NOVARTIS

Novartis Pharma GmbH
Stella-Klein-Löw-Weg 17
1020 Vienna, Austria

Nilotinib (CAMN107, Tasigna®)

CAMN107AAT01

A PROSPECTIVE NON-INTERVENTIONAL SAFETY STUDY IN PATIENTS WITH CHRONIC MYELOID LEUKEMIA RECEIVING NILOTINIB IN DAILY PRACTICE ACCORDING TO UPDATED GUIDELINES

Authors [redacted], Novartis Pharma GmbH

[redacted], Bioconsult GmbH Breitenfurt

Document Status Final

Date of last version of the study report 23 SEP 2016

Table of contents

List of tables

List of abbreviations

ABI	Ankle-Brachial-Index
ADR	Adverse Drug Reaction
AE	Adverse Event
ALAT	Alanine aminotransferase / GPT
AMG	Medicinal Products Act *[Arzneimittelgesetz]*
AP	Accelerated Phase
ASAT	Aspartate aminotransferase / GOT
ATC	Anatomical, Therapeutic, Chemical (classification system)
BC	Blast Crisis
BCR-ABL	Breakpoint Cluster Region – Abelson
CCyR	Complete cytogenetic response
CDC	Centers for Disease Control (and Prevention)
CFR	Code of Federal Regulations
CHR	complete hematologic response
CML	Chronic myeloid leukemia
CP	Chronic phase
CPO	Country Pharma Organization
CPRD	Clinical Practice Research Database
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Clinical Research Organization
CTA	Computed Tomography Angiography
CTCAE	Common Terminology Criteria for Adverse Events
DMP	Data management plan
DSE	Drug Safety and Epidemiology
ECG	Electrocardiography
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
FAS	Full analysis set
FDA	Food and Drug Administration
FISH	Fluorescence *in situ* hybridization
ICD	International Classification of Diseases
IMS	Intercontinental Medical Statistics
MedDRA	Medical Dictionary for Regulatory Activities
MeSH	Medical Subject Headings
MMR	Major molecular response
MRI	Magnet Resonance Imaging
NAMCS	National Ambulatory Medical Care Survey
NCHS	National Center for Health Statistics
NHAMCS	National Hospital Ambulatory Medical Care Survey
NHANES	National Health and Nutrition Examination Survey
NHDS	National Hospital Discharge Survey
NHIS	National Health Interview Survey
NIS	Non-interventional study
PADDS	Processing and Data Delivery System
PAOD	Peripheral Arterial Occlusive Disease
PASS	Post-authorization Safety Study
Ph+	Philadelphia chromosome-positive
PSUR	Periodic Safety Update Report

PT	Preferred term (MedDRA)
QS&E	Quantitative Safety & Epidemiology
RMP	Risk Management Plan
RT-PCR	Reverse Transcription Polymerase Chain Reaction
SAE	Serious Adverse Event
SAP	Statistical analysis plan
SDV	Source data verification
SEER	Surveillance Epidemiology and End Results
SOC	System organ class (MedDRA)
SOP	Standard operating procedure
SPC	Summary of product characteristics
THIN	The Health Improvement Network
WHO	World Health Organization
WP	Working Practice

1 Abstract

Title	CAMN107AAT01: A PROSPECTIVE NON-INTERVENTIONAL SAFETY STUDY IN PATIENTS WITH CHRONIC MYELOID LEUKEMIA RECEIVING NILOTINIB IN DAILY PRACTICE ACCORDING TO UPDATED GUIDELINES
Keywords	Nilotinib, Non-Interventional study, Chronic myeloid Leukemia
Rationale and background	Currently available data confirming the safety of nilotinib in CML treatment is based on controlled clinical studies with a predefined patient population. As the patient population treated in daily clinical routine is not preselected by inclusion and exclusion criteria there is a need to evaluate the safety and the disease management of nilotinib therapy in these patients. The aim of this study was to evaluate the safety of nilotinib as labeled in the SPC under specific consideration of daily clinical practice and current treatment guidelines and recommendations (Baccarani *et al.*, 2009; Valent *et al.*, 2011; Rosti *et al.*, 2011, Kim *et al*., 2012).
Research question and objectives	The aim of this observational study was to collect data from daily clinical practice with respect to tolerability and safety of nilotinib therapy in patients with newly-diagnosed Ph+ CML in CP, as well as in patients with CP Ph+ CML resistant to or intolerant of therapy with imatinib and therefore switch to nilotinib.
Study design	This was a Post Authorization Safety Study according to the EU Volume 9a of the Rules Governing Medicinal Products in the European Union for patients diagnosed with CML in the chronic phase. The study was planned to recruit patients diagnosed with CML in the chronic phase exposed to nilotinib with the objective of enrolling at least 100 patients exposed to nilotinib within 3 years. A minimum follow-up of at least 4 years was planned to be be allowed for all patients enrolled. Nilotinib must not be prescribed for the purpose of participation to the study. The study was conducted in compliance with all applicable national and local regulations and guidelines (Baccarani *et al.*, 2009; Valent *et al.*, 2011; Rosti *et al.*, 2011). This study was non-interventional or observational in nature and did not impose a therapy protocol, diagnostic/therapeutic interventions or a visit schedule. Available data from routine clinical management of the patients were collected at patients' visits to their site. To maintain adequate data collection, the sites were encouraged to provide any updated patient data at baseline (i.e. prior to the start of nilotinib therapy), as well as approximately at months 3, 6, 9, 12, 18, 24, 36 and 48, if available.
Setting	6 sites in [redacted] took part in this Non-Interventional Study (NIS).
Subjects and study size, including dropouts	The following types of patients were suitable for enrollment into this NIS: • Patients who will be treated with nilotinib and: ○ newly diagnosed Philadelphia chromosome positive chronic myeloid leukemia (CML) in the chronic phase

	OR ○ Patients with Philadelphia chromosome positive CML in the chronic phase with resistance to or intolerance of prior therapy including imatinib • Patients who were eligible for and have no contraindication against nilotinib according to the SPC and according to updated local treatment recommendations (e.g. Valent *et al.*, 2011, Kim *et al*., 2012) if applicable; • Patients who received [comprehensive] information about this NIS and signed the Informed Consent Form (ICF); • Patients were not allowed to simultaneously participate in any other clinical study because this does not represent routine clinical practice and it hence defeats the purpose of a NIS. For all enrolled patients, a written informed consent to documentation should be obtained. The SPC should be consulted with respect to the indication of nilotinib therapy as well as regarding contraindications and possible side effects. Nilotinib therapy should not be prescribed for the purpose of inclusion in this NIS, but solely for clinical therapeutic indication. 6 centers in [redacted] were involved, resulting in a total of 9 patients enrolled. According to the design, no formal sample size estimate with respect to statistical comparisons was applicable. The planned sample size had been determined on practical considerations and planned availability of patients and centers.
Variables and data sources	<u>During this non-interventional study, solely the diagnostic measures and clinically indicated examinations conducted in line with the routine clinical practice were documented. The assessment of about 3500 variables was planned</u> <u>Planned variables included but were not limited to:</u> • Demographics (Age, gender, height, body weight, medical history, baseline disease data, concomitant medication) • Adverse events • Diagnostic assessments (for example ECG) • Laboratory values (for example white blood cell count, red blood cell count, platelet count, liver enzymes, renal fasting blood glucose levels, HbA1c, cholesterol, HDL, LDL, TSH, fT3, fT4, pancreatic enzymes) • CML-related deaths and reasons for death events • Progression to AP/BC within 48 months of therapy follow-up • Therapy outcome and management • Molecular and/or cytogenetic response • SOKAL scores • Hasford scores •
Results	9 male patients from 3 [redacted] centers were included. Mean age was 50±16 years. All patients were in accordance with all inclusion and exclusion criteria.

	The inclusion of about 100 patients was planned. As this study was discontinued after inclusion of 9 patients and a median observation time of 6 months due to low enrollment, no representative scientific statement about the variables under consideration is possible. Three SAEs and several AEs were reported. For 8 of 9 patients a complete hematologic remission was documented at the final assessment.
Discussion	The design of an observational study without control group and tests of hypotheses may provide some limitations. In addition this study was discontinued after inclusion of 9 patients and a median observation time of 6 months. The conclusions thus are limited but may support as additional information about treatment and indication examined.
Marketing Authorization Holder	Novartis Europharm Limited Frimley Business Park Camberley GU16 7SR United Kingdom
Name(s) and Affiliation(s) of Principal Investigator(s)	Six centers participated, but only three centers documented patients. The following table contains all participating centers and corresponding PIs, sorted by patient number documented.

Site	PI	Patients
[redacted]		
Total		9

2 Marketing Authorization Holder

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

3 Investigators

3.1 Lead physician

[redacted]
AUSTRIA

3.2 Investigational sites

The study was performed in 6 centers in [redacted], but only 3 centers documented patients.

Site	PI	Patients
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Total		9

3.3 Authors of the protocol

[redacted]

Novartis Oncology Austria
[redacted]
Austria

3.4 Study administration

Mag. Andreas Raffeiner
Raffeiner GmbH
Höhenstraße 27
A-4111 Walding
AUSTRIA

3.5 Medical Advisor Novartis

[redacted]

Novartis Pharma GmbH
[redacted]
AUSTRIA

3.6 Drug safety

[redacted]
Novartis Pharma GmbH
[redacted]
AUSTRIA

3.7 Biometrical Analysis

[redacted]
Bioconsult GmbH
[redacted]

4 Milestones

Table 4-1 Study milestones

Milestone	Planned date	Actual date
Approval by ethics committee	April 2013	May 2013
Start of data collection	10 October 2013	10 October 2013
End of data collection	April 2020	17 December 2015
Draft report no. 1 of study results	August 2016	26 August 2016
Final report of study results	30 September 2016	23 September 2016

5 Rationale and background

5.1 Overview of chronic myeloid leukemia and response criteria

Chronic myeloid leukemia (CML) accounts for approximately 5-10% of myeloid leukemia in adults, and it belongs to the group of chronic myeloproliferative diseases (Faderl et al., 1999; Sawyers, 1999). CML is a clonal myeloproliferative disease of hematopoietic stem cells, leading to an increase in the number of granulocytic and other myeloid (precursor) cells. CML is characterized by a specific chromosomal translocation, the Philadelphia (Ph) chromosome, resulting from exchange of genetic material between chromosomes 9 and 22 (t(9;22)(q34;q11)) (Nowell et al., 1960; Rowley, 1973). The related molecular defect is the fusion of *ABL1* with the *BCR* gene which yields the BCR-ABL1 oncoprotein (Faderl et al., 1999). BCR-ABL1 confers a growth advantage to leukemic cells, increases their proliferation and cytokine-independent growth, inhibits apoptosis and alters adhesion properties of neoplastic cells (Sawyers, 1999; Deininger et al., 2000; Van Etten, 2004). In most patients, the diagnosis is confirmed cytogenetically by demonstrating the presence of the Ph chromosome, and by molecular testing for BCR-ABL1.

The clinical course of CML includes three phases. The relatively stable chronic phase is characterized by an increased number of white blood cells (WBC) and/or platelets, absence of marked basophilia, and less than 10% blasts in blood and bone marrow. Accelerated phase (AP) is defined by 15%-29% blast cells in blood or bone marrow or blast cells plus promyelocytes in blood or bone marrow more than 30%, with blast cells less than 30%, >20% basophils in blood or bone marrow, thrombocytopenia (<100,000/μL) or thrombocytosis (>1,000,000/μL), cytogenetic evidence of clonal evolution in addition to the Ph chromosome and increasing splenomegaly or WBC, unresponsive to therapy (Baccarani et al. 2006). The terminal phase, called blast crisis (BC), is characterized by ≥20% blasts in blood or bone marrow, extramedullary blast proliferation and clusters of blasts in bone marrow biopsy (Vardiman *et al.*, 2002). Once the blast crisis stage is reached, the median survival is only a few months (average duration of 3-6 months according to Enright and McGlave, 2000).

During recent decades therapy of CML contained cytotoxic agents (such as hydroxyurea and busulfan) and interferon-α as well as allogeneic stem cell transplantation. The latter is still recognized as the only curative therapy, albeit it is not always feasible or effective, and it carries an appreciable risk for side effects and complications (Faderl, et al. 1999). Response to CML therapy is measured by assessing different parameters whereas three categories of response have been defined:

- hematologic response, i.e. normalization of hematopoiesis. A complete hematologic response (CHR) is characterized by platelets < 450 000/μL, and WBC count < 10 000/μL, and differential blood count without immature granulocytes and < 5% basophils, and non-palpable spleen
- cytogenetic response: i.e. reduction of Ph+ metaphases in bone marrow (CCyR is 0% Ph+ cells)

- molecular response: i.e. reduction in the BCR-ABL/ABL transcript ratio (major molecular response, MMR, is ≤ 0.1%) in peripheral blood or bone marrow).

5.2 Overview of nilotinib (Tasigna®)

Nilotinib (Tasigna®, AMN107) is a second-generation BCR-ABL tyrosine kinase inhibitor. It is a more potent BCR-ABL inhibitor than imatinib, and it inhibits the catalytic activity of the BCR-ABL molecule in various cell lines with an IC_{50} value of 22-42 nM (imatinib, IC_{50} 196-495 nM). Additionally, nilotinib has an anti-proliferative effect on cell lines, expressing BCR-ABL (nilotinib, IC_{50} 4-34 nM; imatinib, IC_{50} 61-577 nM). Another clinically relevant feature of nilotinib in physiologically relevant concentrations is the inhibition of protein tyrosine kinase activity of certain imatinib-resistant BCR-ABL forms with point mutations in the kinase domain (including E255V, F317L, M351T and F486S) (Weisberg, *et al.* 2005).
In clinical studies, nilotinib demonstrated excellent efficacy and good tolerability in CML patients with imatinib-resistance or -intolerability (Kantarjian *et al.* 2006, Kantarjian *et al.* 2007, Le Coutre *et al.* 2008); hence, it obtained approval in November 2007 as a second-line agent in the treatment of CML. In December 2010, therapy regimen with twice-daily (bid) 300 mg nilotinib received approval as a first-line therapeutic modality in adult patients with newly-diagnosed Philadelphia chromosome-positive myeloid leukemia (Ph+ CML) in the chronic phase (CP). The approval is based on results of the ENESTnd study (CAMN107A2303) which established superiority of nilotinib over imatinib 400 mg q.d. with respect to cytogenetic and molecular response rates (Saglio *et al*., 2010; Kantarjian *et al.*, 2011). Most noteworthy, the progression rate (transition to advanced CML phases—AP and BC) proved to be significantly lower for both nilotinib arms (<1% for both dosage regimens) than for imatinib patients (4%).

