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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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
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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4. 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:	**<u>Criteria for inclusion</u>:** • 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. <u>Criteria for non-inclusion</u>: • 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 ~~i~~nterventional 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 $\alpha = 5\%$. 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.

5. AMENDMENTS AND UPDATES

All substantial amendments to the protocol, including a brief description of the reason for each amendment, the dates of each of the changes and a reference to the section of the protocol targeted by the change are listed in the following table. The amendments are

numbered consecutively. Updates performed by PACL (Protocol Administrative Change Letter) will be described in the table if and when a substantial amendment then is added.

A substantial amendment is a change that may have an impact on the safety of use and physical or psychological well-being of participants in the study or which can affect results of the study and their interpretation, for example, changes to the primary or secondary objectives of the study, the study population, the study design, the source of the data, the method of collection of data, the sample size, definitions of principal exposure, results and confounding factors, as well as the analytical plan as described in the protocol.

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.	

6. 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

7. RATIONALE AND GENERAL CONSIDERATIONS

7.1. 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].

7.2. 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.

7.3. 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.

7.4. 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.

8. 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.

8.1. 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.

8.2. 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.

9. STUDY METHODS

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

9.1. 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.

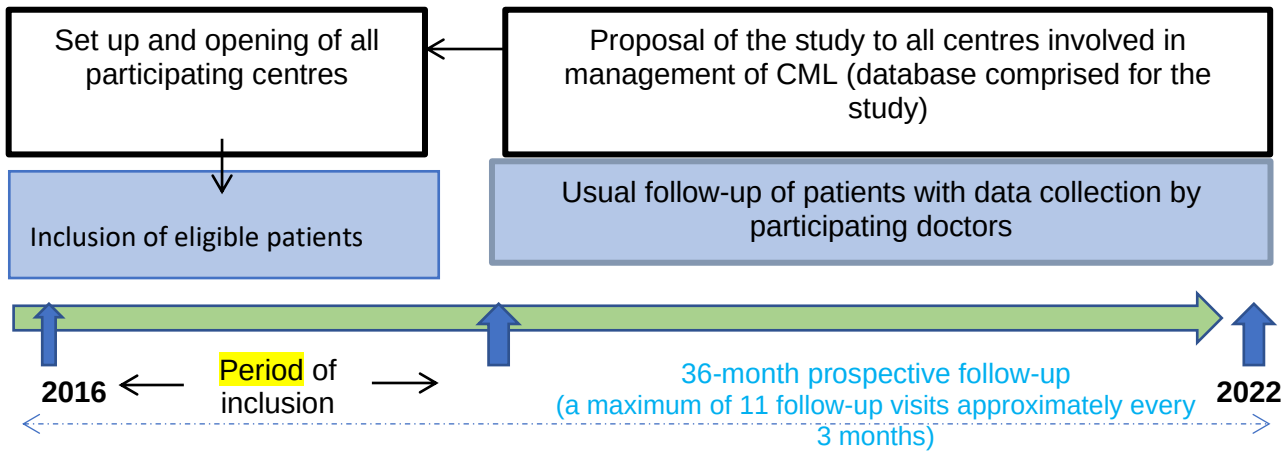
The study will be offered to the totality of patients who satisfy criteria for inclusion and for non-inclusion up to the end of the inclusion period defined as 4 years. About one hundred

(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 1 – Overall study flowchart



9.2. 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*).

9.2.1. 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.

9.2.2. 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.

9.3. 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.

9.4. 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.

9.4.1. 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:	**M0**	**M3**	**M6**	**M9**	**M12**	**M15**	**M18**	**M21**	**M24**	**M27**	**M30**	**M33**	**M36**
Visits completed by the doctor (eCRF)													
Inclusion	**x**												

visit													
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**

9.4.1.1. Inclusion visit

Patients included will undergo collection of medical data indirectly by name (patients' questionnaires completed by the doctor *via* the eCRF).

9.4.1.2. 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.

9.4.1.3. 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

9.4.1.4. 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).

9.4.1.5. 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 **Erreur ! Source du renvoi introuvable.**.

9.4.1.6. 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 **Erreur ! Source du renvoi introuvable.Erreur ! Source du renvoi introuvable.**).

9.4.1.7. Registry of non-inclusion:

Patients eligible but not included must be recorded in a non-inclusion registry (*see ANNEX 3.7: Registry of non-inclusion),* with a minimum of parameters collected:

- Demographic characteristics (year of birth, gender),
- Reason for non-inclusion.

9.5. 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):

- $\leqslant$ 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.

9.6. 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.

9.6.1. 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.

9.6.1.1. 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.

9.6.1.2. 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.

9.6.1.3. 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.

9.6.1.4. 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.

9.6.1.5. 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.

9.6.1.6. 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.

9.7. 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.

