders	Constipation	Grade 2	07/08/2019	No	Recovery	13/09/2019	No	No	BOSULIF	No dose modification		.

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		Musculoskeletal and connective tissue disorders	Rhabdomyolysis	Grade 1	12/07/2019	No	Recovery	02/09/2019	No	No	BOSULIF	No dose modification		.
		Metabolism and nutrition disorders	Malnutrition	Grade 2	13/08/2019	No	Subject not recovered		No	No	BOSULIF	No dose modification		.
		Skin and subcutaneous tissue disorders	Decubitus ulcer	Grade 2	27/08/2019	No	Recovery	13/09/2019	No	No	BOSULIF	No dose modification		.
23-02	01/10/2016	General disorders and administration site conditions	General physical health deterioration	Grade 5	20/10/2016	Yes	Subject not recovered		No	No	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)	PREVISCAN	Withdrawal (temporary or permanent, or deferred administration)
23-03	19/10/2018	Musculoskeletal and connective tissue disorders	Pain in extremity	Grade 1	08/03/2019	No	Recovery	28/06/2019	No	No	BOSULIF	No dose modification		.
		Investigations	Weight decreased	Grade 2	NK/04/2020	No	Recovery	06/09/2021	No	No	BOSULIF	No dose modification		.
		Infections and infestations	Perineal abscess	Grade 3	NK/04/2020	Yes	Recovery	12/05/2020	No	No	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.
		Nervous system disorders	Sciatica	Grade 1	20/01/2020	No	Recovery	05/05/2020	No	No	BOSULIF	No dose modification		.

Patient No.	Date of initiation of bosutinib treatment	SOC name	PT name	CTCAE grade	Date of occurrence	Is the event serious?	Status	Date of recovery	Is it reasonably possible that the event may be related to the study medication?	Is it reasonably possible that the event may be related to a concomitant drug?	Name of the drug (1)	Action taken (1)	Name of the drug (2)	Action taken (2)
		Infections and infestations	Sepsis	Grade 2	16/04/2020	Yes	Recovery	23/04/2020	No	No	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.
		Infections and infestations	Urinary tract infection	Grade 2	NK/04/2020	No	Recovery	23/04/2020	No	No	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.
		Infections and infestations	Orchitis	Grade 1	16/04/2020	No	Recovery	23/04/2020	No	No	BOSULIF	No dose modification		.
		Reproductive system and breast disorders	Benign prostatic hyperplasia	Grade 2	NK/NK/2019	No	Subject not recovered		No	No	BOSULIF	No dose modification		.
		Reproductive system and breast disorders	Pelvic pain	Grade 1	14/10/2019	No	Recovery	23/04/2020	No	No	BOSULIF	No dose modification		.
		Musculoskeletal and connective tissue disorders	Musculoskeletal pain	Grade 1	08/03/2019	No	Recovery	20/01/2020	No	No	BOSULIF	No dose modification		.
		Skin and subcutaneous tissue disorders	Erythema	Grade 1	NK/NK/2021	No	Recovery	06/09/2021	No	No	BOSULIF	No dose modification		.
		Vascular disorders	Pallor	Grade 1	19/11/2020	No	Recovery	06/09/2021	No	No	BOSULIF	No dose modification		.
		Gastrointestinal disorders	Diarrhoea	Grade 2	NK/11/2020	No	Subject not recovered		Yes	Yes	BOSULIF	Dose reduction		.

Patient No.	Date of initiation of bosutinib treatment	SOC name	PT name	CTCAE grade	Date of occurrence	Is the event serious?	Status	Date of recovery	Is it reasonably possible that the event may be related to the study medication?	Is it reasonably possible that the event may be related to a concomitant drug?	Name of the drug (1)	Action taken (1)	Name of the drug (2)	Action taken (2)
24-01	06/03/2017	Reproductive system and breast disorders	Testicular pain	Grade 1	04/07/2017	No	Recovery	10/11/2017	No	No		No dose modification		.
		Nervous system disorders	Paraesthesia	Grade 1	10/11/2017	No	Recovery	06/02/2018	.	No	BOSUTINIB	No dose modification		.
		Metabolism and nutrition disorders	Diabetes mellitus	Grade 1	27/10/2017	No	Subject not recovered		No	No		Not applicable		.
		Musculoskeletal and connective tissue disorders	Limb discomfort	Grade 1	11/10/2017	No	Recovery	17/11/2017	No	No		Not applicable		.
		Hepatobiliary disorders	Hepatocellular injury	Grade 1	14/03/2019	No	Subject not recovered		Yes	No	BOSUTINIB	No dose modification		.
		Infections and infestations	Folliculitis	Grade 2	NK/03/2019	No	Recovery	NK/03/2019	No	No	BOSUTINIB	No dose modification		.
		Gastrointestinal disorders	Diarrhoea	Grade 1	NK/NK/2019	No	Recovery	NK/NK/2019	No	Yes	BOSUTINIB	No dose modification	METFORMINE	Withdrawal (temporary or permanent, or deferred administration)
		General disorders and administration site conditions	Fatigue	Grade 1	19/03/2019	No	Recovery	06/09/2019	No	No	BOSUTINIB	No dose modification		.
		Vascular disorders	Hypertensive crisis	Grade 3	K	No	Subject not recovered		Yes	No	BOSUTINIB	No dose modification		.
24-02	28/03/2017	Gastrointestinal disorders	Diarrhoea	Grade 2	28/03/2017	No	Recovery	04/04/2017	Yes	No	IMMODIUM	No dose modification		.
		Gastrointestinal disorders	Diarrhoea	Grade 1	NK/07/2017	No	Recovery	NK/07/2017	No	No	IMMODIUM	Not applicable		.

Patient No.	Date of initiation of bosutinib treatment	SOC name	PT name	CTCAE grade	Date of occurrence	Is the event serious?	Status	Date of recovery	Is it reasonably possible that the event may be related to the study medication?	Is it reasonably possible that the event may be related to a concomitant drug?	Name of the drug (1)	Action taken (1)	Name of the drug (2)	Action taken (2)
		Gastrointestinal disorders	Diarrhoea	Grade 2	23/02/2018	No	Recovery	28/02/2018	Yes	No	IMMODIUM	No dose modification		.
		Infections and infestations	Malaria	Grade 2	NK/08/2018	Yes	Recovery	NK/08/2018	No	No	BOSULIF	No dose modification		.
24-03	12/04/2017	Reproductive system and breast disorders	Metrorragie	Grade 2	26/04/2017	No	Subject not recovered		Yes	No	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.
		Gastrointestinal disorders	Nausea	Grade 2	13/04/2017	No	Recovery	15/05/2017	Yes	No	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.
24-04	05/12/2017	Investigations	Alanine aminotransferase increased	Grade 3	09/03/2018	No	Recovery	15/12/2018	Yes	No	BOSULIF	Dose reduction		.
		Investigations	Aspartate aminotransferase increased	Grade 3	09/03/2018	No	Recovery	19/06/2018	Yes	No	BOSULIF	Dose reduction		.
		Gastrointestinal disorders	Diarrhoea	Grade 2	05/12/2017	No	Recovery	07/12/2017	Yes	No	BOSULIF	No dose modification		.
		Infections and infestations	Nasopharyngitis	Grade 1	NK/12/2019	No	Recovery	NK/12/2019	No	No	BOSUTINIB	No dose modification		.

Patient No.	Date of initiation of bosutinib treatment	SOC name	PT name	CTCAE grade	Date of occurrence	Is the event serious?	Status	Date of recovery	Is it reasonably possible that the event may be related to the study medication?	Is it reasonably possible that the event may be related to a concomitant drug?	Name of the drug (1)	Action taken (1)	Name of the drug (2)	Action taken (2)
		Infections and infestations	Influenza	Grade 1	NK/NK/2020	No	Recovery	NK/NK/2020	No	No	BOSUTINIB	No dose modification		.
		Infections and infestations	Upper respiratory tract infection	Grade 2	NK/NK/2019	No	Recovery	NK/NK/2019	No	No	BOSUTINIB	No dose modification		.
		Gastrointestinal disorders	Gastritis	Grade 2	NK/04/2018	No	Recovery	09/10/2018	No	No	BOSULIF	No dose modification		.
		General disorders and administration site conditions	Non-cardiac chest pain	Grade 1	NK/06/2018	No	Recovery	NK/06/2018	No	No	BOSULIF	No dose modification		.
		Vascular disorders	Arteriosclerosis	Grade 1	10/09/2018	No	Subject not recovered		No	No	BOSULIF	No dose modification		.
		Cardiac disorders	Coronary artery stenosis	Grade 2	NK/06/2019	Yes	Recovery	NK/06/2019	No	No	BOSUTINIB	No dose modification		.
33-01	04/10/2016	Musculoskeletal and connective tissue disorders	Pain in extremity	Grade 2	NK/10/2016	No	Recovery	02/11/2016	No	No	BOSULIF	No dose modification		.
		Gastrointestinal disorders	Diarrhoea	Grade 1	04/10/2016	No	Recovery	NK/06/2017	Yes	No	BOSULIF	No dose modification		.
		General disorders and administration site conditions	Drug ineffective	Grade 1	24/05/2018	No	Recovery in progress		Yes	No	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.
		Injury, poisoning and procedural complications	Fractured coccyx	Grade 1	NK/NK/2018	No	Recovery	26/02/2018	No	No	BOSULIF	No dose modification		.

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		Gastrointestinal disorders	Constipation	Grade 1	NK/05/2018	No	Recovery	21/08/2018	No	Yes	BOSULIF	Not applicable	ICLUSIG	No dose modification
		Skin and subcutaneous tissue disorders	Skin lesion	Grade 1	NK/NK/2018	No	Recovery	20/12/2018	No	No	PONATINIB	No dose modification		.
33-02	02/05/2017	Musculoskeletal and connective tissue disorders	Arthralgia	Grade 2	12/05/2017	No	Recovery	UK/05/2017	Yes	No		Withdrawal (temporary or permanent, or deferred administration)		.
		Renal and urinary disorders	Renal failure	Grade 1	10/05/2017	Yes	Recovery	21/06/2017	Yes	No		Withdrawal (temporary or permanent, or deferred administration)		.
		General disorders and administration site conditions	Fatigue	Grade 2	12/05/2017	No	Recovery	UK/05/2017	Yes	No		Withdrawal (temporary or permanent, or deferred administration)		.

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		Gastrointestinal disorders	Diarrhoea	Grade 2	12/05/2017	No	Recovery	UK/05/2017	Yes	No		Withdrawal (temporary or permanent, or deferred administration)		.
		Respiratory, thoracic and mediastinal disorders	Dyspnoea	Grade 2	12/05/2017	No	Recovery	UK/05/2017	Yes	No		Withdrawal (temporary or permanent, or deferred administration)		.
		Vascular disorders	Subclavian artery stenosis	Grade 2	UK/05/2017	Yes	Recovery	23/08/2017	No	No		Not applicable		.
		General disorders and administration site conditions	Chills	Grade 1	NK/05/2017	No	Recovery	04/07/2017	Yes	No		Withdrawal (temporary or permanent, or deferred administration)		.
		Skin and subcutaneous tissue disorders	Pruritus	Grade 1	NK/05/2017	No	Recovery	NK/05/2017	No	No	BOSULIF	No dose modification		.
		General disorders and administration site conditions	Oedema	Grade 2	NK/10/2017	No	Unknown		No	Yes	GLIVEC	No dose modification		.
		Renal and urinary disorders	Acute kidney injury	Grade 3	21/11/2018	Yes	Recovery	07/12/2018	No	No	GLIVEC	No dose modification		.

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		Respiratory, thoracic and mediastinal disorders	Dyspnoea	Grade 3	23/10/2018	Yes	Recovery	27/10/2018	No	No	GLIVEC	No dose modification		.
		Metabolism and nutrition disorders	Diabetes mellitus inadequate control	Grade 3	05/07/2018	Yes	Recovery	08/07/2018	No	No	GLIVEC	No dose modification		.
		Skin and subcutaneous tissue disorders	Pruritus	Grade 1	27/12/2017	No	Recovery	17/10/2018	No	No	BOSULIF	Not applicable		.
		Infections and infestations	Bronchitis	Grade 1	07/10/2018	No	Recovery	22/10/2018	No	No		.		.
		Respiratory, thoracic and mediastinal disorders	Upper respiratory tract congestion	Grade 2	07/12/2017	No	Recovery	27/12/2017	No	No	BOSULIF	Not applicable		.
		Renal and urinary disorders	Renal artery stenosis	Grade 3	UK/10/2018	Yes	Recovery	07/02/2019	No	No	BOSULIF	Not applicable		.
		Nervous system disorders	Sciatica	Grade 2	UK/09/2019	No	Recovery	19/02/2020	No	No	BOSULIF	Not applicable		.
		Renal and urinary disorders	Renal failure	Grade 4	03/10/2019	Yes	Subject not recovered		No	No	BOSULIF	Not applicable		.
33-03	04/12/2017	Gastrointestinal disorders	Diarrhoea	Grade 2	NK/01/2018	No	Recovery	23/02/2018	Yes	No	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.

Patient No.	Date of initiation of bosutinib treatment	SOC name	PT name	CTCAE grade	Date of occurrence	Is the event serious?	Status	Date of recovery	Is it reasonably possible that the event may be related to the study medication?	Is it reasonably possible that the event may be related to a concomitant drug?	Name of the drug (1)	Action taken (1)	Name of the drug (2)	Action taken (2)
		Hepatobiliary disorders	Hepatocellular injury	Grade 3	NK/01/2018	No	Recovery	19/02/2019	Yes	No	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.
		Nervous system disorders	Headache	Grade 1	07/04/2020	No	Recovery	18/08/2020	No	No	BOSULIF	Not applicable		.
		Musculoskeletal and connective tissue disorders	Myalgia	Grade 1	07/04/2020	No	Subject not recovered		No	No		No dose modification		.
		Musculoskeletal and connective tissue disorders	Musculoskeletal pain	Grade 1	18/08/2020	No	Subject not recovered		No	No		No dose modification		.
		Musculoskeletal and connective tissue disorders	Arthralgia	Grade 1	18/08/2020	No	Subject not recovered		No	No		No dose modification		.
		General disorders and administration site conditions	Fatigue	Grade 1	18/08/2020	No	Subject not recovered		No	No		Not applicable		Not applicable
		Cardiac disorders	Tachycardia	Grade 2	25/06/2018	No	Recovery	24/09/2018	No	No		Not applicable		.
33-04	28/06/2018	Gastrointestinal disorders	Constipation	Grade 1	26/11/2018	No	Recovery	19/09/2019	Yes	No		No dose modification		.
		Skin and subcutaneous tissue disorders	Dry skin	Grade 1	11/03/2019	No	Recovery	19/06/2019	Yes	No		No dose modification		.
		Gastrointestinal disorders	Reflux gastritis	Grade 1	11/03/2019	No	Recovery	19/06/2019	Yes	No		No dose modification		.
		Infections and infestations	Nasopharyngitis	Grade 1	01/12/2019	No	Recovery	18/03/2020	No	No		No dose modification		.

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33-05	01/09/2018	Musculoskeletal and connective tissue disorders	Myalgia	Grade 1	NK/02/2019	No	Recovery	NK/02/2019	No	No	BOSEVAL	No dose modification		.
		General disorders and administration site conditions	Fatigue	Grade 1	NK/02/2019	No	Recovery	NK/02/2019	No	No	BOSULIF	No dose modification		.
		Gastrointestinal disorders	Diarrhoea	Grade 1	NK/09/2018	No	Recovery	NK/11/2018	Yes	No		No dose modification		.
		Gastrointestinal disorders	Diarrhoea	Grade 1	NK/11/2018	No	Recovery	NK/01/2020	Yes	No	BOSULIF	No dose modification		.
		Investigations	Alanine aminotransferase increased	Grade 2	06/02/2019	No	Recovery	08/01/2020	Yes	No	BOSULIF	No dose modification		.
		Gastrointestinal disorders	Gastrointestinal disorder	Grade 1	NK/02/2019	No	Recovery	NK/02/2019	No	No	BOSULIF	No dose modification		.
		Renal and urinary disorders	Pollakiuria	Grade 1	08/11/2021	No	Subject not recovered		No	No	BOSULIF	No dose modification		.
33-06	05/09/2018	Respiratory, thoracic and mediastinal disorders	Dyspnoea	Grade 2	21/09/2018	Yes	Recovery	26/10/2018	Yes	No	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.
		Skin and subcutaneous tissue disorders	Rash vesicular	Grade 2	25/09/2018	No	Recovery	26/10/2018	No	Yes	WELLVONE	No dose modification		.

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		Metabolism and nutrition disorders	Decreased appetite	Grade 1	24/09/2018	No	Recovery	26/10/2018	Yes	No		Withdrawal (temporary or permanent, or deferred administration)		.
		Infections and infestations	Fungal infection	Grade 1	25/09/2018	No	Recovery	26/10/2018	No	No		No dose modification		.
		Skin and subcutaneous tissue disorders	Dry skin	Grade 1	26/10/2018	No	Recovery	27/11/2018	No	No		Not applicable		.
		Nervous system disorders	Dysgeusia	Grade 1	24/09/2018	No	Recovery	26/10/2018	Yes	No	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.
		General disorders and administration site conditions	Face oedema	Grade 1	NK/12/2018	No	Recovery	NK/NK/2019	No	Yes	IMATINIB	Dose reduction		.
		Gastrointestinal disorders	Nausea	Grade 1	NK/12/2018	No	Recovery	NK/NK/2019	No	Yes	IMATINIB	Dose reduction		.
		Gastrointestinal disorders	Gastrointestinal disorder	Grade 1	NK/12/2018	No	Recovery	NK/NK/2019	No	Yes	IMATINIB	Dose reduction		.
		Metabolism and nutrition disorders	Decreased appetite	Grade 1	NK/12/2018	No	Recovery	NK/NK/2019	No	Yes	IMATINIB	Dose reduction		.
		Eye disorders	Cataract	Grade 2	NK/NK/2020	No	Recovery	11/01/2021	No	No	IMATINIB	No dose modification		.

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		Eye disorders	Cataract	Grade 2	NK/NK/2020	No	Recovery	07/12/2020	No	No	IMATINIB	No dose modification		.
		Injury, poisoning and procedural complications	Procedural pain	Grade 3	08/12/2020	Yes	Recovery	NK/NK/2021	No	No	IMATINIB	No dose modification		.
		General disorders and administration site conditions	Asthenia	Grade 1	05/06/2019	No	Recovery	12/09/2019	No	No	BOSULIF	Not applicable		.
		Psychiatric disorders	Depression	Grade 2	UK/07/2019	No	Recovery	12/09/2019	No	No	BOSULIF	Not applicable		.
		Nervous system disorders	Tremor	Grade 1	12/09/2019	No	Recovery	11/03/2020	No	No	BOSULIF	Not applicable		.
33-07	01/10/2018	Gastrointestinal disorders	Diarrhoea	Grade 1	UK/10/2018	No	Recovery	24/10/2018	Yes	No		No dose modification		.
		Gastrointestinal disorders	Abdominal pain	Grade 1	UK/10/2018	No	Recovery	24/10/2018	Yes	No		No dose modification		.
		Cardiac disorders	Pericardial effusion	Grade 2	06/05/2021	Yes	Recovery	NK/05/2021	Yes	No		No dose modification		.
		Cardiac disorders	Pericarditis	Grade 2	19/10/2021	Yes	Recovery	18/10/2022	Yes	No	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.
		Vascular disorders	Hypertension	Grade 2	08/01/2020	No	Recovery	15/04/2020	No	No	BOSULIF	No dose modification		.
		Metabolism and nutrition disorders	Gout	Grade 2	NK/02/2021	No	Recovery	NK/10/2021	No	No	BOSULIF	No dose modification		.

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33-08	14/10/2019	Respiratory, thoracic and mediastinal disorders	Pleural effusion	Grade 2	21/07/2021	Yes	Recovery	31/08/2021	Yes	No	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.
		Respiratory, thoracic and mediastinal disorders	Dyspnoea	Grade 2	22/05/2021	No	Recovery	21/07/2021	Yes	No	BOSULIF	No dose modification		.
		Musculoskeletal and connective tissue disorders	Musculoskeletal chest pain	Grade 1	30/05/2022	No	Recovery	14/09/2022	No	No	BOSULIF	No dose modification		.
34-01	01/09/2017	Skin and subcutaneous tissue disorders	Rash	Grade 1	07/09/2017	No	Recovery	10/09/2017	Yes	No	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.
		Gastrointestinal disorders	Gingival bleeding	Grade 1	07/09/2017	No	Recovery	21/09/2017	Yes	Yes	BOSULIF	No dose modification		.
		General disorders and administration site conditions	Gait disturbance	Grade 1	07/09/2017	No	Recovery	29/01/2018	Yes	No	BOSULIF	No dose modification		.
		Gastrointestinal disorders	Diarrhoea	Grade 1	07/09/2017	No	Recovery	29/01/2018	Yes	No	BOSULIF	No dose modification		.
		Musculoskeletal and connective tissue disorders	Musculoskeletal pain	Grade 1	07/09/2017	No	Recovery	21/01/2019	Yes	No	BOSULIF	Dose reduction		.
		Psychiatric disorders	Affective disorder	Grade 1	07/09/2017	No	Recovery	19/10/2017	Yes	No	BOSULIF	No dose modification		.

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		Respiratory, thoracic and mediastinal disorders	Pleural effusion	Grade 2	26/02/2018	No	Recovery	11/09/2018	Yes	No	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)	BOSULIF	Dose reduction
		Gastrointestinal disorders	Abdominal pain	Grade 1	26/02/2018	No	Subject not recovered		Yes	No	BOSULIF	No dose modification		.
		Nervous system disorders	Hypersomnia	Grade 1	26/02/2018	No	Recovery	19/03/2018	Yes	No	BOSULIF	No dose modification		.
		General disorders and administration site conditions	Asthenia	Grade 1	29/01/2018	No	Subject not recovered		Yes	No	BOSULIF	Dose reduction		.
		Hepatobiliary disorders	Hepatocellular injury	Grade 2	17/11/2017	No	Recovery	19/03/2018	Yes	No	BOSULIF	No dose modification		.
		Skin and subcutaneous tissue disorders	Dry skin	Grade 1	19/03/2018	No	Recovery	15/06/2018	Yes	No	BOSULIF	No dose modification		.
		Musculoskeletal and connective tissue disorders	Back pain	Grade 1	NK/03/2018	No	Recovery	21/01/2019	No	No	BOSULIF	No dose modification		.
		Respiratory, thoracic and mediastinal disorders	Dyspnoea	Grade 1	15/06/2018	No	Subject not recovered		No	No	BOSULIF	No dose modification		.
		Respiratory, thoracic and mediastinal disorders	Dyspnoea	Grade 1	07/09/2017	No	Recovery	19/10/2017	Yes	No	BOSULIF	No dose modification		.
		Nervous system disorders	Dizziness	Grade 1	07/09/2017	No	Recovery	19/10/2017	Yes	No	BOSULIF	No dose modification		.

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		Skin and subcutaneous tissue disorders	Rash	Grade 1	29/11/2017	No	Recovery	29/01/2018	Yes	No	BOSULIF	Dose reduction		.
		Nervous system disorders	Disturbance in attention	Grade 1	29/11/2017	No	Recovery	29/01/2018	Yes	No	BOSULIF	Dose reduction		.
		General disorders and administration site conditions	Asthenia	Grade 2	13/09/2018	No	Recovery	24/09/2019	No	No	BOSULIF	No dose modification		.
		Gastrointestinal disorders	Abdominal distension	Grade 1	21/01/2019	No	Recovery	24/09/2019	No	No	BOSULIF	No dose modification		.
		Infections and infestations	Herpes zoster	Grade 2	NK/05/2019	No	Recovery	18/05/2020	Yes	No	BOSULIF	No dose modification		.
		Cardiac disorders	Angina pectoris	Grade 3	27/07/2019	Yes	Subject not recovered		No	No	BOSULIF	No dose modification		.
		Gastrointestinal disorders	Abdominal pain upper	Grade 1	19/01/2020	No	Recovery	21/09/2020	Yes	No	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.
34-02	16/01/2019	Infections and infestations	Gastrointestinal infection	Grade 3	06/02/2019	Yes	Recovery	11/02/2019	Yes	No	BOSULIF	Dose reduction		.
		Musculoskeletal and connective tissue disorders	Back pain	Grade 1	28/02/2019	No	Recovery	11/06/2019	No	No	BOSULIF	No dose modification		.
		Nervous system disorders	Dizziness	Grade 1	UK/02/2019	No	Recovery	28/02/2019	Yes	No	BOSULIF	No dose modification		.

Patient No.	Date of initiation of bosutinib treatment	SOC name	PT name	CTCAE grade	Date of occurrence	Is the event serious?	Status	Date of recovery	Is it reasonably possible that the event may be related to the study medication?	Is it reasonably possible that the event may be related to a concomitant drug?	Name of the drug (1)	Action taken (1)	Name of the drug (2)	Action taken (2)
		Musculoskeletal and connective tissue disorders	Bone pain	Grade 1	28/02/2019	No	Recovery	23/04/2019	No	No	BOSULIF	No dose modification		.
		Gastrointestinal disorders	Abdominal pain upper	Grade 1	28/02/2019	No	Recovery	23/04/2019	Yes	No	BOSULIF	No dose modification		.
		General disorders and administration site conditions	Pyrexia	Grade 1	28/02/2019	No	Recovery	09/04/2019	No	No	BOSULIF	No dose modification		.
		Gastrointestinal disorders	Abdominal distension	Grade 1	09/04/2019	No	Recovery	23/04/2019	Yes	No	BOSULIF	No dose modification		.
		General disorders and administration site conditions	Feeling cold	Grade 1	09/04/2019	No	Recovery	23/04/2019	No	No	BOSULIF	No dose modification		.
		Metabolism and nutrition disorders	Hyperphagia	Grade 1	09/04/2019	No	Recovery	23/04/2019	No	No	BOSULIF	No dose modification		.
		Endocrine disorders	Hypothyroidism	Grade 2	15/04/2019	No	Recovery	UK/06/2019	No	No	BOSULIF	No dose modification		.
		Respiratory, thoracic and mediastinal disorders	Dyspnoea	Grade 1	11/06/2019	No	Recovery	08/07/2019	No	No	BOSULIF	No dose modification		.
		Gastrointestinal disorders	Abdominal pain upper	Grade 1	11/06/2019	No	Recovery	08/07/2019	No	No	BOSULIF	No dose modification		.
		Skin and subcutaneous tissue disorders	Rash	Grade 2	08/07/2019	No	Recovery	15/10/2019	Yes	Yes	URAPIDIL	Withdrawal (temporary or permanent, or deferred administration)	BOSULIF	Dose reduction

Patient No.	Date of initiation of bosutinib treatment	SOC name	PT name	CTCAE grade	Date of occurrence	Is the event serious?	Status	Date of recovery	Is it reasonably possible that the event may be related to the study medication?	Is it reasonably possible that the event may be related to a concomitant drug?	Name of the drug (1)	Action taken (1)	Name of the drug (2)	Action taken (2)
		Respiratory, thoracic and mediastinal disorders	Cough	Grade 1	15/10/2019	No	Recovery	16/12/2019	No	No	BOSULIF	No dose modification		.
		Skin and subcutaneous tissue disorders	Rash	Grade 2	27/07/2020	No	Recovery	04/08/2020	Yes	No	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.
		Gastrointestinal disorders	Haemorrhoids	Grade 2	NK/NK/2019	No	Recovery	NK/NK/2019	No	No	BOSULIF	No dose modification		.
		Reproductive system and breast disorders	Pelvic discomfort	Grade 1	NK/NK/2019	No	Recovery	NK/NK/2019	No	No	BOSULIF	No dose modification		.
		Psychiatric disorders	Anxiety	Grade 1	22/08/2019	No	Recovery	NK/08/2019	No	No	BOSULIF	No dose modification		.
		General disorders and administration site conditions	Asthenia	Grade 1	16/12/2019	No	Recovery	13/12/2021	No	No	BOSULIF	No dose modification		.
		Metabolism and nutrition disorders	Iron deficiency	Grade 2	04/08/2021	No	Recovery	NK/11/2021	No	No	BOSULIF	No dose modification		.
		Metabolism and nutrition disorders	Folate deficiency	Grade 2	04/08/2021	No	Recovery	NK/11/2021	No	No	BOSULIF	No dose modification		.
36-01	26/08/2019	Gastrointestinal disorders	Diarrhoea	Grade 3	09/09/2019	No	Recovery	04/10/2019	Yes	No		Dose reduction		.
		General disorders and administration site conditions	Chest pain	Grade 2	09/09/2019	No	Recovery	04/10/2019	Yes	No		Dose reduction		.

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		Hepatobiliary disorders	Hepatocellular injury	Grade 3	01/10/2019	No	Recovery	14/10/2019	Yes	No	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.
		Respiratory, thoracic and mediastinal disorders	Dyspnoea	Grade 2	16/06/2021	No	Recovery in progress		No	Yes	SPRYCELL	No dose modification		.
		Hepatobiliary disorders	Cholestasis	Grade 1	01/10/2019	No	Recovery	05/04/2022	No	No		.		.
		Eye disorders	Cataract	Grade 2	UK/UK/2020	No	Recovery	29/07/2021	No	No		.		.
		Respiratory, thoracic and mediastinal disorders	Pulmonary hypertension	Grade 3	08/09/2020	No	Recovery in progress		No	No		.		.
		Blood and lymphatic system disorders	Thrombocytopenia	Grade 2	UK/06/2021	No	Recovery	14/09/2021	No	No		.		.
		Metabolism and nutrition disorders	Hypertriglyceridaemia	Grade 2	14/09/2021	No	Recovery in progress		Yes	No		.		.
		Reproductive system and breast disorders	Prostatitis	Grade 2	UK/08/2022	Yes	Recovery	06/09/2022	No	Yes	NEORAL	No dose modification		.
		Infections and infestations	Erysipelas	Grade 2	UK/08/2022	No	Recovery	06/09/2022	No	No		.		.
37-01	07/01/2019	Musculoskeletal and connective tissue disorders	Arthralgia	Grade 2	10/04/2019	No	Subject not recovered		Yes	No		No dose modification		.
		Gastrointestinal disorders	Diarrhoea	Grade 2	UK/02/2019	No	Recovery	08/11/2019	Yes	No		No dose modification		.
38-01	14/09/2017	Respiratory, thoracic and mediastinal disorders	Acute respiratory distress syndrome	Grade 3	29/11/2017	Yes	Recovery	06/12/2017	No	No		No dose modification		.

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		Respiratory, thoracic and mediastinal disorders	Pleural effusion	Grade 3	29/11/2017	Yes	Recovery	27/12/2017	No	No		No dose modification		.
		General disorders and administration site conditions	Oedema peripheral	Grade 2	30/11/2017	Yes	Recovery	29/12/2017	No	No	BOSULIF	No dose modification		.
		Psychiatric disorders	Depression	Grade 3	14/12/2017	No	Subject not recovered		No	No	BOSULIF	No dose modification		.
		Infections and infestations	Urinary tract infection	Grade 2	NK/11/2017	No	Recovery	NK/11/2017	No	No	BOSULIF	No dose modification		.
		Infections and infestations	Vulvovaginal mycotic infection	Grade 2	NK/11/2017	No	Recovery	29/12/2017	No	No	BOSULIF	No dose modification		.
		Nervous system disorders	Somnolence	Grade 2	NK/12/2017	No	Recovery	NK/12/2017	No	Yes	BOSULIF	No dose modification	ANTALGIQUE	No dose modification
		Investigations	Blood creatinine increased	Grade 2	19/02/2018	No	Recovery	15/04/2020	No	No	BOSULIF	No dose modification		.
		Injury, poisoning and procedural complications	Limb injury	Grade 2	01/03/2018	No	Recovery	31/03/2018	No	No	BOOSULIF	No dose modification		.
		Injury, poisoning and procedural complications	Limb injury	Grade 4	01/05/2018	Yes	Recovery	13/06/2018	No	No	BOSULIF	No dose modification		.
		Surgical and medical procedures	Foot amputation	Grade 4	22/05/2018	Yes	Recovery	22/05/2018	No	No	BOSULIF	No dose modification		.
		Surgical and medical procedures	Foot amputation	Grade 4	01/06/2018	Yes	Recovery	01/06/2018	No	No	BOSULIF	No dose modification		.
		Skin and subcutaneous tissue disorders	Dermatitis	Grade 4	31/05/2018	Yes	Recovery	11/06/2018	No	No	BOSULIF	No dose modification		.

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		General disorders and administration site conditions	Pyrexia	Grade 2	31/05/2018	No	Recovery	11/06/2018	No	No	BOSULIF	No dose modification		.
		Infections and infestations	Staphylococcal infection	Grade 3	22/05/2018	Yes	Recovery	11/06/2018	No	No	BOSULIF	No dose modification		.
		Infections and infestations	Bacterial infection	Grade 3	01/06/2018	Yes	Recovery	13/06/2018	No	No	BOSULIF	No dose modification		.
		Gastrointestinal disorders	Nausea	Grade 3	06/06/2018	No	Recovery	11/06/2018	No	No	BOSULIF	No dose modification		.
		Gastrointestinal disorders	Vomiting	Grade 3	06/06/2018	No	Recovery	11/06/2018	No	No	BOSULIF	No dose modification		.
		Skin and subcutaneous tissue disorders	Intertrigo	Grade 2	NK/11/2017	No	Recovery	NK/11/2017	No	No	BOSULIF	No dose modification		.
		Infections and infestations	Escherichia infection	Grade 3	14/05/2018	Yes	Recovery	13/06/2018	No	No	BOSULIF	No dose modification		.
		Gastrointestinal disorders	Haemorrhoids	Grade 2	09/08/2018	No	Recovery	20/03/2019	No	No	BOSULIF	No dose modification		.
		Blood and lymphatic system disorders	Thrombocytopenia	Grade 3	02/07/2018	No	Recovery	16/08/2018	Yes	No	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.
		Respiratory, thoracic and mediastinal disorders	Bronchopulmonary disease	Grade 3	10/06/2019	No	Recovery	24/06/2019	No	No	BOSULIF	No dose modification		.

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		Respiratory, thoracic and mediastinal disorders	Dyspnoea	Grade 3	10/06/2019	No	Recovery	24/06/2019	No	No	BOSULIF	No dose modification		.
		Cardiac disorders	Cardiac failure	Grade 3	17/06/2019	Yes	Recovery	24/06/2019	Yes	No	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.
		Cardiac disorders	Tachyarrhythmia	Grade 3	17/06/2019	Yes	Recovery	24/06/2019	Yes	No	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.
		Respiratory, thoracic and mediastinal disorders	Pleural effusion	Grade 3	17/06/2019	Yes	Recovery	31/03/2020	Yes	No	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.
		Cardiac disorders	Left ventricular failure	Grade 3	29/11/2017	Yes	Recovery	06/12/2017	No	No	BOSULIF	No dose modification		.
		Infections and infestations	Klebsiella infection	Grade 2	NK/11/2017	No	Recovery	NK/11/2017	No	No	BOSULIF	No dose modification		.

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		Cardiac disorders	Atrial fibrillation	Grade 3	17/06/2019	Yes	Recovery	24/06/2019	Yes	No	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.
		Gastrointestinal disorders	Diarrhoea	Grade 1	NK/08/2018	No	Recovery	14/09/2018	Yes	No	BOSULIF	No dose modification		.
		Injury, poisoning and procedural complications	Fall	Grade 1	NK/02/2018	No	Recovery	12/06/2018	No	No	BOSULIF	No dose modification		.
38-02	14/08/2018	Social circumstances	Physical disability	Grade 2	NK/03/2019	Yes	Recovery	02/04/2019	No	No	BOSULIF	No dose modification		.
		Gastrointestinal disorders	Inguinal hernia	Grade 2	NK/03/2019	Yes	Subject not recovered		No	No	BOSULIF	No dose modification		.
		Nervous system disorders	Head discomfort	Grade 1	29/01/2019	No	Recovery	02/04/2019	Yes	No	BOSULIF	Dose reduction		.
		Gastrointestinal disorders	Nausea	Grade 1	29/01/2019	No	Recovery	02/04/2019	Yes	No	BOSULIF	Dose reduction		.
		Gastrointestinal disorders	Nausea	Grade 1	NK/10/2019	No	Recovery	18/02/2020	Yes	No	BOSULIF	No dose modification		.
		Gastrointestinal disorders	Vomiting	Grade 1	18/02/2020	No	Recovery	18/06/2020	Yes	No	BOSULIF	No dose modification		.
		Metabolism and nutrition disorders	Decreased appetite	Grade 1	NK/10/2019	No	Recovery	18/06/2020	No	No	BOSULIF	No dose modification		.

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		Nervous system disorders	Headache	Grade 1	18/06/2020	No	Recovery	19/08/2020	No	No	BOSULIF	No dose modification		.
		Nervous system disorders	Balance disorder	Grade 1	18/06/2020	No	Recovery	19/08/2020	No	No	BOSULIF	No dose modification		.
		Gastrointestinal disorders	Pancreatitis acute	Grade 3	19/08/2020	Yes	Recovery	24/08/2020	Yes	No	BOSULIF	No dose modification		.
		Metabolism and nutrition disorders	Diabetes mellitus inadequate control	Grade 3	19/08/2020	Yes	Recovery	24/08/2020	No	No	BOSULIF	No dose modification		.
		Gastrointestinal disorders	Vomiting	Grade 2	19/08/2020	No	Recovery	24/08/2020	Yes	No	BOSULIF	No dose modification		.
		Gastrointestinal disorders	Abdominal pain	Grade 2	19/08/2020	No	Recovery	24/08/2020	No	No	BOSULIF	No dose modification		.
		Musculoskeletal and connective tissue disorders	Neck pain	Grade 1	02/04/2019	No	Recovery	UK/05/2019	No	No	BOSULIF	No dose modification		.
		Nervous system disorders	Head discomfort	Grade 1	UK/09/2021	No	Subject not recovered		Yes	No	BOSULIF	No dose modification		.
39-01	07/09/2018	Gastrointestinal disorders	Diarrhoea	Grade 2	NK/09/2018	No	Recovery	NK/10/2020	Yes	Yes	BOSULIF	Dose reduction	TARDYFERON	No dose modification
		Gastrointestinal disorders	Nausea	Grade 1	NK/10/2019	No	Recovery	16/10/2019	Yes	No	BOSULIF	No dose modification		.
		Blood and lymphatic system disorders	Iron deficiency anaemia	Grade 2	NK/10/2018	No	Recovery	01/06/2021	No	No	BOSULIF	No dose modification		.
		Nervous system disorders	Headache	Grade 1	NK/NK/2019	No	Recovery	NK/03/2019	Yes	No	BOSULIF	No dose modification		.

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		Investigations	Liver function test abnormal	Grade 2	NK/09/2019	No	Recovery	15/03/2021	Yes	No	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.
		Skin and subcutaneous tissue disorders	Dry skin	Grade 1	20/03/2019	No	Recovery	05/02/2020	No	No	BOSULIF	No dose modification		.
		Blood and lymphatic system disorders	Iron deficiency anaemia	Grade 3	19/02/2021	Yes	Recovery	22/02/2021	No	No	BOSULIF	No dose modification		.
		Blood and lymphatic system disorders	Iron deficiency anaemia	Grade 3	15/06/2021	Yes	Recovery	29/06/2021	No	No	BOSULIF	No dose modification		.
		General disorders and administration site conditions	Oedema peripheral	Grade 2	10/06/2021	No	Recovery	NK/06/2021	No	No	BOSULIF	No dose modification		.
		Gastrointestinal disorders	Intestinal polyp	Grade 2	NK/NK/2021	No	Recovery	20/05/2021	No	No	BOSULIF	No dose modification		.
		Blood and lymphatic system disorders	Iron deficiency anaemia	Grade 3	19/05/2021	Yes	Recovery	21/05/2021	No	No	BOSULIF	No dose modification		.
		Gastrointestinal disorders	Gastrointestinal angiodysplasia	Grade 2	20/05/2021	No	Recovery	26/07/2021	No	No	BOSULIF	No dose modification		.
		Gastrointestinal disorders	Reflux gastritis	Grade 2	NK/02/2021	No	Recovery in progress		No	No	BOSULIF	No dose modification		.
42-01	28/11/2017	Gastrointestinal disorders	Functional gastrointestinal disorder	Grade 1	28/11/2017	No	Recovery	28/02/2018	Yes	No	BOSULIF	No dose modification		.