5.3 Rationale of the study

Currently available data confirming the safety of nilotinib in CML treatment is based on controlled clinical studies with a predefined patient population. As the patient population treated in daily clinical routine is not preselected by inclusion and exclusion criteria there is a need to evaluate the safety and the disease management of nilotinib therapy in these patients.
The aim of this study is to evaluate the safety of nilotinib as labeled in SPC under specific consideration of daily clinical practice and current treatment guidelines and recommendations (Baccarani *et al.*, 2009; Valent *et al.*, 2011; Rosti *et al.*, 2011, Kim *et al.* , 2012). Therefore clinical data of CML patients treated with nilotinib shall be collected in addition to available results from clinical trials,
Nilotinib is generally well tolerated, with manageable side effects. Besides hematologic side effects, nilotinib-treated patients may develop increases in pancreatic enzymes, bilirubin, and fasting glucose level (Kantarjian *et al.* 2011). Other non-hematologic adverse events include diarrhea, folliculitis-like skin rash, and bleeding. There are a few reports of severe peripheral arterial occlusive disease (PAOD) and other vascular occlusive events (infarction) in patients receiving nilotinib (Aichberger *et al.*, 2011; Le Coutre *et al.*, 2011; Tefferi and Letendre, 2011, Quintás-Cardama *et al.*, 2012). In the ENESTnd study, 6 cases of PAOD had been reported before the start of this study in both nilotinib arms, while no cases havd been reported in the control imatinib arm (Kantarjian *et al.*, 2011). In light of these reports, Novartis undertook a review and assessment of PAOD cases, and results were discussed with

an external advisory board. In conclusion, a causal relationship between the events and nilotinib could neither be confirmed nor ruled out; hence, a recommendation to exclude patients with a risk of PAOD secondary to therapy with nilotinib was not made. As a consequence the SPC was updated with PAOD being classified as uncommon adverse reaction (≥1/1,000 to <1/100) based on its reported frequency. Moreover, treatment guidelines have been updated to ensure appropriate patient treatment and monitoring (Valent *et al.*, 2011, Kim *et al*. , 2012). This study aims to evaluate the safety of nilotinib as per SPC and the implementation of current guidelines in daily clinical routine (Baccarani *et al.*, 2009, Valent *et al.*, 2011, Rosti *et al.*, 2011, Kim *et al*., 2012).

6 Research question and objectives

The aim of this observational study was to collect data from daily clinical practice with respect to tolerability and safety of nilotinib therapy in patients with newly-diagnosed Ph+ CML in CP, as well as in patients with CP Ph+ CML resistant to or intolerant of therapy with imatinib and therefore switch to nilotinib.
Specifically, the objectives include:

- Assessment of **Safety and tolerability** by documentation of clinical status and reporting of tolerability data and all AEs (serious and non-serious) with a special focus on vascular safety and risk factors
- **Drug utilization and disease management** in daily clinical practice under special consideration of current treatment guidelines and local recommendations

This study was non-interventional or observational in nature and did not impose a therapy protocol, diagnostic/therapeutic interventions or a visit schedule. Available data from routine clinical management of the patients should be collected at patients' visits to their site (e.g. at baseline and after 3, 6, 9, 12, 18, 24, 36 and 48 Month) if available.

7 Amendments and updates to the protocol

Not applicable.

8 Research methods

8.1 Study design

This is a Post Authorization Safety Study according to the EU Volume 9a of the Rules Governing Medicinal Products in the European Union for patients diagnosed with CML in the chronic phase. The study was planned to recruit patients diagnosed with CML in the chronic phase exposed to nilotinib with the objective of enrolling at least 100 patients exposed to nilotinib within 3 years. A minimum follow-up of at least 4 years was planned to be allowed for all patients enrolled. Nilotinib must not be prescribed for the purpose of participation to the study.

The study was conducted in compliance with all applicable national and local regulations and guidelines (Baccarani *et al.*, 2009; Valent *et al.*, 2011; Rosti *et al.*, 2011).

This study was non-interventional or observational in nature and did not impose a therapy protocol, diagnostic/therapeutic interventions or a visit schedule. Available data from routine clinical management of the patients were collected at patients' visits to their site. To maintain adequate data collection, the sites were encouraged to provide any updated patient data at baseline (i.e. prior to the start of nilotinib therapy), as well as approximately at months 3, 6, 9, 12, 18, 24, 36 and 48, if available.

8.2 Setting

Six centers in [redacted] participated in this NIS:

Site	PI	Patients
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Total		9

8.3 Subjects

9 patients, recruited from 3 centers in [redacted] were involved.

Patient population:

This multi-center non-interventional study was planned to be conducted in approximately 10-15 hematology-oncology practices/centers, hence ensuring a representative sample of the population for the involved study centers.
Approximately 100 male or female patients with newly-diagnosed Ph+ CML in the CP, or Ph+ CML CP patients with an inadequate response or toxicities to imatinib (assessed according to current ELN recommendations) were planned to be included (for more details see observational study protocol Version 01).
After inclusion of nine patients the study was stopped due to low enrollment.
The analysis is based on a patient population with documented administration/prescription of nilotinib with a baseline and at least one post-baseline evaluation.
No data will be excluded from these analyses because of protocol violations. This population is analogous to the "Full Analysis Set" (FAS) as described in "International Conference on Harmonization; Guidance on Statistical Principles for Clinical Trials".

8.3.1 Primary source of data. Primary analysis population

The nine patients included (Full Analysis Set, FAS) build the primary analysis population and will be analysed using descriptive methods.

8.3.2 Primary source of data. Secondary analysis population (if needed)

The nine patients included (Full Analysis Set, FAS) build the primary analysis population. No additional analysis population will be defined.

8.3.3 Secondary source of data. Primary and secondary analyses

There are no secondary sources of data.

8.3.4 Study groups/cohorts

8.3.4.1 Active treatment (*or* exposed) group/Main cohort

The nine patients included (Full Analysis Set, FAS) build the primary analysis population and will be analysed using descriptive methods.

8.3.4.2 Comparison group

According to the study design no comparison group is applicable.

8.4 Variables

During this non-interventional study, solely the diagnostic measures and clinically indicated examinations conducted in line with the routine clinical practice were documented.
The assessment of about 3500 variables was planned. As this study was stopped after enrollment of nine patients, only variables really assessed and documented (=variables with data) can be analysed.

8.4.1 Start of observation / baseline examination

- Demographic data (including year of birth and gender);
- Documentation of patient-reported medical history (including documentation of cardiovascular risk factors);
- Documentation of diagnostic assessments (for example ECG, echocardiography, peripheral Doppler sonography, ABI (ankle-brachial-index)) and laboratory values (for example white blood cell count, red blood cell count, platelet count, liver enzymes, renal enzymes, fasting blood glucose levels, HbA1c, cholesterol, HDL, LDL, TSH, fT3, fT4, pancreatic enzymes) in line with the updated guidelines (Valent *et al.*, 2011), if documented;
- Features of disease (including date of diagnosis and its main characteristics, ECOG Performance Status – if conducted) as well as possible pretreatment with hydroxyurea or imatinib;
- Date of the first conventional cytogenetic, molecular biology examination;
- Co-morbidities and concomitant therapies.

8.4.2 Follow-up examinations during the observation period

Taking into consideration the precautions and recommendations specified in the SPC, a complete blood count and serum chemistry (including fasting blood glucose levels, HbA1c, cholesterol, HDL, LDL, TSH, fT3, fT4, pancreatic enzymes) should be performed at regular intervals, and should be documented in the e-CRF.
Follow-up examinations were planned to be performed according to routine clinical practice and recently published guidelines (Baccarani *et al.*, 2009; Valent *et al.*, 2011), and documented for the purposes of this non-interventional study approximately at months 3, 6, 9, 12, 18, 24, 36 and 48 after the start of therapy with nilotinib.
Additional medical examinations used in clinical routine such as ECG, echocardiography and peripheral Doppler sonography, ABI, as well as conventional bone marrow cytogenetics (evaluation of at least 20 metaphases preferred for documentation), and medical examination and hematologic laboratory tests to evaluate the hematologic and molecular response, were also planned to be performed based on published recommendations and routine clinical practice, and planned to be documented.
Dose adjustment and interruption or discontinuation of therapy should be performed according to the summary of product characteristics and based on the individual situation in each case (and at the discretion of the investigator), and were planned to be documented.

8.5 Data sources and measurement

During this non-interventional study, solely the diagnostic measures and clinically indicated examinations conducted in line with the routine clinical practice were planned to be documented.

8.5.1 Start of observation / baseline examination

- Demographic data (including year of birth and gender);
- Documentation of patient-reported medical history (including documentation of cardiovascular risk factors);
- Documentation of diagnostic assessments (for example ECG, echocardiography, peripheral Doppler sonography, ABI (ankle-brachial-index)) and laboratory values (for example white blood cell count, red blood cell count, platelet count, liver enzymes, renal fasting blood glucose levels, HbA1c, cholesterol, HDL, LDL, TSH, fT3, fT4, pancreatic enzymes) in line with the updated guidelines (Valent *et al.*, 2011, Kim *et al.*, 2012), if documented;
- Features of disease (including date of diagnosis and its main characteristics, ECOG Performance Status – if conducted) as well as possible pretreatment with hydroxyurea or imatinib;
- Date of the first cytogenetic, hematologic and molecular examination;
- Co-morbidities and concomitant therapies.

8.5.2 Follow-up examinations during the observation period

Taking into consideration the precautions and recommendations specified in the SPC, a complete blood count and serum chemistry (including fasting blood glucose levels, HbA1c, cholesterol, HDL, LDL, TSH, fT3, fT4, pancreatic enzymes) should be performed at regular intervals.
Follow-up examinations were planned to be be performed according to routine clinical practice and recently published guidelines and recommendations (Baccarani *et al.*, 2009; Valent *et al.*, 2011, Kim *et al.*, 2012), and documented for the purposes of this non-interventional study approximately at months 3, 6, 9, 12, 18, 24, 36 and 48 after the start of nilotinib therapy.
Additional medical examinations used in clinical routine such as ECG, echocardiography and peripheral Doppler sonography, ABI, as well as conventional bone marrow cytogenetic (evaluation of at least 20 metaphases preferred for documentation), and medical examination and hematologic laboratory tests to evaluate the hematologic and molecular response, were also planned to be performed based on published recommendations and routine clinical practice, and were planned to be documented.

Dose adjustment and interruption or discontinuation of therapy should be performed according to the summary of product characteristics and based on the individual situation in each case (and at the discretion of the investigator), and should be reported if documented.

8.5.3 End of observation

Each patient should be followed over a period of up to 48 months. A premature termination should be documented using an electronic documentation form, specifying the date and reason for termination.

8.6 Bias

According to the design of an open, non-interventional retrospective observation study without comparison group and without study hypothesis, a non-comparative bias is expected.

8.7 Study size

According to the study design, no formal sample size estimate with respect to statistical tests of hypotheses is applicable.
The sample size of 100 patients had been determined on practical considerations and availability of patients. This sample size would have been sufficient to have about 80% probability of observing at least one adverse event which has an incidence of 1.5%, and 95% probability of observing at least one adverse event which has an incidence of 3%.
However, due to low enrollment the study was stopped after inclusion of 9 patients.

8.8 Data transformation

No data transformations were performed.

8.9 Data management

Data management was conducted by a CRO (Mag. Andreas Raffeiner GmbH).
All quality assurance measures of the data management plan are contained in a projectspecific data management plan (DMP) and specified for individual data management phases.
All data management processes rest on the SOPs issued by the authorized CRO and Novartis.

8.10 Data analysis

No confirmatory proof of study hypotheses is applicable for this non-interventional observation project. No primary or secondary endpoints were defined. Descriptive statistics will be performed on all variables assessed.
The aim of this observational study was to collect data from daily clinical practice with respect to tolerability and safety of nilotinib therapy in patients with newly-diagnosed Ph+ CML in CP, as well as in patients with CP Ph+ CML resistant to or intolerant of therapy with imatinib and therefore switch to nilotinib. Specifically, the objectives included:

- Assessment of safety and tolerability by documentation of clinical status and reporting of tolerability data and all AEs (serious and non-serious) during with a special focus on vascular safety and risk factors
- Drug utilization and disease management in daily clinical practice under special consideration of current treatment guidelines and local recommendations

The analysis is based on a patient population with documented administration/prescription of nilotinib with a baseline and at least one post-baseline evaluation.

Descriptive statistical tables will be used to present data. Comparisons with historical controls or published data will be done by description of results and not by application of statistical tests.

8.10.1 Statistical methods

No confirmatory proof of study hypotheses is applicable for this non-interventional observational project.
Descriptive statistics will be performed on all variables assessed.

The assessment of about 3500 variables was planned. As this study was stopped after enrollment of nine patients, only variables assessed and documented (=variables with data) can be analysed.

Data were summarized with respect to demographic and baseline characteristics, treatment data, safety observations and measurements, and response observations and measurements. Summary statistics included the mean, N, standard deviation, median, minimum, and maximum values for continuous variables, and frequencies and percentages for categorical variables.
All individual data (including relevant derived variables) were presented by parameter in listings in the statistical appendix of the clinical study report. Missing data were not imputed. Results of descriptive summary statistics were also presented in the statistical parts of the clinical study report.

8.10.1.1 Main Summary Measures

Summary statistics were presented for all efficacy variables including the mean, N, standard deviation, median, minimum, and maximum values for continuous variables, and frequencies and percentages for categorical variables.

8.10.1.2 Main Statistical Methods

As the study was an open label non-interventional post marketing observational study no working hypothesis was allowed. Consequently all variables were evaluated statistically solely on a descriptive basis. No confirmatory proof of study hypotheses was applicable.
Descriptive statistics have been performed on all variables assessed. Data were summarized with respect to demographic and baseline characteristics, safety observations and measurements, and efficacy observations and measurements.

