NOVARTIS

Clinical Study SAP CAMN107ETR02 / NCT01274351

A multicenter, open-label, non-randomized phase II study of nilotinib as a first line treatment in adult patients with newly-diagnosed Philadelphia chromosome-positive (Ph+) and chronic phase myeloid leukemia (CML-CP)

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1 Abbreviations and Definitions

ABL Abelson proto-oncogene
ALT (SGOT) Alanine aminotransferase
AST (SGPT) Aspartat aminotransferase
BCR Breakpoint Cluster Region gene / BCR gene product
BCR-ABL Fusion gene from BCR and ABL/Protein product from BCR-ABL
BID bis in diem/two times daily
SAE Serious adverse event
CTCAE NCI Common Terminology Criteria for Adverse Events
WHO World Health Organization
ECG Electrocardiography
EMEA European Medicines Agency
FDA Food and Drug Administration
GI Gastrointestinal
CTC Common Toxicity Criteria
HDL High-density lipoprotein
HLA Human Leukocyte Antigen
IFN-α Interferon-α
INR International normalization rate
ITT Intent-to-Treat
CP Chronic phase
IRB/IEC/REB Institutional Review Board/Independent Ethics Committee/Research Ethics Board
CML Chronic myeloid leukemia
PCR Partial cytogenetic response
LDH Lactate dehydrogenase
LDL Low-density lipoprotein
MMR Major molecular response
CRR Cytogenetic response rate
mCR Minor cytogenetic response
MCR Major cytogenetic response
ULN Upper limit of normal
CRF Case Report Form
PCR Polymerase chain reaction
Ph+ Philadelphia chromosome-positive
PP Per Protocol
CRO Contract Research Organization
CR Cytogenetic response
CNS Central nervous system
LVEF Left ventricular ejection fraction
CCyR Complete cytogenetic response
VLDL Very low-density lipoprotein

2 Introduction

2.1 Chronic myeloid leukemia

Chronic myeloid leukemia (CML) is a hematologic stem cell disease associated with a specific chromosome translocation known as the Philadelphia chromosome detected in 95% of patients (Nowell 1960, Rowley 1973). Molecular outcome of the translocation is fusion of the Abl proto-oncogene to the Bcr gene, resulting in production of an activated form of Abl protein-tyrosine kinase (Bartram 1983, Heisterkamp 1983). Expression of BCR-ABL protein may cause leukemia in mice, which suggests that this protein is the cause of the disease (Daley 1990, Kelliher 1990). Clinically, CML progresses through three different phases, gradually becoming more resistant to treatment: chronic phase (CP) (median duration 3-4 years, median survival may extent up to 10 years with allogeneic bone marrow transplantation and is 5-6 years with interferon), accelerated phase (AP) (median duration 3-9 months; median survival 8-18 months) and blast crisis (BC) (median survival 3-6 month) (Enright 2000).

In chronic-phase CML, cytogenetic response criteria, which is based on the percentage of Ph+ cells in the bone marrow, is acknowledged as an important indicator of the disease state and treatment and represents the mainstay of monitoring the disease state in CML. Cytogenetic response (CyR) is a known determinant for prognosis in CML management and is used to predict patient outcome.

During the past 25 years, Ph+CML treatment have evolved from treatment with non-specific cytotoxic agents to methods which combine cell destruction and immunologic control of the residual disease and, more recently, to imatinib, which is a tyrosine kinase inhibitor class agent that specifically targets the ABL portion of oncogenic BCR-ABL coded proteins. Conventional treatment may be given by a range of cytotoxic agents, mainly hydroxyurea. The treatment is safe and inexpensive and may be maintained on an outpatient basis and offers a good quality of life but neither prevents nor delays progression from chronic phase to accelerated or blast phases. Thus, all patients treated with conventional chemotherapy die within less than 10 years (median 4.5 years) (Goldman 2003). Conventional treatment is abandoned and may be indicated unless it is impossible to administer other treatments. Preferred treatment approach had been the allogeneic hemopoietic stem cell transplantation for at least 20 years since it was the only treatment procedure which was shown to actually treat the disease. Its use, however, is still limited with patients' age (median age of patients with CML is 58) and requires a HLA-matching donor from patients' families or from the international bone marrow donor registries. Besides, allogeneic hemopoietic stem cell transplantation still constitutes significant toxicity; transplantation-related mortality is approximately 30% and long-term leukemia-free survival is about 50% (Hehlmann 2007, Baccarani 2006, Barret 2003). Based on numerous prospective randomized studies on IFN-α versus conventional chemotherapy, interferon-α (IFN-α) had been the first choice of treatment in CML for about 10 years (1990-2000). Subsequent studies have shown that the efficacy of IFN-α was less in high-risk patients compared to the low-risk patients, who achieve greater benefit from this treatment: complete cytogenetic response was approximately 30% and elongations up to or even more than 10 years were observed.