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		Skin and subcutaneous tissue disorders	Skin odour abnormal	Grade 1	28/11/2017	No	Recovery	28/02/2018	Yes	No	BOSULIF	No dose modification		.
		Gastrointestinal disorders	Abdominal pain	Grade 1	NK/07/2018	No	Recovery	05/12/2018	No	No	BOSULIF	No dose modification		.
		Gastrointestinal disorders	Aphthous stomatitis	Grade 1	NK/07/2018	No	Recovery	05/12/2018	Yes	No	BOSULIF	No dose modification		.
		General disorders and administration site conditions	Asthenia	Grade 2	03/09/2018	No	Subject not recovered		Yes	No	BOSULIF	No dose modification		.
		Skin and subcutaneous tissue disorders	Pruritus	Grade 2	03/09/2018	No	Subject not recovered		Yes	No	BOSULIF	No dose modification		.
		Gastrointestinal disorders	Diarrhoea	Grade 2	05/12/2018	No	Recovery	06/03/2019	No	No	BOSULIF	No dose modification		.
		Infections and infestations	Nasopharyngitis	Grade 1	NK/12/2018	No	Recovery	06/03/2019	No	No	BOSULIF	No dose modification		.
		Hepatobiliary disorders	Hepatocellular injury	Grade 1	17/01/2018	No	Recovery	28/02/2018	Yes	No	BOSULIF	No dose modification		.
		Musculoskeletal and connective tissue disorders	Scoliosis	Grade 1	11/12/2018	No	Subject not recovered		No	No	BOSULIF	No dose modification		.
		Gastrointestinal disorders	Diarrhoea	Grade 2	NK/03/2019	No	Recovery	26/06/2019	Yes	No	BOSULIF	No dose modification		.
		Gastrointestinal disorders	Abdominal pain	Grade 2	NK/03/2019	No	Recovery	26/06/2019	Yes	No	BOSULIF	No dose modification		.
		General disorders and administration site conditions	Chest pain	Grade 1	NK/07/2019	No	Recovery	06/08/2019	No	No	BOSULIF	No dose modification		.

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		Skin and subcutaneous tissue disorders	Erythema	Grade 2	03/09/2018	No	Recovery	05/12/2018	Yes	No	BOSULIF	No dose modification		.
		Musculoskeletal and connective tissue disorders	Intervertebral disc degeneration	Grade 1	11/12/2018	No	Subject not recovered		No	No	BOSULIF	No dose modification		.
		Ear and labyrinth disorders	Hypoacusis	Grade 1	03/09/2019	No	Subject not recovered		No	No	BOSULIF	No dose modification		.
42-02	12/12/2018	Gastrointestinal disorders	Diarrhoea	Grade 2	30/01/2019	No	Recovery	20/03/2019	Yes	No	BOSULIF	No dose modification		.
		Gastrointestinal disorders	Diarrhoea	Grade 2	26/06/2019	No	Recovery	17/06/2020	Yes	No	BOSULIF	No dose modification		.
		Investigations	Aspartate aminotransferase increased	Grade 3	16/09/2019	No	Recovery	23/02/2022	Yes	No	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.
		Investigations	Alanine aminotransferase increased	Grade 3	16/09/2019	No	Recovery	23/02/2022	Yes	No	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.
		Infections and infestations	Genital infection female	Grade 2	01/10/2019	No	Recovery	15/10/2019	No	No	BOSULIF	No dose modification		.
		Musculoskeletal and connective tissue disorders	Myalgia	Grade 1	NK/10/2020	No	Recovery	16/03/2021	No	No	BOSULIG	Not applicable	ASCIMINIB	No dose modification

Patient No.	Date of initiation of bosutinib treatment	SOC name	PT name	CTCAE grade	Date of occurrence	Is the event serious?	Status	Date of recovery	Is it reasonably possible that the event may be related to the study medication?	Is it reasonably possible that the event may be related to a concomitant drug?	Name of the drug (1)	Action taken (1)	Name of the drug (2)	Action taken (2)
43-01	20/11/2018	Infections and infestations	Pneumonia	Grade 2	NK/12/2018	No	Recovery	07/01/2019	No	No	BOSULIF	No dose modification		.
		Gastrointestinal disorders	Nausea	Grade 2	NK/12/2018	No	Recovery	07/01/2019	No	Yes	BOSULIF	No dose modification		.
		Gastrointestinal disorders	Diarrhoea	Grade 2	NK/12/2018	No	Recovery	07/01/2019	No	Yes	BOSULIF	No dose modification		.
		Investigations	Alanine aminotransferase increased	Grade 3	22/03/2019	No	Recovery	08/08/2019	Yes	No	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.
		Investigations	Aspartate aminotransferase increased	Grade 2	22/03/2019	No	Recovery	25/07/2019	Yes	No	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.
		Infections and infestations	Hepatitis E	Grade 2	26/03/2019	No	Subject not recovered		No	No	BOSULIF	No dose modification		.
		Nervous system disorders	Headache	Grade 1	07/03/2019	No	Recovery	18/03/2019	Yes	No	BOSULIF	No dose modification		.
		Gastrointestinal disorders	Nausea	Grade 1	26/03/2019	No	Recovery	15/05/2019	Yes	No	BOSULIF	No dose modification		.
		Gastrointestinal disorders	Vomiting	Grade 1	26/03/2019	No	Recovery	15/05/2019	Yes	No	BOSULIF	No dose modification		.

Patient No.	Date of initiation of bosutinib treatment	SOC name	PT name	CTCAE grade	Date of occurrence	Is the event serious?	Status	Date of recovery	Is it reasonably possible that the event may be related to the study medication?	Is it reasonably possible that the event may be related to a concomitant drug?	Name of the drug (1)	Action taken (1)	Name of the drug (2)	Action taken (2)
		Psychiatric disorders	Anxiety	Grade 1	NK/05/2019	No	Recovery	NK/05/2019	No	No	BOSULIF	No dose modification		.
43-02	01/10/2019	General disorders and administration site conditions	Asthenia	Grade 2	14/10/2019	No	Recovery	09/12/2019	No	No	BOSULIF	No dose modification		.
		Gastrointestinal disorders	Gastroduodenal ulcer	Grade 2	31/07/2020	Yes	Subject not recovered		No	No	BOSULIF	No dose modification		.
		Musculoskeletal and connective tissue disorders	Arthralgia	Grade 2	06/09/2021	No	Subject not recovered		No	No	BOSULIF	No dose modification		.
		Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Bowen's disease	Grade 3	20/05/2021	Yes	Recovery	26/05/2021	No	No	BOSULIF	No dose modification		.
		Infections and infestations	Herpes zoster	Grade 2	UK/UK/2022	No	Recovery	10/10/2022	No	No	BOSULIF	No dose modification		.
		Investigations	Serum ferritin normal	Grade 2	04/04/2022	No	Subject not recovered		No	No	BOSULIF	No dose modification		.
		Reproductive system and breast disorders	Prostatism	Grade 2	10/10/2022	No	Subject not recovered		No	No	BOSULIF	No dose modification		.
		Psychiatric disorders	Mental disorder	Grade 1	10/10/2022	No	Subject not recovered		No	No	BOSULIF	No dose modification		.
47-01	22/01/2019	Infections and infestations	Pneumonia	Grade 2	NK/02/2019	No	Recovery	14/02/2019	No	No	BOSULIF	No dose modification		.
		Musculoskeletal and connective tissue disorders	Pain in extremity	Grade 1	NK/02/2019	No	Recovery	23/04/2019	No	No	BOSULIF	No dose modification		.
		General disorders and administration site conditions	Pyrexia	Grade 2	17/02/2019	No	Recovery	NK/02/2019	No	No	BOSULIF	No dose modification		.

Patient No.	Date of initiation of bosutinib treatment	SOC name	PT name	CTCAE grade	Date of occurrence	Is the event serious?	Status	Date of recovery	Is it reasonably possible that the event may be related to the study medication?	Is it reasonably possible that the event may be related to a concomitant drug?	Name of the drug (1)	Action taken (1)	Name of the drug (2)	Action taken (2)
		Infections and infestations	Pyelonephritis	Grade 3	20/02/2019	Yes	Recovery	22/02/2019	No	No	BOSULIF	No dose modification		.
		Gastrointestinal disorders	Diarrhoea	Grade 1	NK/04/2019	No	Recovery	08/10/2019	Yes	No	BOSULIF	No dose modification		.
		Investigations	Lipase increased	Grade 4	10/01/2020	Yes	Recovery	29/01/2020	Yes	No	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.
		Gastrointestinal disorders	Flatulence	Grade 1	25/05/2020	No	Recovery	05/10/2020	No	No	BOSULIF	No dose modification		.
		Renal and urinary disorders	Renal colic	Grade 2	06/01/2021	Yes	Recovery	04/02/2021	No	No	BOSULIF	No dose modification		.
		Renal and urinary disorders	Nephrolithiasis	Grade 2	04/02/2021	No	Recovery in progress		No	No	BOSULIF	No dose modification		.
		Infections and infestations	Urinary tract infection	Grade 2	01/01/2021	No	Recovery	14/01/2021	No	No	BOSULIF	No dose modification		.
		Infections and infestations	Urinary tract infection	Grade 2	16/08/2021	No	Recovery	NK/03/2022	No	No	BOSULIF	No dose modification		.
47-02	05/03/2019	General disorders and administration site conditions	Asthenia	Grade 2	NK/03/2019	No	Recovery	02/12/2019	Yes	No	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.

Patient No.	Date of initiation of bosutinib treatment	SOC name	PT name	CTCAE grade	Date of occurrence	Is the event serious?	Status	Date of recovery	Is it reasonably possible that the event may be related to the study medication?	Is it reasonably possible that the event may be related to a concomitant drug?	Name of the drug (1)	Action taken (1)	Name of the drug (2)	Action taken (2)
		Gastrointestinal disorders	Diarrhoea	Grade 3	NK/03/2019	No	Recovery	02/09/2019	Yes	No	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.
		Skin and subcutaneous tissue disorders	Night sweats	Grade 2	20/06/2019	No	Recovery	02/09/2021	No	No	BOUSULIF	No dose modification		.
47-03	18/03/2019	Investigations	Aspartate aminotransferase increased	Grade 4	29/04/2019	Yes	Recovery	03/06/2019	Yes	No	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.
		Investigations	Alanine aminotransferase increased	Grade 3	30/04/2019	Yes	Recovery	03/06/2019	Yes	No	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.
		Gastrointestinal disorders	Flatulence	Grade 2	23/04/2019	No	Recovery	13/05/2019	Yes	No	BOSULIF	No dose modification		.
		Gastrointestinal disorders	Abdominal pain	Grade 1	23/04/2019	No	Recovery	13/05/2019	No	No	BOSULIF	No dose modification		.
		Metabolism and nutrition disorders	Decreased appetite	Grade 1	23/04/2019	No	Recovery with sequellae	13/05/2019	Yes	No	BOSULIF	No dose modification		.

Patient No.	Date of initiation of bosutinib treatment	SOC name	PT name	CTCAE grade	Date of occurrence	Is the event serious?	Status	Date of recovery	Is it reasonably possible that the event may be related to the study medication?	Is it reasonably possible that the event may be related to a concomitant drug?	Name of the drug (1)	Action taken (1)	Name of the drug (2)	Action taken (2)
		Gastrointestinal disorders	Nausea	Grade 2	23/04/2019	No	Recovery	13/05/2019	Yes	No	BOSULIF	No dose modification		.
		Psychiatric disorders	Anxiety	Grade 1	27/05/2019	No	Recovery	29/06/2019	No	No	BOSULIF	Not applicable	TASIGNA	No dose modification
		Skin and subcutaneous tissue disorders	Pruritus	Grade 1	11/06/2019	No	Subject not recovered		No	No	TASIGNA	Dose reduction		.
48-01	06/10/2018	Gastrointestinal disorders	Diarrhoea	Grade 3	06/10/2018	No	Recovery	27/10/2018	Yes	No	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.
		Gastrointestinal disorders	Vomiting	Grade 3	06/10/2018	No	Recovery	27/10/2018	Yes	No	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.
		Nervous system disorders	Headache	Grade 2	06/10/2018	No	Recovery	27/10/2018	Yes	No	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.
		Respiratory, thoracic and mediastinal disorders	Rhinorrhoea	Grade 1	31/10/2018	No	Recovery	NK/12/2018	No	No	BOSULIF	Not applicable		.

Patient No.	Date of initiation of bosutinib treatment	SOC name	PT name	CTCAE grade	Date of occurrence	Is the event serious?	Status	Date of recovery	Is it reasonably possible that the event may be related to the study medication?	Is it reasonably possible that the event may be related to a concomitant drug?	Name of the drug (1)	Action taken (1)	Name of the drug (2)	Action taken (2)
		Respiratory, thoracic and mediastinal disorders	Pulmonary pain	Grade 2	NK/10/2018	Yes	Recovery	NK/01/2019	No	No	BOSULIF	Not applicable		.
		General disorders and administration site conditions	Asthenia	Grade 1	NK/11/2018	No	Recovery	NK/11/2018	No	Yes	SPRYCEL	Withdrawal (temporary or permanent, or deferred administration)		.
		Vascular disorders	Hot flush	Grade 1	NK/11/2018	No	Recovery	NK/11/2018	No	Yes	SPRYCEL	Withdrawal (temporary or permanent, or deferred administration)		.
49-01	23/08/2017	Investigations	Alanine aminotransferase increased	Grade 2	03/10/2017	No	Recovery	28/10/2017	Yes	No	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.
		Investigations	Aspartate aminotransferase increased	Grade 3	03/10/2017	No	Recovery	16/10/2017	Yes	No	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.

Patient No.	Date of initiation of bosutinib treatment	SOC name	PT name	CTCAE grade	Date of occurrence	Is the event serious?	Status	Date of recovery	Is it reasonably possible that the event may be related to the study medication?	Is it reasonably possible that the event may be related to a concomitant drug?	Name of the drug (1)	Action taken (1)	Name of the drug (2)	Action taken (2)
		Investigations	Aspartate aminotransferase increased	Grade 3	30/10/2017	No	Recovery	05/12/2017	Yes	No	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.
		Investigations	Alanine aminotransferase increased	Grade 3	30/10/2017	No	Recovery	26/12/2017	Yes	No	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.
		Investigations	Gamma-glutamyltransferase increased	Grade 2	10/10/2017	No	Recovery	09/01/2018	Yes	No	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.
		Investigations	Blood creatinine increased	Grade 2	28/10/2017	No	Recovery	12/01/2018	Yes	No	BOSULIF	Withdrawal (temporary or permanent, or deferred administration)		.
		Nervous system disorders	Headache	Grade 2	15/11/2017	No	Recovery	17/11/2017	Yes	No	BOSULIF	No dose modification		.

Patient No.	Date of initiation of bosutinib treatment	SOC name	PT name	CTCAE grade	Date of occurrence	Is the event serious?	Status	Date of recovery	Is it reasonably possible that the event may be related to the study medication?	Is it reasonably possible that the event may be related to a concomitant drug?	Name of the drug (1)	Action taken (1)	Name of the drug (2)	Action taken (2)
		Renal and urinary disorders	Chromaturia	Grade 2	15/11/2017	No	Recovery	17/11/2017	No	No	BOSULIF	No dose modification		.
		Immune system disorders	Hypersensitivity	Grade 1	NK/10/2017	No	Recovery	22/11/2017	No	No	BOSULIF	No dose modification		.
		General disorders and administration site conditions	Fatigue	Grade 1	NK/11/2017	No	Recovery	12/04/2018	No	No	BOSULIF	No dose modification		.
		Gastrointestinal disorders	Nausea	Grade 1	NK/11/2017	No	Recovery	12/04/2018	No	No	BOSULIF	No dose modification		.

Appendix 7.7 Measures taken to prevent AE - SAF (n=142)

Appendix 7.8 Laboratory listings

Table 83: Biological and Hematological Parameters: ALAT - SAF (n=142)

Variables		2L (N=66)	3L (N=42)	4L+ (N=34)	Total (N=142)
Baseline: ALAT (UI/L)	N	47	27	24	98
	Mean ± SD	21.5 ± 10.6	23.7 ± 13.9	26.5 ± 21.5	23.3 ± 14.8
	Median	19.0	18.0	19.5	19.0
	Q1 ; Q3	15.0 ; 23.0	14.0 ; 34.0	14.5 ; 29.5	15.0 ; 27.0
	Min. ; Max.	6 ; 67	5 ; 57	8 ; 96	5 ; 96
	Missing	19	15	10	44
Month 3: ALAT (UI/L)	N	36	26	20	82
	Mean ± SD	27.9 ± 15.4	34.2 ± 20.9	34.4 ± 25.6	31.5 ± 20.1
	Median	23.0	27.0	23.5	23.5
	Q1 ; Q3	17.5 ; 33.5	18.0 ; 46.0	17.5 ; 48.0	18.0 ; 38.0
	Min. ; Max.	4 ; 70	13 ; 90	3 ; 95	3 ; 95
	Missing	30	16	14	60
Month 6: ALAT (UI/L)	N	30	23	16	69
	Mean ± SD	29.4 ± 16.7	27.2 ± 21.5	37.1 ± 23.4	30.5 ± 20.1
	Median	23.5	18.0	30.5	24.0
	Q1 ; Q3	17.0 ; 34.0	14.0 ; 31.0	19.0 ; 52.5	16.0 ; 36.0
	Min. ; Max.	11 ; 83	8 ; 95	9 ; 89	8 ; 95
	Missing	36	19	18	73
Month 9: ALAT (UI/L)	N	22	16	14	52
	Mean ± SD	27.8 ± 18.0	29.4 ± 20.4	32.6 ± 13.2	29.6 ± 17.4
	Median	22.0	21.5	27.0	26.0
	Q1 ; Q3	14.0 ; 37.0	14.5 ; 39.0	25.0 ; 42.0	15.5 ; 38.0
	Min. ; Max.	8 ; 81	9 ; 85	11 ; 60	8 ; 85
	Missing	44	26	20	90
Month 12: ALAT (UI/L)	N	17	17	14	48
	Mean ± SD	22.9 ± 9.0	26.9 ± 16.7	25.4 ± 10.1	25.0 ± 12.4

Variables		2L (N=66)	3L (N=42)	4L+ (N=34)	Total (N=142)
	Median	21.0	21.0	24.0	22.0
	Q1 ; Q3	15.0 ; 26.0	17.0 ; 32.0	17.0 ; 29.0	16.5 ; 30.5
	Min. ; Max.	12 ; 40	7 ; 62	12 ; 44	7 ; 62
	Missing	49	25	20	94
Month 15: ALAT (UI/L)	N	17	10	14	41
	Mean ± SD	23.9 ± 12.0	22.7 ± 8.9	25.4 ± 12.3	24.1 ± 11.2
	Median	21.0	22.5	24.0	22.0
	Q1 ; Q3	14.0 ; 29.0	17.0 ; 27.0	15.0 ; 36.0	15.0 ; 29.0
	Min. ; Max.	13 ; 52	12 ; 40	9 ; 53	9 ; 53
	Missing	49	32	20	101
Month 18: ALAT (UI/L)	N	8	8	11	27
	Mean ± SD	21.8 ± 7.6	26.9 ± 14.2	21.5 ± 11.6	23.2 ± 11.3
	Median	20.5	23.0	16.0	19.0
	Q1 ; Q3	15.5 ; 29.0	17.0 ; 34.5	13.0 ; 26.0	16.0 ; 28.0
	Min. ; Max.	12 ; 32	11 ; 55	11 ; 52	11 ; 55
	Missing	58	34	23	115
Month 21: ALAT (UI/L)	N	12	4	12	28
	Mean ± SD	19.8 ± 12.5	30.8 ± 17.2	28.3 ± 13.2	25.0 ± 13.7
	Median	16.0	25.0	27.5	18.5
	Q1 ; Q3	11.0 ; 24.5	18.5 ; 43.0	17.5 ; 34.0	15.5 ; 31.0
	Min. ; Max.	9 ; 49	18 ; 55	14 ; 60	9 ; 60
	Missing	54	38	22	114
Month 24: ALAT (UI/L)	N	10	4	11	25
	Mean ± SD	22.4 ± 9.7	21.5 ± 8.4	27.0 ± 17.6	24.3 ± 13.4
	Median	21.0	23.0	21.0	22.0
	Q1 ; Q3	18.0 ; 28.0	16.0 ; 27.0	17.0 ; 38.0	18.0 ; 28.0
	Min. ; Max.	6 ; 40	10 ; 30	9 ; 67	6 ; 67
	Missing	56	38	23	117
Month 27: ALAT (UI/L)	N	8	4	6	18
	Mean ± SD	20.1 ± 4.2	16.8 ± 5.3	26.7 ± 23.4	21.6 ± 13.8
	Median	21.5	18.0	17.5	21.0

Variables		2L (N=66)	3L (N=42)	4L+ (N=34)	Total (N=142)
	Q1 ; Q3	19.0 ; 22.5	12.5 ; 21.0	14.0 ; 23.0	15.0 ; 22.0
	Min. ; Max.	11 ; 24	10 ; 21	14 ; 74	10 ; 74
	Missing	58	38	28	124
Month 30: ALAT (UI/L)	N	9	2	3	14
	Mean ± SD	21.9 ± 10.0	14.5 ± 2.1	16.0 ± 3.5	19.6 ± 8.6
	Median	18.0	14.5	14.0	17.5
	Q1 ; Q3	17.0 ; 24.0	13.0 ; 16.0	14.0 ; 20.0	14.0 ; 20.0
	Min. ; Max.	12 ; 44	13 ; 16	14 ; 20	12 ; 44
	Missing	57	40	31	128
Month 33: ALAT (UI/L)	N	5	0	3	8
	Mean ± SD	19.8 ± 7.2		18.7 ± 9.6	19.4 ± 7.5
	Median	19.0		17.0	18.0
	Q1 ; Q3	15.0 ; 27.0		10.0 ; 29.0	13.0 ; 27.0
	Min. ; Max.	11 ; 27		10 ; 29	10 ; 29
	Missing	61	42	31	134
Month 36: ALAT (UI/L)	N	3	3	2	8
	Mean ± SD	15.0 ± 7.9	12.7 ± 1.5	20.0 ± 12.7	15.4 ± 7.2
	Median	12.0	13.0	20.0	12.5
	Q1 ; Q3	9.0 ; 24.0	11.0 ; 14.0	11.0 ; 29.0	11.0 ; 19.0
	Min. ; Max.	9 ; 24	11 ; 14	11 ; 29	9 ; 29
	Missing	63	39	32	134

Table 15.3.9a Biological and Hematological Parameters: ALAT - SAF (n=142)

Table 84: Biological and Hematological Parameters: ASAT - SAF (n=142)

Variables		2L (N=66)	3L (N=42)	4L+ (N=34)	Total (N=142)
Baseline: ASAT (UI/L)	N	47	27	25	99
	Mean ± SD	23.0 ± 7.0	26.4 ± 10.1	27.9 ± 15.0	25.1 ± 10.5
	Median	23.0	25.0	22.0	24.0
	Q1 ; Q3	18.0 ; 27.0	19.0 ; 33.0	20.0 ; 31.0	19.0 ; 29.0
	Min. ; Max.	8 ; 43	11 ; 58	10 ; 77	8 ; 77
	Missing	19	15	9	43
Month 3: ASAT (UI/L)	N	41	26	22	89
	Mean ± SD	28.7 ± 16.4	31.2 ± 14.7	31.0 ± 19.8	30.0 ± 16.7
	Median	24.0	28.0	27.0	26.0
	Q1 ; Q3	19.0 ; 31.0	21.0 ; 36.0	15.0 ; 41.0	19.0 ; 34.0
	Min. ; Max.	8 ; 83	11 ; 73	6 ; 92	6 ; 92
	Missing	25	16	12	53
Month 6: ASAT (UI/L)	N	30	22	17	69
	Mean ± SD	27.4 ± 12.2	25.0 ± 10.8	30.9 ± 16.3	27.5 ± 12.9
	Median	24.5	22.0	25.0	24.0
	Q1 ; Q3	18.0 ; 34.0	17.0 ; 28.0	19.0 ; 35.0	18.0 ; 34.0
	Min. ; Max.	15 ; 73	9 ; 49	14 ; 61	9 ; 73
	Missing	36	20	17	73
Month 9: ASAT (UI/L)	N	22	17	14	53
	Mean ± SD	24.0 ± 8.9	34.5 ± 23.8	26.4 ± 11.1	28.0 ± 16.0
	Median	23.0	27.0	23.0	23.0
	Q1 ; Q3	17.0 ; 27.0	20.0 ; 39.0	21.0 ; 35.0	20.0 ; 34.0
	Min. ; Max.	8 ; 46	10 ; 99	10 ; 52	8 ; 99
	Missing	44	25	20	89
Month 12: ASAT (UI/L)	N	17	17	14	48
	Mean ± SD	21.8 ± 5.5	30.8 ± 16.7	23.6 ± 8.1	25.5 ± 11.8
	Median	22.0	28.0	23.5	23.0
	Q1 ; Q3	19.0 ; 25.0	22.0 ; 36.0	16.0 ; 31.0	18.5 ; 28.5

Variables		2L (N=66)	3L (N=42)	4L+ (N=34)	Total (N=142)
	Min. ; Max.	13 ; 38	10 ; 85	12 ; 36	10 ; 85
	Missing	49	25	20	94
Month 15: ASAT (UI/L)	N	17	11	14	42
	Mean ± SD	22.5 ± 7.8	31.8 ± 10.4	22.9 ± 6.7	25.1 ± 9.0
	Median	21.0	31.0	22.5	22.5
	Q1 ; Q3	18.0 ; 27.0	21.0 ; 43.0	17.0 ; 27.0	18.0 ; 29.0
	Min. ; Max.	11 ; 41	18 ; 48	14 ; 36	11 ; 48
	Missing	49	31	20	100
Month 18: ASAT (UI/L)	N	8	8	11	27
	Mean ± SD	25.4 ± 5.0	25.9 ± 6.0	22.2 ± 11.3	24.2 ± 8.3
	Median	26.0	26.0	19.0	24.0
	Q1 ; Q3	22.0 ; 29.5	21.0 ; 30.5	15.0 ; 26.0	18.0 ; 29.0
	Min. ; Max.	17 ; 31	17 ; 35	11 ; 52	11 ; 52
	Missing	58	34	23	115
Month 21: ASAT (UI/L)	N	12	4	12	28
	Mean ± SD	21.6 ± 5.8	29.8 ± 7.7	27.7 ± 10.7	25.4 ± 8.9
	Median	21.0	30.5	27.0	23.5
	Q1 ; Q3	17.5 ; 26.0	24.0 ; 35.5	18.0 ; 37.5	19.0 ; 30.5
	Min. ; Max.	12 ; 32	20 ; 38	16 ; 47	12 ; 47
	Missing	54	38	22	114
Month 24: ASAT (UI/L)	N	10	4	11	25
	Mean ± SD	22.6 ± 4.9	21.5 ± 7.6	22.9 ± 9.5	22.6 ± 7.4
	Median	22.0	23.0	21.0	22.0
	Q1 ; Q3	19.0 ; 28.0	16.5 ; 26.5	15.0 ; 31.0	17.0 ; 28.0
	Min. ; Max.	14 ; 28	11 ; 29	13 ; 42	11 ; 42
	Missing	56	38	23	117
Month 27: ASAT (UI/L)	N	8	4	6	18
	Mean ± SD	21.1 ± 5.6	24.8 ± 6.4	37.2 ± 23.1	27.3 ± 15.2
	Median	22.0	25.5	33.5	23.0
	Q1 ; Q3	17.0 ; 23.5	19.5 ; 30.0	18.0 ; 41.0	18.0 ; 31.0
	Min. ; Max.	13 ; 31	17 ; 31	17 ; 80	13 ; 80

Variables		2L (N=66)	3L (N=42)	4L+ (N=34)	Total (N=142)
	Missing	58	38	28	124
Month 30: ASAT (UI/L)	N	9	2	3	14
	Mean ± SD	22.1 ± 7.3	20.5 ± 0.7	23.3 ± 12.5	22.1 ± 7.6
	Median	22.0	20.5	23.0	21.5
	Q1 ; Q3	20.0 ; 27.0	20.0 ; 21.0	11.0 ; 36.0	20.0 ; 27.0
	Min. ; Max.	10 ; 32	20 ; 21	11 ; 36	10 ; 36
	Missing	57	40	31	128
Month 33: ASAT (UI/L)	N	5	0	3	8
	Mean ± SD	22.2 ± 1.6		22.3 ± 11.2	22.3 ± 6.1
	Median	23.0		18.0	22.0
	Q1 ; Q3	21.0 ; 23.0		14.0 ; 35.0	19.0 ; 23.5
	Min. ; Max.	20 ; 24		14 ; 35	14 ; 35
	Missing	61	42	31	134
Month 36: ASAT (UI/L)	N	3	3	2	8
	Mean ± SD	21.7 ± 9.3	25.0 ± 7.9	22.0 ± 4.2	23.0 ± 6.9
	Median	19.0	22.0	22.0	20.5
	Q1 ; Q3	14.0 ; 32.0	19.0 ; 34.0	19.0 ; 25.0	19.0 ; 28.5
	Min. ; Max.	14 ; 32	19 ; 34	19 ; 25	14 ; 34
	Missing	63	39	32	134

Table 15.3.9b Biological and Hematological Parameters: ASAT - SAF (n=142)

Table 85: Biological and Hematological Parameters: Total bilirubin - SAF (n=142)

Variables		2L (N=66)	3L (N=42)	4L+ (N=34)	Total (N=142)
Baseline: Total bilirubin (µmol/L)	N	39	21	22	82
	Mean ± SD	10.042 ± 5.582	11.567 ± 5.172	9.846 ± 5.822	10.380 ± 5.523
	Median	9.000	11.000	8.500	9.000
	Q1 ; Q3	7.000 ; 12.000	7.000 ; 15.700	6.700 ; 11.000	7.000 ; 13.000
	Min. ; Max.	3 ; 32.2	4 ; 21	4 ; 30	3 ; 32.2
	Missing	27	21	12	60
Month 3: Total bilirubin (µmol/L)	N	38	18	22	78
	Mean ± SD	9.863 ± 5.069	9.902 ± 3.892	8.463 ± 3.978	9.477 ± 4.519
	Median	9.000	8.800	7.600	8.600
	Q1 ; Q3	7.000 ; 11.900	6.840 ; 12.900	6.000 ; 10.000	6.840 ; 11.000
	Min. ; Max.	3 ; 25	6 ; 20.7	4 ; 22	3 ; 25
	Missing	28	24	12	64
Month 6: Total bilirubin (µmol/L)	N	27	14	15	56
	Mean ± SD	8.509 ± 3.689	8.230 ± 3.585	10.553 ± 8.344	8.987 ± 5.303
	Median	8.000	6.920	8.000	8.000
	Q1 ; Q3	6.000 ; 11.000	5.400 ; 12.000	6.000 ; 11.000	6.000 ; 11.000
	Min. ; Max.	3 ; 20.5	4 ; 14	3 ; 37	3 ; 37
	Missing	39	28	19	86
Month 9: Total bilirubin (µmol/L)	N	19	11	11	41
	Mean ± SD	8.272 ± 4.014	10.358 ± 5.387	8.073 ± 2.940	8.778 ± 4.197
	Median	7.000	8.900	7.500	7.500
	Q1 ; Q3	5.000 ; 10.260	6.200 ; 15.400	6.100 ; 12.000	6.000 ; 10.900
	Min. ; Max.	3 ; 17	5 ; 22	3 ; 12	3 ; 22
	Missing	47	31	23	101
Month 12: Total bilirubin (µmol/L)	N	13	11	11	35
	Mean ± SD	10.328 ± 7.442	9.258 ± 3.864	7.555 ± 3.144	9.120 ± 5.311
	Median	10.000	7.400	7.000	8.000
	Q1 ; Q3	5.000 ; 13.000	6.840 ; 11.000	4.800 ; 10.000	5.800 ; 11.000

Variables		2L (N=66)	3L (N=42)	4L+ (N=34)	Total (N=142)
	Min. ; Max.	3 ; 32	5.8 ; 17.6	2.9 ; 12	2.9 ; 32
	Missing	53	31	23	107
Month 15: Total bilirubin (µmol/L)	N	14	5	12	31
	Mean ± SD	7.501 ± 2.931	8.686 ± 3.556	8.558 ± 3.208	8.101 ± 3.081
	Median	7.000	9.300	7.750	7.500
	Q1 ; Q3	5.000 ; 10.000	5.130 ; 11.000	7.000 ; 10.000	5.130 ; 10.000
	Min. ; Max.	3 ; 13	5 ; 13	4 ; 16	3 ; 16
	Missing	52	37	22	111
Month 18: Total bilirubin (µmol/L)	N	8	5	10	23
	Mean ± SD	7.619 ± 2.369	10.406 ± 3.365	7.720 ± 4.379	8.269 ± 3.608
	Median	8.475	12.000	5.800	8.400
	Q1 ; Q3	6.500 ; 9.000	9.000 ; 12.900	5.200 ; 11.000	5.200 ; 11.000
	Min. ; Max.	3 ; 10	5.13 ; 13	3 ; 15	3 ; 15
	Missing	58	37	24	119
Month 21: Total bilirubin (µmol/L)	N	9	2	11	22
	Mean ± SD	9.744 ± 3.108	6.650 ± 0.919	7.727 ± 3.072	8.455 ± 3.085
	Median	10.260	6.650	7.000	8.150
	Q1 ; Q3	9.000 ; 12.000	6.000 ; 7.300	5.000 ; 11.000	6.000 ; 11.000
	Min. ; Max.	4 ; 13.2	6 ; 7.3	4 ; 13	4 ; 13.2
	Missing	57	40	23	120
Month 24: Total bilirubin (µmol/L)	N	8	3	10	21
	Mean ± SD	8.933 ± 3.286	8.667 ± 3.512	8.540 ± 3.489	8.708 ± 3.244
	Median	10.000	9.000	8.400	9.000
	Q1 ; Q3	6.000 ; 10.630	5.000 ; 12.000	6.100 ; 10.000	6.100 ; 10.260
	Min. ; Max.	4.2 ; 14	5 ; 12	4 ; 16	4 ; 16
	Missing	58	39	24	121
Month 27: Total bilirubin (µmol/L)	N	7	3	7	17
	Mean ± SD	7.224 ± 4.054	8.367 ± 2.570	7.900 ± 1.992	7.704 ± 2.946
	Median	8.550	8.000	8.000	8.000
	Q1 ; Q3	3.000 ; 10.000	6.000 ; 11.100	6.300 ; 8.000	6.000 ; 9.600
	Min. ; Max.	3 ; 13	6 ; 11.1	6 ; 12	3 ; 13

Variables		2L (N=66)	3L (N=42)	4L+ (N=34)	Total (N=142)
	Missing	59	39	27	125
Month 30: Total bilirubin (µmol/L)	N	5	1	3	9
	Mean ± SD	9.252 ± 1.954	6.900 ± .	11.567 ± 5.056	9.762 ± 3.272
	Median	10.000	6.900	10.700	10.000
	Q1 ; Q3	9.000 ; 10.260	6.900 ; 6.900	7.000 ; 17.000	7.000 ; 10.700
	Min. ; Max.	6 ; 11	6.9 ; 6.9	7 ; 17	6 ; 17
	Missing	61	41	31	133
Month 33: Total bilirubin (µmol/L)	N	4	0	3	7
	Mean ± SD	8.260 ± 1.306		9.700 ± 1.682	8.877 ± 1.545
	Median	8.100		10.300	8.200
	Q1 ; Q3	7.420 ; 9.100		7.800 ; 11.000	7.800 ; 10.300
	Min. ; Max.	6.84 ; 10		7.8 ; 11	6.84 ; 11
	Missing	62	42	31	135
Month 36: Total bilirubin (µmol/L)	N	2	1	2	5
	Mean ± SD	10.00 ± 1.41	5.40 ± .	14.60 ± 4.81	10.92 ± 4.59
	Median	10.00	5.40	14.60	11.00
	Q1 ; Q3	9.00 ; 11.00	5.40 ; 5.40	11.20 ; 18.00	9.00 ; 11.20
	Min. ; Max.	9 ; 11	5.4 ; 5.4	11.2 ; 18	5.4 ; 18
	Missing	64	41	32	137

Table 15.3.9c Biological and Hematological Parameters: Total bilirubin - SAF (n=142)

Table 86: Biological and Hematological Parameters: Conjugated bilirubin - SAF (n=142)

Variables		2L (N=66)	3L (N=42)	4L+ (N=34)	Total (N=142)
Baseline: Conjugated bilirubin (µmol/L)	N	9	3	7	19
	Mean ± SD	4.96 ± 2.81	4.37 ± 0.78	3.76 ± 2.84	4.42 ± 2.57
	Median	4.00	4.60	2.80	3.50
	Q1 ; Q3	3.00 ; 6.50	3.50 ; 5.00	2.00 ; 4.00	2.80 ; 5.00
	Min. ; Max.	1.7 ; 10	3.5 ; 5	1.9 ; 10	1.7 ; 10
	Missing	57	39	27	123
Month 3: Conjugated bilirubin (µmol/L)	N	8	3	9	20
	Mean ± SD	5.04 ± 2.34	3.67 ± 1.86	3.48 ± 1.84	4.13 ± 2.09
	Median	4.00	3.90	3.00	3.60
	Q1 ; Q3	3.55 ; 7.05	1.70 ; 5.40	2.10 ; 3.50	2.55 ; 5.20
	Min. ; Max.	2.3 ; 8.8	1.7 ; 5.4	2 ; 7.7	1.7 ; 8.8
	Missing	58	39	25	122
Month 6: Conjugated bilirubin (µmol/L)	N	5	0	6	11
	Mean ± SD	2.642 ± 1.499		3.500 ± 1.657	3.110 ± 1.572
	Median	2.000		3.050	3.000
	Q1 ; Q3	1.710 ; 3.000		2.000 ; 5.000	1.900 ; 5.000
	Min. ; Max.	1.4 ; 5.1		1.9 ; 6	1.4 ; 6
	Missing	61	42	28	131
Month 9: Conjugated bilirubin (µmol/L)	N	2	2	4	8
	Mean ± SD	1.905 ± 0.276	6.200 ± 5.374	3.150 ± 0.614	3.601 ± 2.677
	Median	1.905	6.200	2.950	2.700
	Q1 ; Q3	1.710 ; 2.100	2.400 ; 10.000	2.700 ; 3.600	2.250 ; 3.600
	Min. ; Max.	1.71 ; 2.1	2.4 ; 10	2.7 ; 4	1.71 ; 10
	Missing	64	40	30	134
Month 12: Conjugated bilirubin (µmol/L)	N	1	2	5	8
	Mean ± SD	9.000 ± .	4.800 ± 0.283	2.698 ± 1.393	4.011 ± 2.467
	Median	9.000	4.800	2.100	3.800
	Q1 ; Q3	9.000 ; 9.000	4.600 ; 5.000	1.700 ; 3.000	1.900 ; 5.000

Variables		2L (N=66)	3L (N=42)	4L+ (N=34)	Total (N=142)
	Min. ; Max.	9 ; 9	4.6 ; 5	1.69 ; 5	1.69 ; 9
	Missing	65	40	29	134
Month 15: Conjugated bilirubin (µmol/L)	N	3	2	2	7
	Mean ± SD	3.707 ± 0.290	7.500 ± 7.778	2.650 ± 0.071	4.489 ± 3.817
	Median	3.700	7.500	2.650	3.420
	Q1 ; Q3	3.420 ; 4.000	2.000 ; 13.000	2.600 ; 2.700	2.600 ; 4.000
	Min. ; Max.	3.42 ; 4	2 ; 13	2.6 ; 2.7	2 ; 13
	Missing	63	40	32	135
Month 18: Conjugated bilirubin (µmol/L)	N	0	1	3	4
	Mean ± SD		8.60 ± .	3.37 ± 1.48	4.68 ± 2.88
	Median		8.60	3.00	4.00
	Q1 ; Q3		8.60 ; 8.60	2.10 ; 5.00	2.55 ; 6.80
	Min. ; Max.		8.6 ; 8.6	2.1 ; 5	2.1 ; 8.6
	Missing	66	41	31	138
Month 21: Conjugated bilirubin (µmol/L)	N	2	0	1	3
	Mean ± SD	3.870 ± 1.598		2.500 ± .	3.413 ± 1.379
	Median	3.870		2.500	2.740
	Q1 ; Q3	2.740 ; 5.000		2.500 ; 2.500	2.500 ; 5.000
	Min. ; Max.	2.74 ; 5		2.5 ; 2.5	2.5 ; 5
	Missing	64	42	33	139
Month 24: Conjugated bilirubin (µmol/L)	N	1	0	2	3
	Mean ± SD	1.50 ± .		3.65 ± 0.21	2.93 ± 1.25
	Median	1.50		3.65	3.50
	Q1 ; Q3	1.50 ; 1.50		3.50 ; 3.80	1.50 ; 3.80
	Min. ; Max.	1.5 ; 1.5		3.5 ; 3.8	1.5 ; 3.8
	Missing	65	42	32	139
Month 27: Conjugated bilirubin (µmol/L)	N	1	1	1	3
	Mean ± SD	3.40 ± .	1.90 ± .	4.80 ± .	3.37 ± 1.45
	Median	3.40	1.90	4.80	3.40
	Q1 ; Q3	3.40 ; 3.40	1.90 ; 1.90	4.80 ; 4.80	1.90 ; 4.80
	Min. ; Max.	3.4 ; 3.4	1.9 ; 1.9	4.8 ; 4.8	1.9 ; 4.8