8.10.1.3 Missing Values

Missing values were not imputed or extrapolated.

8.10.1.4 Sensitivity Analyses

According to the study design, no sensitivity analysis was applicable.

8.10.1.5 Amendments to the Statistical Analysis Plan

Not applicable.

8.10.2 Quality control

The investigators were responsible for the correct documentation of the data from the patient records. The eCRF issued warnings during the documentation process if entered values are completely out of plausible ranges (e.g. age above 120). In addition, the eCRF issued warnings if essential data points were missing (e.g. time of diagnosis).

Monitoring of study sites and source data verification was performed by the CRO Mag. Andreas Raffeiner GmbH in line with the applicable SOPs issued by the authorized CRO and Novartis.

8.10.3 Limitations of the research methods

The design of an observational study without control group and tests of hypotheses may provide some limitations. In addition this study was discontinued after inclusion of 9 patients and a median observation time of 6 months. The conclusions thus are limited but may present additional information about treatment and indication examined.

9 Protection of human subjects

Data protection and privacy regulations were followed in capturing, forwarding, processing, and storing patient data according to local Austrian regulations and laws. Each patient's data collected in the NIS was stored under an assigned unique patient identification number which did not contain any reference to the patient's identity. Even if the study results should be published, personal data would only be available in an anonymized form. Patients will not be traceable to their original data and no such efforts have been undertaken.

All subjects were informed about the study by the respective PI and signed an informed consent form. Approval by the respective ethics committees was obtained prior to study initiation.

Medical personnel responsible for the transfer of data from the patient files was informed about their legal responsibility to safeguard data protection.
This study was designed, implemented and reported in accordance with the Guidelines for Good Pharmacoepidemiology Practices (GPP) of the International Society for Pharmacoepidemiology (ISPE 2008), the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines (Vandenbroucke, et al 2008), and with the ethical principles laid down in the Declaration of Helsinki.

10 Management and reporting of adverse events/adverse reactions

All adverse events (AEs) – including serious adverse events (SAEs) and safety endpoints (where relevant) – had to be collected and recorded in the study database, irrespective of causal association. All safety data AEs and SAEs occurring in association with exposure to a Novartis drug also had to be recorded in the Novartis safety database.

10.1 Adverse event

An adverse event was defined as any untoward medical occurrence in a patient administered Tasigna that does not necessarily have a causal relationship with the treatment.
An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of Tasigna whether or not related to the medicinal product(s).
Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, require therapy (e.g., hematologic abnormality that requires transfusion or hematological stem cell support), or require changes in study medication(s) and/or treatment.
Progression of disease had to be be collected on the Termination / End of Study CRF page.
Progression of disease constituted an adverse event only if it was considered to be causally related to therapy with Tasigna or if any critera for a serious adverse event is fulfilled due to the progression.

Drug of interest included Tasigna and any comparator drug(s) if specified as part of the research objective, given at any time during the study. Medical conditions/diseases present before starting Tasigna were only considered adverse events if they worsened after starting Tasigna.
The occurrence of adverse events should be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments. All adverse events had to be recorded on the Adverse Events case report/case record form (CRF) with the following information:

1. the severity grade (grade 1-4)
2. its relationship to the drug(s) of interest (suspected/not suspected)
3. its duration (start and end dates or if continuing at final exam)
4. whether it constitutes a serious adverse event (SAE)

In addition, all reports of the following special scenarios were also considered an adverse event irrespective if a clinical event has occurred:

- Drug-drug or drug-food interaction, with or without clinical symptoms
- Drug exposure during pregnancy (via the mother or father with or without outcome) see section 6.3,
- Drug use during lactation or breast-feeding,
- Lack of efficacy, with or without clinical symptoms
- Overdose, with or without clinical symptoms
- Drug abuse and misuse, with or without clinical symptoms
- Drug maladministration or accidental exposure,
- Occupational exposure
- Dispensing errors / Medication errors, with or without clinical symptoms
- Withdrawal or rebound symptoms, with or without clinical symptoms
- Unexpected beneficial effect

Any treatment of any adverse event should be recorded on the Adverse Event CRF. Some examples of treatment to be recorded were: no action taken (i.e., further observation only); Tasigna dosage adjusted/temporarily interrupted; Tasigna permanently discontinued due to this adverse event; treatment medication adjusted; non-drug therapy given; patient hospitalized/patient's hospitalization prolonged.
Once an adverse event was detected, it had to be followed until its resolution or until it was judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to Tasigna, the interventions required to treat it, and the outcome.
Information about common adverse effects already known about Tasigna can be found in the Summary of Product Characteristics (SPC). This information was included in the patient informed consent and was planned to be discussed with the patient during the study as needed.
Information on all AEs was included in the individual patient e-CRF which was updated and committed in the study database following each patient visit.

10.2 Serious adverse event reporting

A serious adverse event (SAE) is defined as an event which:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
    - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of Tasigna
    - social reasons and respite care in the absence of any deterioration in the patient's general condition
- is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above e.g. may require treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- transmission of infectious agent via medicinal product

For Tasigna some events are of special interest for targeted follow-up. If necessary, questionnaires had been forwarded to the relevant physicians.
To ensure patient safety, every SAE, regardless of causality assessment, occurring after the patient had provided informed consent and until 30 days after the patient had stopped study participation (defined as time of last dose of Tasigna taken or last visit whichever is later) had to be reported to Novartis within 24 hours of learning of its occurrence.
Any SAEs experienced after this 30 day period should only be reported to Novartis if the treating physician or other involved health care professional suspects a causal relationship to Tasigna.

Recurrent episodes, complications, or progression of the initial SAE had to be reported as follow-up to the original episode, regardless of when the event occurred. This report had to be submitted within 24 hours of the treating physician or other involved health care professional receiving the follow-up information. An SAE that was considered completely unrelated to a previously reported should be reported separately as a new event.

Information about all SAEs was collected and recorded on the Serious Adverse Event Report Form. The treating physician or other involved health care professional must assess the relationship to Tasigna, complete the SAE Report Form and send the completed, signed form electronically in the system within 24 hours to the local Novartis Drug Safety & Epidemiology (DS&E) department.

Follow-up information ws sent to the same person to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the patient continued or withdrew from study participation.

If the SAE was not previously documented in the Package Insert a local DS&E department associate may urgently require further information from the treating physician or other involved health care professional for Health Authority reporting.

11 Plans of disseminating and communicating study results

Upon study completion and finalization of the study report, the results of this non-interventional study may be either submitted for publication and/or posted in a publicly accessible database of results. Publications will comply with internal Novartis standards and the International Committee of Medical Journal Editors (ICMJE) guidelines.

A detailed plan for publication of study results is described in the publication policy charter as a separate document.

12 Results

12.1 Participants

9 male patients from 3 [redacted] centers with newly-diagnosed Ph+ CML in the CP, or Ph+ CML CP patients with an inadequate response or toxicities to imatinib (assessed according to current ELN recommendations) were included.

Informed consent was obtained from all patients.
Mean age was 50±16 years. All patients were in accordance with all inclusion and exclusion criteria.

Table 12.1: Baseline Demographics

Patients included, N	9
Male, %	100.0
Age, years, mean ±SD	50±16

12.2 Demographic Data

12.2.1 Gender

All 9 patients were male

12.2.2 Age (years)

Mean	50.2
S.D.	15.7
Median	45.0
Minimum	24.0
Maximum	73.0
Number	9

12.2.3 Height (cm)

Mean	178.83
S.D.	6.91
Median	178.5
Minimum	172
Maximum	189
Number	6

12.2.4 Weight (kg)

Mean	99
S.D.	9.64
Median	95
Minimum	92
Maximum	110
Number	3

12.3 Baseline data

Due to the prospective nature of this study, only assessments performed after the patient had signed the informed consent could be documented. Therefore, the assessments documented and presented here may not represent all assessments done at baseline for the respective patients. For example, additional assessments used for angiologic risk stratification may have occurred before ICF signature and therefore have been excluded from documentation.

12.3.1 Vital signs at baseline

12.3.1.1 Blood pressure (mmHg)

	Systolic	Diastolic
Mean	123.75	73.5
S.D.	11.09	9.43
Median	125	77
Minimum	110	60
Maximum	135	80
Number	4	4

12.3.1.2 Pulse (bpm)

Mean	77
S.D.	1
Median	77
Minimum	76
Maximum	78
Number	3

12.3.2 Cardiovascular Risk Factors

12.3.2.1 Smoker

	N	%
no	3	33.3
yes	1	11.1
ex-smoker	2	22.2
NA	3	33.3
Total	9	100.0

Ex- smoker since: 0.5 years, 17 years

12.3.2.2 Diabetes mellitus

No patients had diabetes mellitus

12.3.2.3 Hypertension

	N	%
No	7	77.8
yes	2	22.2
Total	9	100.0

12.3.2.3.1 Hypertension since (years)

	N	%
NA	7	77.8
1	1	11.1
10	1	11.1
Total	9	100.0

12.3.2.4 Hypercholesterolemia

	N	%
no	7	77.8
yes	2	22.2
Total	9	100.0

12.3.2.5 Coronary heart disease

For no patient a CHD at baseline was reported.

12.3.2.6 Stroke

For no patient a stroke at baseline was reported.

12.3.2.7 Metabolic Syndrome

For no patient a metabolic syndrome at baseline was reported.

12.3.3 Medical History

Patient	Diagnosis	since	active problem
[redacted]			

12.3.4 Disease history

12.3.4.1 Years since diagnosis of CML

mean	2.4
SD	5.2
median	0.6
min	0.0
maximum	17.1
N	9

12.3.4.2 Has the subject previously been treated for CML?

	N	%
no	2	22.2
yes	7	77.8
Total	9	100.0

12.3.4.2.1 Previous Treatment

Therapy type: 0=Chemotherapy, 1=Hormonal therapy, 2=Immunotherapy, 3=Targeted therapy, 4=Other

	Regimen number	Therapy type	Medication (as entered in the eCRF by the investigator)	Medication (in harmonized terms)	Start date	End date
subject						

12.3.4.3 Peripheral blood (PB) blasts, % at diagnosis

Mean	2.38
S.D.	1.77
Median	2
Minimum	0
Maximum	5
Number	8

12.3.4.4 PB eosinophils, % at diagnosis

Mean	2.85
S.D.	2.24
Median	2.5
Minimum	0
Maximum	7
Number	8

12.3.4.5 PB basophils, % at diagnosis

Mean	5.11
S.D.	2.33
Median	4
Minimum	2
Maximum	9
Number	7

12.3.4.6 Platelets at diagnosis (G/L)

Mean	574.33
S.D.	586.65
Median	400.5
Minimum	83
Maximum	1596
Number	6

12.3.4.7 Spleen size, cm under costal margin

Mean	5.83
S.D.	7.22
Median	3
Minimum	0
Maximum	18
Number	6

12.3.4.8 Sokal Score at diagnosis

.8inkl. : low
.81-1.2 : medium
>1.2 : high

Mean	1.01
S.D.	0.24
Median	0.96
Minimum	0.83
Maximum	1.43
Number	5

12.3.4.8.1 SOKAL Score – categories ‘low’, ‘medium’, ‘high’

	N	%
low	2	22.2
medium	3	33.3
NA	4	44.4
Total	9	100.0

12.3.4.9 Euro (Hasford) score at diagnosis

Mean	833.9
S.D.	566.39
Median	1011.5
Minimum	11
Maximum	1301.6
Number	4

12.3.4.10 Optional Comment

Patient

[redacted]

12.3.5 Cytogenetic Analysis

12.3.5.1 Was a cytogenetic analysis performed?

	N	%
no	2	22.2
yes	7	77.8
Total	9	100.0

12.3.5.2 Date of procedure

	N	%
12.05.2015	1	11.1
13.11.2013	1	11.1
14.01.2015	1	11.1
17.07.2015	1	11.1
21.01.2015	2	22.2
23.12.2014	1	11.1
NA	2	22.2
Total	9	100.0

12.3.5.3 Karyotype formula done

	N	%
Not done	4	44.4
done	3	33.3
NA	2	22.2
Total	9	100.0

If not done or not available, please provide a reason:

no metaphases won	1
Not analysable	1
only 2 metaphases won, diagnostically not utilizable	1
sample condition not sufficient to analyze data	1

12.3.5.4 Number of metaphases examined

	N	%
5	1	11.1
10	1	11.1
22	1	11.1
NA	6	66.7
Total	9	100.0

12.3.5.5 Number of metaphases positive for Philadelphia chromosome

	N	%
0	1	11.1
3	1	11.1
10	1	11.1
NA	6	66.7
Total	9	100.0

12.3.5.6 Number of metaphases negative for Philadelphia chromosome

	N	%
0	1	11.1
2	1	11.1
22	1	11.1
NA	6	66.7
Total	9	100.0

12.3.5.7 Are there any additional aberrations in the Philadelphia positive clone?

	N	%
no	3	33.3
NA	6	66.7
Total	9	100.0

12.3.5.8 Are there any additional aberrations in the Philadelphia negative clone?

	N	%
no	2	22.2
yes	1	11.1
NA	6	66.7
Total	9	100.0

12.3.5.9 Karyotype formula

Patient	Formula
[redacted]	

12.3.6 Bone Marrow Analysis

12.3.6.1 Was a Bone Marrow analysis performed?

	N	%
No	2	22.2
yes	7	77.8
Total	9	100.0

12.3.6.2 Date of procedure

	N	%
13.11.2013	1	11.1
23.12.2014	1	11.1
11.05.2015	1	11.1
14.01.2015	1	11.1
17.07.2015	1	11.1
21.01.2015	2	22.2
NA	2	22.2
Total	9	100.0

12.3.6.3 Type of Bone Marrow Analysis

0=Bone Marrow Aspiration, 1=Bone Marrow Biopsy

	N	%
Bone Marrow Aspiration	6	66.7
Bone Marrow Biopsy	1	11.1
NA	2	22.2
Total	9	100.0

12.3.6.4 Cellularity

0=Aplastic, 1=Hypocellular, 2=Normocellular, 3=Hypercellular, 4=Inadequate sample