IFN-α treatment is safe but toxic and not well-tolerated and about 35% of patients require treatment discontinuation (Baccarani 2003). Tyrosine kinase inhibitors are a new class of components designed and developed to target tyrosine kinase. A tyrosine kinase, imatinib mesylate, which inhibits ABL and other tyrosine kinases, was shown to specifically inhibit Ph+ cells and resulted in impressive number of hematologic and cytogenetic response in all phases of Ph+ leukemias (Hehlman 2007, Goldman 2001, Deininger 2005, Baccarani 2006, Kantarjian 2004, Hochhaus 2008). A prospective, randomized study using imatinib versus IFN-α showed than imatinib was superior to IFN-α by several orders of

magnitude in hematologic response, cytogenetic response, time to progression and toxicity profile (O'Brien 2003, Hughes 2003, Hochhaus 2007). Imatinib thus rapidly become the first choice of treatment for all phases of Ph+ CML, from the early chronic phase to the blastic phase. A range of second generation tyrosine kinase inhibitors were developed including nilotinib and were investigated in preclinical and clinical phases (Martinelli 2005, Kantarjian 2007) (Weisberg 2005, Golemovic 2005, Kantarjian 2006, Kantarjian 2007, Le Coutre 2008).

2.2 Nilotinib

Nilotinib is an orally-available novel aminopyrimidine and an ATP competitive inhibitor of protein tyrosine kinase activity of BCR-ABL, which inhibits activation of BCR-ABL-dependent mitogenic and anti-apoptotic pathways (e.g. PI-3 kinase and STAT5), thereby leading to BCR-ABL genotype demise. Nilotinib also frequently inhibits other oncogenic kinases including FIP1L1-PDGFRA tyrosine kinase, which is associated with hypereosinophilic syndrome and chronic eosinophilic leukemia, and stem cell factor receptor c-Kit tyrosine kinase, which is associated with systemic mastocytosis and gastrointestinal stromal tumors.

Data from preclinical studies indicate that nilotinib reaches higher intracellular concentrations than imatinib and that nilotinib inhibits BCR-ABL tyrosine kinase activity and induce apoptosis at lower concentrations compared to imatinib (Le Coutre 2004, White 2005). In preclinical models, nilotinib was 20 to 50 times more potent than imatinib on CML cell lines sensitive to imatinib and was 3 to 7 times more potent in cell lines resistant to imatinib.

In a phase I dose-escalation study, 119 patients with Ph+ CML and acute lymphocytic leukemia resistant to imatinib were treated with a single oral nilotinib dose of 50-1200 mg or 400 mg and 600 mg nilotinib administered twice daily. Nilotinib produced higher hematologic and cytogenetic response rates in chronic phase CML patients who were resistant to imatinib, 92 and 53% respectively (CCyR in 35%). (AMN107 Investigator Brochure Ed.4.0, 2008).

Initial data from 132 patients resistant or tolerant to imatinib in a phase I study were reported by Kantarjian (2006). In this study, patients were treated with nilotinib for a median period of 226 days (range 3-379 days). Complete hematologic response was achieved in 69% of the patients. Major cytogenetic response was achieved by 42%. Thirty-three patients (22%) achieved complete cytogenetic response.

Nilotinib was also shown to have an acceptable tolerability profile (Kantarjian 2007). In a CML-CP population, the commonest GTC grade 3 hematologic anomalies were decreases in absolute lymphocyte (16.2%), neutrophil (14.8%), white blood cells (12.6%) and platelet (11.2%) counts. The commonest GTC grade 4 anomalies were reductions in platelet count (13.5%), neutrophils (11.6%) and absolute lymphocyte count (7.5%).