Variables		2L (N=66)	3L (N=42)	4L+ (N=34)	Total (N=142)
	Missing	65	41	33	139
Month 30: Conjugated bilirubin (µmol/L)	N	0	0	2	2
	Mean ± SD			3.90 ± 0.14	3.90 ± 0.14
	Median			3.90	3.90
	Q1 ; Q3			3.80 ; 4.00	3.80 ; 4.00
	Min. ; Max.			3.8 ; 4	3.8 ; 4
	Missing	66	42	32	140
Month 33: Conjugated bilirubin (µmol/L)	N	1	0	2	3
	Mean ± SD	1.50 ± .		2.60 ± 1.13	2.23 ± 1.02
	Median	1.50		2.60	1.80
	Q1 ; Q3	1.50 ; 1.50		1.80 ; 3.40	1.50 ; 3.40
	Min. ; Max.	1.5 ; 1.5		1.8 ; 3.4	1.5 ; 3.4
	Missing	65	42	32	139
Month 36: Conjugated bilirubin (µmol/L)	N	0	0	1	1
	Mean ± SD			4.20 ± .	4.20 ± .
	Median			4.20	4.20
	Q1 ; Q3			4.20 ; 4.20	4.20 ; 4.20
	Min. ; Max.			4.2 ; 4.2	4.2 ; 4.2
	Missing	66	42	33	141

Table 15.3.9d Biological and Hematological Parameters: Conjugated bilirubin - SAF (n=142)

Table 87: Biological and Hematological Parameters: LDH - SAF (n=142)

Variables		2L (N=66)	3L (N=42)	4L+ (N=34)	Total (N=142)
Baseline: LDH (UI/L)	N	22	13	14	49
	Mean ± SD	286.0 ± 137.9	300.7 ± 170.6	303.0 ± 119.5	294.8 ± 139.8
	Median	234.5	238.0	279.5	243.0
	Q1 ; Q3	204.0 ; 351.0	208.0 ; 339.0	221.0 ; 393.0	208.0 ; 351.0
	Min. ; Max.	140 ; 674	145 ; 803	142 ; 522	140 ; 803
	Missing	44	29	20	93
Month 3: LDH (UI/L)	N	19	12	11	42
	Mean ± SD	272.4 ± 96.8	271.1 ± 109.3	295.5 ± 146.8	278.1 ± 112.6
	Median	242.0	250.5	215.0	239.5
	Q1 ; Q3	198.0 ; 341.0	185.0 ; 365.0	206.0 ; 478.0	198.0 ; 343.0
	Min. ; Max.	132 ; 456	106 ; 456	136 ; 546	106 ; 546
	Missing	47	30	23	100
Month 6: LDH (UI/L)	N	9	7	9	25
	Mean ± SD	378.7 ± 130.8	285.0 ± 112.9	318.6 ± 106.2	330.8 ± 119.1
	Median	377.0	220.0	358.0	358.0
	Q1 ; Q3	258.0 ; 497.0	183.0 ; 409.0	206.0 ; 401.0	216.0 ; 413.0
	Min. ; Max.	205 ; 564	166 ; 422	193 ; 452	166 ; 564
	Missing	57	35	25	117
Month 9: LDH (UI/L)	N	7	6	4	17
	Mean ± SD	285.3 ± 109.1	340.8 ± 115.9	293.0 ± 114.8	306.7 ± 108.7
	Median	244.0	336.5	300.5	269.0
	Q1 ; Q3	200.0 ; 366.0	249.0 ; 430.0	199.5 ; 386.5	231.0 ; 375.0
	Min. ; Max.	192 ; 495	192 ; 501	159 ; 412	159 ; 501
	Missing	59	36	30	125
Month 12: LDH (UI/L)	N	6	8	5	19
	Mean ± SD	322.3 ± 127.7	238.5 ± 75.9	346.8 ± 147.9	293.5 ± 118.5
	Median	272.5	206.0	402.0	228.0
	Q1 ; Q3	221.0 ; 426.0	186.5 ; 273.5	209.0 ; 428.0	199.0 ; 402.0

Variables		2L (N=66)	3L (N=42)	4L+ (N=34)	Total (N=142)
	Min. ; Max.	218 ; 524	185 ; 391	176 ; 519	176 ; 524
	Missing	60	34	29	123
Month 15: LDH (UI/L)	N	6	4	5	15
	Mean ± SD	333.3 ± 122.7	226.8 ± 17.7	384.8 ± 138.9	322.1 ± 122.5
	Median	313.5	226.5	409.0	261.0
	Q1 ; Q3	259.0 ; 370.0	212.5 ; 241.0	333.0 ; 469.0	218.0 ; 409.0
	Min. ; Max.	200 ; 544	207 ; 247	176 ; 537	176 ; 544
	Missing	60	38	29	127
Month 18: LDH (UI/L)	N	4	4	4	12
	Mean ± SD	319.3 ± 103.8	280.0 ± 89.6	321.8 ± 142.8	307.0 ± 105.3
	Median	294.0	246.0	324.0	269.5
	Q1 ; Q3	249.5 ; 389.0	222.5 ; 337.5	202.0 ; 441.5	226.0 ; 412.0
	Min. ; Max.	224 ; 465	217 ; 411	169 ; 470	169 ; 470
	Missing	62	38	30	130
Month 21: LDH (UI/L)	N	3	1	6	10
	Mean ± SD	360.7 ± 112.4	209.0 ± .	352.2 ± 167.3	340.4 ± 143.2
	Median	377.0	209.0	335.0	335.0
	Q1 ; Q3	241.0 ; 464.0	209.0 ; 209.0	195.0 ; 474.0	209.0 ; 464.0
	Min. ; Max.	241 ; 464	209 ; 209	167 ; 607	167 ; 607
	Missing	63	41	28	132
Month 24: LDH (UI/L)	N	6	2	4	12
	Mean ± SD	301.3 ± 137.4	175.0 ± 42.4	414.5 ± 199.2	318.0 ± 163.8
	Median	230.5	175.0	398.5	230.5
	Q1 ; Q3	219.0 ; 445.0	145.0 ; 205.0	261.0 ; 568.0	202.5 ; 460.0
	Min. ; Max.	178 ; 505	145 ; 205	200 ; 661	145 ; 661
	Missing	60	40	30	130
Month 27: LDH (UI/L)	N	2	1	2	5
	Mean ± SD	240.5 ± 6.4	231.0 ± .	382.5 ± 362.7	295.4 ± 198.1
	Median	240.5	231.0	382.5	236.0
	Q1 ; Q3	236.0 ; 245.0	231.0 ; 231.0	126.0 ; 639.0	231.0 ; 245.0
	Min. ; Max.	236 ; 245	231 ; 231	126 ; 639	126 ; 639

Variables		2L (N=66)	3L (N=42)	4L+ (N=34)	Total (N=142)
	Missing	64	41	32	137
Month 30: LDH (UI/L)	N	4	0	1	5
	Mean ± SD	211.5 ± 27.0		623.0 ± .	293.8 ± 185.5
	Median	217.5		623.0	227.0
	Q1 ; Q3	191.5 ; 231.5		623.0 ; 623.0	208.0 ; 236.0
	Min. ; Max.	175 ; 236		623 ; 623	175 ; 623
	Missing	62	42	33	137
Month 33: LDH (UI/L)	N	1	0	1	2
	Mean ± SD	224.0 ± .		532.0 ± .	378.0 ± 217.8
	Median	224.0		532.0	378.0
	Q1 ; Q3	224.0 ; 224.0		532.0 ; 532.0	224.0 ; 532.0
	Min. ; Max.	224 ; 224		532 ; 532	224 ; 532
	Missing	65	42	33	140
Month 36: LDH (UI/L)	N	0	0	1	1
	Mean ± SD			597.0 ± .	597.0 ± .
	Median			597.0	597.0
	Q1 ; Q3			597.0 ; 597.0	597.0 ; 597.0
	Min. ; Max.			597 ; 597	597 ; 597
	Missing	66	42	33	141

Table 15.3.9e Biological and Hematological Parameters: LDH - SAF (n=142)

Table 88: Biological and Hematological Parameters: Albumin - SAF (n=142)

Variables		2L (N=66)	3L (N=42)	4L+ (N=34)	Total (N=142)
Baseline: Albumin (g/L)	N	9	8	8	25
	Mean ± SD	43.61 ± 2.14	45.06 ± 8.35	43.63 ± 2.56	44.08 ± 4.93
	Median	44.00	43.50	43.50	44.00
	Q1 ; Q3	43.10 ; 45.00	40.55 ; 46.35	42.00 ; 45.00	42.00 ; 45.00
	Min. ; Max.	38.9 ; 46	36 ; 63.7	40 ; 48	36 ; 63.7
	Missing	57	34	26	117
Month 3: Albumin (g/L)	N	7	4	6	17
	Mean ± SD	43.91 ± 2.26	41.50 ± 5.26	40.50 ± 5.17	42.14 ± 4.23
	Median	44.60	43.00	43.00	44.00
	Q1 ; Q3	41.00 ; 45.00	38.00 ; 45.00	35.00 ; 44.00	41.00 ; 45.00
	Min. ; Max.	40.8 ; 47	34 ; 46	33 ; 45	33 ; 47
	Missing	59	38	28	125
Month 6: Albumin (g/L)	N	3	5	4	12
	Mean ± SD	43.93 ± 2.72	41.64 ± 2.46	42.00 ± 2.16	42.33 ± 2.40
	Median	43.00	42.00	41.50	42.00
	Q1 ; Q3	41.80 ; 47.00	39.20 ; 44.00	40.50 ; 43.50	40.50 ; 44.00
	Min. ; Max.	41.8 ; 47	39 ; 44	40 ; 45	39 ; 47
	Missing	63	37	30	130
Month 9: Albumin (g/L)	N	1	3	4	8
	Mean ± SD	42.0 ± .	42.3 ± 1.2	41.0 ± 4.7	41.6 ± 3.2
	Median	42.0	43.0	43.0	43.0
	Q1 ; Q3	42.0 ; 42.0	41.0 ; 43.0	38.5 ; 43.5	41.5 ; 43.0
	Min. ; Max.	42 ; 42	41 ; 43	34 ; 44	34 ; 44
	Missing	65	39	30	134
Month 12: Albumin (g/L)	N	2	3	6	11
	Mean ± SD	43.00 ± 5.66	45.00 ± 1.00	40.30 ± 7.23	42.07 ± 5.85
	Median	43.00	45.00	41.50	44.00
	Q1 ; Q3	39.00 ; 47.00	44.00 ; 46.00	34.00 ; 47.00	39.00 ; 47.00

Variables		2L (N=66)	3L (N=42)	4L+ (N=34)	Total (N=142)
	Min. ; Max.	39 ; 47	44 ; 46	29.8 ; 48	29.8 ; 48
	Missing	64	39	28	131
Month 15: Albumin (g/L)	N	3	1	6	10
	Mean ± SD	43.7 ± 2.9	41.0 ± .	43.7 ± 4.4	43.4 ± 3.6
	Median	42.0	41.0	43.5	42.0
	Q1 ; Q3	42.0 ; 47.0	41.0 ; 41.0	39.0 ; 48.0	41.0 ; 47.0
	Min. ; Max.	42 ; 47	41 ; 41	39 ; 49	39 ; 49
	Missing	63	41	28	132
Month 18: Albumin (g/L)	N	2	0	3	5
	Mean ± SD	46.5 ± 3.5		41.3 ± 4.5	43.4 ± 4.6
	Median	46.5		41.0	44.0
	Q1 ; Q3	44.0 ; 49.0		37.0 ; 46.0	41.0 ; 46.0
	Min. ; Max.	44 ; 49		37 ; 46	37 ; 49
	Missing	64	42	31	137
Month 21: Albumin (g/L)	N	1	0	6	7
	Mean ± SD	43.00 ± .		41.05 ± 4.91	41.33 ± 4.54
	Median	43.00		39.50	40.00
	Q1 ; Q3	43.00 ; 43.00		38.00 ; 46.00	38.00 ; 46.00
	Min. ; Max.	43 ; 43		35.3 ; 48	35.3 ; 48
	Missing	65	42	28	135
Month 24: Albumin (g/L)	N	1	0	5	6
	Mean ± SD	47.00 ± .		43.66 ± 4.54	44.22 ± 4.29
	Median	47.00		45.00	45.00
	Q1 ; Q3	47.00 ; 47.00		42.00 ; 45.00	42.00 ; 47.00
	Min. ; Max.	47 ; 47		37 ; 49.3	37 ; 49.3
	Missing	65	42	29	136
Month 27: Albumin (g/L)	N	1	1	3	5
	Mean ± SD	43.000 ± .	41.460 ± .	40.233 ± 4.131	41.032 ± 3.166
	Median	43.000	41.460	38.000	41.460
	Q1 ; Q3	43.000 ; 43.000	41.460 ; 41.460	37.700 ; 45.000	38.000 ; 43.000
	Min. ; Max.	43 ; 43	41.46 ; 41.46	37.7 ; 45	37.7 ; 45

Variables		2L (N=66)	3L (N=42)	4L+ (N=34)	Total (N=142)
	Missing	65	41	31	137
Month 30: Albumin (g/L)	N	2	0	2	4
	Mean ± SD	46.25 ± 0.92		44.00 ± 4.24	45.13 ± 2.82
	Median	46.25		44.00	46.25
	Q1 ; Q3	45.60 ; 46.90		41.00 ; 47.00	43.30 ; 46.95
	Min. ; Max.	45.6 ; 46.9		41 ; 47	41 ; 47
	Missing	64	42	32	138
Month 33: Albumin (g/L)	N	0	0	2	2
	Mean ± SD			42.0 ± 8.5	42.0 ± 8.5
	Median			42.0	42.0
	Q1 ; Q3			36.0 ; 48.0	36.0 ; 48.0
	Min. ; Max.			36 ; 48	36 ; 48
	Missing	66	42	32	140
Month 36: Albumin (g/L)	N	0	0	2	2
	Mean ± SD			38.0 ± 12.7	38.0 ± 12.7
	Median			38.0	38.0
	Q1 ; Q3			29.0 ; 47.0	29.0 ; 47.0
	Min. ; Max.			29 ; 47	29 ; 47
	Missing	66	42	32	140

Table 15.3.9f Biological and Hematological Parameters: Albumin - SAF (n=142)

Table 89: Biological and Hematological Parameters: Amylase - SAF (n=142)

Variables		2L (N=66)	3L (N=42)	4L+ (N=34)	Total (N=142)
Baseline: Amylase (UI/L)	N	4	3	1	8
	Mean ± SD	57.0 ± 27.9	49.7 ± 16.8	39.0 ± .	52.0 ± 21.3
	Median	55.5	41.0	39.0	43.0
	Q1 ; Q3	35.5 ; 78.5	39.0 ; 69.0	39.0 ; 39.0	39.0 ; 67.5
	Min. ; Max.	26 ; 91	39 ; 69	39 ; 39	26 ; 91
	Missing	62	39	33	134
Month 3: Amylase (UI/L)	N	2	1	1	4
	Mean ± SD	62.5 ± 16.3	63.0 ± .	51.0 ± .	59.8 ± 11.1
	Median	62.5	63.0	51.0	57.0
	Q1 ; Q3	51.0 ; 74.0	63.0 ; 63.0	51.0 ; 51.0	51.0 ; 68.5
	Min. ; Max.	51 ; 74	63 ; 63	51 ; 51	51 ; 74
	Missing	64	41	33	138
Month 6: Amylase (UI/L)	N	1	0	0	1
	Mean ± SD	107.0 ± .			107.0 ± .
	Median	107.0			107.0
	Q1 ; Q3	107.0 ; 107.0			107.0 ; 107.0
	Min. ; Max.	107 ; 107			107 ; 107
	Missing	65	42	34	141
Month 12: Amylase (UI/L)	N	1	0	0	1
	Mean ± SD	110.0 ± .			110.0 ± .
	Median	110.0			110.0
	Q1 ; Q3	110.0 ; 110.0			110.0 ; 110.0
	Min. ; Max.	110 ; 110			110 ; 110
	Missing	65	42	34	141
Month 15: Amylase (UI/L)	N	1	1	0	2
	Mean ± SD	84.0 ± .	38.0 ± .		61.0 ± 32.5
	Median	84.0	38.0		61.0
	Q1 ; Q3	84.0 ; 84.0	38.0 ; 38.0		38.0 ; 84.0

Variables		2L (N=66)	3L (N=42)	4L+ (N=34)	Total (N=142)
	Min. ; Max.	84 ; 84	38 ; 38		38 ; 84
	Missing	65	41	34	140
Month 27: Amylase (UI/L)	N	1	0	0	1
	Mean ± SD	95.0 ± .			95.0 ± .
	Median	95.0			95.0
	Q1 ; Q3	95.0 ; 95.0			95.0 ; 95.0
	Min. ; Max.	95 ; 95			95 ; 95
	Missing	65	42	34	141
Month 30: Amylase (UI/L)	N	1	0	0	1
	Mean ± SD	58.0 ± .			58.0 ± .
	Median	58.0			58.0
	Q1 ; Q3	58.0 ; 58.0			58.0 ; 58.0
	Min. ; Max.	58 ; 58			58 ; 58
	Missing	65	42	34	141
Month 33: Amylase (UI/L)	N	1	0	0	1
	Mean ± SD	77.0 ± .			77.0 ± .
	Median	77.0			77.0
	Q1 ; Q3	77.0 ; 77.0			77.0 ; 77.0
	Min. ; Max.	77 ; 77			77 ; 77
	Missing	65	42	34	141
Month 36: Amylase (UI/L)	N	1	0	0	1
	Mean ± SD	58.0 ± .			58.0 ± .
	Median	58.0			58.0
	Q1 ; Q3	58.0 ; 58.0			58.0 ; 58.0
	Min. ; Max.	58 ; 58			58 ; 58
	Missing	65	42	34	141

Table 15.3.9g Biological and Hematological Parameters: Amylase - SAF (n=142)

Table 90: Biological and Hematological Parameters: Lipase - SAF (n=142)

Variables		2L (N=66)	3L (N=42)	4L+ (N=34)	Total (N=142)
Baseline: Lipase (UI/L)	N	10	11	6	27
	Mean ± SD	42.5 ± 17.4	67.9 ± 64.8	70.8 ± 75.2	59.1 ± 54.6
	Median	36.0	48.0	30.0	41.0
	Q1 ; Q3	28.0 ; 55.0	37.0 ; 80.0	28.0 ; 104.0	28.0 ; 62.0
	Min. ; Max.	28 ; 79	20 ; 254	22 ; 211	20 ; 254
	Missing	56	31	28	115
Month 3: Lipase (UI/L)	N	7	4	4	15
	Mean ± SD	43.9 ± 15.5	60.8 ± 22.6	70.5 ± 55.8	55.5 ± 31.9
	Median	40.0	56.0	55.0	45.0
	Q1 ; Q3	31.0 ; 53.0	42.5 ; 79.0	33.5 ; 107.5	34.0 ; 69.0
	Min. ; Max.	29 ; 73	42 ; 89	22 ; 150	22 ; 150
	Missing	59	38	30	127
Month 6: Lipase (UI/L)	N	6	3	1	10
	Mean ± SD	41.2 ± 20.0	57.0 ± 14.2	76.0 ± .	49.4 ± 20.3
	Median	41.5	52.0	76.0	51.5
	Q1 ; Q3	26.0 ; 55.0	46.0 ; 73.0	76.0 ; 76.0	32.0 ; 68.0
	Min. ; Max.	15 ; 68	46 ; 73	76 ; 76	15 ; 76
	Missing	60	39	33	132
Month 9: Lipase (UI/L)	N	2	3	0	5
	Mean ± SD	32.0 ± 5.7	32.3 ± 11.0		32.2 ± 8.3
	Median	32.0	33.0		33.0
	Q1 ; Q3	28.0 ; 36.0	21.0 ; 43.0		28.0 ; 36.0
	Min. ; Max.	28 ; 36	21 ; 43		21 ; 43
	Missing	64	39	34	137
Month 12: Lipase (UI/L)	N	2	1	0	3
	Mean ± SD	42.0 ± 0.0	38.0 ± .		40.7 ± 2.3
	Median	42.0	38.0		42.0
	Q1 ; Q3	42.0 ; 42.0	38.0 ; 38.0		38.0 ; 42.0

Variables		2L (N=66)	3L (N=42)	4L+ (N=34)	Total (N=142)
	Min. ; Max.	42 ; 42	38 ; 38		38 ; 42
	Missing	64	41	34	139
Month 15: Lipase (UI/L)	N	1	2	0	3
	Mean ± SD	52.0 ± .	38.0 ± 9.9		42.7 ± 10.7
	Median	52.0	38.0		45.0
	Q1 ; Q3	52.0 ; 52.0	31.0 ; 45.0		31.0 ; 52.0
	Min. ; Max.	52 ; 52	31 ; 45		31 ; 52
	Missing	65	40	34	139
Month 18: Lipase (UI/L)	N	0	0	1	1
	Mean ± SD			32.0 ± .	32.0 ± .
	Median			32.0	32.0
	Q1 ; Q3			32.0 ; 32.0	32.0 ; 32.0
	Min. ; Max.			32 ; 32	32 ; 32
	Missing	66	42	33	141
Month 21: Lipase (UI/L)	N	0	0	2	2
	Mean ± SD			37.5 ± 0.7	37.5 ± 0.7
	Median			37.5	37.5
	Q1 ; Q3			37.0 ; 38.0	37.0 ; 38.0
	Min. ; Max.			37 ; 38	37 ; 38
	Missing	66	42	32	140
Month 24: Lipase (UI/L)	N	0	0	1	1
	Mean ± SD			55.0 ± .	55.0 ± .
	Median			55.0	55.0
	Q1 ; Q3			55.0 ; 55.0	55.0 ; 55.0
	Min. ; Max.			55 ; 55	55 ; 55
	Missing	66	42	33	141
Month 27: Lipase (UI/L)	N	1	0	1	2
	Mean ± SD	76.0 ± .		24.0 ± .	50.0 ± 36.8
	Median	76.0		24.0	50.0
	Q1 ; Q3	76.0 ; 76.0		24.0 ; 24.0	24.0 ; 76.0
	Min. ; Max.	76 ; 76		24 ; 24	24 ; 76

Variables		2L (N=66)	3L (N=42)	4L+ (N=34)	Total (N=142)
	Missing	65	42	33	140
Month 30: Lipase (UI/L)	N	4	0	0	4
	Mean ± SD	35.8 ± 7.3			35.8 ± 7.3
	Median	36.5			36.5
	Q1 ; Q3	29.5 ; 42.0			29.5 ; 42.0
	Min. ; Max.	28 ; 42			28 ; 42
	Missing	62	42	34	138
Month 33: Lipase (UI/L)	N	1	0	0	1
	Mean ± SD	57.0 ± .			57.0 ± .
	Median	57.0			57.0
	Q1 ; Q3	57.0 ; 57.0			57.0 ; 57.0
	Min. ; Max.	57 ; 57			57 ; 57
	Missing	65	42	34	141
Month 36: Lipase (UI/L)	N	1	0	0	1
	Mean ± SD	25.0 ± .			25.0 ± .
	Median	25.0			25.0
	Q1 ; Q3	25.0 ; 25.0			25.0 ; 25.0
	Min. ; Max.	25 ; 25			25 ; 25
	Missing	65	42	34	141

Table 15.3.9h Biological and Hematological Parameters: Lipase - SAF (n=142)

Table 91: Biological and Hematological Parameters: Serum creatinine - SAF (n=142)

Variables		2L (N=66)	3L (N=42)	4L+ (N=34)	Total (N=142)
Baseline: Serum creatinine (µmol/L)	N	45	28	27	100
	Mean ± SD	84.522 ± 21.724	89.140 ± 33.366	91.944 ± 32.422	87.819 ± 28.275
	Median	82.000	85.000	80.000	82.105
	Q1 ; Q3	68.000 ; 99.000	61.440 ; 100.390	65.000 ; 113.000	65.650 ; 100.000
	Min. ; Max.	48 ; 159.12	49 ; 169	50.4 ; 159	48 ; 169
	Missing	21	14	7	42
Month 3: Serum creatinine (µmol/L)	N	42	26	25	93
	Mean ± SD	88.309 ± 21.857	95.527 ± 36.665	93.934 ± 37.398	91.839 ± 30.884
	Median	85.375	88.500	85.000	85.750
	Q1 ; Q3	78.000 ; 103.000	69.840 ; 116.000	67.000 ; 112.000	69.900 ; 104.000
	Min. ; Max.	53.04 ; 159.12	50 ; 183	48 ; 185	48 ; 185
	Missing	24	16	9	49
Month 6: Serum creatinine (µmol/L)	N	31	20	17	68
	Mean ± SD	88.202 ± 27.117	87.685 ± 30.681	99.935 ± 38.571	90.983 ± 31.283
	Median	80.000	85.000	89.000	82.605
	Q1 ; Q3	72.000 ; 92.000	68.450 ; 92.500	70.000 ; 118.000	70.500 ; 98.500
	Min. ; Max.	52 ; 177	49 ; 177	51 ; 187	49 ; 187
	Missing	35	22	17	74
Month 9: Serum creatinine (µmol/L)	N	20	17	13	50
	Mean ± SD	90.840 ± 17.898	90.092 ± 38.323	92.215 ± 28.403	90.943 ± 28.320
	Median	89.085	79.000	82.000	84.000
	Q1 ; Q3	80.000 ; 100.000	65.000 ; 102.000	71.000 ; 104.000	72.000 ; 103.000
	Min. ; Max.	56 ; 142	54 ; 185	55.8 ; 157	54 ; 185
	Missing	46	25	21	92
Month 12: Serum creatinine (µmol/L)	N	17	17	13	47
	Mean ± SD	95.825 ± 25.498	89.815 ± 44.157	91.315 ± 32.233	92.404 ± 34.388
	Median	87.520	74.000	92.000	85.750
	Q1 ; Q3	78.000 ; 110.000	63.000 ; 88.000	65.000 ; 97.000	71.000 ; 105.000

Variables		2L (N=66)	3L (N=42)	4L+ (N=34)	Total (N=142)
	Min. ; Max.	65 ; 167.96	51 ; 193	61 ; 179	51 ; 193
	Missing	49	25	21	95
Month 15: Serum creatinine (µmol/L)	N	17	11	12	40
	Mean ± SD	90.760 ± 22.575	89.354 ± 35.220	102.167 ± 37.622	93.795 ± 30.944
	Median	88.000	81.000	89.000	87.315
	Q1 ; Q3	74.000 ; 95.000	60.000 ; 102.000	73.500 ; 130.000	73.500 ; 98.500
	Min. ; Max.	63 ; 150.28	52 ; 168	65 ; 167	52 ; 168
	Missing	49	31	22	102
Month 18: Serum creatinine (µmol/L)	N	6	8	9	23
	Mean ± SD	121.967 ± 42.539	90.626 ± 43.792	105.722 ± 40.332	104.709 ± 42.033
	Median	119.000	74.805	99.000	89.000
	Q1 ; Q3	83.000 ; 155.000	68.200 ; 95.500	70.000 ; 142.000	71.000 ; 147.000
	Min. ; Max.	79 ; 176.8	55 ; 193	60 ; 160	55 ; 193
	Missing	60	34	25	119
Month 21: Serum creatinine (µmol/L)	N	12	4	12	28
	Mean ± SD	98.691 ± 22.842	78.210 ± 15.005	100.833 ± 35.149	96.683 ± 28.300
	Median	96.500	72.920	92.500	94.000
	Q1 ; Q3	85.050 ; 110.000	68.420 ; 88.000	75.500 ; 109.000	73.500 ; 104.000
	Min. ; Max.	67 ; 140	67 ; 100	66 ; 176	66 ; 176
	Missing	54	38	22	114
Month 24: Serum creatinine (µmol/L)	N	10	4	10	24
	Mean ± SD	107.848 ± 33.360	78.478 ± 25.983	98.900 ± 38.926	99.225 ± 34.981
	Median	102.000	75.455	86.500	92.500
	Q1 ; Q3	82.000 ; 116.000	62.000 ; 94.955	78.000 ; 105.000	77.455 ; 113.000
	Min. ; Max.	65 ; 176.8	50 ; 113	61 ; 198	50 ; 198
	Missing	56	38	24	118
Month 27: Serum creatinine (µmol/L)	N	8	4	6	18
	Mean ± SD	94.324 ± 34.743	71.880 ± 4.140	91.500 ± 21.455	88.395 ± 26.824
	Median	83.095	70.260	89.000	82.105
	Q1 ; Q3	77.300 ; 94.000	69.400 ; 74.360	78.000 ; 113.000	70.720 ; 95.000
	Min. ; Max.	69 ; 176.8	69 ; 78	62 ; 118	62 ; 176.8

Variables		2L (N=66)	3L (N=42)	4L+ (N=34)	Total (N=142)
	Missing	58	38	28	124
Month 30: Serum creatinine (µmol/L)	N	10	3	3	16
	Mean ± SD	88.858 ± 31.917	86.333 ± 31.565	78.000 ± 26.287	86.349 ± 29.229
	Median	79.605	75.000	67.000	76.000
	Q1 ; Q3	70.000 ; 98.000	62.000 ; 122.000	59.000 ; 108.000	68.000 ; 99.500
	Min. ; Max.	57.2 ; 171	62 ; 122	59 ; 108	57.2 ; 171
	Missing	56	39	31	126
Month 33: Serum creatinine (µmol/L)	N	6	0	3	9
	Mean ± SD	92.778 ± 10.145		100.333 ± 40.278	95.297 ± 22.004
	Median	93.235		120.000	95.470
	Q1 ; Q3	87.000 ; 101.000		54.000 ; 127.000	87.000 ; 105.200
	Min. ; Max.	77 ; 105.2		54 ; 127	54 ; 127
	Missing	60	42	31	133
Month 36: Serum creatinine (µmol/L)	N	3	3	2	8
	Mean ± SD	81.250 ± 9.808	97.000 ± 30.348	81.000 ± 45.255	87.094 ± 25.505
	Median	85.750	81.000	81.000	83.375
	Q1 ; Q3	70.000 ; 88.000	78.000 ; 132.000	49.000 ; 113.000	74.000 ; 100.500
	Min. ; Max.	70 ; 88	78 ; 132	49 ; 113	49 ; 132
	Missing	63	39	32	134

Table 15.3.9i Biological and Hematological Parameters: Serum creatinine - SAF (n=142)

Table 92: Biological and Hematological Parameters: Blood glucose (fasting) - SAF (n=142)

Variables		2L (N=66)	3L (N=42)	4L+ (N=34)	Total (N=142)
Baseline: Blood glucose (fasting) (mmol/L)	N	8	5	3	16
	Mean ± SD	5.602 ± 1.627	6.238 ± 1.564	6.133 ± 2.323	5.901 ± 1.644
	Median	5.220	5.600	5.050	5.270
	Q1 ; Q3	4.835 ; 5.530	5.320 ; 6.800	4.550 ; 8.800	4.890 ; 6.285
	Min. ; Max.	4.19 ; 9.46	4.77 ; 8.7	4.55 ; 8.8	4.19 ; 9.46
	Missing	58	37	31	126
Month 3: Blood glucose (fasting) (mmol/L)	N	5	3	4	12
	Mean ± SD	5.798 ± 1.874	5.167 ± 0.891	5.342 ± 0.548	5.488 ± 1.258
	Median	5.060	5.050	5.220	5.075
	Q1 ; Q3	4.330 ; 7.100	4.340 ; 6.110	4.960 ; 5.725	4.585 ; 6.105
	Min. ; Max.	4.1 ; 8.4	4.34 ; 6.11	4.83 ; 6.1	4.1 ; 8.4
	Missing	61	39	30	130
Month 6: Blood glucose (fasting) (mmol/L)	N	4	4	1	9
	Mean ± SD	5.505 ± 1.362	5.708 ± 1.062	5.070 ± .	5.547 ± 1.077
	Median	5.900	5.605	5.070	5.400
	Q1 ; Q3	4.510 ; 6.500	4.860 ; 6.555	5.070 ; 5.070	5.070 ; 6.400
	Min. ; Max.	3.62 ; 6.6	4.62 ; 7	5.07 ; 5.07	3.62 ; 7
	Missing	62	38	33	133
Month 9: Blood glucose (fasting) (mmol/L)	N	2	5	2	9
	Mean ± SD	6.715 ± 0.460	5.134 ± 0.858	5.145 ± 0.686	5.488 ± 0.968
	Median	6.715	5.080	5.145	5.370
	Q1 ; Q3	6.390 ; 7.040	4.580 ; 5.370	4.660 ; 5.630	4.660 ; 6.390
	Min. ; Max.	6.39 ; 7.04	4.2 ; 6.44	4.66 ; 5.63	4.2 ; 7.04
	Missing	64	37	32	133
Month 12: Blood glucose (fasting) (mmol/L)	N	1	3	3	7
	Mean ± SD	6.710 ± .	4.493 ± 1.508	5.883 ± 1.702	5.406 ± 1.593
	Median	6.710	4.390	5.300	5.300
	Q1 ; Q3	6.710 ; 6.710	3.040 ; 6.050	4.550 ; 7.800	4.390 ; 6.710

Variables		2L (N=66)	3L (N=42)	4L+ (N=34)	Total (N=142)
	Min. ; Max.	6.71 ; 6.71	3.04 ; 6.05	4.55 ; 7.8	3.04 ; 7.8
	Missing	65	39	31	135
Month 15: Blood glucose (fasting) (mmol/L)	N	3	2	3	8
	Mean ± SD	6.137 ± 0.549	4.620 ± 0.537	4.997 ± 0.352	5.330 ± 0.796
	Median	5.830	4.620	5.200	5.200
	Q1 ; Q3	5.810 ; 6.770	4.240 ; 5.000	4.590 ; 5.200	4.795 ; 5.820
	Min. ; Max.	5.81 ; 6.77	4.24 ; 5	4.59 ; 5.2	4.24 ; 6.77
	Missing	63	40	31	134
Month 21: Blood glucose (fasting) (mmol/L)	N	3	1	3	7
	Mean ± SD	5.400 ± 0.872	6.160 ± .	4.890 ± 1.480	5.290 ± 1.094
	Median	5.270	6.160	4.910	5.270
	Q1 ; Q3	4.600 ; 6.330	6.160 ; 6.160	3.400 ; 6.360	4.600 ; 6.330
	Min. ; Max.	4.6 ; 6.33	6.16 ; 6.16	3.4 ; 6.36	3.4 ; 6.36
	Missing	63	41	31	135
Month 24: Blood glucose (fasting) (mmol/L)	N	2	1	1	4
	Mean ± SD	6.855 ± 0.898	1.020 ± .	7.900 ± .	5.658 ± 3.173
	Median	6.855	1.020	7.900	6.855
	Q1 ; Q3	6.220 ; 7.490	1.020 ; 1.020	7.900 ; 7.900	3.620 ; 7.695
	Min. ; Max.	6.22 ; 7.49	1.02 ; 1.02	7.9 ; 7.9	1.02 ; 7.9
	Missing	64	41	33	138
Month 27: Blood glucose (fasting) (mmol/L)	N	0	2	2	4
	Mean ± SD		5.490 ± 0.707	5.600 ± 1.838	5.545 ± 1.139
	Median		5.490	5.600	5.490
	Q1 ; Q3		4.990 ; 5.990	4.300 ; 6.900	4.645 ; 6.445
	Min. ; Max.		4.99 ; 5.99	4.3 ; 6.9	4.3 ; 6.9
	Missing	66	40	32	138
Month 30: Blood glucose (fasting) (mmol/L)	N	3	3	1	7
	Mean ± SD	5.277 ± 1.095	5.763 ± 0.499	4.600 ± .	5.389 ± 0.814
	Median	4.900	5.870	4.600	5.220
	Q1 ; Q3	4.420 ; 6.510	5.220 ; 6.200	4.600 ; 4.600	4.600 ; 6.200
	Min. ; Max.	4.42 ; 6.51	5.22 ; 6.2	4.6 ; 4.6	4.42 ; 6.51

Variables		2L (N=66)	3L (N=42)	4L+ (N=34)	Total (N=142)
	Missing	63	39	33	135
Month 33: Blood glucose (fasting) (mmol/L)	N	2	0	1	3
	Mean ± SD	7.070 ± 1.146		4.700 ± .	6.280 ± 1.590
	Median	7.070		4.700	6.260
	Q1 ; Q3	6.260 ; 7.880		4.700 ; 4.700	4.700 ; 7.880
	Min. ; Max.	6.26 ; 7.88		4.7 ; 4.7	4.7 ; 7.88
	Missing	64	42	33	139
Month 36: Blood glucose (fasting) (mmol/L)	N	1	3	0	4
	Mean ± SD	6.770 ± .	5.343 ± 0.331		5.700 ± 0.763
	Median	6.770	5.370		5.515
	Q1 ; Q3	6.770 ; 6.770	5.000 ; 5.660		5.185 ; 6.215
	Min. ; Max.	6.77 ; 6.77	5 ; 5.66		5 ; 6.77
	Missing	65	39	34	138

Table 15.3.9j Biological and Hematological Parameters: Blood glucose (fasting) - SAF (n=142)

Table 93: Biological and Hematological Parameters: Blood glucose (non-fasting) - SAF (n=142)

Variables		2L (N=66)	3L (N=42)	4L+ (N=34)	Total (N=142)
Baseline: Blood glucose (non-fasting) (mmol/L)	N	8	13	10	31
	Mean ± SD	7.689 ± 3.877	7.873 ± 7.046	7.216 ± 6.241	7.614 ± 5.927
	Median	7.000	5.300	5.175	5.300
	Q1 ; Q3	4.760 ; 8.695	5.170 ; 6.600	4.800 ; 5.820	4.900 ; 7.700
	Min. ; Max.	4.4 ; 16.2	4.4 ; 30.8	4.1 ; 24.75	4.1 ; 30.8
	Missing	58	29	24	111
Month 3: Blood glucose (non-fasting) (mmol/L)	N	8	11	9	28
	Mean ± SD	7.558 ± 4.357	7.585 ± 3.953	8.434 ± 6.603	7.850 ± 4.878
	Median	5.710	6.600	5.120	5.805
	Q1 ; Q3	5.040 ; 9.080	4.900 ; 8.910	4.900 ; 7.000	4.900 ; 7.955
	Min. ; Max.	4.35 ; 16.45	4.35 ; 17.9	3.8 ; 22	3.8 ; 22
	Missing	58	31	25	114
Month 6: Blood glucose (non-fasting) (mmol/L)	N	4	7	4	15
	Mean ± SD	5.328 ± 1.414	6.587 ± 1.751	6.650 ± 2.922	6.268 ± 1.979
	Median	5.090	6.300	5.450	6.000
	Q1 ; Q3	4.155 ; 6.500	5.300 ; 7.480	5.050 ; 8.250	4.700 ; 7.000
	Min. ; Max.	4.13 ; 7	4.24 ; 9.79	4.7 ; 11	4.13 ; 11
	Missing	62	35	30	127
Month 9: Blood glucose (non-fasting) (mmol/L)	N	4	7	1	12
	Mean ± SD	7.545 ± 5.179	7.894 ± 3.145	5.300 ± .	7.562 ± 3.639
	Median	5.460	6.820	5.300	6.060
	Q1 ; Q3	4.610 ; 10.480	4.700 ; 10.560	5.300 ; 5.300	4.950 ; 10.030
	Min. ; Max.	4.02 ; 15.24	4.46 ; 12.82	5.3 ; 5.3	4.02 ; 15.24
	Missing	62	35	33	130
Month 12: Blood glucose (non-fasting) (mmol/L)	N	4	4	3	11
	Mean ± SD	7.383 ± 4.467	5.243 ± 0.956	5.673 ± 0.297	6.138 ± 2.699
	Median	5.220	5.285	5.600	5.420
	Q1 ; Q3	5.055 ; 9.710	4.440 ; 6.045	5.420 ; 6.000	5.010 ; 6.000