	N	%
1	1	11.1
2	2	22.2
4	2	22.2
NA	4	44.4
Total	9	100.0

12.3.6.5 Percent of blasts

	N	%
	1	11.1
0	1	11.1
1	3	33.3
3.3	1	11.1
OCI:NA	3	33.3
Total	9	100.0

12.3.6.6 Percent of promyelocytes

	N	%
4	1	11.1
5	1	11.1
8	1	11.1
26	1	11.1
NA	5	55.5
Total	9	100.0

12.3.6.7 Percent of basophils

	N	%
0.9	1	11.1
1	1	11.1
2	2	22.2
4	1	11.1
NA	4	44.4
Total	9	100.0

12.3.6.8 Cellularity

0=Aplastic, 1=Hypocellular, 2=Normocellular, 3=Hypercellular, 4=Inadequate sample
V1_F10_Q8

	N	%
3	1	11.1
NA	8	88.9
Total	9	100.0

12.3.6.9 Percent of blasts

V1_F10_Q9

	N	%
MC: Unavailable	1	11.1
OCI:NA	8	88.9
Total	9	100.0

12.3.6.10 Percent of promyelocytes

V1_F10_Q10

	N	%
MC: Unavailable	1	11.1
OCI:NA	8	88.9
Total	9	100.0

12.3.6.11 Percent of basophils

V1_F10_Q11

	N	%
MC: Unavailable	1	11.1
OCI:NA	8	88.9
Total	9	100.0

12.3.6.12 Optional Comment

V1_F10_Q12

	N	%
	3	33.3
Cellularity unknown	1	11.1
Inconclusive sample	1	11.1
Limited conclusiv smear	1	11.1
NA	2	22.2
Percent of basophils <1%	1	11.1
Total	9	100.0

12.3.7 Multiplex PCR for BCR-ABL

12.3.7.1 Was a Multiplex PCR for BCR-ABL performed from peripheral Blood?

V1_F11_Q1

	N	%
no	6	66.7
yes	3	33.3
Total	9	100.0

12.3.7.2 Date test performed

V1_F11_Q2

	N	%
04.09.2015	1	11.1
07.05.2015	1	11.1
23.12.2014	1	11.1
OCI:NA	6	66.7
Total	9	100.0

12.3.7.3 Multiplex PCR for BCR-ABL

V1_F11_Q3
0=Negative, 1=b3a2, 2=b2a2, 3=b3a2 + b2a2, 4=e1a2, 5=e19a2, 6=Inadequate sample, 7=Not done, 8=Other

	N	%
1	1	11.1
2	1	11.1
NA	7	77.8
Total	9	100.0

12.3.7.3.1 Multiplex PCR for BCR-ABL - Please specify

V1_F11_Q4

	N	%
NA	9	100.0
Total	9	100.0

12.3.7.4 Performed at which lab?

V1_F11_Q5

	N	%
	1	11.1
Centre of Medical Genetics Hanusch Hospital	2	22.2
OCI:NA	6	66.7
Total	9	100.0

12.3.7.5 Optional Comment

V1_F11_Q6

No comments were documented.

12.3.8 Prior antineoplastic therapy

12.3.8.1 Has the patient received prior antineoplastic therapies?

	N	%
no	1	11.1
yes	8	88.9
Total	9	100.0

12.3.9 Prior Medications / Significant Non-drug Therapies

12.3.9.1 Has the patient received prior medications/ significant non-drug therapies?

	N	%
NA	1	11.1
no	3	33.3
yes	5	55.6
Total	9	100.0

12.3.9.2 Previous treatment

Therapy type:
0=Chemotherapy, 1=Hormonal therapy, 2=Immunotherapy, 3=Targeted therapy, 4=Other

	Regimen number	Therapy type	Medication (as entered in the eCRF by the investigator)	Medication (in harmonized terms)	Start date	End date
subject						
[redacted]						

12.3.10 Stem cell transplantation

Did the patient receive a stem cell transplantation before study start?

	N	%
no	8	88.9
yes	1	11.1
Total	9	100.0

12.3.11 Tasigna Starting Dose

12.3.11.1 Date of first Tasigna intake

V1_F15_Q1

Patient	Date
[redacted]	

12.3.11.2 Current Tasigna daily dose (total)

V1_F15_Q2

Patient	Date	Dose
[redacted]		

	N	%
600	3	33.3
800	6	66.7
Total	9	100.0

12.3.12 ECOG Performance Status (WHO)

V1_F16_Q1 ECOG Performance Status (WHO): Please tick WHO performance status applicable

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 selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours,
3=Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours,
4=Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair,
5=Dead

	N	%
nd	5	55.6
0	4	44.4
Total	9	100.0

12.3.13 12-lead ECG

12.3.13.1 Was a 12-lead ECG performed?

V1_F17_Q1

	N	%
no	6	66.7
yes	3	33.3
Total	9	100.0

12.3.13.2 Date of ECG

V1_F17_Q2

	N	%
17.07.2015	1	11.1
26.01.2015	1	11.1
MC: unknown	1	11.1
OCI:NA	6	66.7
Total	9	100.0

12.3.13.3 QTcF Interval

V1_F17_Q3

	N	%
382	1	11.1
391	1	11.1
MC: unknown	1	11.1
OCI:NA	6	66.7
Total	9	100.0

12.3.13.4 Are clinically significant ECG abnormalities present?

V1_F17_Q4

	N	%
no	3	33.3
OCI:NA	6	66.7
Total	9	100.0

12.3.14 RQ PCR for BCR-ABL

12.3.14.1 Was a Peripheral Blood RQ PCR for BCR-ABL performed?

V1_F18_Q1

	N	%
no	2	22.2
yes	7	77.8
Total	9	100.0

12.3.14.2 Date test performed

V1_F18_Q2

Patient V1_F18_Q2

12.3.14.3 BCR-ABL

V1_F18_Q3

	N	%
detectable	7	77.8
OCI:NA	2	22.2
Total	9	100.0

12.3.14.4 Mean Number of BCR-ABL copies

V1_F18_Q4

	N	%
	4	44.4
MC: Unavaila	3	33.3
OCI:NA	2	22.2
Total	9	100.0

12.3.14.5 Mean Number of ABL copies

V1_F18_Q5

	N	%
No entry	4	44.4
MC: Unavailable	3	33.3
OCI:NA	2	22.2
Total	9	100.0

12.3.14.6 % BCR-ABL/ABL (raw)

V1_F18_Q6

	N	%
0.109	1	11.1
0.24	1	11.1
0.416	1	11.1
0.608	1	11.1
100	1	11.1
12.82	1	11.1
23.494	1	11.1
OCI:NA	2	22.2
Total	9	100.0

Mean	19.67
S.D.	36.53
Median	0.61
Minimum	0.11
Maximum	100
Number	7

12.3.14.7 % BCR-ABL/ABL (IS)

V1_F18_Q7

	N	%
0.083	1	11.1
0.18	1	11.1
0.316	1	11.1
0.461	1	11.1
17.82	1	11.1
9.727	1	11.1
MC: Unavailable	1	11.1
OCI:NA	2	22.2
Total	9	100.0

Mean	4.76
S.D.	7.43
Median	0.39
Minimum	0.08
Maximum	17.82
Number	6

12.3.14.8 Total Number of ABL copies in all replicates

V1_F18_Q8

	N	%
OCI:NA	9	100.0
Total	9	100.0

12.3.14.9 BCR-ABL mutation status

0=Negative, 1=Positive, 2=Polymorphisms only, 3=Inadequate sample, 4=Not done

V1_F18_Q9

	N	%
0	3	33.3
1	2	22.2
4	2	22.2
OCI:NA	2	22.2
Total	9	100.0

12.3.14.10 Mutation type

V1_F18_Q10

	N	%
OCI:NA	7	77.8
Tyr253Phe	1	11.1
major break point	1	11.1
Total	9	100.0

12.3.14.11 % mutation of BCR-ABL

V1_F18_Q11

	N	%
	1	11.1
MC: Unavailable	1	11.1
OCI:NA	7	77.8
Total	9	100.0

12.3.14.12 Mutation type

V1_F18_Q12

	N	%
No entry	1	11.1
MC: Unavailable	1	11.1
OCI:NA	7	77.8
Total	9	100.0

12.3.14.13 % mutation of BCR-ABL

V1_F18_Q13

	N	%
No entry	1	11.1
MC: Unavailable	1	11.1
OCI:NA	7	77.8
Total	9	100.0

12.3.14.14 Mutation type

V1_F18_Q14

	N	%
No entry	1	11.1
MC: Unavailable	1	11.1
OCI:NA	7	77.8
Total	9	100.0

12.3.14.15 % mutation of BCR-ABL

V1_F18_Q15

	N	%
No entry	1	11.1
MC: Unavailable	1	11.1
OCI:NA	7	77.8
Total	9	100.0

12.3.14.16 Other mutations

V1_F18_Q16
0=Negative, 1=Positive, 2=Polymorphisms only, 3=Inadequate sample, 4=Not done

	N	%
0	1	11.1
4	5	55.6
MC: Unavailable	1	11.1
OCI:NA	2	22.2
Total	9	100.0

12.3.14.17 Mutation type

V1_F18_Q17

	N	%
OCI:NA	9	100.0
Total	9	100.0

12.3.14.18 % mutation

V1_F18_Q18

	N	%
OCI:NA	9	100.0
Total	9	100.0

12.3.14.19 Mutation type

V1_F18_Q19

	N	%
OCI:NA	9	100.0
Total	9	100.0

12.3.14.20 % mutation

V1_F18_Q20

	N	%
OCI:NA	9	100.0
Total	9	100.0

12.3.14.21 Mutation type

V1_F18_Q21

	N	%
OCI:NA	9	100.0
Total	9	100.0

12.3.14.22 % mutation

V1_F18_Q22

	N	%
OCI:NA	9	100.0
Total	9	100.0

12.3.14.23 Performed at which lab?

V1_F18_Q23

	N	%
KIMCL AKH Wien	6	66.7
Krankenhaus der Elisaethinen Linz GmbH	1	11.1
OCI:NA	2	22.2
Total	9	100.0