Furthermore, studies with patients with hematologic malignancies have demonstrated that nilotinib had a potential to mildly elongate QT interval at therapeutic concentrations. On day 8 (steady-state), mean temporal changes in QT interval from baseline ranged from 5.7 msn (CML-CP patients) to 8.4 msn (CML-AP patients).

It should be noted that most of the adverse events reported from the phase II leukemia studies with imatinib have also been reported from the phase I study with nilotinib, although incidence of peripheral edema was very low in the nilotinib study. In the Nilotinib phase I study, 400 mg twice daily (BID) dose level was associated with lower incidence of Grade 3 neutropenia and Grade 3 hyperbilirubinemia compared to the 600 mg BID dose. Initial data from a phase II study with a patient group whose dosage was increased from 400 mg BID to 600 mg BID due to suboptimal response did not demonstrate improved efficacy with the higher dose. Thus, 400 mg BID dose of imatinib was recognized as the dose with optimum efficacy and safety.

Today, nilotinib treatment in patients with Ph+ CML who are resistant or intolerant to imatinib has been approved by the FDA and EMEA (Le Coutre 2008). Nilotinib is now being investigated in many studies as the first line treatment in Ph+ CML comparatively to imatinib.

3 Study objectives

3.1 Primary Objective(s)

- The primary objective of this study is to evaluate the efficacy of Nilotinib by determining the cumulative major molecular response (MMR) rates in 12 months in adult patients with newly-diagnosed Philadelphia chromosome-positive and chronic phase myeloid leukemia.

3.2 Secondary Objective(s)

- To evaluate the rate of complete cytogenetic response (CCyR) at months 6 and 12
- To evaluate periodically the rate of 3-monthly molecular response
- To evaluate complete hematologic response rate
- To evaluate the safety profile of nilotinib treatment
- To evaluate time to MMR and durability of the response
- [redacted]

3.3 Exploratory objective(s)

Not applicable.

4 Study Methods

4.1 General Study Design and Plan

This is a local, multicenter, one-arm and non-randomized phase II clinical trial. This study will evaluate the efficacy and safety of nilotinib in a new group. Newly-diagnosed patients will enter a 2-weeek screening period. Those who meet eligibility criteria will be treated with nilotinib 300 mg BID for 24 months. For efficacy assessments, bone marrow aspiration and/or biopsy will be used for cytogenetic analysis and peripheral blood will be used for RQ-PCR measurements of BCR-ABL transcriptions. Safety assessments will involve adverse events, laboratory profiles (hematology/biochemistry), ECG, and physical examinations. The patients will be evaluated every 15 days during the first 3 months, once every month for up to month 12 and then every three months.

Screening visit: Patients' eligibility (inclusion/exclusion criteria) is assessed at this visit. Subsequent procedures/tests will include informed consent, medical history, inclusion/exclusion criteria, vital findings, physical examination, assessment of extramedullary involvement, concomitant drugs, ECOG performance status, serum pregnancy test, hematology, blood chemistry, bone marrow assessment (within the past 2 months), peripheral blood analysis.

Baseline visit: This visit will be scheduled for 0 to 2 weeks following the screening visit. Baseline assessments will include vital findings, physical examination, additional inclusion/exclusion criteria, concomitant drugs, drug dispensing, ECG, hematology and blood chemistry.

[redacted]

Unscheduled visits: As required. Investigations for the cause of the unscheduled visits will be performed.

[redacted]

All scheduled visits will be performed as close as possible to the scheme given in Figure 4-1. Should deviations from the scheme presented in Figure 4-1 occur, all remaining visits must be performed according to the original plan.

4.2 Study population

All eligible adult patients with Ph+ CML-CP who have been diagnosed cytogenetically during the past six months and who have not received treatment for CML other than anagrelide and hydroxyurea (excluding imatinib treatment for a maximum duration of 31 days) will be enrolled in the study.

A total of 110 patients will be enrolled.

The patients must have fulfilled all inclusion criteria during the 2 weeks prior to the study (bone marrow analyses may have been performed within the last 8 weeks) and should not meet any of the exclusion criteria.