9.7.1. 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.

9.7.2. 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.

9.7.3. 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

Response rate for patients in CP, AP or BP according to treatment line:

- 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 $> 20 \times 10^9/L$ 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.

9.7.4. 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.

9.8. Quality control

9.8.1. 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.

9.8.2. 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 **Erreur ! Source du renvoi introuvable.**)

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.

9.8.3. 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.

9.9. 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.

9.9.1. 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.

9.9.2. 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.

9.9.3. 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.

9.9.4. 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.

9.10. 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.

10. PROTECTION OF PATIENTS

10.1. 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.

10.2. 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.

10.3. 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.

10.4. 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).

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.

At the end of this 5-year period, it will be submitted to another examination by the Ethics Committee and, if applicable, by the National Agency for Medicines and Health Products Safety under conditions stipulated by the Public Health Code.

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.

10.5. 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).

10.6. 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.

10.7. 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

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

11.1. 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.

11.2. 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

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
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.

11.3. 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.

11.4. 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.

11.5. Definition of an adverse event

11.5.1. 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.

<u>Abnormal test results</u>

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.

11.5.2. 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)

11.6. 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.

Exposure during pregnancy (or exposure in utero)

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.

<u>Exposure during lactation</u>

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.

12. PLANS FOR DISCLOSURE AND COMMUNICATION OF RESULTS OF STUDY

12.1. 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.

12.2. Ownership of data

Pfizer will retain ownership of all forms of case reports, data analyses and reports which result from the study.

12.3. 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.

12.4. 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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14. LIST OF TABLES

15. LIST OF FIGURES

ANNEX 1. LIST OF INDEPENDENT DOCUMENTS

Number	Document reference number	Date	Title
1	3.0	15-FEB-2019	Information leaflet and patient consent
2	2.0	15-FEB-2019	Case report forms

ANNEX 2. ENCePP CHECKLIST FOR STUDY PROTOCOLS

Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 2, amended)

Adopted by the ENCePP Steering Group on 14/01/2013

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmaco-epidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the page number(s) of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorization holders when submitting the protocol of a non-interventional post-authorization safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorization safety studies). Note, the Checklist is a supporting document and does not replace the format of the protocol for PASS as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:

Study reference number:

Section 1: Milestones	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the protocol specify timelines for 1.1.1 Start of data collection[1]	☐	☐	☐	

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.

Section 1: Milestones	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1.2 End of data collection[2]	☐	☐	☐	
1.1.3 Study progress report(s)	☐	☐	☐	
1.1.4 Interim progress report(s)	☐	☐	☐	
1.1.5 Registration in the EU PAS register	☐	☐	☐	
1.1.6 Final report of study results.	☐	☐	☐	

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☐	☐	☐	
2.1.2 The objective(s) of the study?	☐	☐	☐	
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalized)	☐	☐	☐	
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☐	☐	☐	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☐	

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Is the study design described? (e.g. cohort, case-control, randomized controlled trial, new or alternative design)	☐	☐	☐	
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☐	☐	☐	
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☐	☐	☐	

Comments:

[2] Date from which the analytical dataset is completely available.

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☐	☐	☐	
4.2 Is the planned study population defined in terms of:	☐	☐	☐	
4.2.1 Study time period?	☐	☐	☐	
4.2.2 Age and sex?	☐	☐	☐	
4.2.3 Country of origin?	☐	☐	☐	
4.2.4 Disease/indication?	☐	☐	☐	
4.2.5 Co-morbidity?	☐	☐	☐	
4.2.6 Seasonality?				
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☐	☐	☐	

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorizing exposure)	☐	☐	☐	
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☐	☐	☐	
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☐	☐	☐	
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☐	
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☐	☐	

Comments:

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
6.1 Does the protocol describe how the endpoints are defined and measured?	☐	☐	☐	

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☐	☐	☐	

Comments:

Section 7: Confounders and effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.1 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☐	☐	☐	
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☐	☐	☐	

Comments:

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☐	☐	☐	
8.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☐	☐	☐	
8.1.3 Covariates?	☐	☐	☐	
8.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☐	☐	☐	
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☐	☐	☐	
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☐	☐	☐	
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☐	☐	☐	
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☐	☐	☐	
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☐	☐	☐	

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☐	

Comments:

Section 9: Study size and power	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Is sample size and/or statistical power calculated?	☐	☐	☐	

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Does the plan include measurement of excess risks?	☐	☐	☐	
10.2 Is the choice of statistical techniques described?	☐	☐	☐	
10.3 Are descriptive analyses included?	☐	☐	☐	
10.4 Are stratified analyses included?	☐	☐	☐	
10.5 Does the plan describe methods for adjusting for confounding?	☐	☐	☐	
10.6 Does the plan describe methods addressing effect modification?	☐	☐	☐	

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.1 Is information provided on the management of missing data?	☐	☐	☐	
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☐	☐	☐	
11.3 Are methods of quality assurance described?	☐	☐	☐	
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☐	☐	☐	
11.5 Is there a system in place for independent	☐	☐	☐	

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
review of study results?				