12.3.14.24 Optional Comment

V1_F18_Q24

	N	%
	7	77.8
OCI:NA	2	22.2
Total	9	100.0

12.3.15 Haematology

12.3.15.1 Erythrocytes (T/L)

V1_F19_Q4

Mean	4.22
S.D.	0.53
Median	4.3
Minimum	3.4
Maximum	4.94
Number	9

12.3.15.2 Hematocrit (%)

V1_F19_Q8

Mean	37.86
S.D.	4
Median	38.9
Minimum	31.9
Maximum	43.9
Number	9

12.3.15.3 Hemoglobin (g/dL)

V1_F19_Q12

Mean	12.69
S.D.	1.28
Median	13.1
Minimum	10.8
Maximum	14.6
Number	9

12.3.15.4 Platelets (G/L)

V1_F19_Q16

Mean	266.44
S.D.	187.33
Median	169
Minimum	95
Maximum	613
Number	9

12.3.15.5 White Blood Count (G/L)

V1_F19_Q20

Mean	10.75
S.D.	7.88
Median	6.29
Minimum	4
Maximum	23.2
Number	8

12.3.15.6 Leukocytes (G/L)

V1_F19_Q24

Mean	14.17
S.D.	19.88
Median	6.27
Minimum	4
Maximum	58.8
Number	7

12.3.15.7 Neutrophils absolute (G/L)

V1_F19_Q28

Mean	9.34
S.D.	10.69
Median	4.5
Minimum	2.1
Maximum	31.8
Number	8

12.3.15.8 Neutrophils (%)

V1_F19_Q32

Mean	61.22
S.D.	14.04
Median	65
Minimum	35
Maximum	85
Number	9

12.3.15.9 Bands absolute (G/L)

V1_F19_Q35

Not assessed

12.3.15.10 Bands (%)

V1_F19_Q39

Mean	0.86
S.D.	1.86
Median	0
Minimum	0
Maximum	5
Number	7

12.3.15.11 Lymphocytes absolute (G/L)

V1_F19_Q42

Mean	2.15
S.D.	0.35
Median	2.15
Minimum	1.9
Maximum	2.4
Number	2

12.3.15.12 Lymphocytes (%)

V1_F19_Q46

Mean	21
S.D.	11.31
Median	24
Minimum	4
Maximum	37
Number	9

12.3.15.13 Eosinophiles absolute (G/L)

V1_F19_Q49

Mean	0.2
S.D.	0
Median	0.2
Minimum	0.2
Maximum	0.2
Number	1

12.3.15.14 Eosinophiles (%)

V1_F19_Q53

Mean	3.13
S.D.	1.36
Median	3.5
Minimum	1
Maximum	5
Number	8

12.3.15.15 Basophiles absolute (G/L)

V1_F19_Q56

Mean	7.1
S.D.	0
Median	7.1
Minimum	7.1
Maximum	7.1
Number	1

12.3.15.16 Basophiles (%)

V1_F19_Q60

Mean	2.13
S.D.	4.16
Median	0
Minimum	0
Maximum	12
Number	8

12.3.15.17 Monocytes absolute (G/L)

V1_F19_Q63

Mean	1.6
S.D.	0.28
Median	1.6
Minimum	1.4
Maximum	1.8
Number	2

12.3.15.18 Monocytes (%)

V1_F19_Q67

Mean	7.56
S.D.	4.48
Median	6
Minimum	2
Maximum	13
Number	9

12.3.15.19 Promyelocytes absolute (G/L)

V1_F19_Q70

Not assessed

12.3.15.20 Promyelocytes (%)

V1_F19_Q74

Mean	0.14
S.D.	0.38
Median	0
Minimum	0
Maximum	1
Number	7

12.3.15.21 Myelocytes absolute (G/L)

V1_F19_Q77

Mean	2.9
S.D.	0
Median	2.9
Minimum	2.9
Maximum	2.9
Number	1

12.3.15.22 Myelocytes (%)

V1_F19_Q81

Mean	2
S.D.	2.88
Median	0
Minimum	0
Maximum	7
Number	8

12.3.15.23 Metamyelocytes absolute (G/L)

V1_F19_Q84

Mean	12.9
S.D.	0
Median	12.9
Minimum	12.9
Maximum	12.9
Number	1

12.3.15.24 Metamyelocytes (%)

V1_F19_Q88

Mean	3.38
S.D.	7.61
Median	0
Minimum	0
Maximum	22
Number	8

12.3.15.25 Blasts absolute (G/L)

V1_F19_Q91

Not assessed

12.3.15.26 Blasts (%)

V1_F19_Q95

Mean	0
S.D.	0
Median	0
Minimum	0
Maximum	0
Number	6

12.3.15.27 Reticolocyte count (G/L)

V1_F19_Q98

Mean	53.49
S.D.	26.23
Median	43.5
Minimum	22.2
Maximum	97.7
Number	7

12.3.16 Biochemistry

12.3.16.1 Urea (mg/dL)

V1_F20_Q4

Not assessed

12.3.16.2 Creatinine (mg/dL)

V1_F20_Q8

Mean	1.04
S.D.	0.2
Median	1.05
Minimum	0.74
Maximum	1.33
Number	9

12.3.16.3 Uric acid (mg/dL)

V1_F20_Q12

Mean	7.83
S.D.	5.95
Median	5.6
Minimum	2.4
Maximum	19.7
Number	8

12.3.16.4 Albumin (g/L)

V1_F20_Q16

Mean	43.98
S.D.	1.89
Median	43.9
Minimum	41.4
Maximum	46.8
Number	6

12.3.16.5 Total Protein (g/L)

V1_F20_Q20

Mean	49.14
S.D.	26.06
Median	61.7
Minimum	6.9
Maximum	66.9
Number	8

12.3.16.6 Total Bilirubin (mg/dL)

V1_F20_Q24

Mean	0.48
S.D.	0.27
Median	0.36
Minimum	0.23
Maximum	1.04
Number	9

12.3.16.7 Direct Bilirubin (mg/dL)

V1_F20_Q28

Not assessed

12.3.16.8 Indirect Bilirubin (mg/dL)

V1_F20_Q32

Not assessed

12.3.16.9 Alkaline phosphatase (U/L)

V1_F20_Q36

Mean	68
S.D.	20.55
Median	67
Minimum	31
Maximum	96
Number	9

12.3.16.10 GOT (AST) (U/L)

V1_F20_Q39

Mean	38.33
S.D.	30.98
Median	28
Minimum	22
Maximum	120
Number	9

12.3.16.11 GPT (ALT) (U/L)

V1_F20_Q42

Mean	50.89
S.D.	71.51
Median	27
Minimum	19
Maximum	241
Number	9

12.3.16.12 Gamma-GT (U/L)

V1_F20_Q44

Mean	37.33
S.D.	24.37
Median	33
Minimum	11
Maximum	93
Number	9

12.3.16.13 Lipase (U/L)

V1_F20_Q48

Mean	62.5
S.D.	51.68
Median	40.5
Minimum	19
Maximum	160
Number	6

12.3.16.14 Amylase (U/L)

V1_F20_Q51

Mean	63.2
S.D.	22.87
Median	74
Minimum	25
Maximum	79
Number	5

12.3.16.15 LDH (U/L)

V1_F20_Q54

Mean	238
S.D.	72.57
Median	215
Minimum	141
Maximum	399
Number	9

12.3.16.16 Sodium (mmol/L)

V1_F20_Q57

Mean	141.56
S.D.	1.94
Median	141
Minimum	139
Maximum	145
Number	9

12.3.16.17 Potassium (mmol/L)

V1_F20_Q61

Mean	4.32
S.D.	0.31
Median	4.33
Minimum	3.73
Maximum	4.7
Number	9

12.3.16.18 Calcium (mmol/L)

V1_F20_Q65

Mean	2.3
S.D.	0.12
Median	2.27
Minimum	2.11
Maximum	2.45
Number	9

12.3.16.19 Magnesium (mmol/L)

V1_F20_Q69

Mean	0.85
S.D.	0.07
Median	0.85
Minimum	0.76
Maximum	0.94
Number	6

12.3.16.20 Cholesterin total (mg/dL)

V1_F20_Q73

Mean	183.56
S.D.	64.11
Median	186
Minimum	92
Maximum	305
Number	9

12.3.16.21 LDL-Cholesterin (mg/dL)

V1_F20_Q77

Mean	108.87
S.D.	53.27
Median	121.8
Minimum	30.2
Maximum	204.4
Number	9

12.3.16.22 HDL-Cholesterin (mg/dL)

V1_F20_Q81

Mean	42.67
S.D.	8.46
Median	38
Minimum	34
Maximum	57
Number	9

12.3.16.23 HbA1c (%)

V1_F20_Q85

Mean	5.36
S.D.	0.18
Median	5.4
Minimum	5.1
Maximum	5.6
Number	5

12.3.16.24 Glucose (fasting) (mg/dL)

V1_F20_Q89

Mean	98.25
S.D.	13.28
Median	96.5
Minimum	84
Maximum	116
Number	4

12.3.16.25 Insulin (fasting 12h)

V1_F20_Q93

Not assessed

12.3.16.26 Fibrinogen (mg/dL)

V1_F20_Q97

Mean	309.33
S.D.	15.14
Median	316
Minimum	292
Maximum	320
Number	3

12.3.16.27 Homocysteine (µmol/L)

V1_F20_Q101

Not assessed.

12.3.16.28 Ferritin (ng/mL)

V1_F20_Q105

Mean	680.18
S.D.	1182.15
Median	224.8
Minimum	117.8
Maximum	3091.1
Number	6

12.3.16.29 TSH (µg/L)

V1_F20_Q109

Mean	2.91
S.D.	0.1
Median	2.91
Minimum	2.84
Maximum	2.98
Number	2

12.3.16.30 Triiodthyronin (fT3) (ng/L)

V1_F20_Q113

Mean	2.64
S.D.	0
Median	2.64
Minimum	2.64
Maximum	2.64
Number	1

12.3.16.31 Thyroxin (ng/L)

V1_F20_Q117

Not assessed

12.3.16.32 CRP (mg/dL)

V1_F20_Q121

Mean	0.4
S.D.	0.61
Median	0.17
Minimum	0.09
Maximum	1.9
Number	8

12.3.17 OGTT

12.3.17.1Was an OGTT performed?

V1_F21_Q1

	N	%
No	8	88.9
Yes	1	11.1
Total	9	100.0

12.3.18 Microalbuminuria

12.3.18.1 Urine Protein (Microalbuminuria / Proteinuria) Test performed

	N	%
no	9	100.0
Total	9	100.0

12.3.19 Echocardiogram

12.3.19.1 Was an Echocardiogram performed?

V1_F23_Q1

	N	%
no	7	77.8
yes	2	22.2
Total	9	100.0

12.3.19.2 Doppler-Sonography

12.3.19.3 Was a Doppler-Sonography performed?

V1_F24_Q1

	N	%
no	8	88.9
yes	1	11.1
Total	9	100.0

12.3.20 Ankle-Brachial Index & Toe-Brachial Index

12.3.20.1 Was the Ankle-Brachial Index measured?

V1_F25_Q1

	N	%
no	9	100.0
Total	9	100.0

12.3.21 Computed Tomography Angiography (CTA)

12.3.21.1 Was a Computed Tomography Angiography (CTA) performed?

V1_F26_Q1

	N	%
no	9	100.0
Total	9	100.0

12.3.22 Magnet Resonance Imaging (MRI)

12.3.22.1 Was a Magnet Resonance Imaging (MRI) performed?

V1_F27_Q1

	N	%
no	9	100.0
Total	9	100.0

12.4 Visits

12.4.1 Total observation time

Site	Patient	Time (months)
[redacted]		
	Mean	6.8
	SD	3.7
	Median	5.9
	Minimum	1.4
	Maximum	13.3
	N	9

12.4.2 Visit dates

Patient	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8
[redacted]								

12.4.2.1 Time differences (months) to visit 1

Patient	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8
[redacted]							

12.4.2.2 Angiologic assessments between baseline and final visit

The following table summarizes relevant angiologic assessments (i.e. Doppler-Sonography, Ankle-Brachial-Index (ABI), Magnet Resonance Imaging (MRI) and Computed Tomography Angiography (CTA)) performed between baseline and final visit (visit 8) in all patients. All documented assessments from visits 2 through 7 are summarized in the table.

Patient	Date	Visit No.	Assessment type	Documented results
[redacted]				

12.5 Concomitant medication

subject Medication Indication Start date ongoing End date Dose Units daily Route for SAE

[redacted]

Is this medication used to treat a SAE?

[redacted]

12.6 Final visit (visit 8) / change to baseline

12.6.1 Completion / Discontinuation

12.6.1.1 Has the Tasigna PASS been terminated prematurely?

1=No = Completion, 2=Yes = Discontinuation

	N	%
no entry	1	11.1
no	1	11.1
yes	7	77.8
Total	9	100.0

Specify:
0=Lack of compliance, 1=withdrawal of consent, 2=loss of contact to patient, 3=No response to therapy, 4=Progression of disease, 5=AE, 6=Worsening of general condition, 7=Death of patient, 8=Infection, 9=Other

V8_F2_Q2

	N	%
3	2	22.2
5	1	11.1
9	5	55.6
OCI_NA	1	11.1
Total	9	100.0

If other, please specify: termination by the sponsor

12.6.2 Physical Examination

No physical examination documented at visit 8.

12.6.3 Cytogenetic Analysis

12.6.3.1 Was a cytogenetic analysis performed?

	N	%
no	0	8
yes	1	1
Total	9	100.0

The results of analysis for patient [redacted] are documented below.

[redacted]

12.6.4 RQ PCR for BCR-ABL

12.6.4.1 Was a Peripheral Blood RQ PCR for BCR-ABL performed?

V8_F6_Q1

	N	%
yes	9	100.0
Total	9	100.0

12.6.4.2 Date test performed

V8_F6_Q2

Patient	V8_F6_Q2
[redacted]	

12.6.4.3 BCR-ABL

V8_F6_Q3

	N	%
detectable	9	100.0
Total	9	100.0

12.6.4.4 Mean Number of BCR-ABL copies

V8_F6_Q4

	N	%
	7	77.8
10	1	11.1
947	1	11.1
Total	9	100.0

12.6.4.5 Mean Number of ABL copies

V8_F6_Q5

	N	%
	7	77.8
142698	1	11.1
46641	1	11.1
Total	9	100.0

12.6.4.6 % BCR-ABL/ABL (raw)

V8_F6_Q6

	N	%
	1	11.1
0.01	1	11.1
0.014	1	11.1
0.021	1	11.1
0.036	1	11.1
0.052	1	11.1
0.664	1	11.1
14.098	1	11.1
40.154	1	11.1
Total	9	100.0

Mean	6.88
S.D.	14.31
Median	0.04
Minimum	0.01
Maximum	40.15
Number	8

12.6.4.7 % BCR-ABL/ABL (IS)

V8_F6_Q7

	N	%
	2	22.2
0.011	1	11.1
0.026	1	11.1
0.027	1	11.1
0.039	1	11.1
0.635	1	11.1
10.693	1	11.1
30.457	1	11.1
Total	9	100.0

Mean	5.98
S.D.	11.49
Median	0.04
Minimum	0.01
Maximum	30.46
Number	7

12.6.4.8 Total Number of ABL copies in all replicates

V8_F6_Q8

	N	%
OCI:NA	9	100.0
Total	9	100.0

12.6.4.9 BCR-ABL mutation status

0=Negative, 1=Positive, 2=Polymorphisms only, 3=Inadequate sample, 4=Not done

V8_F6_Q9

	N	%
1	2	22.2
3	1	11.1
4	6	66.7
Total	9	100.0

12.6.4.10 Mutation type

V8_F6_Q10

	N	%
OCI:NA	7	77.8
Thr253Phe, Thr315Ile	1	11.1
major break point	1	11.1
Total	9	100.0

12.6.4.11% mutation of BCR-ABL

V8_F6_Q11

	N	%
NA	9	100.0
Total	9	100.0

12.6.4.12 Mutation type

V8_F6_Q12

	N	%
NA	9	100.0
Total	9	100.0

12.6.4.13 % mutation of BCR-ABL

V8_F6_Q13

	N	%
NA	9	100.0
Total	9	100.0

12.6.4.14 Mutation type

V8_F6_Q14

	N	%
	1	11.1
NA	9	100.0
Total	9	100.0

12.6.4.15 % mutation of BCR-ABL

V8_F6_Q15

	N	%
	1	11.1
NA	9	100.0
Total	9	100.0

12.6.4.16 Other mutations

V8_F6_Q16

	N	%
Not done	9	100.0
Total	9	100.0

12.6.4.17 Mutation type

V8_F6_Q17

	N	%
OCI:NA	9	100.0
Total	9	100.0

12.6.4.18 % mutation

V8_F6_Q18

	N	%
OCI:NA	9	100.0
Total	9	100.0

12.6.4.19 Mutation type

V8_F6_Q19

	N	%
OCI:NA	9	100.0
Total	9	100.0

12.6.4.20 % mutation

V8_F6_Q20

	N	%
OCI:NA	9	100.0
Total	9	100.0

12.6.4.21 Mutation type

V8_F6_Q21

	N	%
OCI:NA	9	100.0
Total	9	100.0

12.6.4.22 % mutation

V8_F6_Q22

	N	%
OCI:NA	9	100.0
Total	9	100.0

12.6.4.23 Performed at which lab?

V8_F6_Q23

	N	%
KIMCL AKH Wien	6	66.7
Krankenhaus der Elisaethinen Linz GmbH	1	11.1
OCI:NA	2	22.2
Total	9	100.0

12.6.4.24 Optional Comment

V8_F6_Q24

	N	%
	7	77.8
OCI:NA	2	22.2
Total	9	100.0

12.6.5 Response

12.6.5.1 Hematologic remission?

V8_F7_Q1
0=complete (CHR), 1=No (No HR), 2=not assessed

	N	%
0	8	88.9
1	1	11.1
SUMME	9	100.0

12.6.5.2 Cytogenetic Analysis response

V8_F7_Q2
0=CCyR (0% PH+ metaphases), 1=PCyR (1 – 35% PH+ metaphases), 2=mCyR (36 - 65% PH+ metaphases), 3=minCyR (66 - 95% PH+ metaphases), 4=noCyR (95+% PH+ metaphases)

	N	%
No entry	1	11.1
0	4	44.4
4	1	11.1
MC_ Unavailable	3	33.3
Total	9	100.0

12.6.5.3 Peripheral Blood - RQ PCR response

V8_F7_Q3
0=MR < 3 log, 1=MR 3 - 4.5 log, 2=MR > 4.5 log, 3=undetectable

	N	%
No entry	1	11.1
0	1	11.1
1	4	44.4
MC_ Unavailable	3	33.3
Total	9	100.0

12.6.6 Bone Marrow Analysis

12.6.6.1 Was a Bone Marrow analysis performed?

	N	%
No	8	88.9
yes	1	11.1
Total	9	100.0

Yes: patient [redacted]

[redacted]

Comment:
Percent of blasts is below 1%, percent of promyelocytes is below 1%, percent of basophils is below 1%, Bone marrow smear is limited representive without an increase in blastcells, Slight eosinophilia,

12.6.7 ECOG Performance Status (WHO)

Not done at visit 8

12.6.8 12-lead ECG

Not done at visit 8

12.6.9 Hematology

Hematology was performed with all patients at visit 8. The following descriptive tables show visit 1 and visit 8 data together.