4.2.1 Inclusion criteria

- Male and female patients ≥18 years old
- ECOG performance status 0, 1 or 2
- First CML-CP diagnosis should have been made during the past 6 months and Philadelphia chromosome resulting from translocation (9;22) should be confirmed cytogenetically . Standard conventional cytogenetic analysis is required. All of the following criteria of CML-CP diagnosis should be met:
  - <15% blast in peripheral blood and bone marrow
  - <30% blast in peripheral blood and bone marrow plus promyelocyte
  - <20% basophil in peripheral blood
  - ≥100 x 10^9/L (≥100.000/mm^3) platelet
  - No evidence of extramedullary leukemic involvement, except for hepatosplenomegaly
- Should not have received treatment for CML other than anagrelide and hydroxyurea.
- Sufficient end-organ function with the following laboratory criterias:, total bilirubin < 1.5 x ULN; SGOT and SGPT < 2.5 x ULN; creatinine < 1.5 x ULN; serum amylase and lipase ≤ 1.5 x ULN; alkaline phosphatase ≤ 2.5 x ULN unless associated with a tumor
- Serum potassium, magnesium, calcium and phosphorus levels are equal to or above the lower limit of normal before the administration of the first dose of the study treatment.
- Should have provided informed consent in written before ant study-related procedure may be initiated.

4.2.2 Exclusion criteria

- Being treated with tyrosine kinase inhibitors before the study start (awaiting the study start, in cases of emergencies where the disease should be treated, commercial products containing imatinib may be prescribed but the treatment period should not exceed 31 days).
- Known CNS infiltration, confirmed cytopathologically.
- Cardiac dysfunction [presence of any of the following: LVEF <45% (if available), inability to determine QT interval with ECG, acquired long QT syndrome or familial history of long QT syndrome, clinically significant ventricular or atrial tachyarrhythmia or history thereof, clinically significant resting bradycardia (<50 beats/minute), QTc > 450 msn as measured by QTcF in baseline ECG (if QTcF>450 msn and electrolytes are not within normal ranges, the latter should be corrected and the subject should undergo screening again for QTc), history of myocardium infarct within the 12 months before the study start, other clinically significant cardiac disorders (e.g. instable angina, congestive heart failure or uncontrolled hypertension)].
- Serious or uncontrolled medical conditions (e.g., uncontrolled diabetes mellitus, active or uncontrolled infections).
- Acute or chronic hepatic, pancreatic or serious renal diseases not associated with the disease,
- Patients with other primary malignancies; this excludes situations where the tumor is no longer clinically significant or does not necessitate active intervention.
- Significant congenital or acquired bleeding disorders not associated with cancer.
- Previous radiotherapy involving ≥25% of the bone marrow.
- Major surgery during the 4 weeks before the first day of the study or those not recovering following surgery

- Gastrointestinal (GI) dysfunction or GI disease which may significantly alter the absorption of the study drug (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea malabsorption syndrome, small intestine resection or gastric by-pass surgery)
- Patients treated with potent CYP3A4 inhibitors (e.g.; erythromycin, ketoconazole, itraconazole, voriconazole, clarithromycin, telithromycin, ritonavir, mibefradil)
- Patients currently receiving active treatment agents which may potentially prolong QT interval or in whom it is not possible to discontinue the treatment or to switch to another drug before the study start.
- History of noncompliance with medical regimes.
- Pregnant women (positive serum pregnancy test during the 7 days before the start of study treatment for women of childbearing potential) or breastfeeding women
- Fertile male and female patients who are not willing to take contraceptive measures throughout the study (in order to confirm that menopausal women does not have childbearing potential, she should have been amenorrheic for at least 12 months).

4.3 Treatment Blinding

No blinding will be done since this is an open-label study with one treatment arm.

4.4 Study Variables

Period	Screening																				
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Day (d)/Month (m)	D -14 to 1	D1	D15	D30	D45	D60	D75	D90	M4	M5	M6	M 7	M 8	M 9	M1 0	M1 1	M1 2	M1 5	M1 8	M2 1	M2 4
Screening info	X																				
Informed consent	X																				
Inclusion/exclusion criteria	X																				
Demographics	X																				
Relevant medical history, disease history, previous treatments	X																				
ECOG performance status	X			X				X			X			X			X		X		X
Serum pregnancy test	X																				
Vital findings, physical exam., body weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Extramedullary involvement	X			X				X			X			X			X		X		X
ECG	X	X	X	X	X	X	X	X			X			X			X		X		X
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Bone marrow assessments	X							X			X						X				X
Peripheral blood sample	X			X				X			X			X			X	X	X	X	X
Nilotinib dose and compliance		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant drugs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Mutation analysis																					X
Study completion form																					X

5 Sample size

The sample size was calculated using the exact test for single proportion to attain 15% improvement in MMR rates compared to IRIS data.
The sample calculated by 80% confidence interval consists of 110 subjects accounting for a 10% drop-out during the two-year follow-up.