Variables		2L (N=66)	3L (N=42)	4L+ (N=34)	Total (N=142)
	Min. ; Max.	5.01 ; 14.08	4.2 ; 6.2	5.42 ; 6	4.2 ; 14.08
	Missing	62	38	31	131
Month 15: Blood glucose (non-fasting) (mmol/L)	N	3	3	3	9
	Mean ± SD	4.323 ± 1.176	5.537 ± 0.924	6.813 ± 1.845	5.558 ± 1.604
	Median	4.900	5.800	7.640	5.100
	Q1 ; Q3	2.970 ; 5.100	4.510 ; 6.300	4.700 ; 8.100	4.700 ; 6.300
	Min. ; Max.	2.97 ; 5.1	4.51 ; 6.3	4.7 ; 8.1	2.97 ; 8.1
	Missing	63	39	31	133
Month 18: Blood glucose (non-fasting) (mmol/L)	N	2	1	5	8
	Mean ± SD	8.530 ± 5.982	7.260 ± .	5.960 ± 1.868	6.765 ± 2.914
	Median	8.530	7.260	4.800	6.030
	Q1 ; Q3	4.300 ; 12.760	7.260 ; 7.260	4.600 ; 8.000	4.500 ; 8.000
	Min. ; Max.	4.3 ; 12.76	7.26 ; 7.26	4.4 ; 8	4.3 ; 12.76
	Missing	64	41	29	134
Month 21: Blood glucose (non-fasting) (mmol/L)	N	2	2	4	8
	Mean ± SD	5.410 ± 0.410	6.275 ± 1.167	6.873 ± 1.919	6.358 ± 1.486
	Median	5.410	6.275	6.820	5.575
	Q1 ; Q3	5.120 ; 5.700	5.450 ; 7.100	5.220 ; 8.525	5.230 ; 7.700
	Min. ; Max.	5.12 ; 5.7	5.45 ; 7.1	5.1 ; 8.75	5.1 ; 8.75
	Missing	64	40	30	134
Month 24: Blood glucose (non-fasting) (mmol/L)	N	3	1	2	6
	Mean ± SD	8.910 ± 6.198	7.150 ± .	4.550 ± 0.354	7.163 ± 4.467
	Median	5.610	7.150	4.550	5.335
	Q1 ; Q3	5.060 ; 16.060	7.150 ; 7.150	4.300 ; 4.800	4.800 ; 7.150
	Min. ; Max.	5.06 ; 16.06	7.15 ; 7.15	4.3 ; 4.8	4.3 ; 16.06
	Missing	63	41	32	136
Month 27: Blood glucose (non-fasting) (mmol/L)	N	2	2	1	5
	Mean ± SD	7.045 ± 1.167	9.680 ± 2.645	7.700 ± .	8.230 ± 1.978
	Median	7.045	9.680	7.700	7.810
	Q1 ; Q3	6.220 ; 7.870	7.810 ; 11.550	7.700 ; 7.700	7.700 ; 7.870
	Min. ; Max.	6.22 ; 7.87	7.81 ; 11.55	7.7 ; 7.7	6.22 ; 11.55

Variables		2L (N=66)	3L (N=42)	4L+ (N=34)	Total (N=142)
	Missing	64	40	33	137
Month 30: Blood glucose (non-fasting) (mmol/L)	N	1	0	0	1
	Mean ± SD	5.450 ± .			5.450 ± .
	Median	5.450			5.450
	Q1 ; Q3	5.450 ; 5.450			5.450 ; 5.450
	Min. ; Max.	5.45 ; 5.45			5.45 ; 5.45
	Missing	65	42	34	141
Month 33: Blood glucose (non-fasting) (mmol/L)	N	1	1	0	2
	Mean ± SD	4.900 ± .	11.650 ± .		8.275 ± 4.773
	Median	4.900	11.650		8.275
	Q1 ; Q3	4.900 ; 4.900	11.650 ; 11.650		4.900 ; 11.650
	Min. ; Max.	4.9 ; 4.9	11.65 ; 11.65		4.9 ; 11.65
	Missing	65	41	34	140
Month 36: Blood glucose (non-fasting) (mmol/L)	N	1	0	1	2
	Mean ± SD	4.350 ± .		5.800 ± .	5.075 ± 1.025
	Median	4.350		5.800	5.075
	Q1 ; Q3	4.350 ; 4.350		5.800 ; 5.800	4.350 ; 5.800
	Min. ; Max.	4.35 ; 4.35		5.8 ; 5.8	4.35 ; 5.8
	Missing	65	42	33	140

Table 15.3.9k Biological and Hematological Parameters: Blood glucose (non-fasting) - SAF (n=142)

Table 94: Biological and Hematological Parameters: Magnesium - SAF (n=142)

Variables		2L (N=66)	3L (N=42)	4L+ (N=34)	Total (N=142)
Baseline: Magnesium (mmol/L)	N	5	8	5	18
	Mean ± SD	0.838 ± 0.093	0.843 ± 0.082	0.876 ± 0.106	0.851 ± 0.088
	Median	0.800	0.845	0.890	0.845
	Q1 ; Q3	0.780 ; 0.830	0.805 ; 0.865	0.860 ; 0.920	0.780 ; 0.890
	Min. ; Max.	0.78 ; 1	0.71 ; 1	0.71 ; 1	0.71 ; 1
	Missing	61	34	29	124
Month 3: Magnesium (mmol/L)	N	5	6	6	17
	Mean ± SD	0.832 ± 0.184	0.855 ± 0.090	0.918 ± 0.107	0.871 ± 0.127
	Median	0.940	0.870	0.935	0.920
	Q1 ; Q3	0.780 ; 0.950	0.760 ; 0.940	0.880 ; 1.000	0.780 ; 0.950
	Min. ; Max.	0.53 ; 0.96	0.74 ; 0.95	0.73 ; 1.03	0.53 ; 1.03
	Missing	61	36	28	125
Month 6: Magnesium (mmol/L)	N	4	7	3	14
	Mean ± SD	0.910 ± 0.062	0.877 ± 0.124	0.930 ± 0.044	0.898 ± 0.094
	Median	0.890	0.860	0.950	0.890
	Q1 ; Q3	0.875 ; 0.945	0.780 ; 0.910	0.880 ; 0.960	0.860 ; 0.950
	Min. ; Max.	0.86 ; 1	0.73 ; 1.12	0.88 ; 0.96	0.73 ; 1.12
	Missing	62	35	31	128
Month 9: Magnesium (mmol/L)	N	4	3	1	8
	Mean ± SD	0.830 ± 0.134	0.873 ± 0.090	0.860 ± .	0.850 ± 0.102
	Median	0.890	0.920	0.860	0.890
	Q1 ; Q3	0.755 ; 0.905	0.770 ; 0.930	0.860 ; 0.860	0.815 ; 0.915
	Min. ; Max.	0.63 ; 0.91	0.77 ; 0.93	0.86 ; 0.86	0.63 ; 0.93
	Missing	62	39	33	134
Month 12: Magnesium (mmol/L)	N	3	5	3	11
	Mean ± SD	0.867 ± 0.232	0.832 ± 0.110	0.897 ± 0.100	0.859 ± 0.136
	Median	0.900	0.880	0.860	0.880
	Q1 ; Q3	0.620 ; 1.080	0.790 ; 0.890	0.820 ; 1.010	0.790 ; 0.940

Variables		2L (N=66)	3L (N=42)	4L+ (N=34)	Total (N=142)
	Min. ; Max.	0.62 ; 1.08	0.66 ; 0.94	0.82 ; 1.01	0.62 ; 1.08
	Missing	63	37	31	131
Month 15: Magnesium (mmol/L)	N	2	4	6	12
	Mean ± SD	0.740 ± 0.311	0.770 ± 0.111	0.935 ± 0.095	0.848 ± 0.157
	Median	0.740	0.790	0.915	0.875
	Q1 ; Q3	0.520 ; 0.960	0.690 ; 0.850	0.870 ; 1.040	0.790 ; 0.955
	Min. ; Max.	0.52 ; 0.96	0.62 ; 0.88	0.82 ; 1.05	0.52 ; 1.05
	Missing	64	38	28	130
Month 18: Magnesium (mmol/L)	N	2	1	4	7
	Mean ± SD	0.675 ± 0.177	0.690 ± .	0.933 ± 0.063	0.824 ± 0.159
	Median	0.675	0.690	0.940	0.860
	Q1 ; Q3	0.550 ; 0.800	0.690 ; 0.690	0.880 ; 0.985	0.690 ; 0.980
	Min. ; Max.	0.55 ; 0.8	0.69 ; 0.69	0.86 ; 0.99	0.55 ; 0.99
	Missing	64	41	30	135
Month 21: Magnesium (mmol/L)	N	2	1	3	6
	Mean ± SD	0.740 ± 0.297	0.660 ± .	1.000 ± 0.046	0.857 ± 0.210
	Median	0.740	0.660	0.990	0.955
	Q1 ; Q3	0.530 ; 0.950	0.660 ; 0.660	0.960 ; 1.050	0.660 ; 0.990
	Min. ; Max.	0.53 ; 0.95	0.66 ; 0.66	0.96 ; 1.05	0.53 ; 1.05
	Missing	64	41	31	136
Month 24: Magnesium (mmol/L)	N	0	1	3	4
	Mean ± SD		0.610 ± .	1.007 ± 0.055	0.908 ± 0.203
	Median		0.610	1.010	0.980
	Q1 ; Q3		0.610 ; 0.610	0.950 ; 1.060	0.780 ; 1.035
	Min. ; Max.		0.61 ; 0.61	0.95 ; 1.06	0.61 ; 1.06
	Missing	66	41	31	138
Month 27: Magnesium (mmol/L)	N	1	2	4	7
	Mean ± SD	0.830 ± .	0.820 ± 0.311	1.065 ± 0.372	0.961 ± 0.319
	Median	0.830	0.820	0.925	0.860
	Q1 ; Q3	0.830 ; 0.830	0.600 ; 1.040	0.830 ; 1.300	0.800 ; 1.040
	Min. ; Max.	0.83 ; 0.83	0.6 ; 1.04	0.8 ; 1.61	0.6 ; 1.61

Variables		2L (N=66)	3L (N=42)	4L+ (N=34)	Total (N=142)
	Missing	65	40	30	135
Month 30: Magnesium (mmol/L)	N	3	0	1	4
	Mean ± SD	0.780 ± 0.230		0.980 ± .	0.830 ± 0.213
	Median	0.780		0.980	0.880
	Q1 ; Q3	0.550 ; 1.010		0.980 ; 0.980	0.665 ; 0.995
	Min. ; Max.	0.55 ; 1.01		0.98 ; 0.98	0.55 ; 1.01
	Missing	63	42	33	138
Month 33: Magnesium (mmol/L)	N	1	0	1	2
	Mean ± SD	0.910 ± .		0.910 ± .	0.910 ± 0.000
	Median	0.910		0.910	0.910
	Q1 ; Q3	0.910 ; 0.910		0.910 ; 0.910	0.910 ; 0.910
	Min. ; Max.	0.91 ; 0.91		0.91 ; 0.91	0.91 ; 0.91
	Missing	65	42	33	140
Month 36: Magnesium (mmol/L)	N	1	0	1	2
	Mean ± SD	0.880 ± .		0.880 ± .	0.880 ± 0.000
	Median	0.880		0.880	0.880
	Q1 ; Q3	0.880 ; 0.880		0.880 ; 0.880	0.880 ; 0.880
	Min. ; Max.	0.88 ; 0.88		0.88 ; 0.88	0.88 ; 0.88
	Missing	65	42	33	140

Table 15.3.9l Biological and Hematological Parameters: Magnesium - SAF (n=142)

Table 95: Biological and Hematological Parameters: Calcium - SAF (n=142)

Variables		2L (N=66)	3L (N=42)	4L+ (N=34)	Total (N=142)
Baseline: Calcium (mmol/L)	N	24	17	16	57
	Mean ± SD	2.298 ± 0.169	2.347 ± 0.118	2.363 ± 0.141	2.331 ± 0.148
	Median	2.275	2.330	2.345	2.330
	Q1 ; Q3	2.235 ; 2.380	2.280 ; 2.430	2.310 ; 2.450	2.250 ; 2.410
	Min. ; Max.	1.96 ; 2.66	2.13 ; 2.54	2.08 ; 2.64	1.96 ; 2.66
	Missing	42	25	18	85
Month 3: Calcium (mmol/L)	N	19	15	15	49
	Mean ± SD	2.315 ± 0.078	2.329 ± 0.144	2.282 ± 0.104	2.309 ± 0.109
	Median	2.330	2.370	2.300	2.330
	Q1 ; Q3	2.260 ; 2.380	2.260 ; 2.450	2.190 ; 2.370	2.250 ; 2.390
	Min. ; Max.	2.15 ; 2.4	2 ; 2.47	2.11 ; 2.45	2 ; 2.47
	Missing	47	27	19	93
Month 6: Calcium (mmol/L)	N	15	14	7	36
	Mean ± SD	2.287 ± 0.134	2.343 ± 0.105	2.379 ± 0.106	2.326 ± 0.121
	Median	2.330	2.340	2.330	2.330
	Q1 ; Q3	2.210 ; 2.390	2.290 ; 2.410	2.310 ; 2.510	2.270 ; 2.400
	Min. ; Max.	1.99 ; 2.45	2.13 ; 2.53	2.24 ; 2.52	1.99 ; 2.53
	Missing	51	28	27	106
Month 9: Calcium (mmol/L)	N	9	11	6	26
	Mean ± SD	2.338 ± 0.090	2.319 ± 0.073	2.400 ± 0.121	2.344 ± 0.093
	Median	2.350	2.350	2.390	2.355
	Q1 ; Q3	2.270 ; 2.380	2.230 ; 2.380	2.350 ; 2.440	2.270 ; 2.390
	Min. ; Max.	2.21 ; 2.5	2.2 ; 2.41	2.23 ; 2.6	2.2 ; 2.6
	Missing	57	31	28	116
Month 12: Calcium (mmol/L)	N	8	11	7	26
	Mean ± SD	2.266 ± 0.100	2.260 ± 0.387	2.337 ± 0.103	2.283 ± 0.258

Variables		2L (N=66)	3L (N=42)	4L+ (N=34)	Total (N=142)
	Median	2.275	2.350	2.350	2.335
	Q1 ; Q3	2.195 ; 2.325	2.280 ; 2.390	2.290 ; 2.420	2.270 ; 2.390
	Min. ; Max.	2.12 ; 2.42	1.13 ; 2.6	2.15 ; 2.46	1.13 ; 2.6
	Missing	58	31	27	116
Month 15: Calcium (mmol/L)	N	9	6	9	24
	Mean ± SD	2.358 ± 0.079	2.388 ± 0.091	2.333 ± 0.104	2.356 ± 0.090
	Median	2.350	2.400	2.290	2.350
	Q1 ; Q3	2.290 ; 2.370	2.300 ; 2.450	2.260 ; 2.360	2.285 ; 2.450
	Min. ; Max.	2.25 ; 2.5	2.28 ; 2.5	2.24 ; 2.54	2.24 ; 2.54
	Missing	57	36	25	118
Month 18: Calcium (mmol/L)	N	6	3	6	15
	Mean ± SD	2.272 ± 0.120	2.370 ± 0.072	2.340 ± 0.113	2.319 ± 0.111
	Median	2.325	2.350	2.360	2.340
	Q1 ; Q3	2.200 ; 2.340	2.310 ; 2.450	2.290 ; 2.410	2.290 ; 2.400
	Min. ; Max.	2.06 ; 2.38	2.31 ; 2.45	2.15 ; 2.47	2.06 ; 2.47
	Missing	60	39	28	127
Month 21: Calcium (mmol/L)	N	5	1	8	14
	Mean ± SD	2.296 ± 0.154	2.390 ± .	2.345 ± 0.093	2.331 ± 0.113
	Median	2.350	2.390	2.375	2.375
	Q1 ; Q3	2.250 ; 2.400	2.390 ; 2.390	2.265 ; 2.415	2.250 ; 2.410
	Min. ; Max.	2.05 ; 2.43	2.39 ; 2.39	2.2 ; 2.45	2.05 ; 2.45
	Missing	61	41	26	128
Month 24: Calcium (mmol/L)	N	5	4	7	16
	Mean ± SD	2.268 ± 0.144	2.365 ± 0.073	2.373 ± 0.104	2.338 ± 0.115
	Median	2.300	2.375	2.380	2.355
	Q1 ; Q3	2.230 ; 2.360	2.310 ; 2.420	2.330 ; 2.470	2.285 ; 2.420
	Min. ; Max.	2.04 ; 2.41	2.27 ; 2.44	2.18 ; 2.48	2.04 ; 2.48
	Missing	61	38	27	126
Month 27: Calcium (mmol/L)	N	6	4	6	16
	Mean ± SD	2.270 ± 0.134	2.310 ± 0.111	2.317 ± 0.106	2.298 ± 0.113
	Median	2.290	2.315	2.345	2.315

Variables		2L (N=66)	3L (N=42)	4L+ (N=34)	Total (N=142)
	Q1 ; Q3	2.230 ; 2.380	2.235 ; 2.385	2.230 ; 2.410	2.230 ; 2.390
	Min. ; Max.	2.03 ; 2.4	2.17 ; 2.44	2.15 ; 2.42	2.03 ; 2.44
	Missing	60	38	28	126
Month 30: Calcium (mmol/L)	N	5	3	2	10
	Mean ± SD	2.246 ± 0.148	2.250 ± 0.070	2.250 ± 0.099	2.248 ± 0.109
	Median	2.310	2.250	2.250	2.280
	Q1 ; Q3	2.250 ; 2.320	2.180 ; 2.320	2.180 ; 2.320	2.180 ; 2.320
	Min. ; Max.	1.99 ; 2.36	2.18 ; 2.32	2.18 ; 2.32	1.99 ; 2.36
	Missing	61	39	32	132
Month 33: Calcium (mmol/L)	N	4	0	2	6
	Mean ± SD	2.228 ± 0.179		2.320 ± 0.184	2.258 ± 0.168
	Median	2.265		2.320	2.265
	Q1 ; Q3	2.105 ; 2.350		2.190 ; 2.450	2.190 ; 2.400
	Min. ; Max.	1.98 ; 2.4		2.19 ; 2.45	1.98 ; 2.45
	Missing	62	42	32	136
Month 36: Calcium (mmol/L)	N	2	2	2	6
	Mean ± SD	2.260 ± 0.085	2.300 ± 0.184	2.390 ± 0.042	2.317 ± 0.110
	Median	2.260	2.300	2.390	2.340
	Q1 ; Q3	2.200 ; 2.320	2.170 ; 2.430	2.360 ; 2.420	2.200 ; 2.420
	Min. ; Max.	2.2 ; 2.32	2.17 ; 2.43	2.36 ; 2.42	2.17 ; 2.43
	Missing	64	40	32	136

Table 15.3.9m Biological and Hematological Parameters: Calcium - SAF (n=142)

Table 96: Biological and Hematological Parameters: Blood urea - SAF (n=142)

Variables		2L (N=66)	3L (N=42)	4L+ (N=34)	Total (N=142)
Baseline: Blood urea (mmol/L)	N	37	19	22	78
	Mean ± SD	7.118 ± 3.945	6.290 ± 2.825	7.080 ± 3.836	6.905 ± 3.644
	Median	6.100	5.900	5.650	5.940
	Q1 ; Q3	4.880 ; 7.700	4.500 ; 7.200	4.000 ; 9.000	4.800 ; 7.700
	Min. ; Max.	1.74 ; 23.71	3.34 ; 16.3	2.9 ; 17.6	1.74 ; 23.71
	Missing	29	23	12	64
Month 3: Blood urea (mmol/L)	N	33	14	20	67
	Mean ± SD	6.868 ± 3.479	6.693 ± 4.723	6.984 ± 4.706	6.866 ± 4.080
	Median	5.800	5.300	5.255	5.430
	Q1 ; Q3	4.900 ; 8.130	4.200 ; 7.500	4.370 ; 7.925	4.700 ; 8.130
	Min. ; Max.	3.34 ; 20.71	2.5 ; 21.33	2.51 ; 20.71	2.5 ; 21.33
	Missing	33	28	14	75
Month 6: Blood urea (mmol/L)	N	23	13	12	48
	Mean ± SD	6.100 ± 2.968	6.107 ± 1.861	7.380 ± 3.229	6.422 ± 2.786
	Median	5.280	5.900	6.155	5.810
	Q1 ; Q3	4.650 ; 6.800	4.670 ; 6.700	5.250 ; 9.330	4.700 ; 6.925
	Min. ; Max.	3.31 ; 18.2	4 ; 9.85	3.77 ; 14	3.31 ; 18.2
	Missing	43	29	22	94
Month 9: Blood urea (mmol/L)	N	16	10	10	36
	Mean ± SD	7.416 ± 3.858	5.195 ± 2.063	6.614 ± 3.286	6.576 ± 3.334
	Median	6.325	4.900	4.890	5.940
	Q1 ; Q3	5.940 ; 8.050	4.000 ; 5.400	4.300 ; 9.600	4.505 ; 8.125
	Min. ; Max.	4.11 ; 20.8	2.9 ; 9.52	2.84 ; 12.6	2.84 ; 20.8
	Missing	50	32	24	106
Month 12: Blood urea (mmol/L)	N	14	11	9	34
	Mean ± SD	7.387 ± 3.560	5.004 ± 1.550	6.122 ± 3.277	6.281 ± 3.065
	Median	6.450	4.900	5.420	5.640
	Q1 ; Q3	5.680 ; 8.000	3.800 ; 6.010	4.160 ; 6.100	4.600 ; 7.100
	Min. ; Max.	4.5 ; 18.7	2.83 ; 8.52	2.9 ; 12.8	2.83 ; 18.7
	Missing	52	31	25	108

Variables		2L (N=66)	3L (N=42)	4L+ (N=34)	Total (N=142)
Month 15: Blood urea (mmol/L)	N	13	6	10	29
	Mean ± SD	6.775 ± 2.834	5.092 ± 1.597	8.738 ± 5.270	7.103 ± 3.834
	Median	5.500	4.515	6.150	5.500
	Q1 ; Q3	5.300 ; 7.350	4.200 ; 6.500	5.040 ; 11.900	4.830 ; 7.500
	Min. ; Max.	3.34 ; 13.03	3.3 ; 7.52	3.6 ; 18.8	3.3 ; 18.8
	Missing	53	36	24	113
Month 18: Blood urea (mmol/L)	N	6	5	8	19
	Mean ± SD	8.650 ± 3.389	6.152 ± 2.620	9.519 ± 4.693	8.358 ± 3.906
	Median	7.800	6.010	9.000	6.500
	Q1 ; Q3	6.100 ; 9.500	4.000 ; 6.500	5.660 ; 14.000	6.000 ; 10.600
	Min. ; Max.	6 ; 14.7	3.9 ; 10.35	3.3 ; 15.53	3.3 ; 15.53
	Missing	60	37	26	123
Month 21: Blood urea (mmol/L)	N	8	3	9	20
	Mean ± SD	6.974 ± 2.202	6.137 ± 0.409	8.393 ± 5.005	7.487 ± 3.625
	Median	6.800	6.200	7.400	6.455
	Q1 ; Q3	5.345 ; 7.700	5.700 ; 6.510	4.990 ; 10.600	5.345 ; 7.750
	Min. ; Max.	4.6 ; 11.5	5.7 ; 6.51	2.2 ; 17.7	2.2 ; 17.7
	Missing	58	39	25	122
Month 24: Blood urea (mmol/L)	N	8	2	6	16
	Mean ± SD	7.473 ± 3.755	7.090 ± 0.127	10.055 ± 7.675	8.393 ± 5.292
	Median	5.805	7.090	5.700	5.905
	Q1 ; Q3	5.300 ; 8.700	7.000 ; 7.180	5.100 ; 16.700	5.300 ; 8.700
	Min. ; Max.	4.3 ; 15.87	7 ; 7.18	4.53 ; 22.6	4.3 ; 22.6
	Missing	58	40	28	126
Month 27: Blood urea (mmol/L)	N	6	3	5	14
	Mean ± SD	8.868 ± 5.356	5.620 ± 0.122	9.690 ± 8.620	8.466 ± 6.035
	Median	7.100	5.680	6.400	6.250
	Q1 ; Q3	6.100 ; 9.500	5.480 ; 5.700	5.600 ; 6.780	5.600 ; 7.520
	Min. ; Max.	4.2 ; 19.21	5.48 ; 5.7	4.63 ; 25.04	4.2 ; 25.04
	Missing	60	39	29	128

Variables		2L (N=66)	3L (N=42)	4L+ (N=34)	Total (N=142)
Month 30: Blood urea (mmol/L)	N	5	1	3	9
	Mean ± SD	5.462 ± 1.004	5.700 ± .	4.247 ± 0.647	5.083 ± 1.004
	Median	6.100	5.700	4.600	4.640
	Q1 ; Q3	4.400 ; 6.180	5.700 ; 5.700	3.500 ; 4.640	4.400 ; 6.100
	Min. ; Max.	4.33 ; 6.3	5.7 ; 5.7	3.5 ; 4.64	3.5 ; 6.3
	Missing	61	41	31	133
Month 33: Blood urea (mmol/L)	N	2	0	2	4
	Mean ± SD	6.910 ± 0.863		5.980 ± 1.018	6.445 ± 0.939
	Median	6.910		5.980	6.500
	Q1 ; Q3	6.300 ; 7.520		5.260 ; 6.700	5.780 ; 7.110
	Min. ; Max.	6.3 ; 7.52		5.26 ; 6.7	5.26 ; 7.52
	Missing	64	42	32	138
Month 36: Blood urea (mmol/L)	N	2	2	2	6
	Mean ± SD	6.525 ± 0.955	5.650 ± 2.192	5.800 ± 1.131	5.992 ± 1.255
	Median	6.525	5.650	5.800	6.225
	Q1 ; Q3	5.850 ; 7.200	4.100 ; 7.200	5.000 ; 6.600	5.000 ; 7.200
	Min. ; Max.	5.85 ; 7.2	4.1 ; 7.2	5 ; 6.6	4.1 ; 7.2
	Missing	64	40	32	136

Table 15.3.9n Biological and Hematological Parameters: Blood urea - SAF (n=142)

Table 97: Biological and Hematological Parameters: Uric acid - SAF (n=142)

Variables		2L (N=66)	3L (N=42)	4L+ (N=34)	Total (N=142)
Baseline: Uric acid (µmol/L)	N	18	12	12	42
	Mean ± SD	352.664 ± 92.804	350.740 ± 111.567	360.344 ± 151.325	354.309 ± 114.324
	Median	337.505	343.030	380.705	346.005
	Q1 ; Q3	279.580 ; 412.000	257.500 ; 404.500	231.545 ; 469.500	273.630 ; 422.300
	Min. ; Max.	214.15 ; 547.26	206 ; 608	154 ; 653	154 ; 653
	Missing	48	30	22	100
Month 3: Uric acid (µmol/L)	N	15	9	6	30
	Mean ± SD	358.857 ± 139.506	385.416 ± 76.799	407.310 ± 206.079	376.515 ± 136.846
	Median	310.000	418.000	366.930	353.935
	Q1 ; Q3	255.790 ; 425.000	339.060 ; 422.340	280.000 ; 465.000	280.000 ; 425.000
	Min. ; Max.	226 ; 749.51	262 ; 485	184 ; 781	184 ; 781
	Missing	51	33	28	112
Month 6: Uric acid (µmol/L)	N	11	8	3	22
	Mean ± SD	321.009 ± 62.450	345.655 ± 105.272	281.000 ± 98.909	324.515 ± 83.247
	Median	336.000	338.000	230.000	331.500
	Q1 ; Q3	261.000 ; 356.910	273.630 ; 447.490	218.000 ; 395.000	250.900 ; 386.650
	Min. ; Max.	214.15 ; 424	182 ; 465	218 ; 395	182 ; 465
	Missing	55	34	31	120
Month 9: Uric acid (µmol/L)	N	6	7	1	14
	Mean ± SD	331.817 ± 64.811	325.756 ± 61.463	301.000 ± .	326.585 ± 58.502
	Median	344.405	339.060	301.000	329.530
	Q1 ; Q3	306.000 ; 384.000	261.730 ; 373.000	301.000 ; 301.000	301.000 ; 373.000
	Min. ; Max.	220.09 ; 392	233 ; 404.5	301 ; 301	220.09 ; 404.5
	Missing	60	35	33	128
Month 12: Uric acid (µmol/L)	N	5	5	3	13
	Mean ± SD	330.506 ± 95.711	353.318 ± 84.333	401.430 ± 246.123	355.647 ± 127.710
	Median	300.000	376.000	276.000	300.000
	Q1 ; Q3	258.000 ; 416.400	291.000 ; 410.450	243.290 ; 685.000	258.000 ; 416.400
	Min. ; Max.	231.99 ; 446.14	243 ; 446.14	243.29 ; 685	231.99 ; 685
	Missing	61	37	31	129

Variables		2L (N=66)	3L (N=42)	4L+ (N=34)	Total (N=142)
Month 15: Uric acid (µmol/L)	N	6	3	4	13
	Mean ± SD	351.630 ± 76.906	334.337 ± 15.147	381.500 ± 127.715	356.830 ± 83.206
	Median	368.000	341.000	350.000	345.010
	Q1 ; Q3	309.000 ; 386.650	317.000 ; 345.010	285.500 ; 477.500	309.000 ; 386.650
	Min. ; Max.	226.04 ; 452.09	317 ; 345.01	272 ; 554	226.04 ; 554
	Missing	60	39	30	129
Month 18: Uric acid (µmol/L)	N	4	2	3	9
	Mean ± SD	387.103 ± 42.218	319.660 ± 14.623	433.000 ± 148.253	387.414 ± 90.094
	Median	380.705	319.660	443.000	368.810
	Q1 ; Q3	356.405 ; 417.800	309.320 ; 330.000	280.000 ; 576.000	330.000 ; 443.000
	Min. ; Max.	344 ; 443	309.32 ; 330	280 ; 576	280 ; 576
	Missing	62	40	31	133
Month 21: Uric acid (µmol/L)	N	3	0	4	7
	Mean ± SD	373.337 ± 36.112		417.750 ± 117.333	398.716 ± 88.779
	Median	361.000		425.500	395.000
	Q1 ; Q3	345.010 ; 414.000		332.500 ; 503.000	345.010 ; 456.000
	Min. ; Max.	345.01 ; 414		270 ; 550	270 ; 550
	Missing	63	42	30	135
Month 24: Uric acid (µmol/L)	N	4	2	3	9
	Mean ± SD	364.690 ± 134.457	358.005 ± 18.378	411.333 ± 83.936	378.752 ± 95.852
	Median	344.880	358.005	382.000	371.000
	Q1 ; Q3	270.000 ; 459.380	345.010 ; 371.000	346.000 ; 506.000	345.010 ; 382.000
	Min. ; Max.	225 ; 544	345.01 ; 371	346 ; 506	225 ; 544
	Missing	62	40	31	133
Month 27: Uric acid (µmol/L)	N	3	2	1	6
	Mean ± SD	433.453 ± 92.210	323.030 ± 22.670	255.000 ± .	366.903 ± 97.137
	Median	416.400	323.030	255.000	345.010
	Q1 ; Q3	350.960 ; 533.000	307.000 ; 339.060	255.000 ; 255.000	307.000 ; 416.400
	Min. ; Max.	350.96 ; 533	307 ; 339.06	255 ; 255	255 ; 533
	Missing	63	40	33	136

Variables		2L (N=66)	3L (N=42)	4L+ (N=34)	Total (N=142)
Month 30: Uric acid (µmol/L)	N	4	0	1	5
	Mean ± SD	360.115 ± 73.623		280.000 ± .	344.092 ± 73.137
	Median	349.530		280.000	339.060
	Q1 ; Q3	310.730 ; 409.500		280.000 ; 280.000	282.400 ; 360.000
	Min. ; Max.	282.4 ; 459		280 ; 280	280 ; 459
	Missing	62	42	33	137
Month 33: Uric acid (µmol/L)	N	2	0	1	3
	Mean ± SD	426.75 ± 31.47		258.00 ± .	370.50 ± 99.94
	Median	426.75		258.00	404.50
	Q1 ; Q3	404.50 ; 449.00		258.00 ; 258.00	258.00 ; 449.00
	Min. ; Max.	404.5 ; 449		258 ; 258	258 ; 449
	Missing	64	42	33	139
Month 36: Uric acid (µmol/L)	N	1	0	1	2
	Mean ± SD	398.550 ± .		194.000 ± .	296.275 ± 144.639
	Median	398.550		194.000	296.275
	Q1 ; Q3	398.550 ; 398.550		194.000 ; 194.000	194.000 ; 398.550
	Min. ; Max.	398.55 ; 398.55		194 ; 194	194 ; 398.55
	Missing	65	42	33	140

Table 15.3.9o Biological and Hematological Parameters: Uric acid - SAF (n=142)

Table 98: Biological and Hematological Parameters: Hemoglobin - SAF (n=142)

Variables		2L (N=66)	3L (N=42)	4L+ (N=34)	Total (N=142)
Baseline: Hemoglobin (g/dL)	N	51	32	30	113
	Mean ± SD	12.816 ± 2.331	13.200 ± 1.997	13.107 ± 1.835	13.002 ± 2.105
	Median	12.700	13.500	13.450	13.200
	Q1 ; Q3	12.000 ; 14.600	12.450 ; 14.200	12.200 ; 14.000	12.200 ; 14.300
	Min. ; Max.	1.13 ; 17	4.9 ; 16.8	9.4 ; 17.8	1.13 ; 17.8
	Missing	15	10	4	29
Month 3: Hemoglobin (g/dL)	N	44	30	26	100
	Mean ± SD	13.08 ± 2.34	12.92 ± 1.08	12.64 ± 1.79	12.92 ± 1.89
	Median	13.45	12.95	13.00	13.10
	Q1 ; Q3	12.20 ; 14.35	12.40 ; 13.80	11.70 ; 13.70	12.20 ; 14.00
	Min. ; Max.	1.2 ; 16.1	9.8 ; 14.5	7.7 ; 16	1.2 ; 16.1
	Missing	22	12	8	42
Month 6: Hemoglobin (g/dL)	N	32	24	18	74
	Mean ± SD	13.142 ± 2.625	12.273 ± 3.672	13.139 ± 1.673	12.859 ± 2.827
	Median	13.450	13.150	13.400	13.300
	Q1 ; Q3	12.150 ; 14.900	12.100 ; 13.900	11.700 ; 14.400	12.100 ; 14.400
	Min. ; Max.	1.13 ; 15.7	1.17 ; 17	9.3 ; 15.6	1.13 ; 17
	Missing	34	18	16	68
Month 9: Hemoglobin (g/dL)	N	22	17	15	54
	Mean ± SD	13.404 ± 3.142	13.106 ± 0.982	13.113 ± 2.385	13.229 ± 2.393
	Median	14.200	13.000	13.600	13.700
	Q1 ; Q3	12.400 ; 14.900	12.900 ; 13.800	12.100 ; 14.300	12.600 ; 14.300
	Min. ; Max.	1.09 ; 16.6	10.3 ; 14.5	7.6 ; 16.5	1.09 ; 16.6
	Missing	44	25	19	88
Month 12: Hemoglobin (g/dL)	N	17	17	16	50
	Mean ± SD	13.39 ± 2.68	12.63 ± 3.33	13.06 ± 1.95	13.03 ± 2.69
	Median	14.30	13.60	13.50	13.70
	Q1 ; Q3	12.10 ; 15.00	12.30 ; 14.00	11.05 ; 14.30	12.10 ; 14.70
	Min. ; Max.	5 ; 15.7	1.2 ; 16.2	10.1 ; 16.5	1.2 ; 16.5
	Missing	49	25	18	92

Variables		2L (N=66)	3L (N=42)	4L+ (N=34)	Total (N=142)
Month 15: Hemoglobin (g/dL)	N	17	12	14	43
	Mean ± SD	12.526 ± 3.246	12.917 ± 1.454	12.264 ± 3.980	12.550 ± 3.088
	Median	12.800	13.150	13.750	13.200
	Q1 ; Q3	11.900 ; 14.100	12.500 ; 13.400	10.500 ; 14.500	11.900 ; 14.200
	Min. ; Max.	1.05 ; 15.5	9.3 ; 15.3	1 ; 16.5	1 ; 16.5
	Missing	49	30	20	99
Month 18: Hemoglobin (g/dL)	N	9	10	11	30
	Mean ± SD	13.62 ± 1.05	13.25 ± 1.44	13.11 ± 1.83	13.31 ± 1.47
	Median	13.50	12.95	13.80	13.40
	Q1 ; Q3	13.30 ; 13.70	12.60 ; 14.20	11.60 ; 14.80	11.80 ; 14.20
	Min. ; Max.	11.8 ; 15.7	11.4 ; 16.3	10.5 ; 15.9	10.5 ; 16.3
	Missing	57	32	23	112
Month 21: Hemoglobin (g/dL)	N	13	4	11	28
	Mean ± SD	13.22 ± 1.96	12.88 ± 0.86	13.34 ± 1.64	13.22 ± 1.68
	Median	13.40	12.65	13.80	13.35
	Q1 ; Q3	11.90 ; 14.50	12.35 ; 13.40	11.60 ; 14.60	12.00 ; 14.45
	Min. ; Max.	9.6 ; 16.2	12.1 ; 14.1	10.8 ; 15.7	9.6 ; 16.2
	Missing	53	38	23	114
Month 24: Hemoglobin (g/dL)	N	10	4	11	25
	Mean ± SD	11.926 ± 4.032	13.075 ± 1.646	13.573 ± 1.955	12.834 ± 2.938
	Median	13.200	12.400	13.400	13.300
	Q1 ; Q3	11.200 ; 14.200	12.050 ; 14.100	11.500 ; 15.500	12.000 ; 14.400
	Min. ; Max.	1.46 ; 15.4	12 ; 15.5	10.7 ; 16	1.46 ; 16
	Missing	56	38	23	117
Month 27: Hemoglobin (g/dL)	N	9	4	7	20
	Mean ± SD	12.63 ± 1.39	12.55 ± 0.64	13.10 ± 2.63	12.78 ± 1.77
	Median	12.30	12.80	14.10	12.90
	Q1 ; Q3	11.50 ; 14.00	12.20 ; 12.90	11.20 ; 14.60	11.55 ; 14.15
	Min. ; Max.	10.7 ; 14.3	11.6 ; 13	8.1 ; 15.9	8.1 ; 15.9
	Missing	57	38	27	122

Variables		2L (N=66)	3L (N=42)	4L+ (N=34)	Total (N=142)
Month 30: Hemoglobin (g/dL)	N	10	3	3	16
	Mean ± SD	13.75 ± 1.40	11.77 ± 0.60	13.03 ± 1.96	13.24 ± 1.53
	Median	14.00	11.70	13.20	13.50
	Q1 ; Q3	13.40 ; 14.70	11.20 ; 12.40	11.00 ; 14.90	11.75 ; 14.60
	Min. ; Max.	11 ; 15.4	11.2 ; 12.4	11 ; 14.9	11 ; 15.4
	Missing	56	39	31	126
Month 33: Hemoglobin (g/dL)	N	6	0	3	9
	Mean ± SD	12.92 ± 1.30		13.10 ± 3.12	12.98 ± 1.87
	Median	13.15		14.10	13.40
	Q1 ; Q3	11.60 ; 13.90		9.60 ; 15.60	11.60 ; 14.10
	Min. ; Max.	11.2 ; 14.5		9.6 ; 15.6	9.6 ; 15.6
	Missing	60	42	31	133
Month 36: Hemoglobin (g/dL)	N	4	3	2	9
	Mean ± SD	13.85 ± 1.29	11.70 ± 2.04	13.15 ± 2.19	12.98 ± 1.81
	Median	14.05	11.00	13.15	13.90
	Q1 ; Q3	13.00 ; 14.70	10.10 ; 14.00	11.60 ; 14.70	11.60 ; 14.20
	Min. ; Max.	12.1 ; 15.2	10.1 ; 14	11.6 ; 14.7	10.1 ; 15.2
	Missing	62	39	32	133

Table 15.3.9p Biological and Hematological Parameters: Hemoglobin - SAF (n=142)

Table 99: Biological and Hematological Parameters: Hematocrit - SAF (n=142)