12.6.9.1 Erythrocytes (T/L)

	Visit1	Visit 8
Mean	4.2	4.7
S.D.	0.5	0.6
Median	4.3	5.0
Minimum	3.4	3.8
Maximum	4.9	5.5
Number	9	9

12.6.9.2 Hematocrit (%)

	Visit1	Visit 8
Mean	37.9	39.8
S.D.	3.8	4.7
Median	38.9	39.6
Minimum	31.9	33.2
Maximum	43.9	46.0
Number	9	9

12.6.9.3 Hemoglobin (g/dL)

	Visit1	Visit 8
Mean	12.7	13.5
S.D.	1.2	1.5
Median	13.1	13.3
Minimum	10.8	11.5
Maximum	14.6	15.4
Number	9	9

12.6.9.4 Platelets (G/L)

	Visit1	Visit 8
Mean	266.4	244.0
S.D.	176.6	146.1
Median	169.0	175.0
Minimum	95.0	107.0
Maximum	613.0	616.0
Number	9	9

12.6.9.5 White Blood Count (G/L)

	Visit1	Visit 8
Mean	10.7	10.6
S.D.	7.4	5.1
Median	6.3	8.2
Minimum	4.0	6.9
Maximum	23.2	21.8
Number	8	7

12.6.9.6 Leucocytes (G/L)

	Visit1	Visit 8
Mean	14.2	11.0
S.D.	18.4	5.0
Median	6.3	8.3
Minimum	4.0	6.9
Maximum	58.8	21.8
Number	7	9

12.6.9.7 Neutrophils absolute (G/L)

	Visit1	Visit 8
Mean	9.3	8.3
S.D.	10.0	4.7
Median	4.5	5.7
Minimum	2.1	3.9
Maximum	31.8	17.8
Number	8	8

12.6.9.8 Neutrophils (%)

	Visit1	Visit 8
Mean	61.2	65.1
S.D.	13.2	11.8
Median	65.0	58.1
Minimum	35.0	50.0
Maximum	85.0	83.0
Number	9	9

12.6.9.9 Bands absolute (G/L)

Not assessed

12.6.9.10 Bands (%)

	Visit1	Visit 8
Mean	0.9	1.6
S.D.	1.7	3.5
Median	0.0	0.0
Minimum	0.0	0.0
Maximum	5.0	10.0
Number	7	7

12.6.9.11 Lymphocytes absolute (G/L)

	Visit1	Visit 8
Mean	2.2	2.7
S.D.	0.3	0.0
Median	2.2	2.7
Minimum	1.9	2.7
Maximum	2.4	2.7
Number	2	2

12.6.9.12 Lymphocytes (%)

	Visit1	Visit 8
Mean	21.0	20.9
S.D.	10.7	11.7
Median	24.0	17.0
Minimum	4.0	5.0
Maximum	37.0	38.0
Number	9	9

12.6.9.13 Eosinophiles absolute (G/L)

	Visit1	Visit 8
Mean	0.2	0.3
S.D.	0.0	0.1
Median	0.2	0.3
Minimum	0.2	0.2
Maximum	0.2	0.4
Number	1	2

12.6.9.14 Eosinophiles (%)

	Visit1	Visit 8
Mean	3.1	3.0
S.D.	1.3	2.3
Median	3.5	2.2
Minimum	1.0	0.0
Maximum	5.0	6.9
Number	8	9

12.6.9.15 Basophiles absolute (G/L)

	Visit1	Visit 8
Mean	7.1	0.1
S.D.	0.0	0.0
Median	7.1	0.1
Minimum	7.1	0.1
Maximum	7.1	0.1
Number	1	2

12.6.9.16 Basophiles (%)

	Visit1	Visit 8
Mean	2.1	0.4
S.D.	3.9	0.4
Median	0.0	0.4
Minimum	0.0	0.0
Maximum	12.0	1.0
Number	8	9

12.6.9.17 Monocytes absolute (G/L)

	Visit1	Visit 8
Mean	1.6	1.1
S.D.	0.2	0.4
Median	1.6	1.1
Minimum	1.4	0.7
Maximum	1.8	1.4
Number	2	2

12.6.9.18 Monocytes (%)

	Visit1	Visit 8
Mean	7.6	6.9
S.D.	4.2	2.0
Median	6.0	7.5
Minimum	2.0	2.0
Maximum	13.0	9.0
Number	9	9

12.6.9.19 Promyelocytes absolute (G/L)

Not assessed

12.6.9.20 Promyelocytes (%)

	Visit1	Visit 8
Mean	0.1	0.0
S.D.	0.3	0.0
Median	0.0	0.0
Minimum	0.0	0.0
Maximum	1.0	0.0
Number	7	7

12.6.9.21 Myelocytes absolute (G/L)

	Visit1	Visit 8
Mean	2.9	
S.D.	0.0	
Median	2.9	
Minimum	2.9	
Maximum	2.9	
Number	1	0

12.6.9.22 Myelocytes (%)

	Visit1	Visit 8
Mean	2.0	2.0
S.D.	2.7	4.5
Median	0.0	0.0
Minimum	0.0	0.0
Maximum	7.0	13.0
Number	8	7

12.6.9.23 Metamyelocytes absolute (G/L)

	Visit1	Visit 8
Mean	12.9	
S.D.	0.0	
Median	12.9	
Minimum	12.9	
Maximum	12.9	
Number	1	0

12.6.9.24 Metamyelocytes (%)

	Visit1	Visit 8
Mean	3.4	0.9
S.D.	7.1	2.1
Median	0.0	0.0
Minimum	0.0	0.0
Maximum	22.0	6.0
Number	8	7

12.6.9.25 Blasts absolute (G/L)

Not assessed

12.6.9.26 Blasts (%)

	Visit1	Visit 8
Mean	0.0	0.1
S.D.	0.0	0.3
Median	0.0	0.0
Minimum	0.0	0.0
Maximum	0.0	1.0
Number	6	7

12.6.9.27 Reticolocyte count (G/L)

	Visit1	Visit 8
Mean	53.5	66.3
S.D.	24.3	37.3
Median	43.5	54.0
Minimum	22.2	29.2
Maximum	97.7	144.7
Number	7	6

12.6.10 Biochemistry

12.6.10.1 Urea (mg/dL)

Not assessed

12.6.10.2 Creatinine (mg/dL)

	Visit1	Visit 8
Mean	1.0	1.0
S.D.	0.2	0.1
Median	1.1	1.0
Minimum	0.7	0.7
Maximum	1.3	1.2
Number	9	9

12.6.10.3 Uric acid (mg/dL)

	Visit1	Visit 8
Mean	7.8	5.4
S.D.	5.6	1.1
Median	5.6	5.8
Minimum	2.4	3.0
Maximum	19.7	6.5
Number	8	8

12.6.10.4 Albumin (g/L)

	Visit1	Visit 8
Mean	44.0	38.1
S.D.	1.7	13.5
Median	43.9	43.5
Minimum	41.4	5.1
Maximum	46.8	45.8
Number	6	7

12.6.10.5 Total Protein (g/L)

	Visit1	Visit 8
Mean	49.1	52.3
S.D.	24.4	25.9
Median	61.7	66.9
Minimum	6.9	7.2
Maximum	66.9	68.2
Number	8	8

12.6.10.6 Total Bilirubin (mg/dL)

	Visit1	Visit 8
Mean	0.5	0.9
S.D.	0.3	0.4
Median	0.4	0.9
Minimum	0.2	0.4
Maximum	1.0	1.5
Number	9	9

12.6.10.7 Direct Bilirubin (mg/dL)

Not assessed

12.6.10.8 Indirect Bilirubin (mg/dL)

Not assessed

12.6.10.9 Alkaline phosphatase (U/L)

	Visit1	Visit 8
Mean	68.0	77.9
S.D.	19.4	21.1
Median	67.0	82.0
Minimum	31.0	38.0
Maximum	96.0	107.0
Number	9	9

12.6.10.10 GOT (AST) (U/L)

	Visit1	Visit 8
Mean	38.3	31.6
S.D.	29.2	18.0
Median	28.0	26.0
Minimum	22.0	16.0
Maximum	120.0	79.0
Number	9	9

12.6.10.11 GPT (ALT) (U/L)

	Visit1	Visit 8
Mean	50.9	46.0
S.D.	67.4	32.7
Median	27.0	31.0
Minimum	19.0	21.0
Maximum	241.0	122.0
Number	9	9

12.6.10.12 Gamma-GT (U/L)

	Visit1	Visit 8
Mean	37.3	60.9
S.D.	23.0	30.3
Median	33.0	43.0
Minimum	11.0	25.0
Maximum	93.0	103.0
Number	9	9

12.6.10.13 Lipase (U/L)

	Visit1	Visit 8
Mean	62.5	30.8
S.D.	47.2	9.9
Median	40.5	31.5
Minimum	19.0	15.0
Maximum	160.0	46.0
Number	6	6

12.6.10.14 Amylase (U/L)

	Visit1	Visit 8
Mean	63.2	63.7
S.D.	20.5	17.3
Median	74.0	61.5
Minimum	25.0	41.0
Maximum	79.0	85.0
Number	5	6

12.6.10.15 LDH (U/L)

	Visit1	Visit 8
Mean	238.0	205.8
S.D.	68.4	56.0
Median	215.0	182.0
Minimum	141.0	137.0
Maximum	399.0	313.0
Number	9	9

12.6.10.16 Sodium (mmol/L)

	Visit1	Visit 8
Mean	141.6	141.1
S.D.	1.8	1.5
Median	141.0	141.0
Minimum	139.0	138.0
Maximum	145.0	143.0
Number	9	9

12.6.10.17 Potassium (mmol/L)

	Visit1	Visit 8
Mean	4.3	4.3
S.D.	0.3	0.2
Median	4.3	4.3
Minimum	3.7	3.8
Maximum	4.7	4.5
Number	9	9

12.6.10.18 Calcium (mmol/L)

	Visit1	Visit 8
Mean	2.3	2.3
S.D.	0.1	0.1
Median	2.3	2.3
Minimum	2.1	2.2
Maximum	2.5	2.4
Number	9	8

12.6.10.19 Magnesium (mmol/L)

	Visit1	Visit 8
Mean	0.9	0.9
S.D.	0.1	0.1
Median	0.9	0.9
Minimum	0.8	0.8
Maximum	0.9	1.1
Number	6	5

12.6.10.20 Cholesterin total (mg/dL)

	Visit1	Visit 8
Mean	183.6	161.5
S.D.	60.4	36.3
Median	186.0	180.0
Minimum	92.0	108.0
Maximum	305.0	196.0
Number	9	6

12.6.10.21 LDL-Cholesterin (mg/dL)

	Visit1	Visit 8
Mean	108.9	83.2
S.D.	50.2	25.8
Median	121.8	90.4
Minimum	30.2	49.0
Maximum	204.4	110.4
Number	9	5

12.6.10.22 HDL-Cholesterin (mg/dL)

	Visit1	Visit 8
Mean	42.7	49.8
S.D.	8.0	21.3
Median	38.0	46.0
Minimum	34.0	25.0
Maximum	57.0	87.0
Number	9	5

12.6.10.23 HbA1c (%)

	Visit1	Visit 8
Mean	5.4	5.6
S.D.	0.2	0.4
Median	5.4	5.8
Minimum	5.1	5.0
Maximum	5.6	6.0
Number	5	3

12.6.10.24 Glucose (fasting) (mg/dL)

	Visit1	Visit 8
Mean	98.3	87.0
S.D.	11.5	2.0
Median	96.5	87.0
Minimum	84.0	85.0
Maximum	116.0	89.0
Number	4	2

12.6.10.25 Insulin (fasting 12h)

Not assessed

12.6.10.26 Fibrinogen (mg/dL)

	Visit1	Visit 8
Mean	309.3	
S.D.	12.4	
Median	316.0	
Minimum	292.0	
Maximum	320.0	
Number	3	0

12.6.10.27 Homocysteine (µmol/L)

Not assessed

12.6.10.28 Ferritin (µg/L)

	Visit1	Visit 8
Mean	680.2	405.0
S.D.	1079.2	648.8
Median	224.8	183.5
Minimum	117.8	77.1
Maximum	3091.1	2116.4
Number	6	8

12.6.10.29 TSH (µg/L)

	Visit1	Visit 8
Mean	2.9	1.6
S.D.	0.1	0.0
Median	2.9	1.6
Minimum	2.8	1.6
Maximum	3.0	1.6
Number	2	1

12.6.10.30 Triiodthyronin (fT3) (ng/L)

	Visit1	Visit 8
Mean	2.6	
S.D.	0.0	
Median	2.6	
Minimum	2.6	
Maximum	2.6	
Number	1	0

12.6.10.31 Thyroxin (ng/L)

Not assessed

12.6.10.32 CRP (mg/dL)

	Visit1	Visit 8
Mean	0.4	13.0
S.D.	0.6	33.0
Median	0.2	0.4
Minimum	0.1	0.2
Maximum	1.9	100.4
Number	8	8

12.7 Treatment log

Reason for dose change
0=Adverse Event, 1=inadequate response, 2=concomitant medication (e.g. CYP3A4-inhibitor), 3=other

Dose schedule: 0=once daily, 1=twice daily

subject	Reason for dose change	please specify	Start date	End date	Dose/day	Dose/ schedule	Tablets á 150 mg	Tablets á 200 mg
[redacted]								