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.1 Does the protocol discuss: 12.1.1 Selection biases? 12.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☐ ☐	☐ ☐	☐ ☐	
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☐	☐	☐	
12.3 Does the protocol address other limitations?	☐	☐	☐	

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
13.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☐	☐	☐	
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☐	
13.3 Have data protection requirements been described?	☐	☐	☐	

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Page Number(s)**
14.1 Does the protocol include a section to document future amendments and deviations?	☐	☐	☐	

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Page Number(s)**

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Page Number(s)**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☐	☐	☐	
15.2 Are plans described for disseminating study results externally, including publication?	☐	☐	☐	

Comments:

Name of the main author of the protocol: _____

Date: / /

Signature: _____

ANNEX 3. ADDITIONAL INFORMATION

Annex 3.1: ECOG Performance Status

ECOG Performance Status

These scales and criteria are used by doctors and researchers to assess how a patient's disease is progressing, to assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis. They are included here for health care professionals to access.

ECOG PERFORMANCE STATUS*	
Grade	**ECOG**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

* As published in Am. J. Clin. Oncol.: *Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.*

The ECOG Performance Status is in the public domain therefore available for public use. To duplicate the scale, please cite the reference above and credit the Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

Annex 3.2 SOKAL Index

The SOKAL index is calculated based on the following parameters before start of any treatment:

- Age (years)
- Spleen size (cm under the costal border)
- Platelet count before and at start of treatment (10^9/l)
- Percent of blast in peripheral blood (%)

The SOKAL index is calculated according to the following formula:

exp [0.116 (age-43.4)] + 0.0345(spleen size-7.51) + 0.188[(platelets/700) ^{2} – 0.563] + 0.0887(% blasts - 2.1)

After calculation of the SOKAL index, patients will be evaluated as follows:

- At low risk if SOKAL Score is less than 0.8
- At intermediate risk of SOKAL Score is between 0.8 - 1.2
- At high risk if SOKAL Score is greater than 1.2

ref: Sokal JE, Cox EB, Baccarani M, Tura S, Gomez GA, Robertson JE, et al. Prognostic discrimination in "good-risk" chronic granulocytic leukemia. Blood 1984;63:789-99

Annex 3.3: Morisky 8-item questionnaire on adherence to treatment

Questionnaire in relation to your treatment

(Mark only one response per question)

	Yes	No
1. Do you ever forget to take your treatment?	❑	❑
2. Sometimes some persons do not take their medicinal products for reasons other than forgetfulness. By thinking about the last two weeks, have there been any days when you did not take your treatment?	❑	❑
3. Has it ever happened for you to reduce the dose or to discontinue taking your treatment without telling your doctor because you feel less well by taking it?	❑	❑
4. When you travel or when you leave the house, does it happen that you forget to take your treatment with you?	❑	❑
5. Have you taken your treatment yesterday?	❑	❑
6. When you experience much less or even not at all your symptoms, does it happen sometimes for you to stop taking your treatment?	❑	❑
7. Does the fact of having to take your treatment everyday represent a real inconvenience for certain patients? The fact of having to take your treatment every day represents a real inconvenience for certain patients. Does it sometimes happen for each to be upset by the fact of having to adhere to your treatment?	❑	❑
8. Does it happen that you have difficulty in remembering to take your treatment? ❑ Never/Rarely ❑ From time to time ❑ Sometimes ❑ Regularly ❑ All the time		

ANNEX 3.4: FACT-leu questionnaire 4th version

You will find below a list of comments that other persons with the same illness as yours have considered important. **Please indicate your response by circling a single figure per line and by taking into account the last 7 days.**

	PHYSICAL WELL-BEING	**Not at all**	**A little**	**Moderately**	**Much**	**Enormously**
GP1	I lack energy……	0	1	2	3	4
GP2	I have nausea.....	0	1	2	3	4
GP3	Because of my physical condition, I have difficulty in responding to the needs of my family	0	1	2	3	4
GP4	I have pain.....	0	1	2	3	4
GP5	I am bothered by the side effects of treatment	0	1	2	3	4
GP6	I feel ill.....	0	1	2	3	4
GP7	I must spend time lying down……	0	1	2	3	4

	SOCIAL/FAMILIAL WELL-BEING	**Not at all**	**A little**	**Moderately**	**Much**	**Enormously**
GS1	I feel close to my friends	0	1	2	3	4
GS2	My family provides me with moral support	0	1	2	3	4
GS3	My friends support me.....	0	1	2	3	4
GS4	My family has accepted my illness.....	0	1	2	3	4
GS5	I am satisfied by communication with my family on subject of my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my principal caregiver).....	0	1	2	3	4
Q1	*Whatever your degree of sexual activity at this time, please respond to the following question.* *If you prefer to not respond to it, tick this box and go on to the next section.*					
GS7	I am satisfied with my sex life……..	0	1	2	3	4