Variables		2L (N=66)	3L (N=42)	4L+ (N=34)	Total (N=142)
Baseline: Hematocrit (%)	N	50	32	30	112
	Mean ± SD	39.30 ± 4.40	40.13 ± 5.52	39.56 ± 4.89	39.61 ± 4.84
	Median	39.00	40.40	40.10	39.70
	Q1 ; Q3	36.30 ; 42.20	38.20 ; 43.45	35.80 ; 42.00	36.80 ; 42.15
	Min. ; Max.	28.9 ; 49.4	16.8 ; 49.4	30.6 ; 52	16.8 ; 52
	Missing	16	10	4	30
Month 3: Hematocrit (%)	N	44	30	26	100
	Mean ± SD	40.073 ± 3.826	39.573 ± 2.758	38.488 ± 4.898	39.511 ± 3.881
	Median	39.950	39.250	39.300	39.500
	Q1 ; Q3	36.700 ; 43.000	38.000 ; 41.400	36.000 ; 42.000	37.000 ; 42.050
	Min. ; Max.	33.8 ; 47.4	31.4 ; 44.1	24.7 ; 46	24.7 ; 47.4
	Missing	22	12	8	42
Month 6: Hematocrit (%)	N	32	24	18	74
	Mean ± SD	40.66 ± 4.15	40.17 ± 4.08	39.65 ± 4.24	40.25 ± 4.11
	Median	40.95	39.95	40.80	40.00
	Q1 ; Q3	37.70 ; 43.45	37.80 ; 42.05	36.50 ; 42.70	37.40 ; 43.10
	Min. ; Max.	30.9 ; 47.8	33.7 ; 51.4	30 ; 45.1	30 ; 51.4
	Missing	34	18	16	68
Month 9: Hematocrit (%)	N	22	16	15	53
	Mean ± SD	41.80 ± 4.67	39.44 ± 2.74	39.55 ± 6.74	40.45 ± 4.95
	Median	42.95	39.75	40.30	40.70
	Q1 ; Q3	38.00 ; 45.40	38.15 ; 41.20	37.60 ; 43.40	38.00 ; 43.40
	Min. ; Max.	34 ; 49.8	32 ; 42.6	25.2 ; 49	25.2 ; 49.8
	Missing	44	26	19	89
Month 12: Hematocrit (%)	N	16	17	15	48
	Mean ± SD	41.93 ± 4.43	40.40 ± 3.96	39.73 ± 5.23	40.70 ± 4.54
	Median	43.05	40.50	41.00	42.00
	Q1 ; Q3	39.25 ; 45.00	38.00 ; 42.20	34.00 ; 43.90	37.50 ; 44.05
	Min. ; Max.	33.4 ; 47.8	32 ; 48	32.1 ; 49	32 ; 49
	Missing	50	25	19	94

Variables		2L (N=66)	3L (N=42)	4L+ (N=34)	Total (N=142)
Month 15: Hematocrit (%)	N	17	12	13	42
	Mean ± SD	38.41 ± 7.98	39.17 ± 4.20	39.49 ± 6.74	38.96 ± 6.57
	Median	37.50	40.05	40.10	40.05
	Q1 ; Q3	36.70 ; 44.00	37.25 ; 41.50	33.80 ; 43.60	36.30 ; 42.80
	Min. ; Max.	11.9 ; 47.1	30 ; 46	26.5 ; 48.4	11.9 ; 48.4
	Missing	49	30	21	100
Month 18: Hematocrit (%)	N	9	10	11	30
	Mean ± SD	41.57 ± 3.10	40.55 ± 4.63	39.71 ± 4.63	40.55 ± 4.15
	Median	40.80	40.30	41.00	40.80
	Q1 ; Q3	40.50 ; 43.00	37.30 ; 42.40	35.50 ; 42.80	37.20 ; 42.80
	Min. ; Max.	37.2 ; 47.9	33 ; 50.1	33.7 ; 47	33 ; 50.1
	Missing	57	32	23	112
Month 21: Hematocrit (%)	N	13	4	11	28
	Mean ± SD	39.63 ± 5.13	38.55 ± 2.64	40.68 ± 4.42	39.89 ± 4.50
	Median	41.00	38.95	40.00	39.80
	Q1 ; Q3	36.50 ; 42.40	36.75 ; 40.35	38.20 ; 43.40	37.35 ; 42.75
	Min. ; Max.	29.8 ; 46.8	35 ; 41.3	34.3 ; 48.1	29.8 ; 48.1
	Missing	53	38	23	114
Month 24: Hematocrit (%)	N	10	4	11	25
	Mean ± SD	39.51 ± 4.49	42.15 ± 5.26	40.68 ± 5.19	40.45 ± 4.81
	Median	40.25	43.30	40.80	41.00
	Q1 ; Q3	37.40 ; 43.20	38.30 ; 46.00	35.10 ; 45.80	37.40 ; 44.50
	Min. ; Max.	29.9 ; 45	35 ; 47	32.9 ; 48.1	29.9 ; 48.1
	Missing	56	38	23	117
Month 27: Hematocrit (%)	N	9	4	7	20
	Mean ± SD	38.58 ± 3.02	39.35 ± 2.95	38.64 ± 8.02	38.76 ± 5.06
	Median	37.60	39.40	42.00	39.50
	Q1 ; Q3	36.70 ; 41.00	36.80 ; 41.90	34.30 ; 43.80	36.65 ; 42.05
	Min. ; Max.	35 ; 43	36.6 ; 42	22.6 ; 46	22.6 ; 46
	Missing	57	38	27	122

Variables		2L (N=66)	3L (N=42)	4L+ (N=34)	Total (N=142)
Month 30: Hematocrit (%)	N	8	3	3	14
	Mean ± SD	41.50 ± 5.22	36.67 ± 0.58	38.83 ± 5.00	39.89 ± 4.78
	Median	42.45	37.00	38.90	39.75
	Q1 ; Q3	38.20 ; 44.50	36.00 ; 37.00	33.80 ; 43.80	36.00 ; 43.80
	Min. ; Max.	32.6 ; 49.1	36 ; 37	33.8 ; 43.8	32.6 ; 49.1
	Missing	58	39	31	128
Month 33: Hematocrit (%)	N	6	0	3	9
	Mean ± SD	39.02 ± 3.65		38.87 ± 7.60	38.97 ± 4.77
	Median	39.90		41.50	40.90
	Q1 ; Q3	35.00 ; 42.00		30.30 ; 44.80	35.00 ; 42.00
	Min. ; Max.	34.3 ; 43		30.3 ; 44.8	30.3 ; 44.8
	Missing	60	42	31	133
Month 36: Hematocrit (%)	N	4	3	2	9
	Mean ± SD	42.18 ± 4.36	37.57 ± 4.62	39.95 ± 5.44	40.14 ± 4.55
	Median	43.35	35.00	39.95	42.50
	Q1 ; Q3	39.25 ; 45.10	34.80 ; 42.90	36.10 ; 43.80	36.00 ; 43.80
	Min. ; Max.	36 ; 46	34.8 ; 42.9	36.1 ; 43.8	34.8 ; 46
	Missing	62	39	32	133

Table 15.3.9q Biological and Hematological Parameters: Hematocrit - SAF (n=142)

Table 100: Biological and Hematological Parameters: Leukocytes - SAF (n=142)

Variables		2L (N=66)	3L (N=42)	4L+ (N=34)	Total (N=142)
Baseline: Leukocytes (g/L)	N	51	31	29	111
	Mean ± SD	10.2467 ± 15.2753	8.6526 ± 9.0548	10.7834 ± 12.2861	9.9417 ± 12.9438
	Median	6.2000	6.4000	6.3000	6.3200
	Q1 ; Q3	5.0000 ; 8.7000	5.3400 ; 8.8000	5.4000 ; 8.4000	5.2000 ; 8.7000
	Min. ; Max.	3.4 ; 92.3	4.26 ; 55.8	3.94 ; 63.478	3.4 ; 92.3
	Missing	15	11	5	31
Month 3: Leukocytes (g/L)	N	43	30	26	99
	Mean ± SD	7.198 ± 1.867	7.475 ± 2.526	6.663 ± 2.016	7.142 ± 2.125
	Median	6.490	7.310	6.450	6.600
	Q1 ; Q3	5.930 ; 8.420	5.380 ; 9.200	5.460 ; 7.020	5.650 ; 8.510
	Min. ; Max.	4.2 ; 11.68	3.25 ; 14.54	4.5 ; 13.3	3.25 ; 14.54
	Missing	23	12	8	43
Month 6: Leukocytes (g/L)	N	29	24	18	71
	Mean ± SD	7.558 ± 2.388	7.348 ± 2.486	6.926 ± 1.551	7.327 ± 2.227
	Median	7.340	7.450	6.750	7.170
	Q1 ; Q3	5.900 ; 8.400	5.130 ; 9.440	6.200 ; 7.400	5.660 ; 8.400
	Min. ; Max.	4.1 ; 16.22	3.51 ; 11.2	4.7 ; 11.6	3.51 ; 16.22
	Missing	37	18	16	71
Month 9: Leukocytes (g/L)	N	21	17	15	53
	Mean ± SD	7.859 ± 2.407	6.466 ± 2.140	7.835 ± 4.296	7.405 ± 3.005
	Median	7.420	6.140	6.800	6.800
	Q1 ; Q3	6.100 ; 8.900	4.990 ; 7.100	5.700 ; 8.600	5.600 ; 8.400
	Min. ; Max.	4.6 ; 14.3	3.73 ; 11.25	3.9 ; 22.1	3.73 ; 22.1
	Missing	45	25	19	89
Month 12: Leukocytes (g/L)	N	17	17	16	50
	Mean ± SD	8.386 ± 3.484	7.818 ± 3.818	7.489 ± 2.475	7.906 ± 3.277
	Median	7.200	6.500	7.450	7.150
	Q1 ; Q3	6.330 ; 9.800	6.200 ; 8.400	6.000 ; 8.940	6.200 ; 9.480
	Min. ; Max.	4.72 ; 17.9	3.23 ; 19.83	3.5 ; 12.24	3.23 ; 19.83
	Missing	49	25	18	92

Variables		2L (N=66)	3L (N=42)	4L+ (N=34)	Total (N=142)
Month 15: Leukocytes (g/L)	N	16	12	13	41
	Mean ± SD	7.996 ± 2.868	7.598 ± 3.043	6.838 ± 2.570	7.512 ± 2.803
	Median	7.370	7.550	5.740	7.040
	Q1 ; Q3	5.750 ; 9.800	5.295 ; 9.350	5.200 ; 7.800	5.350 ; 8.530
	Min. ; Max.	4.8 ; 13.64	3.36 ; 14.5	3.4 ; 12.1	3.36 ; 14.5
	Missing	50	30	21	101
Month 18: Leukocytes (g/L)	N	9	10	11	30
	Mean ± SD	7.462 ± 2.274	6.148 ± 1.641	6.910 ± 2.338	6.822 ± 2.105
	Median	5.900	6.400	6.800	6.650
	Q1 ; Q3	5.800 ; 9.300	5.240 ; 6.940	5.500 ; 8.600	5.500 ; 8.600
	Min. ; Max.	5.3 ; 11.46	2.76 ; 8.6	3 ; 11.1	2.76 ; 11.46
	Missing	57	32	23	112
Month 21: Leukocytes (g/L)	N	13	4	11	28
	Mean ± SD	7.198 ± 1.385	6.678 ± 1.458	6.421 ± 2.348	6.819 ± 1.808
	Median	6.600	7.355	6.360	6.750
	Q1 ; Q3	6.300 ; 8.520	5.855 ; 7.500	4.200 ; 8.600	5.420 ; 8.510
	Min. ; Max.	5.2 ; 9	4.5 ; 7.5	3.6 ; 10.9	3.6 ; 10.9
	Missing	53	38	23	114
Month 24: Leukocytes (g/L)	N	10	4	11	25
	Mean ± SD	7.792 ± 2.381	7.248 ± 4.181	7.461 ± 2.753	7.559 ± 2.741
	Median	7.400	5.450	6.700	6.700
	Q1 ; Q3	6.100 ; 8.600	5.000 ; 9.495	5.500 ; 8.000	5.500 ; 8.380
	Min. ; Max.	5.07 ; 12.03	4.6 ; 13.49	4.5 ; 13.2	4.5 ; 13.49
	Missing	56	38	23	117
Month 27: Leukocytes (g/L)	N	9	4	7	20
	Mean ± SD	7.211 ± 2.468	8.428 ± 3.187	6.854 ± 1.572	7.330 ± 2.301
	Median	6.610	6.960	6.600	6.655
	Q1 ; Q3	6.100 ; 8.860	6.650 ; 10.205	5.600 ; 7.900	5.850 ; 8.380
	Min. ; Max.	3.51 ; 11.37	6.6 ; 13.19	5.5 ; 9.8	3.51 ; 13.19
	Missing	57	38	27	122

Variables		2L (N=66)	3L (N=42)	4L+ (N=34)	Total (N=142)
Month 30: Leukocytes (g/L)	N	9	3	3	15
	Mean ± SD	6.449 ± 1.779	7.933 ± 1.080	6.033 ± 0.551	6.663 ± 1.574
	Median	6.260	8.390	6.300	6.400
	Q1 ; Q3	4.900 ; 7.700	6.700 ; 8.710	5.400 ; 6.400	5.400 ; 8.100
	Min. ; Max.	4 ; 9.5	6.7 ; 8.71	5.4 ; 6.4	4 ; 9.5
	Missing	57	39	31	127
Month 33: Leukocytes (g/L)	N	6	0	3	9
	Mean ± SD	6.772 ± 1.506		7.080 ± 0.688	6.874 ± 1.249
	Median	6.570		7.200	7.140
	Q1 ; Q3	5.890 ; 8.280		6.340 ; 7.700	6.000 ; 7.700
	Min. ; Max.	4.72 ; 8.6		6.34 ; 7.7	4.72 ; 8.6
	Missing	60	42	31	133
Month 36: Leukocytes (g/L)	N	4	3	2	9
	Mean ± SD	5.915 ± 1.594	8.387 ± 0.677	8.500 ± 0.707	7.313 ± 1.700
	Median	5.550	8.100	8.500	7.960
	Q1 ; Q3	4.650 ; 7.180	7.900 ; 9.160	8.000 ; 9.000	6.400 ; 8.100
	Min. ; Max.	4.6 ; 7.96	7.9 ; 9.16	8 ; 9	4.6 ; 9.16
	Missing	62	39	32	133

Table 15.3.9r Biological and Hematological Parameters: Leukocytes - SAF (n=142)

Table 101: Biological and Hematological Parameters: Platelets - SAF (n=142)

Variables		2L (N=66)	3L (N=42)	4L+ (N=34)	Total (N=142)
Baseline: Platelets (g/L)	N	50	30	29	109
	Mean ± SD	262.7 ± 137.9	309.1 ± 337.2	305.9 ± 196.8	287.0 ± 222.9
	Median	231.5	233.0	258.0	237.0
	Q1 ; Q3	178.0 ; 293.0	215.0 ; 294.0	197.0 ; 333.0	195.0 ; 304.0
	Min. ; Max.	51 ; 913	139 ; 2066	63 ; 1075	51 ; 2066
	Missing	16	12	5	33
Month 3: Platelets (g/L)	N	44	30	26	100
	Mean ± SD	220.2 ± 77.6	261.7 ± 105.1	244.9 ± 91.7	239.1 ± 91.1
	Median	214.5	238.0	230.0	223.5
	Q1 ; Q3	166.0 ; 259.5	200.0 ; 297.0	187.0 ; 291.0	182.5 ; 281.0
	Min. ; Max.	39 ; 493	142 ; 705	72 ; 478	39 ; 705
	Missing	22	12	8	42
Month 6: Platelets (g/L)	N	28	24	17	69
	Mean ± SD	211.0 ± 72.8	237.7 ± 67.9	235.5 ± 75.9	226.3 ± 72.0
	Median	203.0	227.0	243.0	212.0
	Q1 ; Q3	176.5 ; 237.5	180.0 ; 304.0	185.0 ; 286.0	184.0 ; 266.0
	Min. ; Max.	31 ; 440	135 ; 372	94 ; 407	31 ; 440
	Missing	38	18	17	73
Month 9: Platelets (g/L)	N	20	17	15	52
	Mean ± SD	209.5 ± 67.6	223.1 ± 61.4	253.1 ± 83.7	226.5 ± 71.7
	Median	201.0	233.0	243.0	207.0
	Q1 ; Q3	167.5 ; 217.0	165.0 ; 275.0	195.0 ; 299.0	182.0 ; 258.0
	Min. ; Max.	138 ; 426	125 ; 324	113 ; 432	113 ; 432
	Missing	46	25	19	90
Month 12: Platelets (g/L)	N	16	17	16	49
	Mean ± SD	209.8 ± 55.6	252.3 ± 83.2	248.9 ± 87.5	237.3 ± 77.7
	Median	203.5	255.0	217.5	224.0
	Q1 ; Q3	180.5 ; 237.0	192.0 ; 278.0	188.5 ; 295.0	192.0 ; 262.0
	Min. ; Max.	123 ; 351	128 ; 478	136 ; 445	123 ; 478
	Missing	50	25	18	93

Variables		2L (N=66)	3L (N=42)	4L+ (N=34)	Total (N=142)
Month 15: Platelets (g/L)	N	15	12	13	40
	Mean ± SD	201.1 ± 59.4	252.0 ± 83.4	240.8 ± 76.2	229.3 ± 74.3
	Median	194.0	250.0	254.0	219.5
	Q1 ; Q3	159.0 ; 231.0	194.0 ; 293.5	196.0 ; 267.0	177.5 ; 268.0
	Min. ; Max.	90 ; 348	122 ; 423	136 ; 419	90 ; 423
	Missing	51	30	21	102
Month 18: Platelets (g/L)	N	9	10	11	30
	Mean ± SD	189.6 ± 45.2	245.9 ± 60.9	216.2 ± 68.8	218.1 ± 62.2
	Median	184.0	256.0	181.0	216.0
	Q1 ; Q3	154.0 ; 234.0	198.0 ; 283.0	158.0 ; 273.0	165.0 ; 269.0
	Min. ; Max.	118 ; 250	131 ; 339	132 ; 321	118 ; 339
	Missing	57	32	23	112
Month 21: Platelets (g/L)	N	12	4	11	27
	Mean ± SD	206.9 ± 46.4	265.0 ± 52.2	234.3 ± 48.8	226.7 ± 50.7
	Median	208.5	264.5	234.0	230.0
	Q1 ; Q3	182.0 ; 238.0	229.5 ; 300.5	191.0 ; 266.0	191.0 ; 257.0
	Min. ; Max.	116 ; 290	202 ; 329	154 ; 322	116 ; 329
	Missing	54	38	23	115
Month 24: Platelets (g/L)	N	9	4	11	24
	Mean ± SD	190.2 ± 41.5	297.0 ± 64.9	241.7 ± 54.5	231.6 ± 62.5
	Median	205.0	284.5	252.0	226.5
	Q1 ; Q3	168.0 ; 210.0	258.0 ; 336.0	207.0 ; 265.0	203.5 ; 265.0
	Min. ; Max.	108 ; 246	232 ; 387	127 ; 329	108 ; 387
	Missing	57	38	23	118
Month 27: Platelets (g/L)	N	9	4	7	20
	Mean ± SD	208.9 ± 30.9	272.3 ± 30.4	239.3 ± 54.6	232.2 ± 45.9
	Median	215.0	283.5	252.0	226.5
	Q1 ; Q3	202.0 ; 221.0	252.5 ; 292.0	210.0 ; 290.0	207.0 ; 270.5
	Min. ; Max.	161 ; 264	228 ; 294	134 ; 294	134 ; 294
	Missing	57	38	27	122

Variables		2L (N=66)	3L (N=42)	4L+ (N=34)	Total (N=142)
Month 30: Platelets (g/L)	N	9	3	3	15
	Mean ± SD	205.8 ± 44.6	240.7 ± 1.5	202.0 ± 57.7	212.0 ± 42.8
	Median	225.0	241.0	182.0	225.0
	Q1 ; Q3	173.0 ; 235.0	239.0 ; 242.0	157.0 ; 267.0	173.0 ; 242.0
	Min. ; Max.	126 ; 252	239 ; 242	157 ; 267	126 ; 267
	Missing	57	39	31	127
Month 33: Platelets (g/L)	N	6	0	3	9
	Mean ± SD	213.8 ± 30.3		203.0 ± 61.7	210.2 ± 39.4
	Median	227.0		184.0	226.0
	Q1 ; Q3	185.0 ; 238.0		153.0 ; 272.0	184.0 ; 238.0
	Min. ; Max.	167 ; 239		153 ; 272	153 ; 272
	Missing	60	42	31	133
Month 36: Platelets (g/L)	N	4	3	2	9
	Mean ± SD	211.5 ± 21.6	348.0 ± 60.7	284.5 ± 21.9	273.2 ± 72.0
	Median	212.0	353.0	284.5	269.0
	Q1 ; Q3	193.0 ; 230.0	285.0 ; 406.0	269.0 ; 300.0	228.0 ; 300.0
	Min. ; Max.	190 ; 232	285 ; 406	269 ; 300	190 ; 406
	Missing	62	39	32	133

Table 15.3.9s Biological and Hematological Parameters: Platelets - SAF (n=142)

Table 102: Biological and Hematological Parameters: Blasts (peripheral blood) - SAF (n=142)

Variables		2L (N=66)	3L (N=42)	4L+ (N=34)	Total (N=142)
Baseline: Blasts (peripheral blood) (%)	N	18	12	11	41
	Mean ± SD	0.14 ± 0.48	0.00 ± 0.00	0.55 ± 1.29	0.21 ± 0.75
	Median	0.00	0.00	0.00	0.00
	Q1 ; Q3	0.00 ; 0.00	0.00 ; 0.00	0.00 ; 0.00	0.00 ; 0.00
	Min. ; Max.	0 ; 2	0 ; 0	0 ; 4	0 ; 4
	Missing	48	30	23	101
Month 3: Blasts (peripheral blood) (%)	N	9	8	10	27
	Mean ± SD	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
	Median	0.0	0.0	0.0	0.0
	Q1 ; Q3	0.0 ; 0.0	0.0 ; 0.0	0.0 ; 0.0	0.0 ; 0.0
	Min. ; Max.	0 ; 0	0 ; 0	0 ; 0	0 ; 0
	Missing	57	34	24	115
Month 6: Blasts (peripheral blood) (%)	N	4	5	6	15
	Mean ± SD	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
	Median	0.0	0.0	0.0	0.0
	Q1 ; Q3	0.0 ; 0.0	0.0 ; 0.0	0.0 ; 0.0	0.0 ; 0.0
	Min. ; Max.	0 ; 0	0 ; 0	0 ; 0	0 ; 0
	Missing	62	37	28	127
Month 9: Blasts (peripheral blood) (%)	N	4	4	5	13
	Mean ± SD	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
	Median	0.0	0.0	0.0	0.0
	Q1 ; Q3	0.0 ; 0.0	0.0 ; 0.0	0.0 ; 0.0	0.0 ; 0.0
	Min. ; Max.	0 ; 0	0 ; 0	0 ; 0	0 ; 0
	Missing	62	38	29	129
Month 12: Blasts (peripheral blood) (%)	N	2	3	5	10
	Mean ± SD	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
	Median	0.0	0.0	0.0	0.0
	Q1 ; Q3	0.0 ; 0.0	0.0 ; 0.0	0.0 ; 0.0	0.0 ; 0.0
	Min. ; Max.	0 ; 0	0 ; 0	0 ; 0	0 ; 0
	Missing	64	39	29	132

Variables		2L (N=66)	3L (N=42)	4L+ (N=34)	Total (N=142)
Month 15: Blasts (peripheral blood) (%)	N	3	3	3	9
	Mean ± SD	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
	Median	0.0	0.0	0.0	0.0
	Q1 ; Q3	0.0 ; 0.0	0.0 ; 0.0	0.0 ; 0.0	0.0 ; 0.0
	Min. ; Max.	0 ; 0	0 ; 0	0 ; 0	0 ; 0
	Missing	63	39	31	133
Month 18: Blasts (peripheral blood) (%)	N	2	2	3	7
	Mean ± SD	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
	Median	0.0	0.0	0.0	0.0
	Q1 ; Q3	0.0 ; 0.0	0.0 ; 0.0	0.0 ; 0.0	0.0 ; 0.0
	Min. ; Max.	0 ; 0	0 ; 0	0 ; 0	0 ; 0
	Missing	64	40	31	135
Month 21: Blasts (peripheral blood) (%)	N	2	1	2	5
	Mean ± SD	0.0 ± 0.0	0.0 ± .	0.0 ± 0.0	0.0 ± 0.0
	Median	0.0	0.0	0.0	0.0
	Q1 ; Q3	0.0 ; 0.0	0.0 ; 0.0	0.0 ; 0.0	0.0 ; 0.0
	Min. ; Max.	0 ; 0	0 ; 0	0 ; 0	0 ; 0
	Missing	64	41	32	137
Month 24: Blasts (peripheral blood) (%)	N	2	1	0	3
	Mean ± SD	0.0 ± 0.0	0.0 ± .		0.0 ± 0.0
	Median	0.0	0.0		0.0
	Q1 ; Q3	0.0 ; 0.0	0.0 ; 0.0		0.0 ; 0.0
	Min. ; Max.	0 ; 0	0 ; 0		0 ; 0
	Missing	64	41	34	139
Month 27: Blasts (peripheral blood) (%)	N	4	1	1	6
	Mean ± SD	0.045 ± 0.090	0.000 ± .	0.000 ± .	0.030 ± 0.073
	Median	0.000	0.000	0.000	0.000
	Q1 ; Q3	0.000 ; 0.090	0.000 ; 0.000	0.000 ; 0.000	0.000 ; 0.000
	Min. ; Max.	0 ; 0.18	0 ; 0	0 ; 0	0 ; 0.18
	Missing	62	41	33	136

Variables		2L (N=66)	3L (N=42)	4L+ (N=34)	Total (N=142)
Month 30: Blasts (peripheral blood) (%)	N	4	0	1	5
	Mean ± SD	0.020 ± 0.040		0.000 ± .	0.016 ± 0.036
	Median	0.000		0.000	0.000
	Q1 ; Q3	0.000 ; 0.040		0.000 ; 0.000	0.000 ; 0.000
	Min. ; Max.	0 ; 0.08		0 ; 0	0 ; 0.08
	Missing	62	42	33	137
Month 33: Blasts (peripheral blood) (%)	N	2	0	1	3
	Mean ± SD	0.5 ± 0.7		0.0 ± .	0.3 ± 0.6
	Median	0.5		0.0	0.0
	Q1 ; Q3	0.0 ; 1.0		0.0 ; 0.0	0.0 ; 1.0
	Min. ; Max.	0 ; 1		0 ; 0	0 ; 1
	Missing	64	42	33	139
Month 36: Blasts (peripheral blood) (%)	N	2	0	1	3
	Mean ± SD	0.0 ± 0.0		0.0 ± .	0.0 ± 0.0
	Median	0.0		0.0	0.0
	Q1 ; Q3	0.0 ; 0.0		0.0 ; 0.0	0.0 ; 0.0
	Min. ; Max.	0 ; 0		0 ; 0	0 ; 0
	Missing	64	42	33	139

Table 15.3.9t Biological and Hematological Parameters: Blasts (peripheral blood) - SAF (n=142)

Table 103: Biological and Hematological Parameters: Basophils - SAF (n=142)

Variables		2L (N=66)	3L (N=42)	4L+ (N=34)	Total (N=142)
Baseline: Basophils (g/L)	N	51	32	30	113
	Mean ± SD	0.64856 ± 1.35671	0.29187 ± 0.54452	0.42683 ± 0.84643	0.48869 ± 1.05500
	Median	0.08060	0.08000	0.05500	0.08000
	Q1 ; Q3	0.02000 ; 0.80000	0.03500 ; 0.30000	0.02000 ; 0.60000	0.03000 ; 0.60000
	Min. ; Max.	0 ; 6.1	0 ; 2.79	0 ; 4.2	0 ; 6.1
	Missing	15	10	4	29
Month 3: Basophils (g/L)	N	44	30	26	100
	Mean ± SD	0.2636 ± 0.4892	0.1600 ± 0.2762	0.2010 ± 0.2885	0.2162 ± 0.3864
	Median	0.0500	0.0700	0.0700	0.0600
	Q1 ; Q3	0.0200 ; 0.3000	0.0300 ; 0.1000	0.0400 ; 0.2000	0.0300 ; 0.1600
	Min. ; Max.	0 ; 2.2	0 ; 1.2	0 ; 1.1	0 ; 2.2
	Missing	22	12	8	42
Month 6: Basophils (g/L)	N	32	24	18	74
	Mean ± SD	0.4272 ± 0.9644	0.1620 ± 0.2883	0.2147 ± 0.3085	0.2895 ± 0.6770
	Median	0.0600	0.0500	0.0460	0.0500
	Q1 ; Q3	0.0300 ; 0.4000	0.0350 ; 0.0800	0.0200 ; 0.3000	0.0300 ; 0.3000
	Min. ; Max.	0 ; 4.7	0 ; 1.2	0 ; 1	0 ; 4.7
	Missing	34	18	16	68
Month 9: Basophils (g/L)	N	22	17	14	53
	Mean ± SD	0.6990 ± 2.3175	0.1312 ± 0.2278	0.2649 ± 0.3565	0.4022 ± 1.5110
	Median	0.0600	0.0600	0.0650	0.0600
	Q1 ; Q3	0.0370 ; 0.4000	0.0400 ; 0.0700	0.0400 ; 0.4000	0.0400 ; 0.3000
	Min. ; Max.	0 ; 11	0.01 ; 0.9	0 ; 1	0 ; 11
	Missing	44	25	20	89
Month 12: Basophils (g/L)	N	16	17	15	48
	Mean ± SD	0.1600 ± 0.2785	0.1740 ± 0.3320	0.2443 ± 0.4322	0.1913 ± 0.3454
	Median	0.0500	0.0600	0.0500	0.0500
	Q1 ; Q3	0.0300 ; 0.0850	0.0400 ; 0.0900	0.0400 ; 0.3300	0.0350 ; 0.1150
	Min. ; Max.	0 ; 0.9	0 ; 1.3	0 ; 1.6	0 ; 1.6
	Missing	50	25	19	94

Variables		2L (N=66)	3L (N=42)	4L+ (N=34)	Total (N=142)
Month 15: Basophils (g/L)	N	17	12	13	42
	Mean ± SD	0.189 ± 0.309	0.192 ± 0.291	0.393 ± 0.406	0.253 ± 0.342
	Median	0.040	0.065	0.130	0.060
	Q1 ; Q3	0.030 ; 0.080	0.050 ; 0.140	0.050 ; 0.800	0.040 ; 0.400
	Min. ; Max.	0.01 ; 1.1	0.02 ; 0.9	0.02 ; 1	0.01 ; 1.1
	Missing	49	30	21	100
Month 18: Basophils (g/L)	N	8	9	11	28
	Mean ± SD	0.264 ± 0.247	0.161 ± 0.282	0.289 ± 0.423	0.241 ± 0.330
	Median	0.245	0.060	0.040	0.060
	Q1 ; Q3	0.045 ; 0.400	0.040 ; 0.090	0.000 ; 0.600	0.030 ; 0.400
	Min. ; Max.	0.03 ; 0.7	0.02 ; 0.9	0 ; 1.2	0 ; 1.2
	Missing	58	33	23	114
Month 21: Basophils (g/L)	N	13	4	11	28
	Mean ± SD	0.168 ± 0.288	0.178 ± 0.216	0.366 ± 0.424	0.247 ± 0.344
	Median	0.060	0.080	0.060	0.060
	Q1 ; Q3	0.020 ; 0.080	0.060 ; 0.295	0.040 ; 0.700	0.035 ; 0.450
	Min. ; Max.	0 ; 1	0.05 ; 0.5	0.02 ; 1.2	0 ; 1.2
	Missing	53	38	23	114
Month 24: Basophils (g/L)	N	10	4	11	25
	Mean ± SD	0.4490 ± 0.6685	0.3600 ± 0.4982	0.3489 ± 0.3845	0.3907 ± 0.5124
	Median	0.0750	0.1550	0.1100	0.1100
	Q1 ; Q3	0.0400 ; 0.7000	0.0700 ; 0.6500	0.0200 ; 0.7000	0.0400 ; 0.7000
	Min. ; Max.	0.02 ; 2	0.03 ; 1.1	0 ; 1	0 ; 2
	Missing	56	38	23	117
Month 27: Basophils (g/L)	N	9	4	6	19
	Mean ± SD	0.221 ± 0.314	0.050 ± 0.047	0.592 ± 0.480	0.302 ± 0.392
	Median	0.030	0.055	0.700	0.090
	Q1 ; Q3	0.020 ; 0.400	0.010 ; 0.090	0.030 ; 0.900	0.020 ; 0.600
	Min. ; Max.	0 ; 0.9	0 ; 0.09	0.02 ; 1.2	0 ; 1.2
	Missing	57	38	28	123

Variables		2L (N=66)	3L (N=42)	4L+ (N=34)	Total (N=142)
Month 30: Basophils (g/L)	N	8	3	3	14
	Mean ± SD	0.228 ± 0.370	0.067 ± 0.025	0.033 ± 0.042	0.151 ± 0.287
	Median	0.045	0.070	0.020	0.045
	Q1 ; Q3	0.020 ; 0.345	0.040 ; 0.090	0.000 ; 0.080	0.020 ; 0.090
	Min. ; Max.	0 ; 1	0.04 ; 0.09	0 ; 0.08	0 ; 1
	Missing	58	39	31	128
Month 33: Basophils (g/L)	N	6	0	3	9
	Mean ± SD	0.3667 ± 0.4017		0.0363 ± 0.0292	0.2566 ± 0.3583
	Median	0.2700		0.0200	0.0400
	Q1 ; Q3	0.0400 ; 0.6000		0.0190 ; 0.0700	0.0200 ; 0.5000
	Min. ; Max.	0.02 ; 1		0.019 ; 0.07	0.019 ; 1
	Missing	60	42	31	133
Month 36: Basophils (g/L)	N	4	3	2	9
	Mean ± SD	0.173 ± 0.285	0.100 ± 0.017	0.030 ± 0.014	0.117 ± 0.185
	Median	0.030	0.110	0.030	0.040
	Q1 ; Q3	0.030 ; 0.315	0.080 ; 0.110	0.020 ; 0.040	0.030 ; 0.110
	Min. ; Max.	0.03 ; 0.6	0.08 ; 0.11	0.02 ; 0.04	0.02 ; 0.6
	Missing	62	39	32	133

Table 15.3.9u Biological and Hematological Parameters: Basophils - SAF (n=142)

Table 104: Biological and Hematological Parameters: Eosinophils - SAF (n=142)

Variables		2L (N=66)	3L (N=42)	4L+ (N=34)	Total (N=142)
Baseline: Eosinophils (g/L)	N	51	32	30	113
	Mean ± SD	1.82291 ± 4.06600	0.95688 ± 2.27631	0.89633 ± 1.37630	1.33167 ± 3.08317
	Median	0.40000	0.16000	0.26500	0.24000
	Q1 ; Q3	0.13000 ; 2.10000	0.08500 ; 0.31500	0.12000 ; 1.00000	0.12000 ; 1.30000
	Min. ; Max.	0 ; 26.4	0 ; 11.5	0 ; 5.7	0 ; 26.4
	Missing	15	10	4	29
Month 3: Eosinophils (g/L)	N	44	30	26	100
	Mean ± SD	0.9195 ± 1.5171	0.7023 ± 1.4954	1.0792 ± 1.9494	0.8959 ± 1.6232
	Median	0.2200	0.1650	0.1350	0.1945
	Q1 ; Q3	0.1300 ; 0.9000	0.1000 ; 0.4200	0.1000 ; 0.8000	0.1100 ; 0.6100
	Min. ; Max.	0 ; 7.9	0 ; 6.2	0.05 ; 7.8	0 ; 7.9
	Missing	22	12	8	42
Month 6: Eosinophils (g/L)	N	32	24	18	74
	Mean ± SD	0.9121 ± 1.2892	0.7472 ± 1.6636	1.3928 ± 1.9291	0.9755 ± 1.5831
	Median	0.2150	0.2200	0.3440	0.2650
	Q1 ; Q3	0.1200 ; 1.4250	0.0950 ; 0.4800	0.1600 ; 2.2000	0.1100 ; 0.9000
	Min. ; Max.	0 ; 5.9	0 ; 6.2	0.06 ; 6.4	0 ; 6.4
	Missing	34	18	16	68
Month 9: Eosinophils (g/L)	N	22	17	15	54
	Mean ± SD	0.9342 ± 1.2454	0.4729 ± 1.0057	1.4609 ± 1.8530	0.9353 ± 1.4049
	Median	0.2610	0.1400	0.3000	0.2450
	Q1 ; Q3	0.1100 ; 1.6000	0.1200 ; 0.3600	0.1900 ; 3.1000	0.1200 ; 1.0200
	Min. ; Max.	0 ; 4.4	0 ; 4.3	0.09 ; 5.2	0 ; 5.2
	Missing	44	25	19	88
Month 12: Eosinophils (g/L)	N	17	17	15	49
	Mean ± SD	1.0453 ± 2.6637	0.9546 ± 1.5188	0.6127 ± 1.0081	0.8814 ± 1.8613
	Median	0.2000	0.2800	0.2330	0.2200
	Q1 ; Q3	0.1000 ; 0.2800	0.1600 ; 0.9400	0.1500 ; 0.4000	0.1400 ; 0.4700
	Min. ; Max.	0 ; 11	0.04 ; 4.8	0 ; 3.6	0 ; 11
	Missing	49	25	19	93

Variables		2L (N=66)	3L (N=42)	4L+ (N=34)	Total (N=142)
Month 15: Eosinophils (g/L)	N	17	12	13	42
	Mean ± SD	1.569 ± 3.194	0.866 ± 1.306	1.784 ± 2.157	1.435 ± 2.438
	Median	0.200	0.215	0.360	0.235
	Q1 ; Q3	0.170 ; 0.340	0.110 ; 1.080	0.160 ; 4.100	0.160 ; 1.700
	Min. ; Max.	0.04 ; 11.3	0.06 ; 3.6	0 ; 5.4	0 ; 11.3
	Missing	49	30	21	100
Month 18: Eosinophils (g/L)	N	8	9	11	28
	Mean ± SD	3.328 ± 4.383	0.976 ± 1.473	1.210 ± 1.733	1.740 ± 2.792
	Median	1.570	0.260	0.300	0.295
	Q1 ; Q3	0.250 ; 5.200	0.250 ; 0.430	0.140 ; 2.400	0.165 ; 2.950
	Min. ; Max.	0.08 ; 12.5	0.06 ; 3.9	0.1 ; 5.2	0.06 ; 12.5
	Missing	58	33	23	114
Month 21: Eosinophils (g/L)	N	13	4	11	28
	Mean ± SD	0.796 ± 1.145	1.038 ± 1.708	1.427 ± 1.623	1.079 ± 1.404
	Median	0.240	0.190	0.440	0.260
	Q1 ; Q3	0.170 ; 0.630	0.175 ; 1.900	0.140 ; 3.000	0.165 ; 2.150
	Min. ; Max.	0.05 ; 3.7	0.17 ; 3.6	0.09 ; 4.4	0.05 ; 4.4
	Missing	53	38	23	114
Month 24: Eosinophils (g/L)	N	10	4	11	25
	Mean ± SD	1.7820 ± 2.1467	0.8975 ± 0.9158	1.6761 ± 2.0098	1.5939 ± 1.9012
	Median	0.4150	0.7200	0.3100	0.3400
	Q1 ; Q3	0.2700 ; 3.6000	0.1950 ; 1.6000	0.2870 ; 3.7000	0.2870 ; 2.7000
	Min. ; Max.	0.15 ; 6.1	0.05 ; 2.1	0.12 ; 5.9	0.05 ; 6.1
	Missing	56	38	23	117
Month 27: Eosinophils (g/L)	N	9	4	6	19
	Mean ± SD	2.553 ± 4.301	0.463 ± 0.253	2.060 ± 1.795	1.957 ± 3.132
	Median	0.180	0.415	1.850	0.500
	Q1 ; Q3	0.120 ; 4.200	0.275 ; 0.650	0.530 ; 3.300	0.180 ; 3.300
	Min. ; Max.	0.04 ; 12.8	0.22 ; 0.8	0.13 ; 4.7	0.04 ; 12.8
	Missing	57	38	28	123

Variables		2L (N=66)	3L (N=42)	4L+ (N=34)	Total (N=142)
Month 30: Eosinophils (g/L)	N	8	3	3	14
	Mean ± SD	1.200 ± 1.945	0.237 ± 0.197	0.200 ± 0.090	0.779 ± 1.516
	Median	0.220	0.160	0.200	0.200
	Q1 ; Q3	0.140 ; 1.740	0.090 ; 0.460	0.110 ; 0.290	0.110 ; 0.380
	Min. ; Max.	0.1 ; 5.3	0.09 ; 0.46	0.11 ; 0.29	0.09 ; 5.3
	Missing	58	39	31	128
Month 33: Eosinophils (g/L)	N	6	0	3	9
	Mean ± SD	2.7933 ± 3.0249		0.2230 ± 0.1446	1.9366 ± 2.7158
	Median	2.2550		0.1400	0.2100
	Q1 ; Q3	0.1400 ; 5.0000		0.1390 ; 0.3900	0.1400 ; 4.3000
	Min. ; Max.	0.11 ; 7		0.139 ; 0.39	0.11 ; 7
	Missing	60	42	31	133
Month 36: Eosinophils (g/L)	N	4	3	2	9
	Mean ± SD	1.128 ± 1.982	0.360 ± 0.090	0.160 ± 0.000	0.657 ± 1.296
	Median	0.160	0.360	0.160	0.160
	Q1 ; Q3	0.125 ; 2.130	0.270 ; 0.450	0.160 ; 0.160	0.160 ; 0.360
	Min. ; Max.	0.09 ; 4.1	0.27 ; 0.45	0.16 ; 0.16	0.09 ; 4.1
	Missing	62	39	32	133