12.7.1 OGTT

Not done at visit 8

12.7.2 Microalbuminuria

12.7.2.1 Urine Protein (Microalbuminuria / Proteinuria) test performed

	N	%
no	9	100.0
Total	9	100.0

12.7.3 Echocardiogram

12.7.3.1 Was an Echocardiogram performed?

	N	%
no	9	100.0
Total	9	100.0

12.7.4 Doppler-Sonography

12.7.4.1 Was a Doppler-Sonography performed?

	N	%
no	9	100.0
Total	9	100.0

12.7.5 Ankle-Brachial Index & Toe-Brachial Index

12.7.5.1 Was the Ankle-Brachial Index measured?

	N	%
no	9	100.0
Total	9	100.0

12.7.6 Computed Tomography Angiography (CTA)

12.7.6.1 Was a Computed Tomography Angiography (CTA) performed?

	N	%
no	9	100.0
Total	9	100.0

12.7.7 Magnet Resonance Imaging (MRI)

12.7.7.1 Was a Magnet Resonance Imaging (MRI) performed?

	N	%
no	9	100.0
Total	9	100.0

12.7.8 Tasigna Therapy

12.7.8.1 Has Tasigna been taken constantly without any change in dose since the last visit?

V8_F20_Q1
0=No, 1=Yes

	N	%
	1	11.1
0	1	11.1
1	7	77.8
Total	9	100.0

12.7.8.2 Will the dose be changed or is a therapy pause planned?

V8_F20_Q2
0=No, 1=Yes

	N	%
0	6	66.7
1	3	33.3
Total	9	100.0

12.7.8.3 Will the patient continue to take Tasigna?

V8_F20_Q3
0=No, 1=Yes

	N	%
0	4	44.4
1	5	55.6
Total	9	100.0

12.7.9 Additional Concomitant Medication

12.7.9.1 Concomitant medication changed?

V8_F21_Q1
0=No, 1=Yes

	N	%
0	4	44.4
1	5	55.6
Total	9	100.0

12.7.10 New Medical Conditions / Worsening of Existing Medical Conditions

12.7.10.1 New medical conditions or already existing medical conditions worsened?

V8_F22_Q1
0=No, 1=Yes

	N	%
	1	11.1
0	6	66.7
1	2	22.2
Total	9	100.0

13 Adverse events

13.1 Serious adverse events (SAEs)

13.1.1 Codes

Report type	1=Initial, 2=Follow-Up
Was the treatment code broken?	1=Yes, please enter in section 6, 0=No, 2=Not applicable (i.e. open study)
Sex	1=Male, 2=Female
Ethnicity	1=Caucasian, 2=Black, 3=Hispanic, 4=Asian, 5=Other, 6=Unknown
Frequency	1=once daily, 2=twice daily, 3=other
Action taken	1=1. Study treatment continued unchanged, 2=2. Study treatment withdrawn**, 3=3. Study treatment dose reduced**, 4=4. Study treatment dose increased**, 5=5. Study treatment interrupted**, 6=6. Unknown
Event improved	1=yes, 0=no
Study treatment restarted	1=yes, 2=no
Did the event reoccur?	1=yes, 0=no
Visit name before onset of SAE	1=V1, 2=V2, 3=V3, 4=V4, 5=V5, 6=V6, 7=V7, 8=V8/ET
Action taken	1=1. Medication continued unchanged, 2=2. Medication withdrawn**, 3=3. Medication dose reduced**, 4=4. Medication dose increased**, 5=5. Medication interrupted**, 6=6. Unknown
Action taken	1=1. Medication continued unchanged, 2=2. Medication withdrawn**, 3=3. Medication dose reduced**, 4=4. Medication dose increased**, 5=5. Medication interrupted**, 6=6. Unknown
Is this a diagnosis?	1=yes, 0=no
Seriousness criteria	1=1. Death, 2=2. Life threatening, 3=3. Involved or prolonged inpatient hospitalization, 4=4. Results in persistent or significant disability/incapacity, 5=5. Congenital anomaly/birth defect., 6=6. Medically significant event
Outcome	1. Not recovered / Not resolved / Unchanged=1. Not recovered / Not resolved / Unchanged, 2. Condition deteriorating=2. Condition deteriorating, 3. Recovered / resolved=3. Recovered / resolved, 4. Improving / recovering / resolving=4. Improving / recovering / resolving, 5. Recovered with sequelae (please specify sequelae in section 10 or 15)=5. Recovered with sequelae (please specify sequelae in section 10 or 15), 6. Fatal=6. Fatal, 7. Unknown=7. Unknown
Is there a reasonable possibility that the study treatment caused the event?	1=yes, 0=no
Other possible contr butory factors	1=1. Lack of efficacy to study treatment, 2=2. Progression of study indication*, 3=3. Progression of concomitant disease (specify disease in box)., 4=4. Aggravation of study indication (specify cause of aggravation in box)., 5=5. Study conduct (please specify in box)., 6=6. Other (please specify in box)., 7=7. None.
11. Did the subject die?	0=No, 1=Yes
If subject died, was an autopsy performed?	1=Yes *, 0=No, 2=Unknown
* If yes, date of autopsy	

13.1.2 Individual SAEs ([redacted])

Country	[redacted]
Centre Number	
Indication	
Study ID	
Report type	
Was the treatment code broken?	
Subject ID	
Year of Birth	
Age	
Sex	
Ethnicity	
Weight	
Height	
Condition	
Onset date	
Ongoing at time of SAE?	
If no, End date	
Study treatment	
Date dose first received	
Date this dose last taken prior to SAE	
Dosage	
Frequency	
If other frequency, please specify	
Action taken	
Event improved	
Study treatment restarted	
Date study treatment restarted	
Did the event reoccur?	
Visit name before onset of SAE	
Treatment name	
Reason for use	
Date dose first received	
Date this dose last taken prior to SAE	
Dosage	
Action taken	
Date	
Treatment name	
Reason for use	
Date dose first received	
Date this dose last taken prior to SAE	
Dosage	
Action taken	

	[redacted]
Date	
Serious Adverse Event specify diagnosis, if possible, otherwise note key signs and symptom(s)	
Is this a diagnosis?	
Seriousness criteria	
Onset date	
Outcome	
Date	
Is there a reasonable possibility that the study treatment caused the event?	
Treatment name	
Other possible contributory factors	
Specify	
9. Please provide rationale for causality assessment to study treatment	
10. Description of the event(s) including all hospitalization start and stop dates	
11. Did the subject die?	
If subject died, was an autopsy performed?	
* If yes, date of autopsy	
Details of drug &amp, non-drug treatment	
Start	
Stop	
Dosage	
Details of drug &amp, non-drug treatment	
Start	
Stop	
Dosage	
Details of drug &amp, non-drug treatment	
Start	
Stop	
Dosage	
Details of drug &amp, non-drug treatment	
Start	
Stop	
Dosage	
Details of drug	

&amp, non-drug treatment	[redacted]
Start	
Stop	
Dosage	
Details of drug &amp, non-drug treatment	
Start	
Stop	
Dosage	
Details of drug &amp, non-drug treatment	
Start	
Stop	
Dosage	
Date	
Test	
Results	
Lower Limit Normal Range	
Upper Limit Normal Range	
CTCAE grade	
Date	
Test	
Results	
Lower Limit Normal Range	
Upper Limit Normal Range	
CTCAE grade	
Date	
Test	
Results	
Lower Limit Normal Range	
Upper Limit Normal Range	
CTCAE grade	
Date	
Test	
Results	
Lower Limit Normal Range	
Upper Limit Normal Range	
CTCAE grade	
Date	
Test	
Results	
Lower Limit Normal Range	
Upper Limit Normal Range	

CTCAE grade	[redacted]
Date	
Test	
Results	
Lower Limit Normal Range	
Upper Limit Normal Range	
CTCAE grade	
Date	
Test	
Results	
Lower Limit Normal Range	
Upper Limit Normal Range	
CTCAE grade	
Date	
Test	
Results	
Lower Limit Normal Range	
Upper Limit Normal Range	
CTCAE grade	
Date	
Test	
Results	
Lower Limit Normal Range	
Upper Limit Normal Range	
CTCAE grade	

13.2 Non-serious adverse events

Patient	[redacted]
Country	
Centre number	
Subject ID	
Indication	
Study ID	
Report type	
1. Age or Age Group	
2. Gender	
3. Onset of first symptoms of AE	
4. Adverse Event	
5. Outcome of the adverse event	
Date of recovery	
6. NOVARTIS DRUG(S)	
7. Doses at or before onset of AE	
8. Route of administration	
from	
to	
10. Indication(s) for NOVARTIS drug(s)	
Drug name(s)	
Dose	
Therapy dates	
Reason for use	
Drug name(s)	
Dose	
Therapy dates	
Reason for use	
Drug name(s)	
Dose	
Therapy dates	
Reason for use	
Drug name(s)	
Dose	
Therapy dates	
Reason for use	
Drug name(s)	
Dose	
Therapy dates	
Reason for use	
Drug name(s)	
Dose	
Therapy dates	
Reason for use	
Drug name(s)	

Patient	[redacted]
Dose	
Therapy dates	
Reason for use	
Drug name(s)	
Dose	
Therapy dates	
Reason for use	
12. Comment	
13. Patient&#039,s relevant medical history	
14. Action taken	
Test name	
Date	
Result	
Lower Limit Normal Range	
Upper Limit Normal Range	
16. Assessment of causality	
Specify Novartis suspected drug(s)	

Patient	[redacted]
Country	
Centre number	
Subject ID	
Indication	
Study ID	
Report type	
1. Age or Age Group	
2. Gender	
3. Onset of first symptoms of AE	
4. Adverse Event	
5. Outcome of the adverse event	
Date of recovery	
6. NOVARTIS DRUG(S)	
7. Doses at or before onset of AE	
8. Route of administration	
from	
to	
10. Indication(s) for NOVARTIS drug(s)	
Drug name(s)	
Dose	
Therapy dates	
Reason for use	
Drug name(s)	
Dose	
Therapy dates	
Reason for use	
Drug name(s)	
Dose	
Therapy dates	
Reason for use	
Drug name(s)	

Patient	[redacted]
Dose	
Therapy dates	
Reason for use	
Drug name(s)	
Dose	
Therapy dates	
Reason for use	
Drug name(s)	
Dose	
Therapy dates	
Reason for use	
Drug name(s)	
Dose	
Therapy dates	
Reason for use	
Drug name(s)	
Dose	
Therapy dates	
Reason for use	
12. Comment	
13. Patient&#039,s relevant medical history	
14. Action taken	
Test name	
Date	
Result	
Lower Limit Normal Range	
Upper Limit Normal Range	
16. Assessment of causality	
Specify Novartis suspected drug(s)	

Patient	[redacted]
Country	
Centre number	
Subject ID	
Indication	
Study ID	
Report type	
1. Age or Age Group	
2. Gender	
3. Onset of first symptoms of AE	
4. Adverse Event	
5. Outcome of the adverse event	
Date of recovery	
6. NOVARTIS DRUG(S)	
7. Doses at or before onset of AE	
8. Route of administration	
from	
to	
10. Indication(s) for NOVARTIS drug(s)	
Drug name(s)	
Dose	

Patient	[redacted]
Therapy dates	
Reason for use	
Drug name(s)	
Dose	
Therapy dates	
Reason for use	
Drug name(s)	
Dose	
Therapy dates	
Reason for use	
Drug name(s)	
Dose	
Therapy dates	
Reason for use	
Drug name(s)	
Dose	
Therapy dates	
Reason for use	
Drug name(s)	
Dose	
Therapy dates	
Reason for use	
Drug name(s)	
Dose	
Therapy dates	
Reason for use	
Drug name(s)	
Dose	
Therapy dates	
Reason for use	
12. Comment	
13. Patient&#039,s relevant medical history	
14. Action taken	
Test name	
Date	
Result	
Lower Limit Normal Range	
Upper Limit Normal Range	
16. Assessment of causality	
Specify Novartis suspected drug(s)	

Patient	[redacted]
Country	
Centre number	
Subject ID	
Indication	
Study ID	
Report type	

Patient	[redacted]
1. Age or Age Group	
2. Gender	
3. Onset of first symptoms of AE	
4. Adverse Event	
5. Outcome of the adverse event	
Date of recovery	
6. NOVARTIS DRUG(S)	
7. Doses at or before onset of AE	
8. Route of administration	
from	
to	
10. Indication(s) for NOVARTIS drug(s)	
Drug name(s)	
Dose	
Therapy dates	
Reason for use	
Drug name(s)	
Dose	
Therapy dates	
Reason for use	
Drug name(s)	
Dose	
Therapy dates	
Reason for use	
Drug name(s)	
Dose	
Therapy dates	
Reason for use	
Drug name(s)	
Dose	
Therapy dates	
Reason for use	
Drug name(s)	
Dose	
Therapy dates	
Reason for use	
Drug name(s)	
Dose	
Therapy dates	
Reason for use	
Drug name(s)	
Dose	
Therapy dates	
Reason for use	
12. Comment	
13. Patient&#039,s relevant medical history	
14. Action taken	
Test name	
Date	
Result	
Lower Limit Normal Range	
Upper Limit Normal Range	

Patient	[redacted]
16. Assessment of causality	
Specify Novartis suspected drug(s)	

Patient	[redacted]
Country	
Centre number	
Subject ID	
Indication	
Study ID	
Report type	
1. Age or Age Group	
2. Gender	
3. Onset of first symptoms of AE	
4. Adverse Event	
5. Outcome of the adverse event	
Date of recovery	
6. NOVARTIS DRUG(S)	
7. Doses at or before onset of AE	
8. Route of administration	
from	
to	
10. Indication(s) for NOVARTIS drug(s)	
Drug name(s)	
Dose	
Therapy dates	
Reason for use	
Drug name(s)	
Dose	
Therapy dates	
Reason for use	
Drug name(s)	
Dose	
Therapy dates	
Reason for use	
Drug name(s)	
Dose	
Therapy dates	
Reason for use	
Drug name(s)	
Dose	
Therapy dates	
Reason for use	
Drug name(s)	
Dose	
Therapy dates	
Reason for use	
Drug name(s)	
Dose	