6 General Considerations

6.1 Timing of Analyses

The final analysis will be performed when 110 subjects have completed visit 24 or dropped out prior to visit 24.

6.2 Analysis Populations

The analyses in this study will be conducted in three seperate groups. First group will be the safety population, which will consist of all subjects who received at least one dose of study drug and have at least one post-baseline safety assessment. A report by a subject indicating no adverse experience will constitute a safety assessment.
The second group will be the ITT population, which will consist of all subjects who provided informed consent form.
And the last group of analyses will be conducted in the per protocol population, which will consist of all subjects in the ITT population with no major protocol violation reported. All reported protocol violations will be classified as major or minor in a review meeting before database lock.
The population intended to be treated for demographical and baseline characteristics will be used in all ITT efficacy evaluations. Per protocol population will be used for per protocol analyses for primary efficacy endpoint and some important secondary efficacy variables.

Safety analysis will be performed with the safety population.

6.3 Covariates and Subgroups

Since this is an open-label study with one treatment arm and disease-specific inclusion and exclusion criteria, no sub-groups will be formed, and no stratification will be made during the interim analysis. The major aim in the interim analyses is to determine the molecular and hematological response rates, and to determine the major adverse event rates in the study population. [redacted] The final analyses of the study will be conducted in aforementioned three separate groups (safety, ITT, and per protocol populations) and stratifications will be made at this stage. The sub-groups (or strata) will be formed according to clinically important demographic and clinical variables (such as age, gender, major adverse events, progression of the disease, etc.). For the sake of preventing the inflation of statistical significance, the interim analyses will be conducted for descriptive statistics only. But, if the findings in these analyses shows significant results for unfavored high frequency of adverse events or decreased survival, necessary analytical statistical analyses should be performed. In this case, alpha-spending considerations will be subject to the determination of statistical significance, and preferably O'Brien-Fleming approach should be utilized for calculating the p values of inferential statistical analyses.

6.4 Missing Data

Subjects who withdraw prematurely or those who fail to provide data for the study for other reasons will be designated as premature withdrawal or inevaluable, respectively, and will be included in the ITT analysis as non-responders. Only those who achieve MMR by month 12 will be considered as responders.

6.5 Interim Analyses and Data Monitoring

6.5.1 Purpose of Interim Analyses

Interim analyses will be conducted to inform the steering committee about the descriptive data of primary outcome measure – namely MMR, adverse event frequency and survival of the patients. If no critical values of adverse events and/or survival data is determined, no revisions will be needed in the protocol of the study. But if needed, descriptive data, and some on-demand inferential statistics may be used for deciding the revisions on the protocol.

6.5.2 Planned Schedule of Interim Analyses

An interim analysis is planned when 30% of the targeted number of subjects for this study is reached and these patients received nilotinib treatment for 6 months. Only one interim analyse should be performed during the study. This interim analyse will be mainly focused on descriptive characteristics of the treatment effects of Nilotinib, and the analyses will be particulary performed to determine the molecular and hematological response rates, and to determine the major adverse event rates in the study population. [redacted]

6.5.3 Scope of Adaptations

If the interim analyses show significant adverse effects and/or decreased survival in patients treated with Nilotinib, then the analyses should be detailed according to the demographic and key clinical characteristics of the study population, and additional data should be provided to help the steering committee to decide the necessary revisions in the protocol. The scope of adaptations should be constituted according to the following outcomes of the study:

- Molecular Response Rate
  This data will be provided as follows:

Cumulative MMR rate

N=	n (%)
3rd Month (Visit 8)	
6th Month (Visit 11)	
9th Month (Visit 14)	
12th Month (Visit 17)	

- Cytogenetic Response Rate
  This data will be provided as follows:

Cytogenetic response rate

			80% Confidence Interval	
	N	Mean (SD)	Lower Bound	Upper Bound
CRR at 6th Month				
CRR at 12th Month				

- Survival rates
  This data will be provided as follows:

Survival rates

	Cumulative Survival Rate	
Time	Estimate	Standart Error
…	…	…

- Adverse events
  This data will be provided as follows:

Adverse Events

	Frequency	Percent
Elevated bilirubins		
Leucocytosis		
Ischemic heart disease		
Total		100,0

6.5.4 Stopping Rules

The study will not be stopped due to the findings in the interim analyses, unless unexpected high mortality rates or adverse events are reported. In the case of elevated adverse event rates or mortality, which will still be in the acceptable limits, some modifications may be applied in the treatment protocol according to the steering committee.

6.5.5 Analysis Methods to Minimise Bias

Since this is an open-label study with one treatment arm, statistical analyses will primarily include descriptive data of the study population. As the descriptive analyses will not include subgroup comparisons, bias will be automatically avoided. Key analyses of primary and secondary efficacy and safety parameters will also include individual patient data to elucidate the unfavored situations. At the final pooled analyses of the study ITT, PP and safety group analyses will be performed separately, to cover the all spectrum of the clinical aspects of the treatment, and this will also prevent the biased results of the outcomes of the trial.

6.5.6 Adjustment of Confidence Intervals and p-values

The interim analyses will mainly provide descriptive data about the primary and secondary efficacy and safety parameters, and 80% confidence intervals of means will be provided when needed. As the descriptive analyses will have no analytical statistics, p values will not be modified for the interim analyses. But, if the descriptive date provides critical information about efficacy or safety profile of the treatment, then analytical statistics will be performed in subgroup analyses, and according to the alpha-spending function approach, O'Brien Fleming method will be used to determine the critical p value to be used in analytical statistics.

6.5.7 Interim Analysis for Sample Size Adjustment

Sample size will not be adjusted according to the interim analyses, since no power analyses will be performed in interim analyses.

6.5.8 Practical Measures to Minimise Bias

Data management will only be performed by a CRO responsible for data management. Data captured from the CRFs will be entered to the database through an electronic verification system with a single entry.
No blinding will be done since this is an open-label study with one treatment arm.

6.5.9 Documentation of Interim Analyses

Interim analyses will be conducted by the responsible CRO and the documents will be preserved for future use.

6.6 Multi-centre Studies

This is a multicenter study with 15 participating institutions.

6.7 Multiple Testing

The first set of analyses in this study will primarily based on to provide descriptive data about the study and its effects in study population. Therefore, no subgroups will be formed for the comparative analyses. But, if descriptive data of the primary and secondary endpoints reveal clinically significant findings, then the multiple group comparisons may be subject to the inferential analyses. In such a case, a Type-I error level of 5% will be preserved for multiple group comparisons, and Bonferroni correction will be utilized for preventing the statistical significance inflation in post-hoc pairwise comparisons.

7 Summary of Study Data

The data gathered in this study will be presented in summary tables. The central tendency of numerical variables will be presented in means or medians, and the dispersion will be presented as standart deviations, interquartile ranges or minimum-maximum values, where appropriate. Categorical variables will be shown in frequency (n) and percents. Examples of both the numerical and categorical data is shown below:

Cytogenetic response rate

			80% Confidence Interval	
	N	Mean (SD)	Lower Bound	Upper Bound
CRR at 6th Month				
CRR at 12th Month				