Table 15.3.9v Biological and Hematological Parameters: Eosinophils - SAF (n=142)

Table 105: Biological and Hematological Parameters: Neutrophils - SAF (n=142)

Variables		2L (N=66)	3L (N=42)	4L+ (N=34)	Total (N=142)
Baseline: Neutrophils (g/L)	N	51	32	30	113
	Mean ± SD	24.82776 ± 27.72139	17.28844 ± 23.25400	18.29440 ± 23.45132	20.95821 ± 25.45013
	Median	6.04000	4.74000	4.99000	5.10000
	Q1 ; Q3	3.03000 ; 54.00000	3.08000 ; 24.15500	3.19000 ; 35.00000	3.15000 ; 46.60000
	Min. ; Max.	1.75 ; 78	2.2 ; 67.9	2.12 ; 70.8	1.75 ; 78
	Missing	15	10	4	29
Month 3: Neutrophils (g/L)	N	44	30	26	100
	Mean ± SD	22.9236 ± 29.5993	15.6337 ± 22.5621	12.7592 ± 20.8772	18.0939 ± 25.6787
	Median	4.6220	5.3000	4.1100	4.6800
	Q1 ; Q3	3.7200 ; 58.7000	4.0400 ; 7.4200	3.1700 ; 5.4000	3.7700 ; 7.7400
	Min. ; Max.	2.56 ; 83.8	1.63 ; 71.6	2.48 ; 71.1	1.63 ; 83.8
	Missing	22	12	8	42
Month 6: Neutrophils (g/L)	N	32	24	18	74
	Mean ± SD	20.9595 ± 27.7909	11.7060 ± 18.2975	15.9368 ± 22.4075	16.7366 ± 23.8051
	Median	5.3550	5.3050	4.6305	5.2050
	Q1 ; Q3	4.0330 ; 27.2500	4.0770 ; 6.3900	3.5700 ; 8.0800	4.0200 ; 8.6500
	Min. ; Max.	2.95 ; 83.6	2.18 ; 69.4	2.34 ; 65.8	2.18 ; 83.6
	Missing	34	18	16	68
Month 9: Neutrophils (g/L)	N	22	17	15	54
	Mean ± SD	22.3090 ± 29.5120	9.7900 ± 15.7888	18.8701 ± 23.4456	17.4126 ± 24.3874
	Median	4.9250	3.9900	4.7000	4.7100
	Q1 ; Q3	3.9800 ; 61.9000	3.3900 ; 5.6000	3.5300 ; 43.8000	3.5300 ; 8.2000
	Min. ; Max.	2.52 ; 76.3	2.39 ; 54.7	1.786 ; 62.3	1.786 ; 76.3
	Missing	44	25	19	88
Month 12: Neutrophils (g/L)	N	17	17	16	50
	Mean ± SD	12.7041 ± 19.4572	19.5547 ± 28.3422	19.9099 ± 27.0006	17.3392 ± 24.9078
	Median	5.3300	4.9400	5.7100	5.3700
	Q1 ; Q3	4.2400 ; 7.3800	3.7700 ; 7.2500	4.0650 ; 30.8780	4.0300 ; 9.1560
	Min. ; Max.	2.9 ; 65.5	1.36 ; 77.2	1.677 ; 78	1.36 ; 78
	Missing	49	25	18	92

Variables		2L (N=66)	3L (N=42)	4L+ (N=34)	Total (N=142)
Month 15: Neutrophils (g/L)	N	17	12	13	42
	Mean ± SD	20.277 ± 28.177	15.688 ± 25.146	21.448 ± 24.873	19.328 ± 25.811
	Median	5.000	5.505	6.580	5.270
	Q1 ; Q3	3.960 ; 10.200	3.750 ; 7.560	3.340 ; 44.000	3.730 ; 18.910
	Min. ; Max.	2.91 ; 72.7	2.28 ; 70.8	2.09 ; 65.5	2.09 ; 72.7
	Missing	49	30	21	100
Month 18: Neutrophils (g/L)	N	9	9	11	29
	Mean ± SD	38.9389 ± 33.7236	18.2500 ± 28.6594	15.5367 ± 24.6803	23.6415 ± 29.7913
	Median	55.0000	4.3700	4.7200	4.7200
	Q1 ; Q3	3.6700 ; 69.1000	3.7500 ; 5.0700	3.2300 ; 8.6000	3.5900 ; 57.9000
	Min. ; Max.	3.18 ; 74.4	3.17 ; 78.1	1.6 ; 70.2	1.6 ; 78.1
	Missing	57	33	23	113
Month 21: Neutrophils (g/L)	N	13	4	11	28
	Mean ± SD	14.286 ± 23.735	21.390 ± 34.680	18.908 ± 26.780	17.117 ± 25.642
	Median	4.620	4.525	3.180	4.525
	Q1 ; Q3	4.180 ; 5.470	3.785 ; 38.995	2.120 ; 51.000	3.295 ; 7.230
	Min. ; Max.	3.41 ; 73	3.11 ; 73.4	1.53 ; 66.1	1.53 ; 73.4
	Missing	53	38	23	114
Month 24: Neutrophils (g/L)	N	10	4	11	25
	Mean ± SD	31.4060 ± 35.4858	35.5075 ± 35.3199	20.8758 ± 27.9344	27.4290 ± 31.4713
	Median	5.1550	33.1650	5.0000	5.3200
	Q1 ; Q3	3.5700 ; 70.6000	5.4150 ; 65.6000	2.9900 ; 54.5000	3.5700 ; 61.6000
	Min. ; Max.	2.94 ; 77.7	2.8 ; 72.9	2.34 ; 74.7	2.34 ; 77.7
	Missing	56	38	23	117
Month 27: Neutrophils (g/L)	N	9	4	6	19
	Mean ± SD	24.396 ± 31.396	23.580 ± 36.749	30.667 ± 29.771	26.204 ± 30.318
	Median	4.000	6.410	29.070	4.550
	Q1 ; Q3	3.490 ; 62.800	3.725 ; 43.435	3.330 ; 56.100	3.330 ; 62.800
	Min. ; Max.	1.3 ; 70	2.9 ; 78.6	3.33 ; 63.1	1.3 ; 78.6
	Missing	57	38	28	123

Variables		2L (N=66)	3L (N=42)	4L+ (N=34)	Total (N=142)
Month 30: Neutrophils (g/L)	N	10	3	3	16
	Mean ± SD	17.017 ± 26.786	4.790 ± 1.071	3.813 ± 0.506	12.249 ± 21.707
	Median	4.745	4.290	4.000	4.295
	Q1 ; Q3	4.230 ; 5.610	4.060 ; 6.020	3.240 ; 4.200	4.030 ; 5.455
	Min. ; Max.	1.96 ; 68.6	4.06 ; 6.02	3.24 ; 4.2	1.96 ; 68.6
	Missing	56	39	31	126
Month 33: Neutrophils (g/L)	N	6	0	3	9
	Mean ± SD	35.0050 ± 34.0563		4.9590 ± 0.4984	24.9897 ± 30.8326
	Median	32.9100		5.1900	5.3000
	Q1 ; Q3	3.6600 ; 67.9000		4.3870 ; 5.3000	4.3870 ; 60.0000
	Min. ; Max.	2.75 ; 69.9		4.387 ; 5.3	2.75 ; 69.9
	Missing	60	42	31	133
Month 36: Neutrophils (g/L)	N	4	3	2	9
	Mean ± SD	19.903 ± 31.086	4.590 ± 0.835	6.105 ± 1.704	11.732 ± 20.575
	Median	4.970	4.990	6.105	4.990
	Q1 ; Q3	3.600 ; 36.205	3.630 ; 5.150	4.900 ; 7.310	4.030 ; 5.910
	Min. ; Max.	3.17 ; 66.5	3.63 ; 5.15	4.9 ; 7.31	3.17 ; 66.5
	Missing	62	39	32	133

Table 15.3.9w Biological and Hematological Parameters: Neutrophils - SAF (n=142)

Table 106: Biological and Hematological Parameters: Monocytes - SAF (n=142)

Variables		2L (N=66)	3L (N=42)	4L+ (N=34)	Total (N=142)
Baseline: Monocytes (g/L)	N	50	32	30	112
	Mean ± SD	3.15100 ± 3.86813	2.18531 ± 3.11134	2.25483 ± 4.16081	2.63505 ± 3.74819
	Median	0.74500	0.70000	0.60000	0.65500
	Q1 ; Q3	0.39000 ; 6.68000	0.47000 ; 1.03500	0.46000 ; 1.37000	0.41500 ; 4.05000
	Min. ; Max.	0.18 ; 14.7	0.24 ; 10.9	0 ; 20	0 ; 20
	Missing	16	10	4	30
Month 3: Monocytes (g/L)	N	44	30	26	100
	Mean ± SD	2.6746 ± 3.3676	2.0313 ± 2.9649	2.3450 ± 4.0421	2.3959 ± 3.4209
	Median	0.6900	0.6450	0.5810	0.6350
	Q1 ; Q3	0.5100 ; 5.7500	0.5100 ; 1.2300	0.5000 ; 0.8700	0.5035 ; 1.5450
	Min. ; Max.	0.14 ; 9.7	0.1 ; 9.6	0.18 ; 16.5	0.1 ; 16.5
	Missing	22	12	8	42
Month 6: Monocytes (g/L)	N	32	24	18	74
	Mean ± SD	2.5911 ± 3.3824	1.7128 ± 3.0982	2.8123 ± 4.5973	2.3601 ± 3.6078
	Median	0.8700	0.5550	0.6350	0.6400
	Q1 ; Q3	0.4745 ; 3.0500	0.4350 ; 0.9300	0.4000 ; 1.0670	0.4360 ; 1.4600
	Min. ; Max.	0.321 ; 11.2	0.16 ; 12.7	0.23 ; 15.5	0.16 ; 15.5
	Missing	34	18	16	68
Month 9: Monocytes (g/L)	N	22	17	15	54
	Mean ± SD	2.7052 ± 3.7366	1.3012 ± 2.1068	3.3534 ± 4.7285	2.4432 ± 3.6687
	Median	0.7000	0.4700	0.8000	0.5950
	Q1 ; Q3	0.5100 ; 3.1000	0.3900 ; 0.8700	0.5300 ; 8.7000	0.4600 ; 1.4500
	Min. ; Max.	0.3 ; 12	0.33 ; 6.9	0.242 ; 13.8	0.242 ; 13.8
	Missing	44	25	19	88
Month 12: Monocytes (g/L)	N	17	17	15	49
	Mean ± SD	2.2000 ± 3.3514	2.1975 ± 2.9167	2.5080 ± 4.2967	2.2934 ± 3.4619
	Median	0.6600	0.7300	0.6200	0.6600
	Q1 ; Q3	0.5300 ; 1.1300	0.5500 ; 1.2900	0.4000 ; 1.0200	0.5300 ; 1.1900

Variables		2L (N=66)	3L (N=42)	4L+ (N=34)	Total (N=142)
	Min. ; Max.	0.45 ; 9.7	0.32 ; 9.7	0.17 ; 14.5	0.17 ; 14.5
	Missing	49	25	19	93
Month 15: Monocytes (g/L)	N	17	12	13	42
	Mean ± SD	2.466 ± 3.388	2.027 ± 3.429	3.808 ± 4.759	2.756 ± 3.848
	Median	0.650	0.565	0.720	0.650
	Q1 ; Q3	0.510 ; 1.350	0.440 ; 1.235	0.520 ; 8.300	0.490 ; 3.600
	Min. ; Max.	0.37 ; 10.1	0.22 ; 11.4	0.21 ; 13.4	0.21 ; 13.4
	Missing	49	30	21	100
Month 18: Monocytes (g/L)	N	8	9	11	28
	Mean ± SD	4.200 ± 3.926	2.440 ± 3.674	2.205 ± 3.859	2.851 ± 3.779
	Median	3.690	0.530	0.460	0.540
	Q1 ; Q3	0.605 ; 7.800	0.470 ; 1.430	0.400 ; 0.910	0.440 ; 6.800
	Min. ; Max.	0.41 ; 9	0.42 ; 10.3	0.3 ; 10.3	0.3 ; 10.3
	Missing	58	33	23	114
Month 21: Monocytes (g/L)	N	13	4	11	28
	Mean ± SD	1.6892 ± 2.6717	2.6600 ± 4.4280	3.2239 ± 4.8082	2.4308 ± 3.8003
	Median	0.5500	0.4850	0.6800	0.6050
	Q1 ; Q3	0.4600 ; 0.9000	0.3700 ; 4.9500	0.3900 ; 8.5000	0.4100 ; 0.9900
	Min. ; Max.	0.34 ; 8.4	0.37 ; 9.3	0.23 ; 13.9	0.23 ; 13.9
	Missing	53	38	23	114
Month 24: Monocytes (g/L)	N	10	4	11	25
	Mean ± SD	3.3200 ± 3.5216	5.9150 ± 6.1916	3.3390 ± 4.8057	3.7436 ± 4.4723
	Median	0.9650	5.6050	0.8610	0.9500
	Q1 ; Q3	0.4900 ; 7.2000	0.5800 ; 11.2500	0.4500 ; 7.7000	0.4900 ; 7.7000
	Min. ; Max.	0.32 ; 8.4	0.45 ; 12	0.3 ; 14	0.3 ; 14
	Missing	56	38	23	117
Month 27: Monocytes (g/L)	N	9	4	6	19
	Mean ± SD	3.239 ± 4.309	3.373 ± 4.910	5.247 ± 5.595	3.901 ± 4.675
	Median	0.510	1.190	4.535	0.550
	Q1 ; Q3	0.490 ; 7.200	0.595 ; 6.150	0.360 ; 8.700	0.410 ; 8.600
	Min. ; Max.	0.21 ; 11	0.41 ; 10.7	0.25 ; 13.1	0.21 ; 13.1

Variables		2L (N=66)	3L (N=42)	4L+ (N=34)	Total (N=142)
	Missing	57	38	28	123
Month 30: Monocytes (g/L)	N	8	3	3	14
	Mean ± SD	2.3925 ± 3.6459	0.8030 ± 0.8251	0.4333 ± 0.0764	1.6321 ± 2.8477
	Median	0.5150	0.5300	0.4500	0.4850
	Q1 ; Q3	0.3300 ; 3.9050	0.1490 ; 1.7300	0.3500 ; 0.5000	0.3500 ; 0.8100
	Min. ; Max.	0.24 ; 9.4	0.149 ; 1.73	0.35 ; 0.5	0.149 ; 9.4
	Missing	58	39	31	128
Month 33: Monocytes (g/L)	N	6	0	3	9
	Mean ± SD	3.9000 ± 4.0202		0.4877 ± 0.1665	2.7626 ± 3.6082
	Median	2.3650		0.4900	0.6530
	Q1 ; Q3	0.5900 ; 8.6000		0.3200 ; 0.6530	0.4900 ; 4.0000
	Min. ; Max.	0.48 ; 9		0.32 ; 0.653	0.32 ; 9
	Missing	60	42	31	133
Month 36: Monocytes (g/L)	N	4	3	2	9
	Mean ± SD	2.658 ± 4.098	1.107 ± 0.378	0.625 ± 0.049	1.689 ± 2.686
	Median	0.690	1.310	0.625	0.670
	Q1 ; Q3	0.505 ; 4.810	0.670 ; 1.340	0.590 ; 0.660	0.590 ; 1.310
	Min. ; Max.	0.45 ; 8.8	0.67 ; 1.34	0.59 ; 0.66	0.45 ; 8.8
	Missing	62	39	32	133

Table 107: Biological and Hematological Parameters: Lymphocytes - SAF (n=142)

Variables		2L (N=66)	3L (N=42)	4L+ (N=34)	Total (N=142)
Baseline: Lymphocytes (g/L)	N	51	32	30	113
	Mean ± SD	10.04565 ± 13.12168	7.92281 ± 12.59985	8.27030 ± 13.79161	8.97316 ± 13.07779
	Median	2.29000	2.01000	1.93000	2.19300
	Q1 ; Q3	1.42000 ; 15.80000	1.34000 ; 3.57000	1.46000 ; 3.80900	1.40000 ; 11.00000
	Min. ; Max.	0.73 ; 47.4	0.4 ; 44.4	0.21 ; 51.6	0.21 ; 51.6
	Missing	15	10	4	29
Month 3: Lymphocytes (g/L)	N	44	30	26	100
	Mean ± SD	7.6738 ± 10.7839	7.4183 ± 13.0314	6.2452 ± 10.3502	7.2257 ± 11.2987
	Median	1.8300	2.0000	1.4900	1.8300
	Q1 ; Q3	1.3950 ; 15.8000	1.0300 ; 3.0000	1.1300 ; 2.6800	1.2800 ; 3.1000
	Min. ; Max.	0.8 ; 46	0.19 ; 52.1	0.29 ; 35.2	0.19 ; 52.1
	Missing	22	12	8	42
Month 6: Lymphocytes (g/L)	N	32	24	18	74
	Mean ± SD	7.6802 ± 11.6344	5.0269 ± 9.8107	7.6293 ± 12.1171	6.8073 ± 11.1149
	Median	1.9350	1.9450	1.7090	1.8545
	Q1 ; Q3	1.4100 ; 8.3500	1.0650 ; 3.0150	1.1510 ; 2.9000	1.3400 ; 3.1500
	Min. ; Max.	0.984 ; 43.2	0.41 ; 41.9	0.71 ; 36.8	0.41 ; 43.2
	Missing	34	18	16	68
Month 9: Lymphocytes (g/L)	N	22	16	15	53
	Mean ± SD	5.5232 ± 6.8583	4.2456 ± 10.7314	9.3578 ± 13.9581	6.2228 ± 10.4362
	Median	2.1900	1.6250	1.5000	1.7700
	Q1 ; Q3	1.5200 ; 5.5000	0.8750 ; 2.3050	1.3970 ; 25.6000	1.4100 ; 2.5600
	Min. ; Max.	0.8 ; 21.1	0.6 ; 44.4	1.21 ; 41.9	0.6 ; 44.4
	Missing	44	26	19	89
Month 12: Lymphocytes (g/L)	N	17	17	15	49
	Mean ± SD	4.2741 ± 6.6861	6.1660 ± 8.7357	6.4188 ± 10.5401	5.5870 ± 8.5841
	Median	1.5900	2.2800	1.5420	1.6100
	Q1 ; Q3	1.1200 ; 2.2600	1.3700 ; 3.7000	1.1990 ; 2.3000	1.1990 ; 2.6900
	Min. ; Max.	0.83 ; 25.4	0.6 ; 29.6	0.48 ; 28.5	0.48 ; 29.6
	Missing	49	25	19	93

Variables		2L (N=66)	3L (N=42)	4L+ (N=34)	Total (N=142)
Month 15: Lymphocytes (g/L)	N	17	12	13	42
	Mean ± SD	4.842 ± 6.467	4.338 ± 6.336	10.071 ± 14.334	6.316 ± 9.682
	Median	1.870	1.900	1.810	1.860
	Q1 ; Q3	1.470 ; 2.270	0.945 ; 3.285	1.450 ; 21.000	1.170 ; 3.910
	Min. ; Max.	0.97 ; 21.5	0.74 ; 21.1	0.42 ; 42.4	0.42 ; 42.4
	Missing	49	30	21	100
Month 18: Lymphocytes (g/L)	N	8	9	11	28
	Mean ± SD	8.5025 ± 7.6342	5.4578 ± 9.5169	4.4402 ± 8.1897	5.9279 ± 8.3502
	Median	7.0150	1.7500	1.6000	1.7300
	Q1 ; Q3	1.4450 ; 15.4000	1.1300 ; 2.4200	1.1320 ; 2.7000	1.2560 ; 7.5000
	Min. ; Max.	1.1 ; 19.2	0.82 ; 30.1	0.45 ; 28.6	0.45 ; 30.1
	Missing	58	33	23	114
Month 21: Lymphocytes (g/L)	N	13	4	11	28
	Mean ± SD	4.6015 ± 7.5966	4.5225 ± 5.8171	12.5213 ± 16.9653	7.7016 ± 12.3125
	Median	1.6200	2.0600	1.5300	1.6900
	Q1 ; Q3	1.3700 ; 2.5900	1.3850 ; 7.6600	1.2200 ; 26.6000	1.3000 ; 7.9850
	Min. ; Max.	0.79 ; 26.3	0.77 ; 13.2	0.39 ; 49.5	0.39 ; 49.5
	Missing	53	38	23	114
Month 24: Lymphocytes (g/L)	N	10	4	11	25
	Mean ± SD	7.0880 ± 7.7608	11.8250 ± 12.0423	7.3209 ± 10.3333	7.9484 ± 9.3913
	Median	2.4100	9.0500	1.5300	2.4000
	Q1 ; Q3	1.5600 ; 12.1000	2.7500 ; 20.9000	1.1090 ; 16.3000	1.3710 ; 13.8000
	Min. ; Max.	1.06 ; 22.7	1.2 ; 28	0.36 ; 27.2	0.36 ; 28
	Missing	56	38	23	117
Month 27: Lymphocytes (g/L)	N	9	4	6	19
	Mean ± SD	7.014 ± 7.870	4.105 ± 3.360	15.330 ± 15.219	9.028 ± 10.696
	Median	2.360	2.755	14.220	2.730
	Q1 ; Q3	1.720 ; 12.500	2.270 ; 5.940	1.580 ; 27.300	1.720 ; 17.400
	Min. ; Max.	1.28 ; 21.3	1.81 ; 9.1	1.46 ; 33.2	1.28 ; 33.2
	Missing	57	38	28	123

Variables		2L (N=66)	3L (N=42)	4L+ (N=34)	Total (N=142)
Month 30: Lymphocytes (g/L)	N	8	3	3	14
	Mean ± SD	5.771 ± 8.344	1.907 ± 0.402	1.503 ± 0.188	4.029 ± 6.473
	Median	1.410	1.690	1.400	1.590
	Q1 ; Q3	0.875 ; 9.550	1.660 ; 2.370	1.390 ; 1.720	1.300 ; 2.370
	Min. ; Max.	0.6 ; 21.9	1.66 ; 2.37	1.39 ; 1.72	0.6 ; 21.9
	Missing	58	39	31	128
Month 33: Lymphocytes (g/L)	N	6	0	3	9
	Mean ± SD	10.9150 ± 11.4163		1.3503 ± 0.3548	7.7268 ± 10.2156
	Median	8.6500		1.1500	1.7600
	Q1 ; Q3	1.2500 ; 16.7000		1.1410 ; 1.7600	1.2400 ; 15.5000
	Min. ; Max.	1.24 ; 29		1.141 ; 1.76	1.141 ; 29
	Missing	60	42	31	133
Month 36: Lymphocytes (g/L)	N	4	3	2	9
	Mean ± SD	5.878 ± 9.424	2.223 ± 0.312	1.565 ± 0.983	3.701 ± 6.146
	Median	1.380	2.300	1.565	1.880
	Q1 ; Q3	0.895 ; 10.860	1.880 ; 2.490	0.870 ; 2.260	1.040 ; 2.300
	Min. ; Max.	0.75 ; 20	1.88 ; 2.49	0.87 ; 2.26	0.75 ; 20
	Missing	62	39	32	133

Table 15.3.9y Biological and Hematological Parameters: Lymphocytes - SAF (n=142)

Appendix 7.9: Subject with accelerated or blast phase

Table 108: Subjects with Accelerated or Blast Phase - All Subjects

Patient No.	Current phase	Date of initiation of bosutinib treatment	SOC name	PT name	CTCAE grade	Date of occurrence	Is the event serious?	Serious event	Status	Date of recovery	Is it reasonably possible that the event may be related to the study medication?	Is it reasonably possible that the event may be related to a concomitant drug?
09-10	Accelerated	21/09/2017	Gastrointestinal disorders	Diarrhoea	Grade 2	20/10/2017	No		Recovery	08/02/2018	Yes	No
			Gastrointestinal disorders	Nausea	Grade 2	05/12/2017	No		Recovery	30/04/2018	Yes	No
			Skin and subcutaneous tissue disorders	Dermatitis bullous	Grade 1	27/10/2017	No		Recovery with sequellae	22/12/2017	No	No
			Vascular disorders	Haemorrhage	Grade 4	03/05/2018	Yes	Endangerment of vital prognosis/Hospitalization or extension of hospitalization	Recovery	05/05/2018	No	No
			General disorders and administration site conditions	General physical health deterioration	Grade 2	07/06/2018	No		Subject not recovered		No	No
			Infections and infestations	Bronchitis	Grade 1	19/05/2018	No		Recovery	30/06/2018	No	No
			Gastrointestinal disorders	Vomiting	Grade 2	04/06/2018	No		Recovery	05/06/2018	Yes	No
			General disorders and administration site conditions	Therapeutic response decreased	Grade 2	03/04/2018	No		Subject not recovered		No	No

Patient No.	Current phase	Date of initiation of bosutinib treatment	SOC name	PT name	CTCAE grade	Date of occurrence	Is the event serious?	Serious event	Status	Date of recovery	Is it reasonably possible that the event may be related to the study medication?	Is it reasonably possible that the event may be related to a concomitant drug?
			Gastrointestinal disorders	Diarrhoea	Grade 1	09/02/2018	No		Recovery	10/08/2018	Yes	Yes
			Skin and subcutaneous tissue disorders	Acne	Grade 1	21/12/2017	No		Recovery	NK/04/2018	No	No
			Injury, poisoning and procedural complications	Arteriovenous fistula occlusion	Grade 3	15/02/2018	No		Recovery	28/02/2018	No	No
			Injury, poisoning and procedural complications	Thermal burn	Grade 1	25/03/2018	No		Recovery	NK/NK/2018	No	No
			General disorders and administration site conditions	General physical health deterioration	Grade 5	01/02/2018	Yes	Death/Hospitalization or extension of hospitalization	Subject not recovered		No	No
			General disorders and administration site conditions	Malaise	Grade 3	07/02/2019	Yes	Hospitalization or extension of hospitalization	Recovery	07/02/2019	No	No
			Gastrointestinal disorders	Constipation	Grade 2	NK/07/2018	No		Recovery	10/08/2018	No	No
			Psychiatric disorders	Depression	Grade 2	NK/08/2018	No		Subject not recovered		No	No
			Injury, poisoning and procedural complications	Wound	Grade 2	30/10/2018	No		Subject not recovered		No	No
			Metabolism and nutrition disorders	Malnutrition	Grade 4	22/09/2017	Yes	Hospitalization or extension of hospitalization	Subject not recovered		Yes	No
			Infections and infestations	Staphylococcal infection	Grade 3	05/02/2019	Yes	Hospitalization or extension of hospitalization	Subject not recovered		No	No
			Metabolism and nutrition disorders	Malnutrition	Grade 2	26/02/2019	No		Recovery	01/03/2019	No	No

Patient No.	Current phase	Date of initiation of bosutinib treatment	SOC name	PT name	CTCAE grade	Date of occurrence	Is the event serious?	Serious event	Status	Date of recovery	Is it reasonably possible that the event may be related to the study medication?	Is it reasonably possible that the event may be related to a concomitant drug?
			Infections and infestations	Oral fungal infection	Grade 2	NK/02/2019	No		Unknown		No	No
			Blood and lymphatic system disorders	Pancytopenia	Grade 4	21/02/2019	Yes	Endangerment of vital prognosis/Hospitalization or extension of hospitalization	Subject not recovered		No	Yes
			General disorders and administration site conditions	Malaise	Grade 4	26/02/2019	Yes	Hospitalization or extension of hospitalization	Subject not recovered		No	No
			Skin and subcutaneous tissue disorders	Dermatitis bullous	Grade 2	01/02/2018	No		Recovery	NK/NK/2018	No	No
			Metabolism and nutrition disorders	Folate deficiency	Grade 3	15/02/2019	Yes	Significant medical event	Recovery in progress		No	No
			Blood and lymphatic system disorders	Anaemia	Grade 2	03/05/2018	No		Recovery	NK/NK/2018	No	No
13-01	Blast-phase	26/03/2016	Blood and lymphatic system disorders	Anaemia	Grade 3	13/04/2016	Yes	Hospitalization or extension of hospitalization	Recovery	13/07/2016	Yes	No
			General disorders and administration site conditions	Pyrexia	Grade 2	13/04/2016	No		Recovery	17/04/2016	No	No
			Psychiatric disorders	Paranoia	Grade 3	19/04/2016	No		Recovery	25/05/2016	No	Yes
			Injury, poisoning and procedural complications	Head injury	Grade 1	21/04/2016	No		Recovery	21/04/2016	No	No
			Infections and infestations	Urinary tract infection	Grade 2	26/04/2016	No		Recovery	25/05/2016	No	No
			Gastrointestinal disorders	Constipation	Grade 2	22/05/2016	No		Recovery	22/05/2016	No	No

Patient No.	Current phase	Date of initiation of bosutinib treatment	SOC name	PT name	CTCAE grade	Date of occurrence	Is the event serious?	Serious event	Status	Date of recovery	Is it reasonably possible that the event may be related to the study medication?	Is it reasonably possible that the event may be related to a concomitant drug?
			Skin and subcutaneous tissue disorders	Rash	Grade 1	11/05/2016	No		Recovery	24/05/2016	No	No
			General disorders and administration site conditions	Oedema peripheral	Grade 1	13/04/2016	No		Recovery	NK/NK/2016	No	No
			Psychiatric disorders	Insomnia	Grade 1	14/04/2016	No		Recovery	18/06/2016	No	No
			Metabolism and nutrition disorders	Hypokalaemia	Grade 1	15/04/2016	No		Recovery	22/04/2016	Yes	No
			General disorders and administration site conditions	General physical health deterioration	Grade 5	26/07/2016	Yes	Death	Subject not recovered		No	No

Table 109: Treatment and Follow-up

Patient No.	Date of initiation of bosutinib treatment	Current phase	Dosage initiation	Was the patient on monitored for the 36 months of the study?	Has treatment with bosutinib been finally withdrawn	Date of withdrawal	Died	Date of death	Cause of death	Cause of death: Other, specify
09-10	21/09/2017	Accelerated	200mg/day	No	Yes	05/06/2018	Ticked	02/03/2019	Related to the illness	
13-01	26/03/2016	Blast-phase	200mg/day	No	.		Ticked	29/07/2016	Other, specify	AEG

Appendix 7.10: Death-SAF

Table 110: Death - SAF (n=142)

Patient No.	Date of initiation of bosutinib treatment	Has treatment with bosutinib been finally withdrawn	Date of withdrawal	Date of death	Cause of death	Cause of death: Other, specify
01-01	24/02/2016	Yes	03/03/2016	23/01/2017	Related to the illness	
09-10	21/09/2017	Yes	05/06/2018	02/03/2019	Related to the illness	
13-01	26/03/2016	.		29/07/2016	Other, specify	AEG
13-04	15/03/2018	.		02/02/2020	Other, specify	COMORBIDITES
16-03	24/07/2016	Yes	28/10/2018	30/10/2018	Other, specify	DEFAILLANCE MULTIORGANE
16-08	30/01/2019	Yes	17/09/2019	27/06/2021	Other, specify	DECOMPENSATION RESPIRATOIRE
23-02	01/10/2016	Yes	NK/10/2016	02/11/2016	Other, specify	ADENOCARCINOME POLYLMETASTATIQUE

Appendix 7.8 Death - SAF (n=142)

Appendix 7.11: Missing dose

Table 111: Missing dose (duration of interruption missing) - FAS (n=139)

Patient No.	Discontinuation date	Duration
03-01	NK/NK/2018	.
04-03	NK/NK/2019	.
	NK/NK/2020	.
	NK/NK/2021	.
09-21	NK/12/2019	.
11-01	NK/05/2016	.
11-22	24/09/2020	.
12-03	NK/07/2016	.
33-03	NK/12/2017	.
39-01	NK/09/2018	.

Appendix 7.9a Missing dose (duration of interruption missing) - FAS (n=139)

Table 112: Missing dose (new dose missing) - FAS (n=139)

Patient No.	Modification date	New dose	New dose: Other, specify	New dosage
09-10	03/05/2018	Other, specify : mg/day	200MG PAR JOUR LES VEILLES DE DYALYSE ET 300 MG PAR JOUR LES AUTRES JOURS	.
11-23	14/04/2020	Other, specify : mg/day	100MG 1JOUR/2	.
34-01	NK/11/2017	Other, specify : mg/day	200 MG CERTAINS JOURS	.

Appendix 7.9b Missing dose (new dose missing) - FAS (n=139)

Appendix 7.12 Subjects non-included

Table 113: Reasons for Non-Inclusion - All Subjects

Center No.	Date of consultation	Sex	Age (years)	Reason for non-inclusion	Reason for non-inclusion, specify
01	06/07/2017	Male	76	Other, specify	OUBLI DU MEDECIN
03	13/06/2019	Female	73	Other, specify	DELAI INITIATION > 7 JOURS
07	20/02/2018	Male	67	Other, specify	OUBLI
07	12/02/2018	Male	72	Other, specify	OUBLI
11	13/12/2019	Female	51	.	
12	13/08/2018	Male	70	Other, specify	OUBLI DU DR COITEUX
15	22/01/2018	Male	69	Other, specify	COMPLIANCE DIFFICILE POUR SUIVI ET TRAITEMENT
17	13/11/2018	Female	42	Other, specify	PATIENTE NON INFORMEE (NON JOIGNABLE PAR TEL)
22	14/02/2018	Female	80	Other, specify	SURCHARGE DE TRAVAIL
24	21/11/2016	Male	49	Refusal of the patient	
36	27/06/2018	Male	.	Other, specify	OUBLI DOCTEUR
36	25/10/2018	Male	54	Other, specify	OUBLI DOCTEUR
36	05/01/2018	Male	.	Other, specify	OUBLI DOCTEUR

Appendix 7.2 Reasons for Non-Inclusion - All Subjects

Appendix 7.13 Reasons for treatment change

Table 114: Reasons for temporary discontinuation of treatment - SAF (n=142)

Variables		2L (N=65)	3L (N=35)	4L+ (N=32)	Total (N=132)
Reasons for temporary discontinuation	STOP BY THE PATIENT DUE TO A BLISTERING SKIN LESION ON THE FINGER.	1 (1.5%)	0 (0%)	0 (0%)	1 (0.8%)
	STOP BY THE PATIENT FOR THE HOLIDAYS.	1 (1.5%)	0 (0%)	0 (0%)	1 (0.8%)
	ADVERSE EVENT	47 (72.3%)	30 (85.7%)	24 (75%)	101 (76.5%)
	PATIENT CHOICE	0 (0%)	1 (2.9%)	0 (0%)	1 (0.8%)
	COLOSCOPIE	1 (1.5%)	0 (0%)	0 (0%)	1 (0.8%)
	PATIENT'S DECISION FOR HER COMFORT ON THE DAY OF THE HOSPITAL CONSULTATION.	0 (0%)	1 (2.9%)	0 (0%)	1 (0.8%)
	PATIENT’S DECISION	0 (0%)	0 (0%)	5 (15.6%)	5 (3.8%)
	PATIENT’S DECISION	1 (1.5%)	0 (0%)	0 (0%)	1 (0.8%)
	DEPLACEMENT	0 (0%)	0 (0%)	1 (3.1%)	1 (0.8%)
	DESIR OF PREGNANCY	0 (0%)	0 (0%)	1 (3.1%)	1 (0.8%)
	PATIENT’S DECISION	1 (1.5%)	0 (0%)	0 (0%)	1 (0.8%)
	FIBROMYALGIA KNOWN BEFORE TREATMENT	1 (1.5%)	0 (0%)	0 (0%)	1 (0.8%)
	UNKNOWN	0 (0%)	2 (5.7%)	0 (0%)	2 (1.5%)
	POOR COMPLAINCE AND POOR COMPLIANCE	1 (1.5%)	0 (0%)	0 (0%)	1 (0.8%)

Variables		2L (N=65)	3L (N=35)	4L+ (N=32)	Total (N=132)
	POOR COMPLAINCE	2 (3.1%)	0 (0%)	0 (0%)	2 (1.5%)
	FORGOT	2 (3.1%)	0 (0%)	0 (0%)	2 (1.5%)
	PATIENT FORGOTFULNESS	0 (0%)	0 (0%)	1 (3.1%)	1 (0.8%)
	PATIENT FORGOTFULNESS	2 (3.1%)	0 (0%)	0 (0%)	2 (1.5%)
	PATIENT FORGOTFULNESS	1 (1.5%)	0 (0%)	0 (0%)	1 (0.8%)
	INVESTIGATOR S DECISION	0 (0%)	1 (2.9%)	0 (0%)	1 (0.8%)
	SOTCKOUT	1 (1.5%)	0 (0%)	0 (0%)	1 (0.8%)
	STOCKOUT	1 (1.5%)	0 (0%)	0 (0%)	1 (0.8%)
	INVESTIGATOR S DECISION	1 (1.5%)	0 (0%)	0 (0%)	1 (0.8%)
	UNKNOWN	1 (1.5%)	0 (0%)	0 (0%)	1 (0.8%)

Table 15.4.2d Reasons for temporary discontinuation of treatment - SAF (n=142)

Table 115: Reasons for dose reduction - SAF (n=142)

Variables		2L (N=48)	3L (N=34)	4L+ (N=30)	Total (N=112)
Reasons for dose reduction	AGGRAVATION OF CHRONIC RENAL INSUFFICIENCY	1 (2.1%)	0 (0%)	0 (0%)	1 (0.9%)
	WEIGHT LOSS	0 (0%)	0 (0%)	1 (3.3%)	1 (0.9%)
	AFTER STOPPING, PATIENT RESUMED AT 300 MG DUE TO RESPONSE	1 (2.1%)	0 (0%)	0 (0%)	1 (0.9%)
	GOOD RESPONSE	0 (0%)	1 (2.9%)	0 (0%)	1 (0.9%)
	INVESTIGATOR'S CHOICE	1 (2.1%)	0 (0%)	0 (0%)	1 (0.9%)

Variables		2L (N=48)	3L (N=34)	4L+ (N=30)	Total (N=112)
	PATIENT'S CHOICE	1 (2.1%)	0 (0%)	0 (0%)	1 (0.9%)
	COMMON DECISION OF HEMATOLOGIST AND PNEUMOLOGIST TO ASSESS THE FOLLOW-UP OF PLEURAL EFFUSIONS	0 (0%)	1 (2.9%)	0 (0%)	1 (0.9%)
	PHYSICIAN'SDECISION	0 (0%)	1 (2.9%)	0 (0%)	1 (0.9%)
	PATIENT'S CHOICE	1 (2.1%)	0 (0%)	0 (0%)	1 (0.9%)
	AE	36 (75%)	30 (88.2%)	23 (76.7%)	89 (79.5%)
	IN AGREEMENT WITH NEPHROLOGIST	1 (2.1%)	0 (0%)	0 (0%)	1 (0.9%)
	DUE TO TRAMADOL	1 (2.1%)	0 (0%)	0 (0%)	1 (0.9%)
	THE PATIENT SOMETIMES TAKES 200MG	0 (0%)	0 (0%)	1 (3.3%)	1 (0.9%)
	NOT PRECISED	0 (0%)	1 (2.9%)	0 (0%)	1 (0.9%)
	PATIENT STATES TAKING 100MG /DAY	0 (0%)	0 (0%)	1 (3.3%)	1 (0.9%)
	MOLECULAR REPONSE	1 (2.1%)	0 (0%)	0 (0%)	1 (0.9%)
	RESUMPTION AFTER TEMPORARY STOP DUE TO PLEURAL EFFUSION	1 (2.1%)	0 (0%)	0 (0%)	1 (0.9%)
	RESUMPTION AFTER AE	1 (2.1%)	0 (0%)	0 (0%)	1 (0.9%)
	RESUMPTION AFTER PREGNANCY	0 (0%)	0 (0%)	1 (3.3%)	1 (0.9%)
	RESUMPTION OF BOSUTINIB	0 (0%)	0 (0%)	1 (3.3%)	1 (0.9%)
	RESUMPTION OF BOSUTINIB	0 (0%)	0 (0%)	1 (3.3%)	1 (0.9%)
	RM5 LESIONS	0 (0%)	0 (0%)	1 (3.3%)	1 (0.9%)
	SUPPLY SHORTAGE	1 (2.1%)	0 (0%)	0 (0%)	1 (0.9%)
	THROMBOPENIA	1 (2.1%)	0 (0%)	0 (0%)	1 (0.9%)