Patient	[redacted]
Therapy dates	
Reason for use	
Drug name(s)	
Dose	
Therapy dates	
Reason for use	
12. Comment	
13. Patient&#039,s relevant medical history	
14. Action taken	
Test name	
Date	
Result	
Lower Limit Normal Range	
Upper Limit Normal Range	
16. Assessment of causality	
Specify Novartis suspected drug(s)	

Patient	[redacted]
Country	
Centre number	
Subject ID	
Indication	
Study ID	
Report type	
1. Age or Age Group	
2. Gender	
3. Onset of first symptoms of AE	
4. Adverse Event	
5. Outcome of the adverse event	
Date of recovery	
6. NOVARTIS DRUG(S)	
7. Doses at or before onset of AE	
8. Route of administration	
from	
to	
10. Indication(s) for NOVARTIS drug(s)	
Drug name(s)	
Dose	
Therapy dates	
Reason for use	
Drug name(s)	
Dose	
Therapy dates	
Reason for use	
Drug name(s)	
Dose	
Therapy dates	
Reason for use	
Drug name(s)	
Dose	
Therapy dates	

Patient	[redacted]
Reason for use	
Drug name(s)	
Dose	
Therapy dates	
Reason for use	
Drug name(s)	
Dose	
Therapy dates	
Reason for use	
Drug name(s)	
Dose	
Therapy dates	
Reason for use	
Drug name(s)	
Dose	
Therapy dates	
Reason for use	
Drug name(s)	
Dose	
Therapy dates	
Reason for use	
12. Comment	
13. Patient&#039,s relevant medical history	
14. Action taken	
Test name	
Date	
Result	
Lower Limit Normal Range	
Upper Limit Normal Range	
16. Assessment of causality	
Specify Novartis suspected drug(s)	

Patient	[redacted]
Country	
Centre number	
Subject ID	
Indication	
Study ID	
Report type	
1. Age or Age Group	
2. Gender	
3. Onset of first symptoms of AE	
4. Adverse Event	
5. Outcome of the adverse event	
Date of recovery	
6. NOVARTIS DRUG(S)	
7. Doses at or before onset of AE	
8. Route of administration	
from	
to	
10. Indication(s) for NOVARTIS drug(s)	
Drug name(s)	
Dose	
Therapy dates	

Patient	[redacted]
Reason for use	
Drug name(s)	
Dose	
Therapy dates	
Reason for use	
Drug name(s)	
Dose	
Therapy dates	
Reason for use	
Drug name(s)	
Dose	
Therapy dates	
Reason for use	
Drug name(s)	
Dose	
Therapy dates	
Reason for use	
Drug name(s)	
Dose	
Therapy dates	
Reason for use	
Drug name(s)	
Dose	
Therapy dates	
Reason for use	
Drug name(s)	
Dose	
Therapy dates	
Reason for use	
Drug name(s)	
Dose	
Therapy dates	
Reason for use	
12. Comment	
13. Patient&#039,s relevant medical history	
14. Action taken	
Test name	
Date	
Result	
Lower Limit Normal Range	
Upper Limit Normal Range	
16. Assessment of causality	
Specify Novartis suspected drug(s)	

14 Discussion

This was a Post Authorization Safety Study according to the EU Volume 9a of the Rules Governing Medicinal Products in the European Union for patients diagnosed with CML in the chronic phase. The study was conducted in compliance with all applicable national and local regulations and guidelines (Baccarani et al., 2009; Valent et al., 2011; Rosti et al., 2011). The aim of this observational study was to collect data from daily clinical practice with respect to tolerability and safety of nilotinib therapy in patients with newly-diagnosed Ph+ CML in CP, as well as in patients with CP Ph+ CML resistant to or intolerant of therapy with imatinib and therefore switch to nilotinib.

The study was planned to recruit patients diagnosed with CML in the chronic phase exposed to nilotinib with the objective of enrolling at least 100 patients exposed to nilotinib within 3 years. However, due to low enrollment and unsuccessful expansion of the study to additional sites, only 9 patients could be recruited over a period of more than 2 years. Therefore the decision was made to prematurely terminate the trial due to low enrollment. The analysis presented here includes all 9 patients that had been documented before the termination of the trial. Due to the low patient number, no statistically substantiated conclusions can be drawn from the obtained data, and no comparisons with other published data can be made.

14.1 Key results

14.1.1 Efficacy

Due to the nature of this study as a non-interventional, observational safety study, efficacy was not part of the objectives of the study. Nonetheless, measures of response were documented as this constitutes an important factor in therapy management. At the final visit, 8 out of 9 patients displayed a complete hematologic remission, 4 out of 9 patients had a molecular response of at least 3 log reduction in BCR-ABL/ABL on the international scale (= MR3/ MMR).

Due to the low patient number of 9 documented patients and the correspondingly low statistical significance, no comparison of the obtained results with published data can be made.

14.1.2 Safety

Serious adverse events were reported in one patient: cAVK IV (central arterial occlusive disease IV) and pAVK II (peripheral arterial occlusive disease II), which were both unresolved at the time of last reporting, associated with a partial loss of visus – Amaurosis fugax right side, which was resolved at the time of last reporting. For all three events the treating investigator reported that there was a reasonable possibility that the study treatment (Tasigna) caused the event. Further details on these events can be found in section 13.1.2.

Several non-serious adverse events were reported: Hypercholesterolemia (reported three times), Headache occipital right side, Arterial Hypertension, Pain in knees, Cramping lower extremities, Dry skin, Loose pivot tooth, Common cold disease, Hyperlipidemia, Konjunktivitis, Erysipel, Trembling, CRP increased, Stomach Pain, Exanthema, Gastric hyperacidity, Itching Eye, and worsening of cholesterinemia.

The most frequently reported AE hypercholesterinemia was reported previously in clinical trials (see Tasigna Fachinformation/SMPC, dated May 2016). Due to the low patient number however, no conclusions about the frequency of this adverse event in a non-selected patient population can be drawn.

In summary, due to the low patient number and short observation time (less than 18 months in most patients) documented in this trial, no conclusions could be drawn and no new hypotheses could be raised regarding the safety profile of Tasigna.

14.1.3 Evaluation of results

As described above, the patient number in this analysis was much lower than originally planned. Only documented data could be analysed. According to §2 (3) of the Austrian Pharmaceutical Act this was an observational study, without testing of hypotheses and without control group. Missing CRF data were not queried, resulting in a deliberate number of missing data.
The design of an observational study without control group and tests of hypotheses may provide some limitations.

14.2 Limitations

According to §2 (3) of the Austrian Pharmaceutical Act this was an observational study, without testing of hypotheses and without control group. Missing CRF data were not queried, resulting in a deliberately number of missing data.

14.3 Interpretation

No general interpretations of the data were made due to the low patient number resulting in a lack of significance of the results presented here. Moreover, the design of an observational study without control group and tests of hypotheses may provide some limitations.

14.4 Generalizability

Limitations are described in Section 10.2, regarding study design. Moreover, due to the small sample size and therefore non-representative patient population, the results obtained here lack generalizability to the general patient population.

15 Other information

The complete eCRF data are available as separate files.

16 References

- Le Coutre P, Rea D, Abruzzese E, Dombret H, Trawinska MM, Herndlhofer S, Dörken B, Valent P. Severe peripheral arterial disease during nilotinib therapy. J Natl Cancer Inst. 2011 Sep 7;103(17):1347-8.
- Aichberger KJ, Herndlhofer S, Schernthaner GH, Schillinger M, Mitterbauer-Hohendanner G, Sillaber C, Valent P. Progressive peripheral arterial occlusive disease and other vascular events during nilotinib therapy in CML. Am J Hematol. 2011 Jul;86(7):531-2
- Baccarani M, Cortes J, Pane F, et al (2009) Chronic myeloid leukemia: An update of concepts and management recommendations of European Leukemia Net. JCO; 27(35):6041-6051.
- Buchdunger E, Matter A, Druker BJ (2001) Bcr-Abl inhibition as a modality of CML therapeutics. Biochem Biophys Acta; 1551(1):M11-8.
- Cortes, E, Jones, E O'Brien, SG *et al.* Nilotinib as front-line treatment for patients with chronic myeloid leukemia in early chronic phase. J Clin Oncol, 28 (3) (2010), pp. 392–397
- Deininger MWN, Goldman JM, Melo JV The molecular biology of CML. Blood 2000; 96:3343-3356.
- Deininger M, O'Brien SG, Guilhot F, et al (2009) International Randomized Study of Interferon and STI571 (IRIS) 8-Year Follow-Up: Sustained survival and low risk for progression or events in patients with newly diagnosed chronic myeloid leukemia in chronic phase treated with imatinib. Blood; 114(22):462. Abstract # 1126.
- Enright H, McGlave P (2000) Chronic myelogenous leukemia. In: Hoffmann R, Benz EJ, Shattil SJ, et al (2000) Hem: Bas Princ and Pract; 3rd ed.: 1155-1171.
- Faderl S, Talpaz M, Estrov Z, et al (1999) The biology of CML. N Engl J Med; 1999:164-172.
- Hochhaus A, O'Brien SG, Guilhot F, et al (2009) Six-year follow-up of patients receiving imatinib for the first-line treatment of chronic myeloid leukemia. Leukemia; 23:1054-1061.
- Kantarjian HM, Giles F, Wunderle L, et al (2006) Nilotinib in imatinib-resistant CML and Philadelphia chromosome-positive ALL. N Engl J Med; 354(24):2542-2551.

- Kantarjian HM, Giles F, Gattermann N, et al (2007) Nilotinib (formerly AMN107), a highly selective BCR-ABL tyrosine kinase inhibitor, is effective in patients with Philadelphia chromosome-positive chronic myelogenous leukemia in chronic phase following imatinib resistance and intolerance. Blood; 110(10):3540-3546.
- Kantarjian HM, Hochhaus A, Saglio G, et al., Nilotinib versus imatinib for the treatment of patients with newly diagnosed chronic phase, Philadelphia chromosome-positive, chronic myeloid leukaemia: 24-month minimum follow-up of the phase 3 randomised ENESTnd trial. Lancet Oncol. 2011 Sep;12(9):841-51
- Kim TD, le Coutre P, Schwarz M, et al., Clinical cardiac safety profile of nilotinib. Haematologica. 2012 Jun;97(6):883-9
- Lavallade H de, Apperley JF, Khorashad JS et al (2008) Imatinib for newly diagnosed patients with chronic myeloid leukemia: incidence of sustained responses in an intention-to-treat analysis. J Clin Oncol; 26(20):3358–3363.
- Le Coutre P, Ottmann OG, Giles F, et al (2008) Nilotinib (formerly AMN107), a highly selective BCR-ABL tyrosine kinase inhibitor, is active in patients with imatinib-resistant or intolerant accelerated-phase chronic myelogenous leukemia. Blood; 111:1834-39.
- Nowell PC, Hungerford DA (1960) A minute chromosome in human chronic granulocytic leukemia. Science; 132:1497-1501.
- O'Brien SG, Guilhot F, Larson RA, et al (2003) Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. N Engl J Med; 348(11):994-1004.
- Quintás-Cardama A, Kantarjian H, Cortes J. (2012) Nilotinib-Associated Vascular Events. Clin Lymphoma Myeloma Leuk. 2012 May 23. [Epub ahead of print]
- Rowley JD (1973) A new consistent chromosomal abnormality in chronic myelogenous leukemia identified by quinacrine fluorescence and Giemsa staining. Nature; 243:290-293.
- Rosti, G, Palandri, F, Castagnetti F. *et al.* Nilotinib for the frontline treatment of Ph(+) chronic myeloid leukemia Blood, 114 (24) (2009), pp. 4933–4938
- Rosti G, Castagnetti F, Gugliotta G, Palandri F, Baccarani M. (2011) Physician's guide to the clinical management of adverse events on nilotinib therapy for the treatment of CML. Cancer Treatment Reviews, Available online 12 August 2011
- Saglio G, Kim DW, Issaragrisil S, et al (2010) Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. N Engl J Med.; 362(24);2251-9. Epub 2010 Jun 5.

- Sawyers CL (1999) Chronic Myeloid Leukaemia. N Engl J Med; 340(17):1330-1340.
- Nilotinib Summary of Product Characteristics, Available at:
- http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000798/human_med_001079.jsp&mid=WC0b01ac058001d124&murl=menus/medicines/medicines.jsp, Accessed on February 17, 2012
- Tefferi A, Letendre L. Nilotinib treatment-associated peripheral artery disease and sudden death: yet another reason to stick to imatinib as front-line therapy for chronic myelogenous leukemia. Am J Hematol. 2011 Jul;86(7):610-1.
- Valent P. Severe adverse events associated with the use of second-line BCR/ABL tyrosine kinase inhibitors: preferential occurrence in patients with comorbidities. Haematologica. 2011 Oct;96(10):1395-7. a)
- Valent P, Gastl G, Geissler K, Greil R, Hantschel O, Lang A, Linkesch W, Lion T, Petzer AL, Pittermann E, Pleyer L, Thaler J, Wolf D. Nilotinib as frontline and second-line therapy in chronic myeloid leukemia: Open questions. Crit Rev Oncol Hematol. 2011 Sep 6. b)
- Valent P. Standard treatment of Ph+ CML in 2010: how, when and where not to use what BCR/ABL1 kinase inhibitor? Eur J Clin Invest. 2010 Oct;40(10):918-31.
- Van Etten RA (2004) Mechanisms of transformation by the BCR-ABL oncogene: new perspectives in the post-imatinib era. Leukemia Res; 28(Supplement1):21-28.
- Vardiman, JW, Harris, NL, Brunning, RD, The World Health Organization (WHO) classification of the myeloid neoplasms, Blood 100(7):2292-2302
- Weisberg E, Manley PW, Breitenstein W, et al (2005) Characterization of AMN107, a selective inhibitor of native and mutant Bcr-Abl. Cancer Cell; 7(2):129-141.
- *CPMP/ICH/363/96:* "Statistical Principles for Clinical Trials", ICH Guideline Topic E9, Note For Guidance on Statistical Principles for Clinical Trials, current version
- *CPMP/ICH/137/95*: "Structure and Content of Clinical Study Reports", ICH Guideline Topic E3; Note For Guidance on Structure and Content of Clinical Study Reports, current version