	EMOTIONAL WELL-BEING	**Not at all**	**A little**	**Moderately**	**Much**	**Enormously**
GE1	I feel sad……..	0	1	2	3	4
GE2	I am satisfied with the manner in which I face my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous 0	0	1	2	3	4
GE5	I am concerned by the thought of dying 0	0	1	2	3	4
GE6	I am concerned by the thought that my health condition may worsen.....	0	1	2	3	4

	FUNCTIONAL WELL-BEING	**Not at all**	**A little**	**Moderately**	**Much**	**Enormously**
GF1	I am able to work (including housework).....	0	1	2	3	4
GF2	My work (including housework) gives me satisfaction..	0	1	2	3	4
GF3	I am able to obtain benefit from life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I sleep well.....	0	1	2	3	4
GF6	I appreciate my usual leisure	0	1	2	3	4
GF7	I am satisfied with my current quality of life	0	1	2	3	4

	OTHER SUBJECTS OF CONCERN	**Not at all**	**A little**	**Moderately**	**Much**	**Enormously**
BRM3	I am bothered by fever	0	1	2	3	4
P2	Some parts of my body are painful	0	1	2	3	4
BRM 2	I am bothered by chills	0	1	2	3	4
ES3	I have night sweats	0	1	2	3	4
LEU 1	I am bothered by lumps or swelling in certain parts of my body (for example, neck, armpits or groin)	0	1	2	3	4
TH1	I bleed easily	0	1	2	3	4
TH2	I easily bruise	0	1	2	3	4
HI 12	I feel general weakness	0	1	2	3	4
BMT 6	I tire easily	0	1	2	3	4
C2	I lose weight	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
An7	I am able to perform my usual activities	0	1	2	3	4

N3	I am concerned by the thought of contracting an infection.....	0	1	2	3	4
LEU 5	I experience uncertainty regarding my future health.....	0	1	2	3	4
LEU 6	I am concerned about the idea of the occurrence of new symptoms of my illness	0	1	2	3	4
BRM 9	Emotionally, I experience highs and lows.....	0	1	2	3	4
LEU 7	I feel isolated from others because of my illness or because of my treatment.....	0	1	2	3	4

ANNEX 3.5: Bosutinib SmPC

Available online:
http://wvpartner.pfizer.com/webviewer/labelcentral/Labels/EUBPI/France/French/FRA%20BOSU%20031%20MLG%20LONGUES%20%20v005%2015Nov2018.pdf

ANNEX 3.7: Registry of non-inclusion

Registry of non-inclusion

OBJECTIVES OF THE REGISTRY OF NON-INCLUSION
The registry of non-inclusion makes it possible to compare patients who will be included in the BosEVAL study to patients who will not be included.
This comparison makes it possible to have an evaluation of an inclusion bias, as well as to measure their impact on the representativeness of the studied population.
Consequently, the statistical results will be totally utilizable and can be published.

INSTRUCTIONS FOR COMPLETING THE REGISTRY OF NON-INCLUSION
the registry of non-inclusion is to be completed during the inclusion period of the BosEVAL study for all adult patients who satisfy criteria for inclusion and for non-inclusion but who have not wanted to participate in the study.

CHARACTERISTICS OF PATIENTS NOT INCLUDED IN THE STUDY

CENTRE No.: |_|_|

	Date of consultation	Date of birth	Gender	Reason for non-inclusion
1	___ / ___ / _____ (DD/MM/YYYY)	___ / _____ (MM/YYYY)	☐ Male ☐ Female	☐ Patient refusal ☐ Other, specify: ___
2	___ / ___ / _____ (DD/MM/YYYY)	___ / _____ (MM/YYYY)	☐ Male ☐ Female	☐ Patient refusal ☐ Other, specify: ___
3	___ / ___ / _____ (DD/MM/YYYY)	___ / _____ (MM/YYYY)	☐ Male ☐ Female	☐ Patient refusal ☐ Other, specify: ___
4	___ / ___ / _____ (DD/MM/YYYY)	___ / _____ (MM/YYYY)	☐ Male ☐ Female	☐ Patient refusal ☐ Other, specify: ___
5	___ / ___ / _____ (DD/MM/YYYY)	___ / _____ (MM/YYYY)	☐ Male ☐ Female	☐ Patient refusal ☐ Other, specify: ___

Please complete date and sign electronically the registry of non-inclusion.
Date of electronic signature: ___ / ___ / _____ (DD/MM/YYYY)