Table 15.4.2b Reasons for dose reduction - SAF (n=142)

Table 116: Reasons for dose increase - SAF (n=142)

Variables		2L (N=143)	3L (N=82)	4L+ (N=56)	Total (N=281)
Reasons for dose increase	ADAPTATION	2 (1.4%)	0 (0%)	0 (0%)	2 (0.7%)
	DOSE ADAPTATION	0 (0%)	1 (1.2%)	0 (0%)	1 (0.4%)
	ADAPTATION FOR EFFECTIVE DOSE	2 (1.4%)	0 (0%)	0 (0%)	2 (0.7%)
	PROGRESSIVE IMPROVEMENT OF LIVER FUNCTION	0 (0%)	1 (1.2%)	0 (0%)	1 (0.4%)
	PREVENTIVE TREATMENT DISCONTINUATION DUE TO TRAVELLING ABROAD	0 (0%)	0 (0%)	2 (3.6%)	2 (0.7%)
	PROGRESSIVE INCREASE	0 (0%)	3 (3.7%)	0 (0%)	3 (1.1%)
	PLANNED INCREASE	3 (2.1%)	0 (0%)	0 (0%)	3 (1.1%)
	DOSE INCREASE	0 (0%)	0 (0%)	1 (1.8%)	1 (0.4%)
	DOSE INCREASE AFTER DISCONTINUATION	0 (0%)	0 (0%)	1 (1.8%)	1 (0.4%)
	INCREASE FOR EFFECTIVE DOSE	1 (0.7%)	0 (0%)	0 (0%)	1 (0.4%)
	GRADUAL INCREASE AFTER INITIATION OF TREATMENT	0 (0%)	0 (0%)	1 (1.8%)	1 (0.4%)
	GRADUAL INCREASE ACCORDING TO PHYSICIAN S DECISION	0 (0%)	2 (2.4%)	0 (0%)	2 (0.7%)
	INCREASE ACCORDING TO RCP	2 (1.4%)	0 (0%)	0 (0%)	2 (0.7%)
	GOOD TOLERANCE	1 (0.7%)	0 (0%)	1 (1.8%)	2 (0.7%)
	GOOD TOLERANCE	11 (7.7%)	14 (17.1%)	6 (10.7%)	31 (11%)
	GOOD TOLERANCE	1 (0.7%)	0 (0%)	0 (0%)	1 (0.4%)
	GOOD TOLERANCE	1 (0.7%)	0 (0%)	0 (0%)	1 (0.4%)
	GOOD TOLERANCE	2 (1.4%)	0 (0%)	2 (3.6%)	4 (1.4%)

Variables		2L (N=143)	3L (N=82)	4L+ (N=56)	Total (N=281)
	GOOD TOLERANCE	0 (0%)	1 (1.2%)	0 (0%)	1 (0.4%)
	GOOD TOLERANCE	0 (0%)	1 (1.2%)	0 (0%)	1 (0.4%)
	GOOD TOLERANCE	1 (0.7%)	0 (0%)	0 (0%)	1 (0.4%)
	GOOD TOLERANCE	0 (0%)	1 (1.2%)	0 (0%)	1 (0.4%)
	GOOD TOLERANCE	0 (0%)	0 (0%)	1 (1.8%)	1 (0.4%)
	GOOD TOLERANCE	2 (1.4%)	0 (0%)	0 (0%)	2 (0.7%)
	PRESCRIPTION CONFORMITY	0 (0%)	1 (1.2%)	0 (0%)	1 (0.4%)
	INVESTIGATOR S DECISION	0 (0%)	1 (1.2%)	0 (0%)	1 (0.4%)
	INVESTIGATOR S DECISION	0 (0%)	1 (1.2%)	0 (0%)	1 (0.4%)
	INVESTIGATOR S DECISION	2 (1.4%)	1 (1.2%)	2 (3.6%)	5 (1.8%)
	INVESTIGATOR S DECISION	2 (1.4%)	3 (3.7%)	4 (7.1%)	9 (3.2%)
	INVESTIGATOR S DECISION	0 (0%)	1 (1.2%)	0 (0%)	1 (0.4%)
	INVESTIGATOR S DECISION ACCORDING TO PROTOCOL	1 (0.7%)	0 (0%)	0 (0%)	1 (0.4%)
	INVESTIGATOR S DECISION ACCORDING TO PROTOCOL	1 (0.7%)	0 (0%)	0 (0%)	1 (0.4%)
	INVESTIGATOR S DECISION	0 (0%)	2 (2.4%)	0 (0%)	2 (0.7%)
	INVESTIGATOR S DECISION	0 (0%)	7 (8.5%)	0 (0%)	7 (2.5%)
	INVESTIGATOR S DECISION	2 (1.4%)	1 (1.2%)	0 (0%)	3 (1.1%)
	INVESTIGATOR S DECISION	7 (4.9%)	6 (7.3%)	1 (1.8%)	14 (5%)
	INVESTIGATOR S DECISION	0 (0%)	1 (1.2%)	0 (0%)	1 (0.4%)
	DISAPPEARANCE OF DIARRHEA	1 (0.7%)	0 (0%)	0 (0%)	1 (0.4%)
	NON OPTIMAL DOSE	2 (1.4%)	0 (0%)	0 (0%)	2 (0.7%)
	OPTIMAL DOSAGE NOT REACHED	1 (0.7%)	0 (0%)	0 (0%)	1 (0.4%)

Variables		2L (N=143)	3L (N=82)	4L+ (N=56)	Total (N=281)
	NON OPTIMAL DOSE	2 (1.4%)	0 (0%)	0 (0%)	2 (0.7%)
	AE	1 (0.7%)	2 (2.4%)	1 (1.8%)	4 (1.4%)
	PLANNED DOSE ESCALATION	2 (1.4%)	0 (0%)	0 (0%)	2 (0.7%)
	DISEASE PROGRESSION	1 (0.7%)	0 (0%)	0 (0%)	1 (0.4%)
	GOOD TOLERANCE	1 (0.7%)	0 (0%)	0 (0%)	1 (0.4%)
	THE PATIENT SHOULD INCREASE TO 300 MG AFTER 15 DAYS OF TREATMENT	0 (0%)	1 (1.2%)	0 (0%)	1 (0.4%)
	TOO HIGH RESIDUAL DISEASE	0 (0%)	1 (1.2%)	0 (0%)	1 (0.4%)
	Lack of efficacy / Suboptimal response	4 (2.8%)	2 (2.4%)	1 (1.8%)	7 (2.5%)
	NOT SPECIFIED	0 (0%)	1 (1.2%)	0 (0%)	1 (0.4%)
	NEW DOSE AFTER INITIATION	0 (0%)	0 (0%)	1 (1.8%)	1 (0.4%)
	DOSE OPTIMISATION	2 (1.4%)	2 (2.4%)	0 (0%)	4 (1.4%)
	OPTIMISATION DE LA DOSE DU TRAITEMENT	1 (0.7%)	0 (0%)	0 (0%)	1 (0.4%)
	OPTIMISATION EN FONCTION DE SON BILAN BIOLOGIQUE	0 (0%)	1 (1.2%)	0 (0%)	1 (0.4%)
	OPTIMISATION THERAPEUTIQUE	0 (0%)	1 (1.2%)	0 (0%)	1 (0.4%)
	TREATMENT INITIATION	0 (0%)	0 (0%)	2 (3.6%)	2 (0.7%)
	BOSUTINIB STEP	3 (2.1%)	0 (0%)	0 (0%)	3 (1.1%)
	BOSUTINIB STEP	2 (1.4%)	0 (0%)	2 (3.6%)	4 (1.4%)
	PROTOCOL STEP	2 (1.4%)	0 (0%)	0 (0%)	2 (0.7%)
	BOSUTINIB STEP	2 (1.4%)	0 (0%)	0 (0%)	2 (0.7%)
	PER PROTOCOLE	15 (10.5%)	5 (6.1%)	5 (8.9%)	25 (8.9%)
	PLANNED PROGRESSIVE DOSAGE	2 (1.4%)	0 (0%)	0 (0%)	2 (0.7%)
	TO OBTAIN GOOD EFFICACY	2 (1.4%)	0 (0%)	0 (0%)	2 (0.7%)

Variables		2L (N=143)	3L (N=82)	4L+ (N=56)	Total (N=281)
	MEDICALE PRECRIPTION	1 (0.7%)	0 (0%)	0 (0%)	1 (0.4%)
	MEDICALE PRESCRIPTION	2 (1.4%)	0 (0%)	0 (0%)	2 (0.7%)
	MEDICALE PRESCRIPTION	4 (2.8%)	0 (0%)	0 (0%)	4 (1.4%)
	PLANNED	16 (11.2%)	7 (8.5%)	0 (0%)	23 (8.2%)
	PLANNED IN THE PROTOCOL	3 (2.1%)	0 (0%)	0 (0%)	3 (1.1%)
	PROGRAMME	0 (0%)	0 (0%)	2 (3.6%)	2 (0.7%)
	PLANNED IN THE PROTOCOL	3 (2.1%)	0 (0%)	5 (8.9%)	8 (2.8%)
	PLANNED IN THE PROTOCOL	3 (2.1%)	0 (0%)	1 (1.8%)	4 (1.4%)
	PROTOCOL TO ACHIEVE EFFECTIVE DOSE	1 (0.7%)	0 (0%)	0 (0%)	1 (0.4%)
	PLANNED IN THE PROTOCOL	0 (0%)	0 (0%)	4 (7.1%)	4 (1.4%)
	LOSS OF RESPONSE	1 (0.7%)	3 (3.7%)	6 (10.7%)	10 (3.6%)
	RCP	3 (2.1%)	0 (0%)	0 (0%)	3 (1.1%)
	RCP	0 (0%)	2 (2.4%)	2 (3.6%)	4 (1.4%)
	DOSE REINCREASE FOR BETTER EFFICACY/ DOSE OPTIMISATION	1 (0.7%)	0 (0%)	0 (0%)	1 (0.4%)
	REPONSE SUBOPTIMALE/ DOSE OPTIMISATION	0 (0%)	0 (0%)	1 (1.8%)	1 (0.4%)
	RESUMPTION	2 (1.4%)	1 (1.2%)	0 (0%)	3 (1.1%)
	RESUMPTION	0 (0%)	0 (0%)	1 (1.8%)	1 (0.4%)
	RESUMPTION	0 (0%)	1 (1.2%)	0 (0%)	1 (0.4%)
	RESUMPTION	1 (0.7%)	0 (0%)	0 (0%)	1 (0.4%)
	RESUMPTION	1 (0.7%)	0 (0%)	0 (0%)	1 (0.4%)
	RESOLUTION AE	0 (0%)	1 (1.2%)	0 (0%)	1 (0.4%)
	DOSE ESCALATION SCHEME	2 (1.4%)	0 (0%)	0 (0%)	2 (0.7%)

Variables		2L (N=143)	3L (N=82)	4L+ (N=56)	Total (N=281)
	SELON L'ORDONNACE CAR BONNE TOLERANCE/ GOOD TOLERANCE	0 (0%)	1 (1.2%)	0 (0%)	1 (0.4%)
	PLANNED IN THE PROTOCOL	3 (2.1%)	0 (0%)	0 (0%)	3 (1.1%)
	PLANNED IN THE PROTOCOL	3 (2.1%)	0 (0%)	0 (0%)	3 (1.1%)
	STABLE MOLECULAR RESPONSE	0 (0%)	1 (1.2%)	0 (0%)	1 (0.4%)
	THERAPEUTIC SCHEME	2 (1.4%)	0 (0%)	0 (0%)	2 (0.7%)
	VERIFICATION OF TREATMENT TOLERANCE	1 (0.7%)	0 (0%)	0 (0%)	1 (0.4%)

Table 15.4.2c Reasons for dose increase - SAF (n=142)

Appendix 7.14 Cytogenetic response

Table 117: Cumulative cytogenetic responses to Bosutinib - FAS (n=139)

Variables		2L (N=64)	3L (N=42)	4L+ (N=33)	Total (N=139)
Minor cumulative cytogenetic response (mCyR)	No	63 (98.4%)	41 (97.6%)	33 (100%)	137 (98.6%)
	Yes	1 (1.6%)	1 (2.4%)	0 (0%)	2 (1.4%)
Partial cumulative cytogenetic response (PCyR)	No	63 (98.4%)	41 (97.6%)	32 (97%)	136 (97.8%)
	Yes	1 (1.6%)	1 (2.4%)	1 (3%)	3 (2.2%)
Complete cumulative cytogenetic response (CCyR)	No	57 (89.1%)	37 (88.1%)	32 (97%)	126 (90.6%)
	Yes	7 (10.9%)	5 (11.9%)	1 (3%)	13 (9.4%)
Major cumulative cytogenetic response (MCyR)	No	56 (87.5%)	36 (85.7%)	31 (93.9%)	123 (88.5%)
	Yes	8 (12.5%)	6 (14.3%)	2 (6.1%)	16 (11.5%)
Cumulative cytogenetic response (CyR)	No	55 (85.9%)	35 (83.3%)	31 (93.9%)	121 (87.1%)
	Yes	9 (14.1%)	7 (16.7%)	2 (6.1%)	18 (12.9%)

Table 15.2.1c Cumulative cytogenetic responses to Bosutinib - FAS (n=139)

Table 118: Cumulative cytogenetic responses to Bosutinib according to mean dose received during the follow up - FAS (n=139)

Variables		<=200 (N=16)	]200-300] (N=50)	]300-400] (N=33)	>400 (N=29)	Missing dose (N=11)	Total (N=139)
Minor cumulative cytogenetic response (mCyR)	No	16 (100%)	50 (100%)	32 (97%)	29 (100%)	10 (90.9%)	137 (98.6%)
	Yes	0 (0%)	0 (0%)	1 (3%)	0 (0%)	1 (9.1%)	2 (1.4%)
Partial cumulative cytogenetic response (PCyR)	No	16 (100%)	50 (100%)	32 (97%)	27 (93.1%)	11 (100%)	136 (97.8%)
	Yes	0 (0%)	0 (0%)	1 (3%)	2 (6.9%)	0 (0%)	3 (2.2%)
Complete cumulative cytogenetic response (CCyR)	No	16 (100%)	45 (90%)	30 (90.9%)	24 (82.8%)	11 (100%)	126 (90.6%)
	Yes	0 (0%)	5 (10%)	3 (9.1%)	5 (17.2%)	0 (0%)	13 (9.4%)
Major cumulative cytogenetic response (MCyR)	No	16 (100%)	45 (90%)	29 (87.9%)	22 (75.9%)	11 (100%)	123 (88.5%)
	Yes	0 (0%)	5 (10%)	4 (12.1%)	7 (24.1%)	0 (0%)	16 (11.5%)
Cumulative cytogenetic response (CyR)	No	16 (100%)	45 (90%)	28 (84.8%)	22 (75.9%)	10 (90.9%)	121 (87.1%)
	Yes	0 (0%)	5 (10%)	5 (15.2%)	7 (24.1%)	1 (9.1%)	18 (12.9%)

Table 15.2.1d Cumulative cytogenetic responses to Bosutinib according to the mean dose received during the follow-up - FAS (n=139)

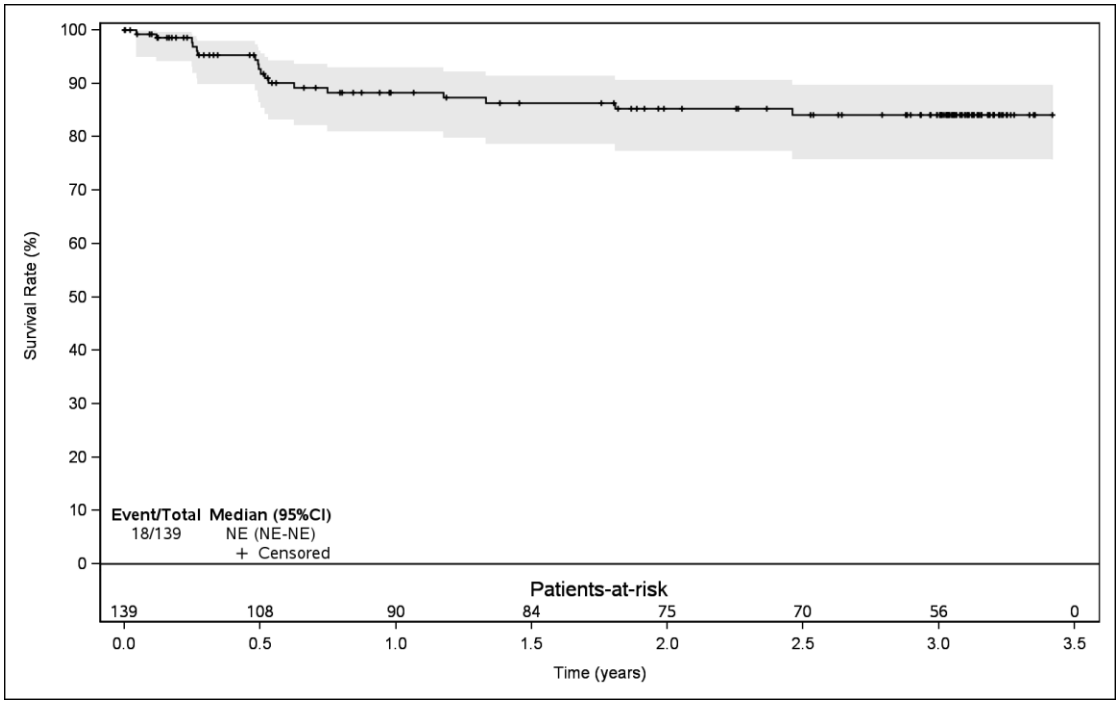
Table 119: Time-to-cytogenetic Response - FAS (n=139)

Variables		2L (N=64)	3L (N=42)	4L+ (N=33)	Total (N=139)
Event cytogenetic (time to response)	No	55 (85.9%)	35 (83.3%)	31 (93.9%)	121 (87.1%)
	Yes	9 (14.1%)	7 (16.7%)	2 (6.1%)	18 (12.9%)
Event/censoring cytogenetic (time to response)	Death during bosutinib	0 (0%)	0 (0%)	2 (6.1%)	2 (1.4%)
	Lost to follow-up	31 (48.4%)	19 (45.2%)	18 (54.5%)	68 (48.9%)
	Permanent discontinuation of bosutinib	24 (37.5%)	16 (38.1%)	11 (33.3%)	51 (36.7%)
	Response to bosutinib (all types)	9 (14.1%)	7 (16.7%)	2 (6.1%)	18 (12.9%)

Timepoint	Real time	Survival	[CI95%]	Failure	Erreur type de survie	Number Failed	Number Left	Estimate
1 year	0.75	0.88	[0.81-0.93]	0.12	0.0295	14	90	
2 years	1.81	0.85	[0.77-0.91]	0.15	0.0333	17	75	
3 years	2.46	0.84	[0.76-0.9]	0.16	0.0349	18	56	
Median [CI95%]	.				.	.	.	Not evaluable

Table 15.2.2b Time-to-cytogenetic Response - FAS (n=139)

Figure 15: Time-to-cytogenetic Response - FAS (n=139)



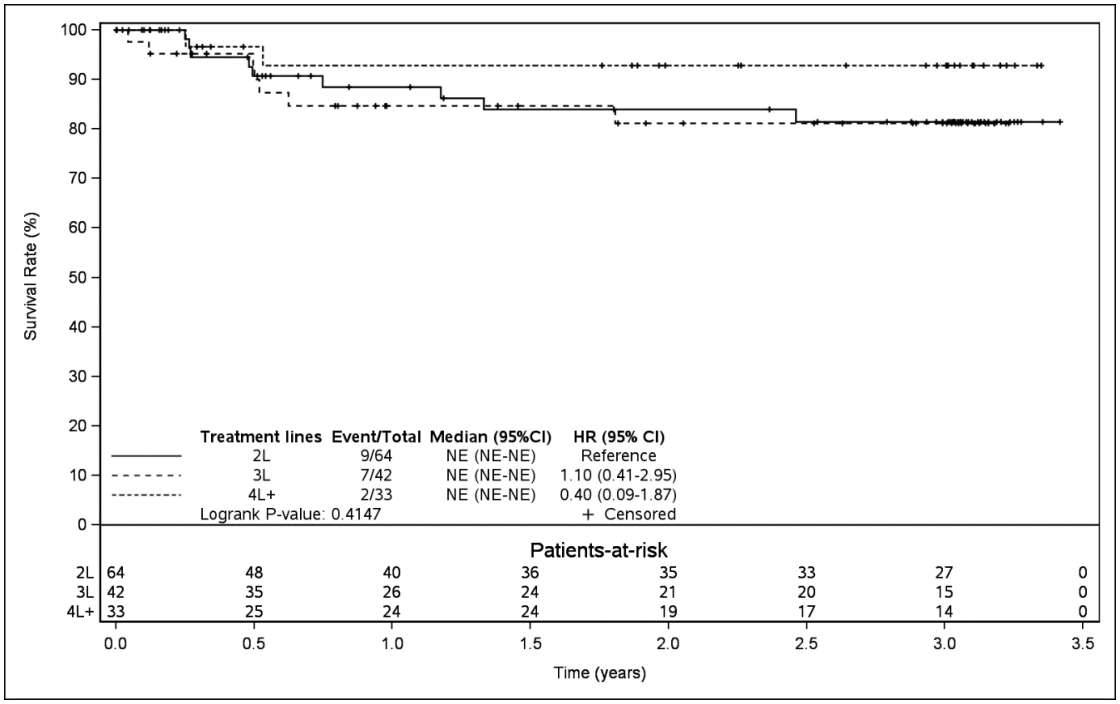


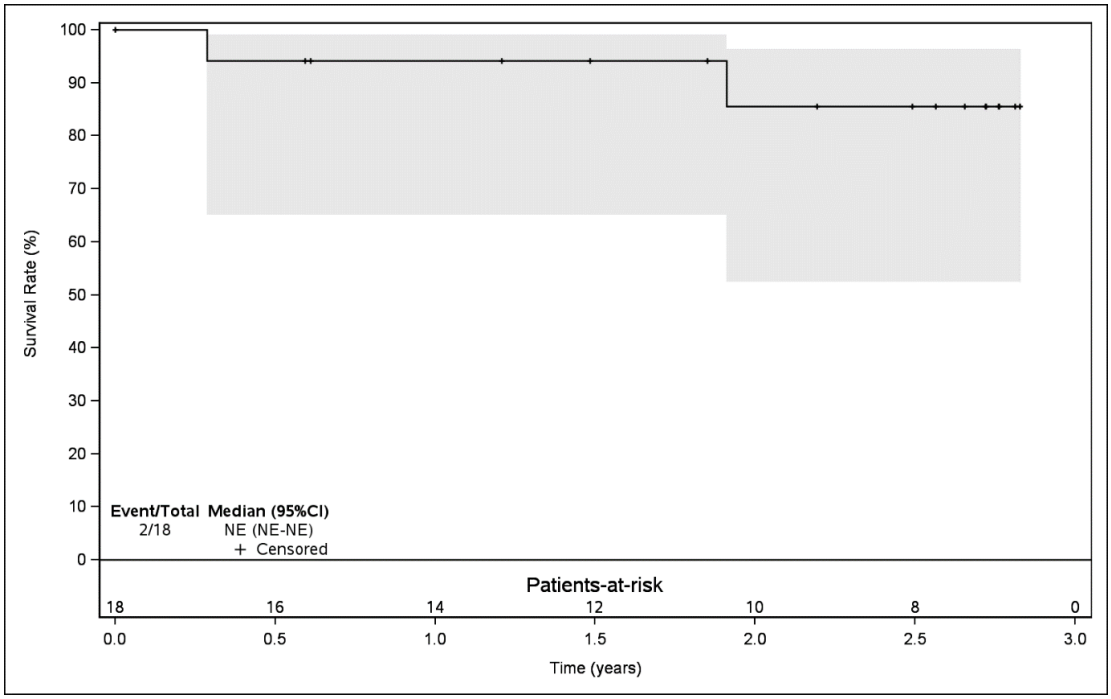
Table 120: Duration of cytogenetic Response - FAS (n=139)

Variables		2L (N=64)	3L (N=42)	4L+ (N=33)	Total (N=139)
Cumulative cytogenetic response (CyR)	No	55 (85.9%)	35 (83.3%)	31 (93.9%)	121 (87.1%)
	Yes	9 (14.1%)	7 (16.7%)	2 (6.1%)	18 (12.9%)
Event cytogenetic (duration of response)	No	8 (88.9%)	6 (85.7%)	2 (100%)	16 (88.9%)
	Yes	1 (11.1%)	1 (14.3%)	0 (0%)	2 (11.1%)
Event/censoring cytogenetic (duration of response)	Alive at end of follow-up or lost to follow-up	8 (88.9%)	6 (85.7%)	2 (100%)	16 (88.9%)
	Death while responding	0 (0%)	1 (14.3%)	0 (0%)	1 (5.6%)
	Disease progression	1 (11.1%)	0 (0%)	0 (0%)	1 (5.6%)

Timepoint	Real time	Survival	[CI95%]	Failure	Erreur type de survie	Number Failed	Number Left	Estimate
1 year	0.29	0.94	[0.65-0.99]	0.06	0.0571	1	14	
2 years	1.91	0.86	[0.52-0.96]	0.14	0.0967	2	10	
3 years	.				.	2	0	
Median [CI95%]	.				.	.	.	Not evaluable

Table 15.2.3b Duration of cytogenetic Response - FAS (n=139)

Figure 16: Duration of cytogenetic Response - FAS (n=139)



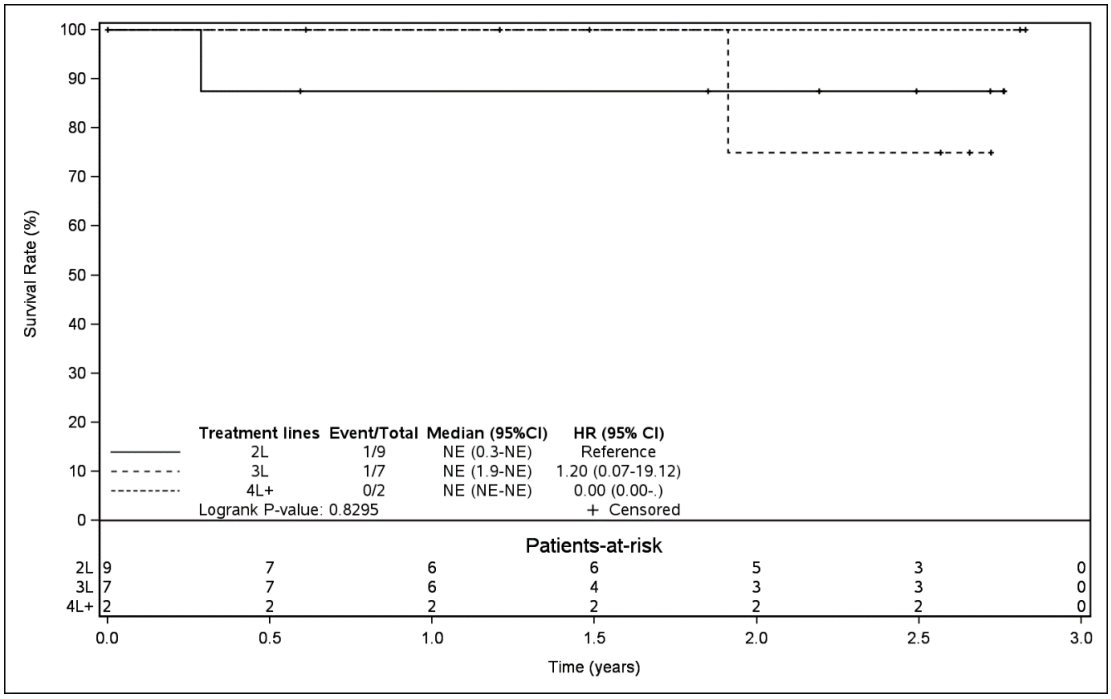


Table 121: Prognostic Factors for cytogenetic Response - Univariable analysis - FAS (n=139)

Variable	Comparison	Pvalue (ML)	OR [95%CI] (ML)	Number of observations used (%)
Age (years)		0.4339	0.99 [0.95-1.02]	139 (100%)
Sex	Male vs Female	0.3282	1.67 [0.61-5.05]	139 (100%)
Weight (kg)		0.4410	1.01 [0.98-1.04]	118 (84.9%)
Height (cm)		0.3316	1.03 [0.97-1.10]	134 (96.4%)
BMI (kg/m²)		0.6627	1.02 [0.93-1.12]	116 (83.5%)
ECOG score		0.6407		112 (80.6%)
ECOG score	1 vs 0	.	0.52 [0.11-1.89]	
ECOG score	2-3 vs 0	.	0.68 [0.03-4.31]	
BCR-ABL mutations		0.9178		139 (100%)
BCR-ABL mutations	BCR vs ABL	.	0.90 [0.13-3.75]	
BCR-ABL mutations	Oth vs ABL	.	0.76 [0.16-2.58]	
SOKAL score		**0.0993**		**126 (90.6%)**
SOKAL score	High vs Low	.	1.10 [0.15-5.57]	
SOKAL score	Intermediate vs Low	.	3.24 [1.06-11.14]	
Time between initial diagnosis and initiation of bosutinib treatment (years)		**0.0637**	**0.91 [0.79-1.00]**	**139 (100%)**
Bone marrow karyotype	**Yes vs No/Unknown**	**0.0295**	**Not evaluable**	**139 (100%)**
Rearrangement t(9,22) present	Yes vs No/Unknown	0.8624	1.20 [0.20-23.03]	139 (100%)
Concomitant medication	Yes vs No	0.4546	Not evaluable	139 (100%)
Number of concomitant medication		0.9700	1.00 [0.95-1.04]	139 (100%)
Antecedent or comorbidities	Yes vs No	0.4546	Not evaluable	139 (100%)

Variable	Comparison	Pvalue (ML)	OR [95%CI] (ML)	Number of observations used (%)
Number of antecedent or comorbidities		0.8659	1.01 [0.92-1.09]	139 (100%)
Treatment line		0.3984		139 (100%)
Treatment line	3L vs 2L	.	1.22 [0.40-3.58]	
Treatment line	4L+ vs 2L	.	0.39 [0.06-1.65]	
Last therapy		0.4002		139 (100%)
Last therapy	Dasatinib vs Imatinib	.	0.42 [0.11-1.31]	
Last therapy	Nilotinib vs Imatinib	.	0.37 [0.05-1.49]	
Last therapy	Ponatinib vs Imatinib	.	0.00 [NE-7.59]	
Hematological response in last line	Response vs No response/Unknown	0.2343	Not evaluable	139 (100%)
Cytogenetic response in last line	Response vs No response/Unknown	0.8098	1.17 [0.35-5.36]	139 (100%)
Molecular response in last line	**Response vs No response/Unknown**	**0.0044**	**0.23 [0.07-0.64]**	**139 (100%)**
Reason for change of line in last line		0.2164		139 (100%)
Reason for change of line in last line	Intolerance vs Lack of response	.	0.15 [0.02-1.23]	
Reason for change of line in last line	Loss of response vs Lack of response	.	0.32 [0.03-3.23]	
Reason for change of line in last line	Other, specify vs Lack of response	.	0.00 [NE-1.31]	
Reason for change of line in last line	Suboptimum response vs Lack of response	.	0.44 [0.06-4.05]	
Baseline: ALAT (UI/L)		0.6554	0.99 [0.94-1.03]	101 (72.7%)
Baseline: ASAT (UI/L)		0.5697	0.98 [0.92-1.04]	102 (73.4%)
Baseline: Total bilirubin (µmol/L)		0.3700	1.04 [0.95-1.15]	84 (60.4%)
Baseline: Conjugated bilirubin (µmol/L)		0.2907	1.27 [0.79-2.05]	20 (14.4%)
Baseline: LDH (UI/L)		0.4714	1.00 [1.00-1.01]	50 (36%)

Variable	Comparison	Pvalue (ML)	OR [95%CI] (ML)	Number of observations used (%)
Baseline: Albumin (g/L)		**0.0012**	**0.11 [0.00-0.68]**	**25 (18%)**
Baseline: Lipase (UI/L)		0.3716	0.99 [0.94-1.01]	27 (19.4%)
Baseline: Serum creatinine (µmol/L)		0.4519	1.01 [0.99-1.03]	103 (74.1%)
Baseline: Blood glucose (fasting) (mmol/L)		**0.0007**	**Not evaluable**	**18 (12.9%)**
Baseline: Blood glucose (non-fasting) (mmol/L)		**0.0587**	**1.14 [1.00-1.36]**	**31 (22.3%)**
Baseline: Magnesium (mmol/L)		0.9222	0.42 [0.00-14731237]	18 (12.9%)
Baseline: Calcium (mmol/L)		**0.0367**	**0.00 [0.00-0.69]**	**59 (42.4%)**
Baseline: Blood urea (mmol/L)		0.8416	0.98 [0.81-1.14]	81 (58.3%)
Baseline: Uric acid (µmol/L)		0.7567	1.00 [0.99-1.01]	42 (30.2%)
Baseline: Hemoglobin (g/dL)		0.9821	1.00 [0.79-1.32]	116 (83.5%)
Baseline: Hematocrit (%)		0.8620	0.99 [0.89-1.11]	115 (82.7%)
Baseline: Leukocytes (g/L)		0.8511	1.00 [0.95-1.04]	113 (81.3%)
Baseline: Platelets (g/L)		0.1649	1.00 [1.00-1.00]	111 (79.9%)
Baseline: Blasts (peripheral blood) (%)		0.3522	0.00 [NE-2.10]	41 (29.5%)
Baseline: Basophils (g/L)		**0.0155**	**1.62 [1.10-2.52]**	**116 (83.5%)**
Baseline: Eosinophils (g/L)		0.8542	0.98 [0.73-1.14]	116 (83.5%)
Baseline: Neutrophils (g/L)		**0.0178**	**1.02 [1.00-1.04]**	**116 (83.5%)**
Baseline: Monocytes (g/L)		0.1662	1.09 [0.96-1.24]	115 (82.7%)
Baseline: Lymphocytes (g/L)		**0.0400**	**1.04 [1.00-1.07]**	**116 (83.5%)**

Table 15.2.4c Prognostic Factors for cytogenetic Response - Univariable analysis - FAS (n=139)

Table 122: Prognostic Factors for cytogenetic Response - Multivariable analysis (effects removed) - FAS (n=139)

Step	Effect deleted	Pvalue (Wald)
1	Bone marrow karyotype	0.9668
2	Time between initial diagnosis and initiation of bosutinib treatment (years)	0.8988
3	Baseline: Neutrophils (g/L)	0.7884
4	Baseline: Basophils (g/L)	0.2008
5	SOKAL score	0.0860

Table 15.2.4d Prognostic Factors for cytogenetic Response - Multivariable analysis (effects removed) - FAS (n=139)

Table 123: Prognostic Factors for cytogenetic Response - Multivariable analysis - FAS (n=139)

Number of observations used (%)	Variable	Comparison	Pvalue (Wald)	OR [95%CI]
116 (83.5%)	Molecular response in last line	Response vs No response/Unknown	0.0010	0.10 [0.02-0.36]
	Baseline: Lymphocytes (g/L)		0.0135	1.05 [1.01-1.10]

Table 15.2.4e Prognostic Factors for cytogenetic Response - Multivariable analysis - FAS (n=139)

Appendix 7.15 Follow-up duration analyses

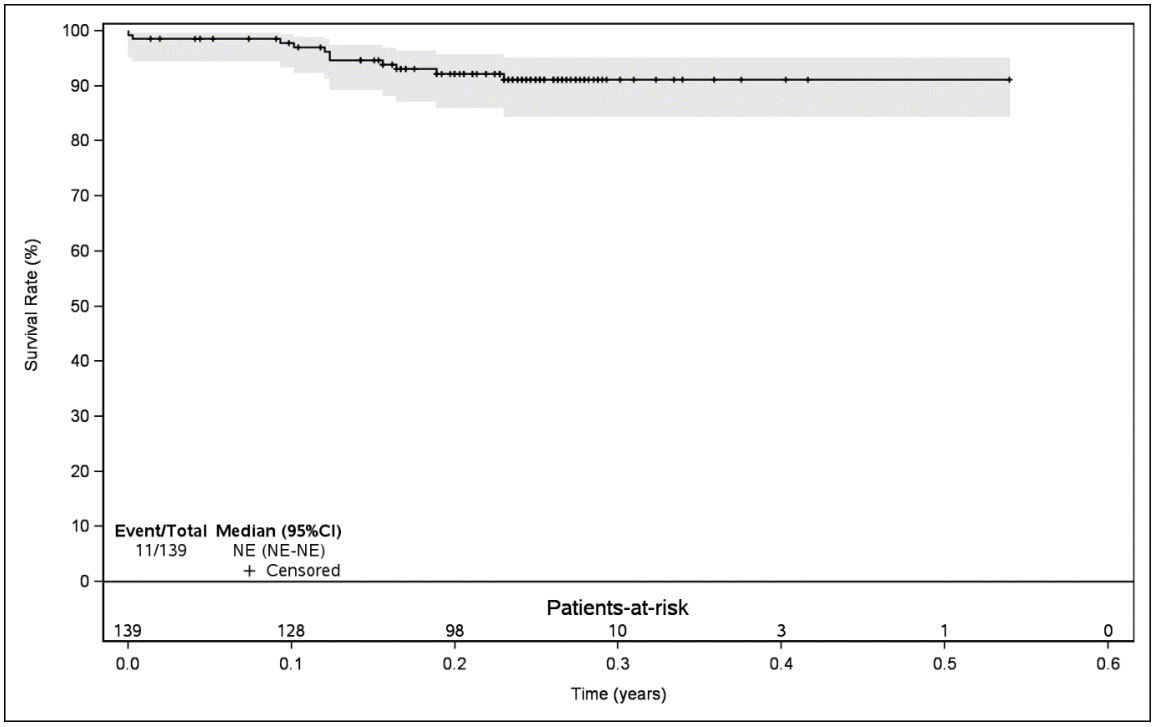
Table 124: Follow-up duration (reverse Time-to-hematological Response) - FAS (n=139)

Variables		2L (N=64)	3L (N=42)	4L+ (N=33)	Total (N=139)
Event hematological (follow-up duration)	No	56 (87.5%)	41 (97.6%)	31 (93.9%)	128 (92.1%)
	Yes	8 (12.5%)	1 (2.4%)	2 (6.1%)	11 (7.9%)
Event/censoring hematological (follow-up duration)	Permanent discontinuation of bosutinib	8 (12.5%)	1 (2.4%)	2 (6.1%)	11 (7.9%)
	Response to bosutinib (all types)	56 (87.5%)	41 (97.6%)	31 (93.9%)	128 (92.1%)

Timepoint	Real time	Survival [CI95%]	Failure	Erreur type de survie	Number Failed	Number Left	Estimate
1 year	.		.		11	0	
2 years	.		.		11	0	
3 years	.		.		11	0	
Mean +/- Std	.		.		.	.	0.22 +/- 0
Median [CI95%]	.		.		.	.	Not evaluable

Table 15.2.2d Follow-up duration (reverse Time-to-hematological Response) - FAS (n=139)

Figure 17: Follow-up duration (reverse Time-to-hematological Response) - FAS (n=139)