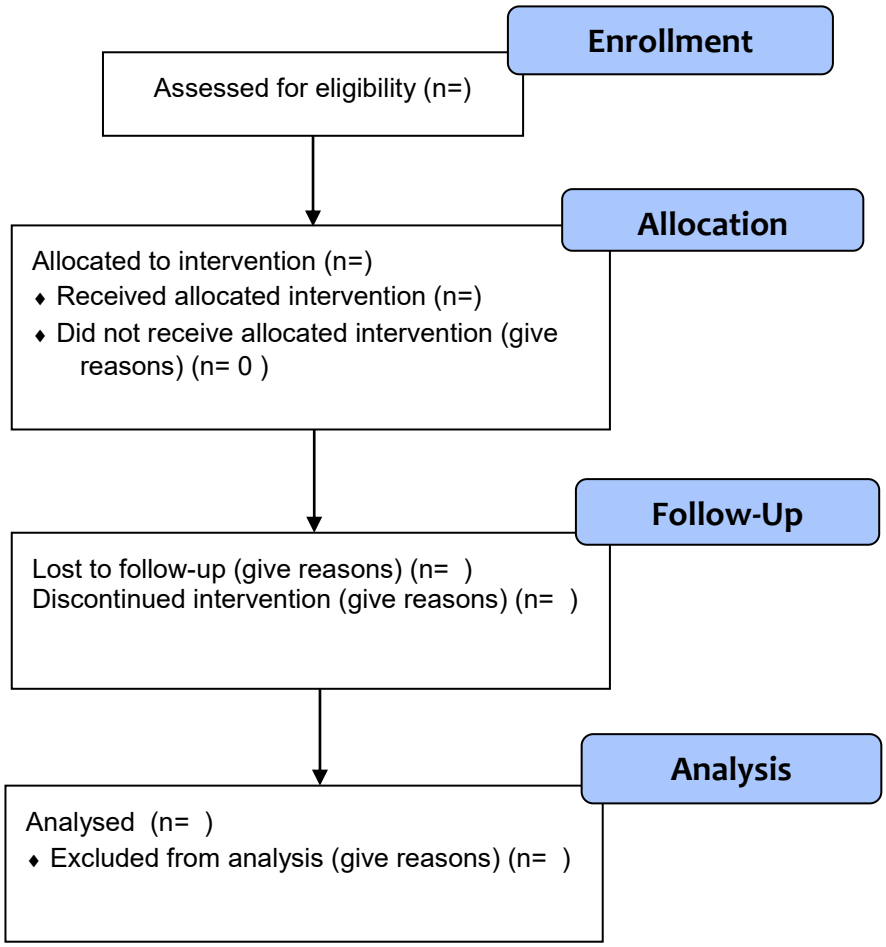
Cumulative MMR rate

N=	n (%)
3rd Month (Visit 8)	
6th Month (Visit 11)	
9th Month (Visit 14)	
12th Month (Visit 17)	

Since the objective of the statistical analyses in this study is providing the descriptive data about the primary and secondary endpoints, no stratifications will be made in the descriptive tables. But, if further comparative analyses will be necessary according to the relevant demographic or clinical vairables, the descriptive tables should be stratified according to these variables.

7.1 Subject Disposition

The numbers in the following chart will be completed upon the interim and final analyses.



7.2 Protocol Deviations

Subjects who discontinue treatment with the study drug will be considered as withdrawals after the final visit assessments or if they are lost to follow up. The subjects may withdraw from the study prematurely due to any of the following reasons:

- Adverse event(s)
- Abnormal laboratory value(s)
- Abnormal test result(s)
- Disease progression
- Nilotinib inefficacy based on the criteria for this study.
- Subject's condition no longer requires treatment (may be beneficial in patients undergoing bone marrow transplantation).
- Protocol violation

- Subject withdraws informed consent
- Lost to follow-up
- Pregnancy
- Executive issues
- Death

7.3 Demographic and Baseline Variables

Subject's age and gender will be documented in the relevant page of the CRF. Bone marrow screening to confirm CCyR will be performed during the last 8 weeks following administration of last study treatment. Peripheral blood sample analysis to measure molecular response should be performed within 28 days after the administration of the first study dose. Bone Marrow Analysis CRF will be used to collect information on the cytogenetic status and Previous antineoplastic agents CRF will be used to collect information on previous medications.
Relevant conditions and surgeries during the 5 years before the study (a longer period of time for disease-related history, if feasible) as well as concomitant conditions, date of diagnosis/surgery and information whether there is an ongoing problem will be recorded.
Information on surgeries, including previous antineoplastic agents, radiotherapy and surgical biopsies will be collected.

Date of first CML diagnosis and the best previous response will be collected.

7.4 Concurrent Illnesses and Medical Conditions

The summary statistics will be produced in accordance with section 7.3.

7.5 Prior and Concurrent Medications

Concomitant medications given before and after treatment with study drug will be summarized by treatment groups. WHO Drug Reference List will be used to code medications. All prescription and non-prescription medicinal products including vitamins and blood transfusions will be entered in the Concomitant medications/non drug therapies CRF. The records will include the trade name of the medicines, start date and end date and the rationale for administration.