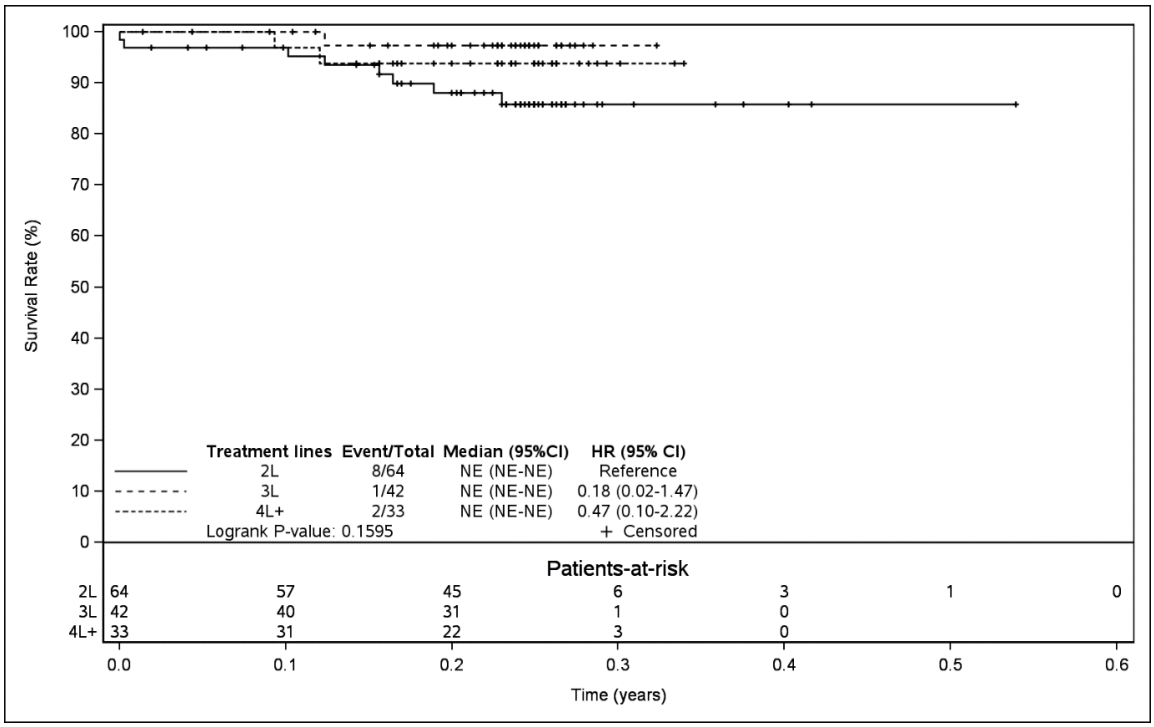


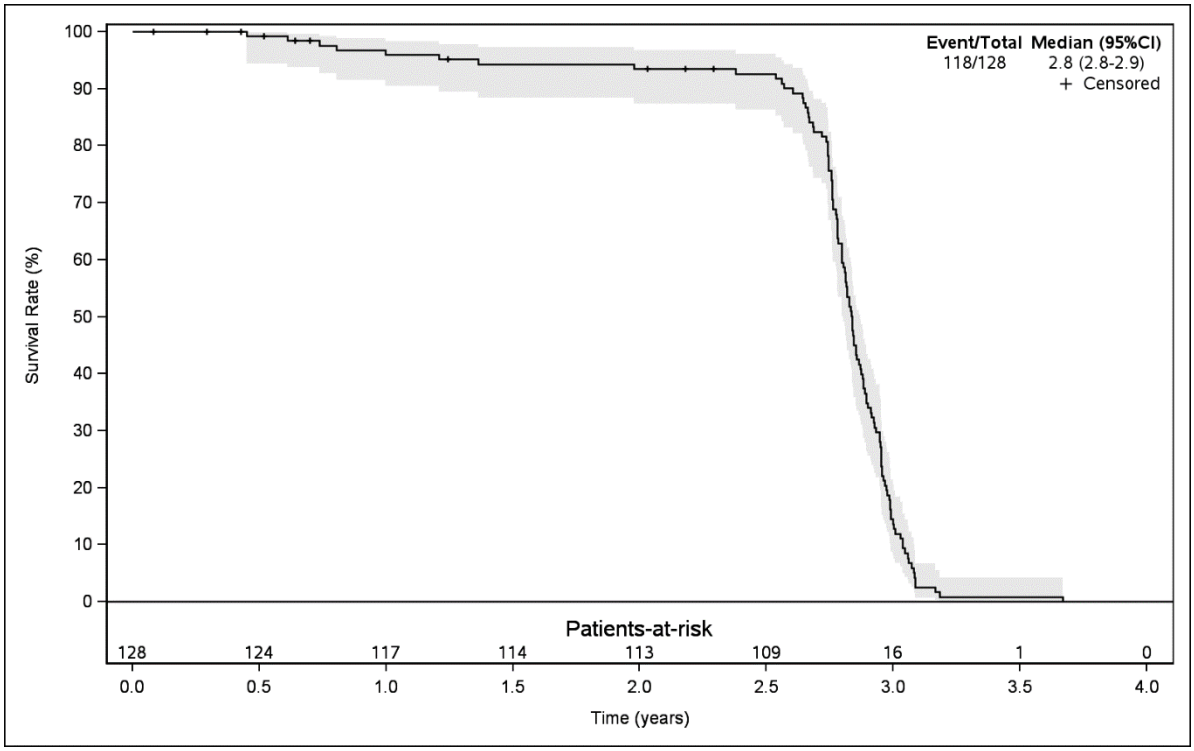
Table 125: Follow-up duration (reverse Duration of hematological Response) - FAS (n=139)

Variables		2L (N=64)	3L (N=42)	4L+ (N=33)	Total (N=139)
Cumulative hematological response	No	8 (12.5%)	1 (2.4%)	2 (6.1%)	11 (7.9%)
	Yes	56 (87.5%)	41 (97.6%)	31 (93.9%)	128 (92.1%)
Event hematological (duration of response)	No	4 (7.1%)	2 (4.9%)	4 (12.9%)	10 (7.8%)
	Yes	52 (92.9%)	39 (95.1%)	27 (87.1%)	118 (92.2%)
Event/censoring hematological (duration of response)	Alive at end of follow-up or lost to follow-up	52 (92.9%)	39 (95.1%)	27 (87.1%)	118 (92.2%)
	Death while responding	0 (0%)	1 (2.4%)	2 (6.5%)	3 (2.3%)
	Disease progression	4 (7.1%)	0 (0%)	1 (3.2%)	5 (3.9%)
	Loss of response	0 (0%)	1 (2.4%)	1 (3.2%)	2 (1.6%)

Timepoint	Real time	Survival	[CI95%]	Failure	Erreur type de survie	Number Failed	Number Left	Estimate
1 year	1	0.96	[0.91-0.98]	0.04	0.0178	5	117	
2 years	1.98	0.93	[0.87-0.97]	0.07	0.0224	8	113	
3 years	3	0.14	[0.08-0.2]	0.86	0.0316	102	16	
Mean +/- Std	.				.	.	.	2.74 +/- 0.04
Median [CI95%]	.				.	.	.	2.84 [2.8-2.87]

Table 15.2.3d Follow-up duration (reverse Duration of hematological Response) - FAS (n=139)

Figure 18: Follow-up duration (reverse Duration of hematological Response) - FAS (n=139)



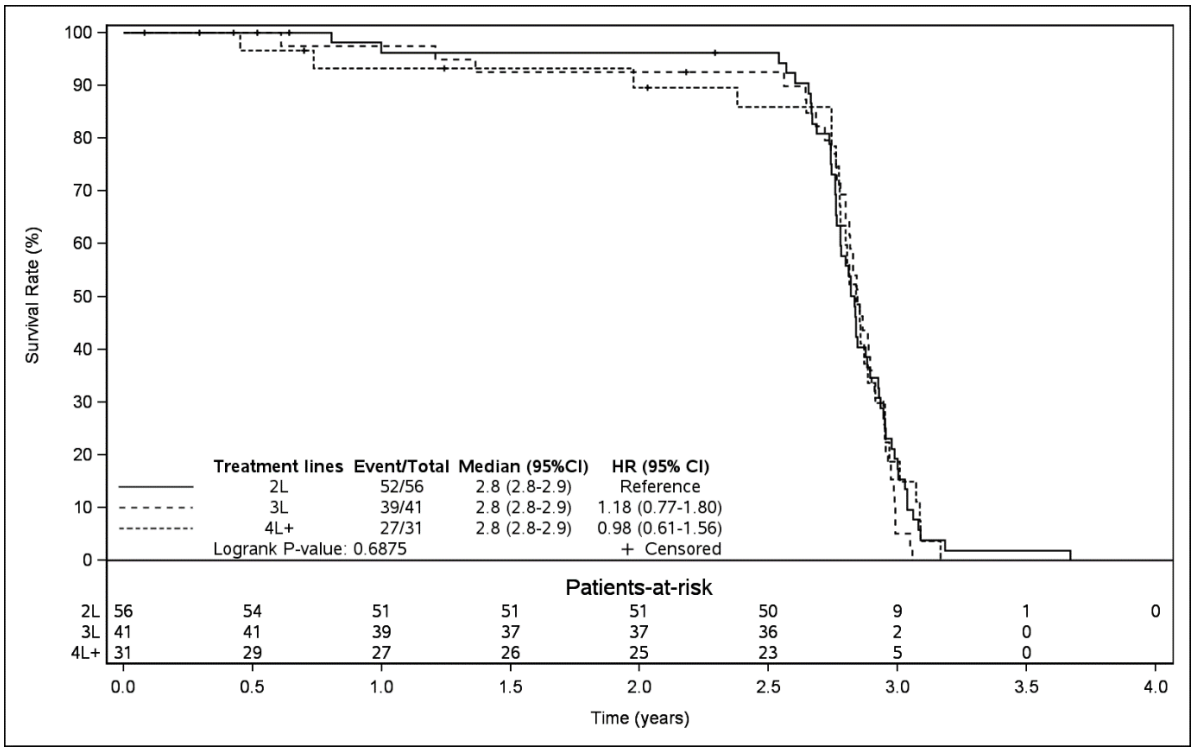


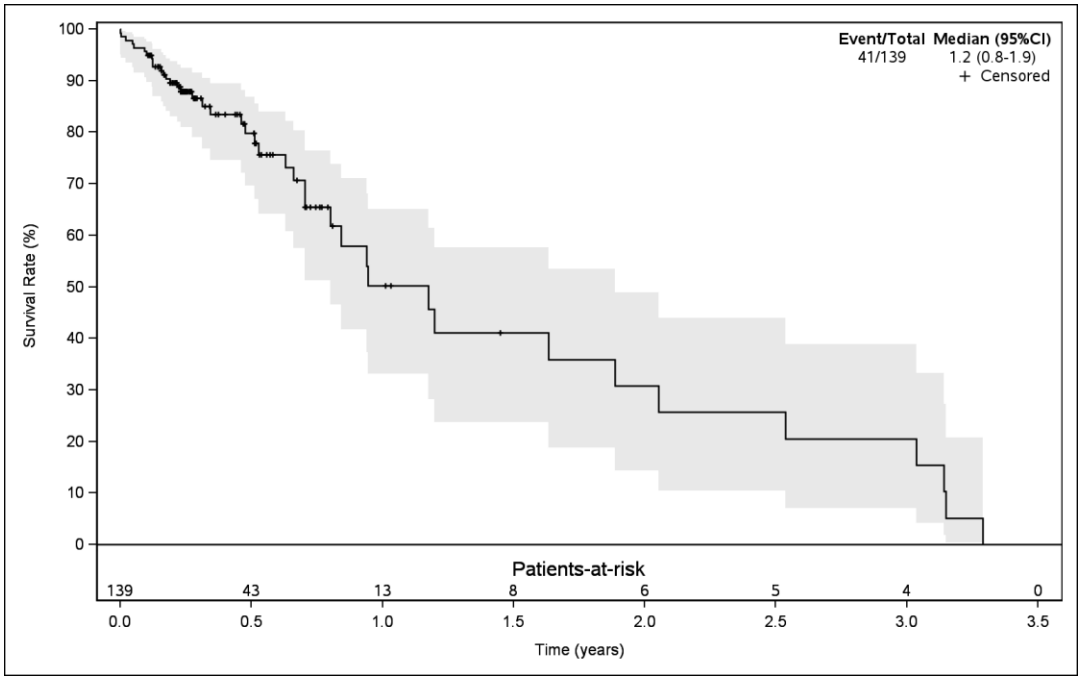
Table 126: Follow-up duration (reverse Time-to-molecular Response) - FAS (n=139)

Variables		2L (N=64)	3L (N=42)	4L+ (N=33)	Total (N=139)
Event molecular (follow-up duration)	No	43 (67.2%)	31 (73.8%)	24 (72.7%)	98 (70.5%)
	Yes	21 (32.8%)	11 (26.2%)	9 (27.3%)	41 (29.5%)
Event/censoring molecular (follow-up duration)	Death during bosutinib	0 (0%)	0 (0%)	2 (6.1%)	2 (1.4%)
	Lost to follow-up	1 (1.6%)	1 (2.4%)	1 (3%)	3 (2.2%)
	Permanent discontinuation of bosutinib	20 (31.3%)	10 (23.8%)	6 (18.2%)	36 (25.9%)
	Response to bosutinib (all types)	43 (67.2%)	31 (73.8%)	24 (72.7%)	98 (70.5%)

Timepoint	Real time	Survival	[CI95%]	Failure	Erreur type de survie	Number Failed	Number Left	Estimate
1 year	0.94	0.50	[0.33-0.65]	0.50	0.0831	31	13	
2 years	1.89	0.31	[0.14-0.49]	0.69	0.0920	35	6	
3 years	2.54	0.21	[0.07-0.39]	0.79	0.0853	37	4	
Mean +/- Std	.				.	.	.	1.44 +/- 0.19
Median [CI95%]	.				.	.	.	1.17 [0.8-1.89]

Figure 15.2.2f Follow-up duration (reverse Time-to-molecular Response) - FAS (n=139)

Figure 19: Follow-up duration (reverse Time-to-molecular Response) - FAS (n=139)



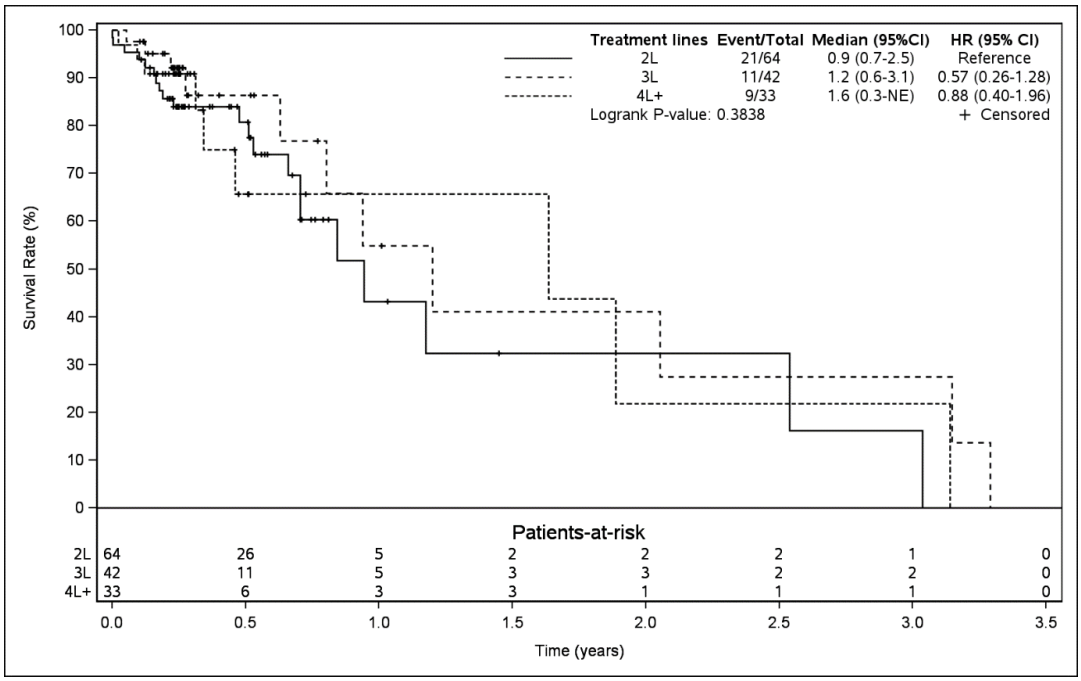


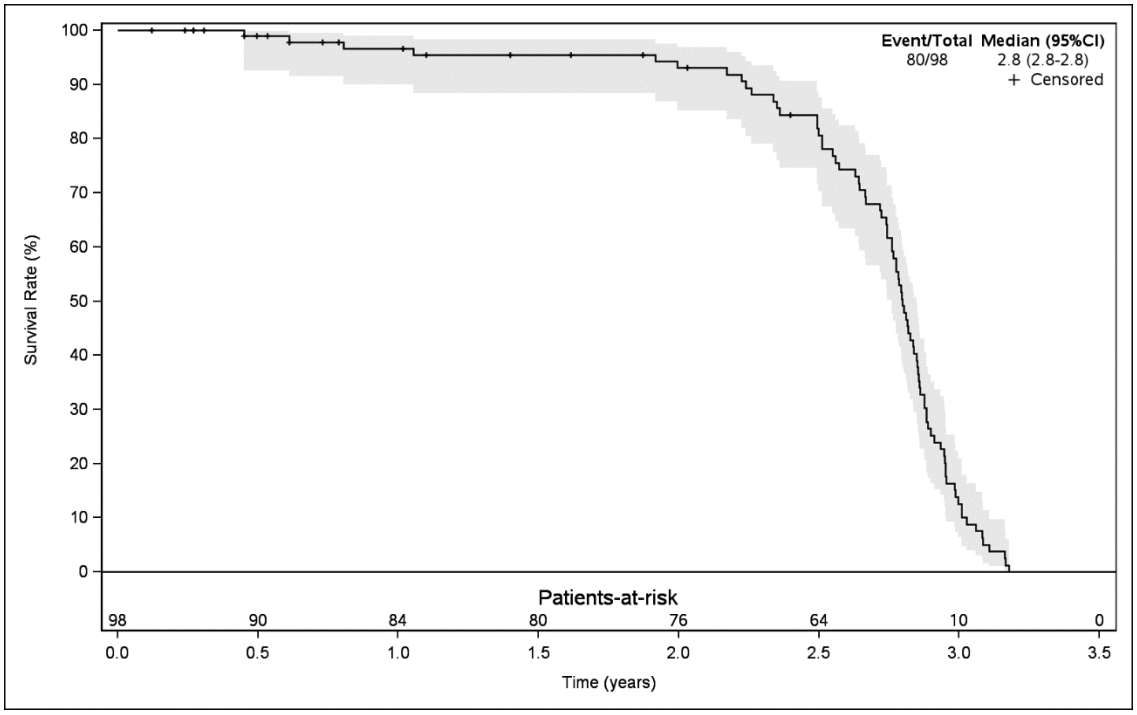
Table 127: Follow-up duration (reverse Duration of molecular Response) - FAS (n=139)

Variables		2L (N=64)	3L (N=42)	4L+ (N=33)	Total (N=139)
Cumulative molecular response	No	21 (32.8%)	11 (26.2%)	9 (27.3%)	41 (29.5%)
	Yes	43 (67.2%)	31 (73.8%)	24 (72.7%)	98 (70.5%)
Event molecular (duration of response)	No	11 (25.6%)	4 (12.9%)	3 (12.5%)	18 (18.4%)
	Yes	32 (74.4%)	27 (87.1%)	21 (87.5%)	80 (81.6%)
Event/censoring molecular (duration of response)	Alive at end of follow-up or lost to follow-up	32 (74.4%)	27 (87.1%)	21 (87.5%)	80 (81.6%)
	Death while responding	0 (0%)	0 (0%)	1 (4.2%)	1 (1%)
	Loss of response	11 (25.6%)	4 (12.9%)	2 (8.3%)	17 (17.3%)

Timepoint	Real time	Survival	[CI95%]	Failure	Erreur type de survie	Number Failed	Number Left	Estimate
1 year	0.8	0.97	[0.9-0.99]	0.03	0.0190	3	84	
2 years	2	0.93	[0.85-0.97]	0.07	0.0274	6	76	
3 years	3	0.13	[0.06-0.21]	0.87	0.0372	70	10	
Mean +/- Std	.				.	.	.	2.67 +/- 0.05
Median [CI95%]	.				.	.	.	2.8 [2.76-2.85]

Table 15.2.3f Follow-up duration (reverse Duration of molecular Response) - FAS (n=139)

Figure 20: Follow-up duration (reverse Duration of molecular Response) - FAS (n=139)



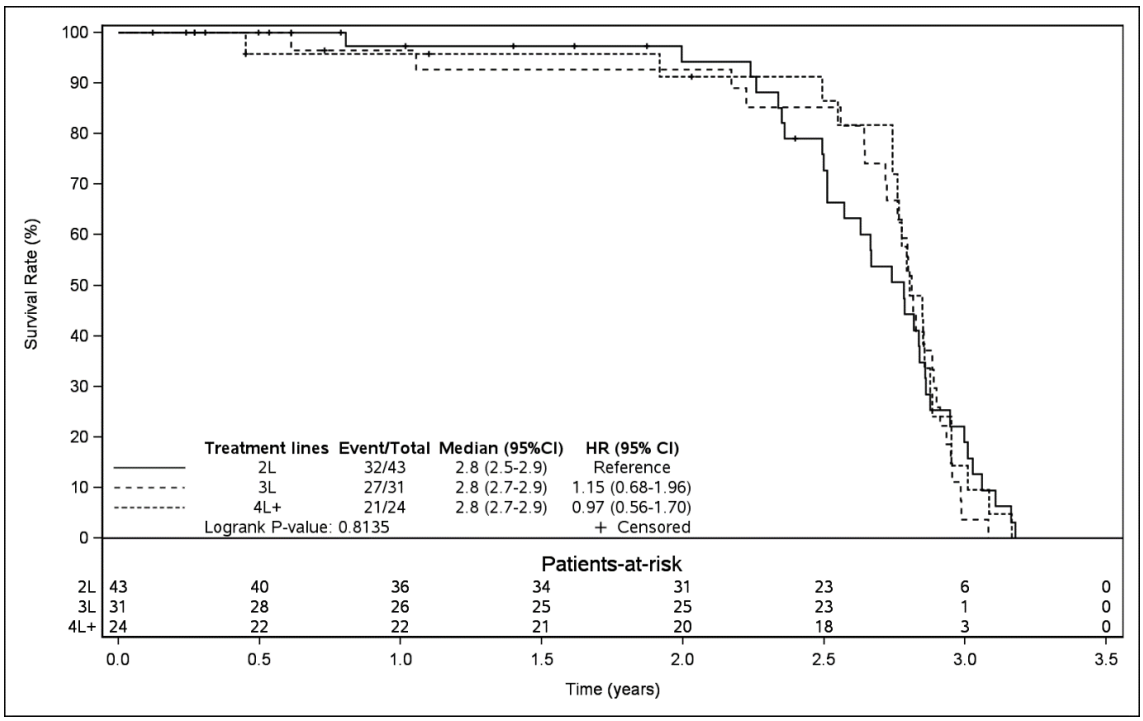


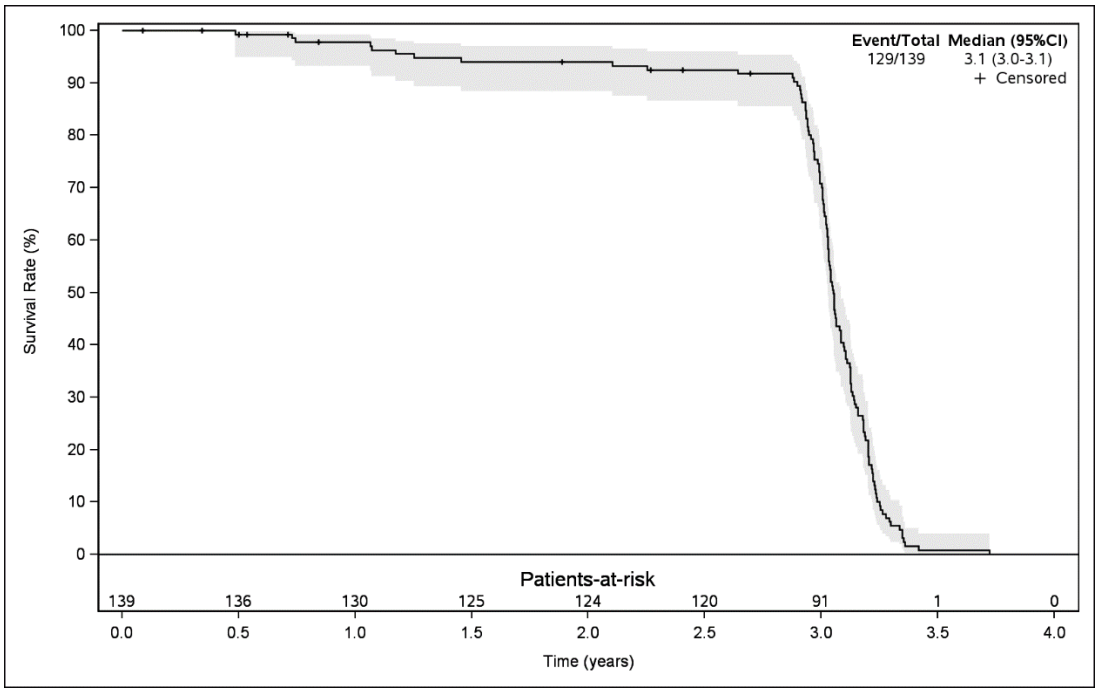
Table 128: Follow-up duration (reverse Progression Free Survival) - FAS (n=139)

Variables		2L (N=64)	3L (N=42)	4L+ (N=33)	Total (N=139)
Event Progression Free Survival (PFS)	No	5 (7.8%)	1 (2.4%)	4 (12.1%)	10 (7.2%)
	Yes	59 (92.2%)	41 (97.6%)	29 (87.9%)	129 (92.8%)
Event/censoring Progression Free Survival (PFS)	Alive at end of follow-up or lost to follow-up	59 (92.2%)	41 (97.6%)	29 (87.9%)	129 (92.8%)
	Death after permanent discontinuation treatment	1 (1.6%)	1 (2.4%)	1 (3%)	3 (2.2%)
	Death during bosutinib	0 (0%)	0 (0%)	2 (6.1%)	2 (1.4%)
	Disease progression after permanent discontinuation treatment	0 (0%)	0 (0%)	1 (3%)	1 (0.7%)
	Disease progression during bosutinib	4 (6.3%)	0 (0%)	0 (0%)	4 (2.9%)

Timepoint	Real time	Survival	[CI95%]	Failure	Erreur type de survie	Number Failed	Number Left	Estimate
1 year	0.74	0.98	[0.93-0.99]	0.02	0.0127	3	130	
2 years	1.45	0.94	[0.88-0.97]	0.06	0.0205	8	124	
3 years	2.99	0.71	[0.62-0.78]	0.29	0.0400	38	91	
Mean +/- Std	.				.	.	.	2.95 +/- 0.05
Median [CI95%]	.				.	.	.	3.05 [3.03-3.09]

Table 15.2.6b Follow-up duration (reverse Progression Free Survival) - FAS (n=139)

Figure 21: Follow-up duration (reverse Progression Free Survival) - FAS (n=139)



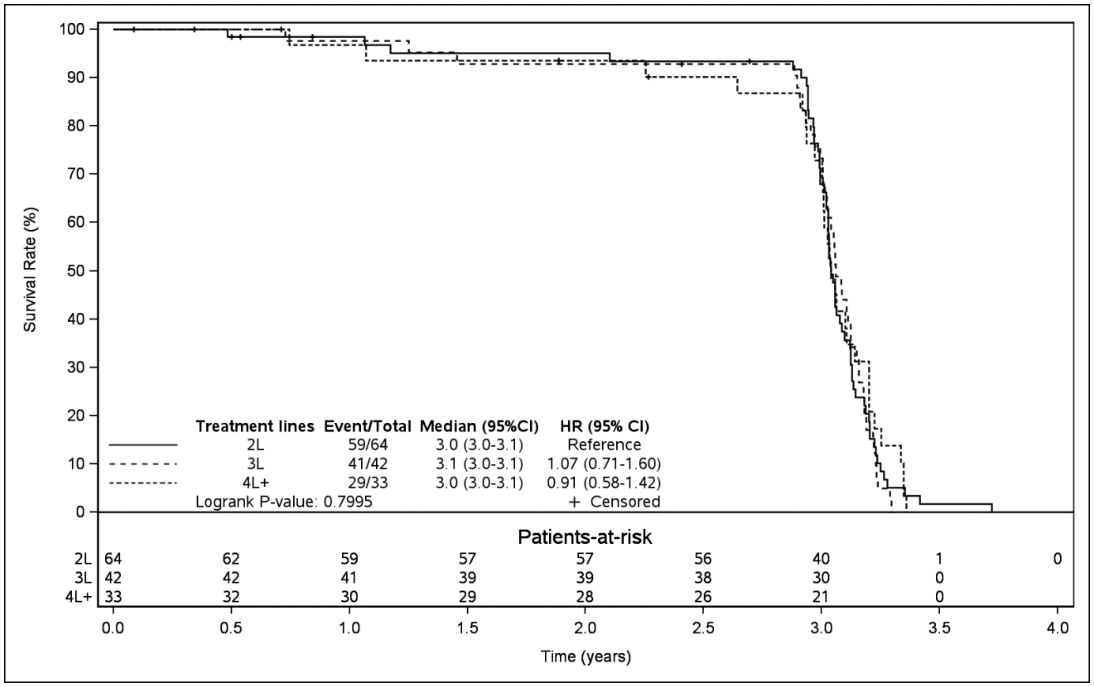


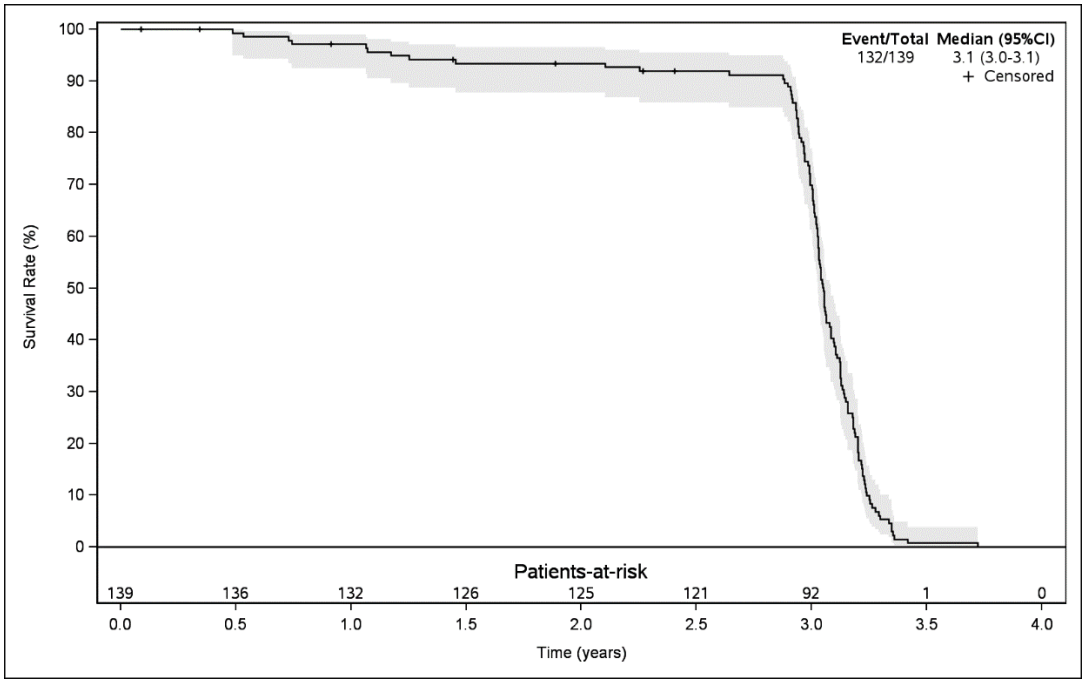
Table 129: Follow-up duration (reverse Overall Survival) - FAS (n=139)

Variables		2L (N=64)	3L (N=42)	4L+ (N=33)	Total (N=139)
Event Overall Survival (OS)	No	2 (3.1%)	1 (2.4%)	4 (12.1%)	7 (5%)
	Yes	62 (96.9%)	41 (97.6%)	29 (87.9%)	132 (95%)
Event/censoring Overall Survival (OS)	Alive at end of follow-up or lost to follow-up	62 (96.9%)	41 (97.6%)	29 (87.9%)	132 (95%)
	Death after permanent discontinuation treatment	2 (3.1%)	1 (2.4%)	2 (6.1%)	5 (3.6%)
	Death during bosutinib	0 (0%)	0 (0%)	2 (6.1%)	2 (1.4%)

Timepoint	Real time	Survival	[CI95%]	Failure	Erreur type de survie	Number Failed	Number Left	Estimate
1 year	0.74	0.97	[0.92-0.99]	0.03	0.0144	4	132	
2 years	1.45	0.93	[0.88-0.97]	0.07	0.0213	9	125	
3 years	2.99	0.70	[0.61-0.77]	0.30	0.0399	40	92	
Mean +/- Std	.				.	.	.	2.94 +/- 0.05
Median [CI95%]	.				.	.	.	3.05 [3.03-3.09]

Table 15.2.7b Follow-up duration (reverse Overall Survival) - FAS (n=139)

Figure 22: Follow-up duration (reverse Overall Survival) - FAS (n=139)



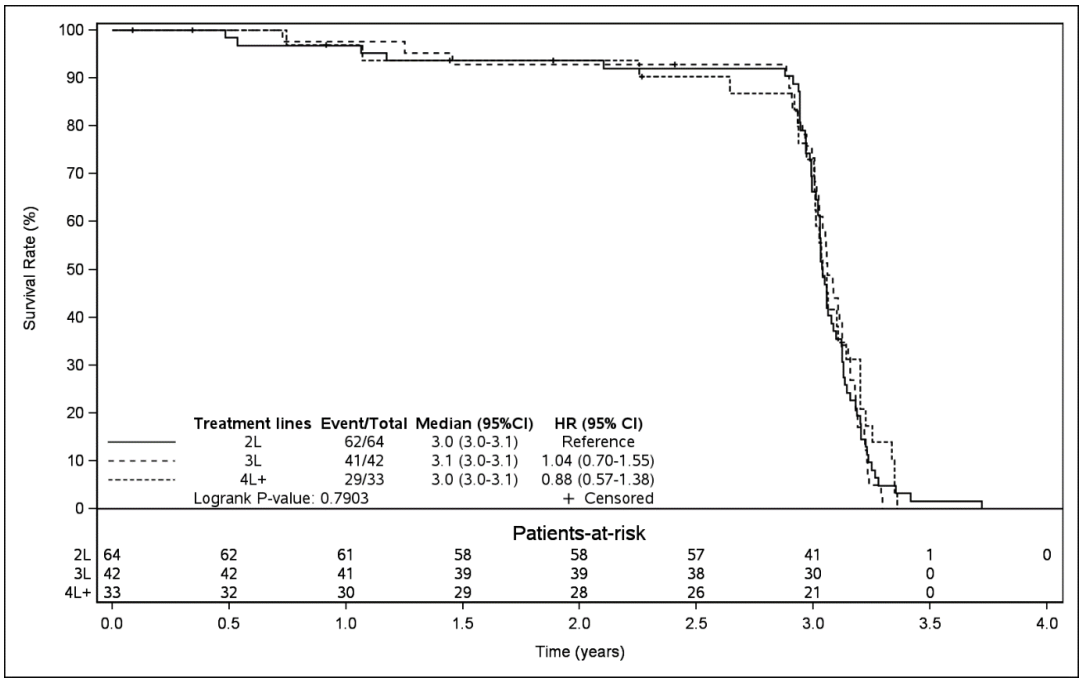


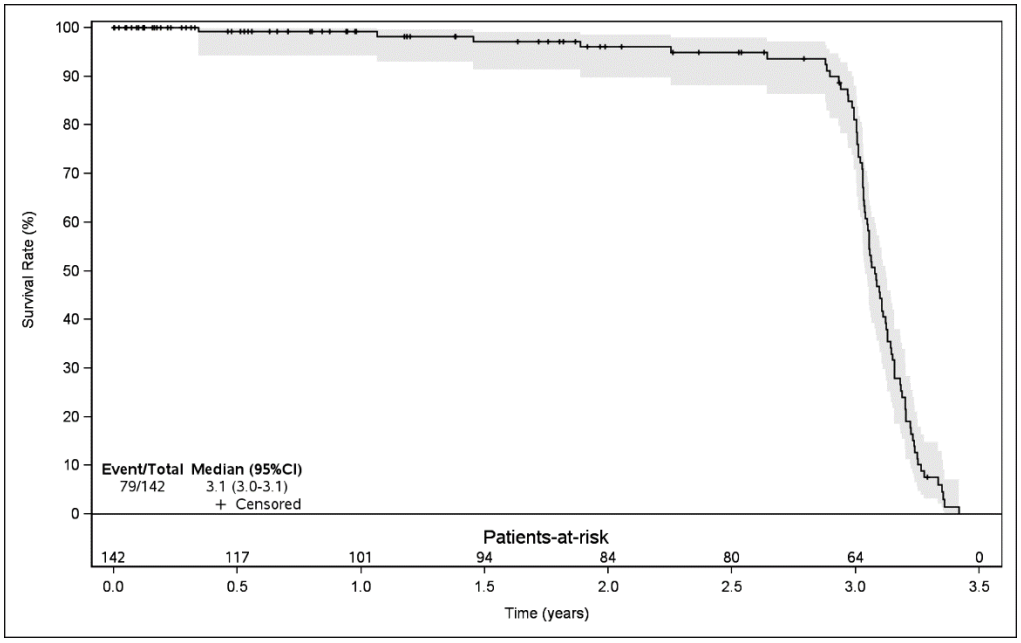
Table 130: Follow-up duration (reverse Time-to-Treatment Failure) - SAF (n=142)

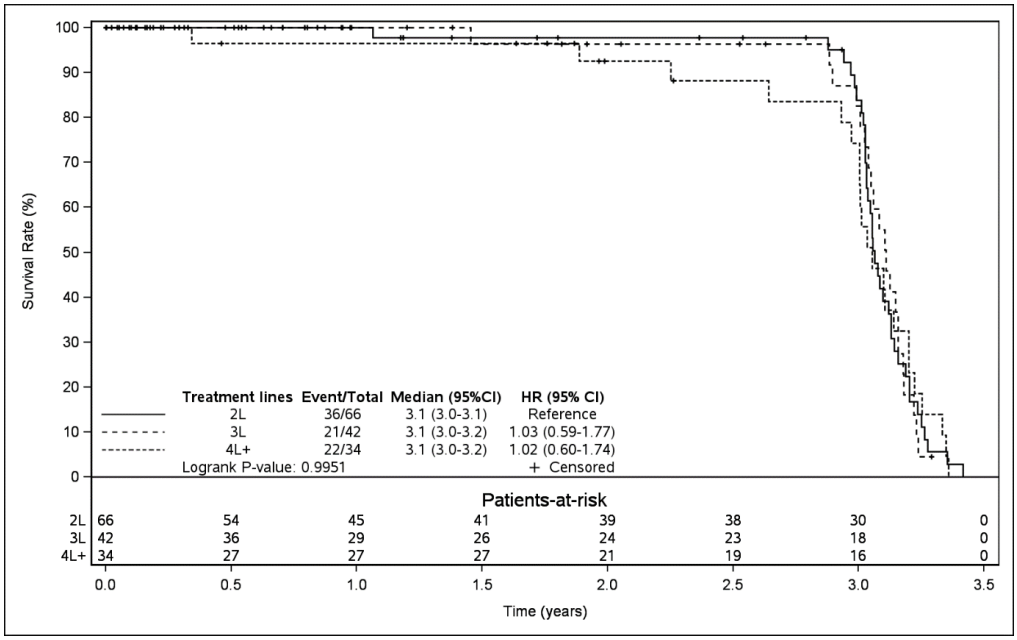
Variables		2L (N=66)	3L (N=42)	4L+ (N=34)	Total (N=142)
Event Time to treatment failure (TTF)	No	30 (45.5%)	21 (50%)	12 (35.3%)	63 (44.4%)
	Yes	36 (54.5%)	21 (50%)	22 (64.7%)	79 (55.6%)
Event/censoring Time to treatment failure (TTF)	Alive and treated with bosutinib	36 (54.5%)	21 (50%)	20 (58.8%)	77 (54.2%)
	Death during bosutinib	0 (0%)	0 (0%)	2 (5.9%)	2 (1.4%)
	Permanent Bosutinib discontinuation (all causes)	30 (45.5%)	21 (50%)	12 (35.3%)	63 (44.4%)

Timepoint	Real time	Survival	[CI95%]	Failure	Erreur type de survie	Number Failed	Number Left	Estimate
1 year	0.34	0.99	[0.94-1]	0.01	0.00830	1	101	
2 years	1.89	0.96	[0.9-0.99]	0.04	0.0195	4	84	
3 years	2.99	0.81	[0.71-0.88]	0.19	0.0430	16	64	
Mean +/- Std	.				.	.	.	3.02 +/- 0.04
Median [CI95%]	.				.	.	.	3.08 [3.04-3.12]

Table 15.3.2b Follow-up duration (reverse Time-to-Treatment Failure) - SAF (n=142)

Figure 23: Follow-up duration (reverse Time-to-Treatment Failure) - SAF (n=142)





APPENDIX 8. Suspect AEs and SAEs reports

This study report contains narratives printed in a CIOMS format with a “Draft” watermark. This watermark signifies that these narratives were not produced for the submission of individual case

safety reports to a regulatory agency. The narratives contain the information available at the time of database lock and are considered final. CIOMS are provided into a separate document.