7.6 Treatment Compliance

Treatment compliance will be evaluated by the investigator and/or study personnel by examining the number of capsules and the information provided by the subject. This information will be recorded on source documents at every visit.

8 Efficacy Analyses

8.1 Primary Efficacy Analysis

The primary efficacy endpoint in this study is the best cumulative MMR rate at month 12, measured as RQ-PCR and defined as ≤0.1% BCR-ABL/% control gene reported in % on the international scale.

8.2 Secondary Efficacy Analyses

Efficacy variables for secondary variables will be analyzed descriptively using summary statistics. Summary statistics will include n (number of observations), mean, standard deviation, median,

minimum and maximum values for continuous variables as well as frequency and percentages for categorical variables. Missing values for secondary endpoints will not be replaced. All ratios will be assessed at month 6 and 12, and then once every year if data is available and the ratio is the cumulative ratio up to a specific time point.

Time variables up to any event will be shown with Kaplan-Meier curves.

8.3 Exploratory Efficacy Analyses

Not applicable

9 Safety Analyses

All safety analyses will be performed on the safety population. Safety assessment will be based on primarily the incidence of adverse events and the number of subjects with laboratory values outside predetermined rates and number of patients with clinically significant ECG findings.

9.1 Extent of Exposure

Physical examination findings consistent with extramedullary leukemia involvement (e.g., lymph nodes, liver and spleen sizes) will be recorded. Only those lymph nodes considered related to the disease will be taken into account.
If the only evidence of a blast crisis is an extramedullary involvement outside liver and spleen, this must be confirmed histologically and/or by biology (particularly for lymph nodes) and the data should be entered in the CRF.

9.2 Adverse Events

A serious adverse event is an undesirable sign, symptom, or medical condition defined according to the following criteria:

- is fatal or life-threatening
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- 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

These events will not constitute an adverse event if the hospitalization is for:

- the medical care was scheduled before enrollment
- elective treatment for a pre-existing condition that is unrelated to the indication under study
- 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)
- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
- social reasons and respite care in the absence of any deterioration in the patient's general condition

9.3 Deaths, Serious Adverse Events and other Significant Adverse Events

The summary statistics will be produced in accordance with section 9.2.

9.4 Pregnancies

Women of childbearing potential are required to undergo a serum pregnancy test at screening. In order to confirm that menopausal woman does not have childbearing potential, she should have been amenorrheic for at least 12 months.

9.5 Clinical Laboratory Evaluations

Blood chemistry laboratory assessments will be performed by a certified central laboratory. Biochemistry will include urea or BUN, creatinine, uric acid, albumin, total protein, total bilirubin (direct or indirect), alkaline phosphatase, AST (SGOT), ALT (SGPT), LDH, sodium, chloride, (fasting) glucose, calcium, lipase, amylase, potassium, magnesium and phosphor and lipid profile (HDL, LDL, VLDL, triglycerides and total cholesterol), INR (International Normalization Ratio) and Hemoglobin A1c.

In addition to the routine biochemistry assessments outlined in the visit schedule, subjects must have their serum potassium and magnesium levels in case of QTc elongation or at the discretion of the investigator. Routine biochemistry assessments outlined in the visit schedule will be recorded in the CRF. Additional electrolyte results (potassium and magnesium) will not be entered in the CRF or clinical database unless they require supportive treatment or substitution treatment. If supportive treatment and substitution treatment required, the laboratory anomaly should be documented in the CRF as scheduled or unscheduled laboratory result and should also be recorded as an adverse event. If supportive treatment and substitution treatment is given, these should be indicated as concomitant medication. Other additional results should be included only in the source documentation at the study center.

9.6 Other Safety Measures

Not applicable

10 Pharmacokinetics

Not applicable

11 Other Analyses

Min, max and mean values of treatment duration from the first dose through out the treatment period.

Number of patients having dose reductions and/or which AEs lead to dose reductions.

Details of cardiovascular events with MedDRA coding.

Details of laboratory values of the patients having mutations.

Details of laboratory values of the patients having study treatment related thrombocytopenia.

Analysis of the patients having hyperglycemia.

Patient numbers by socal risk groups.

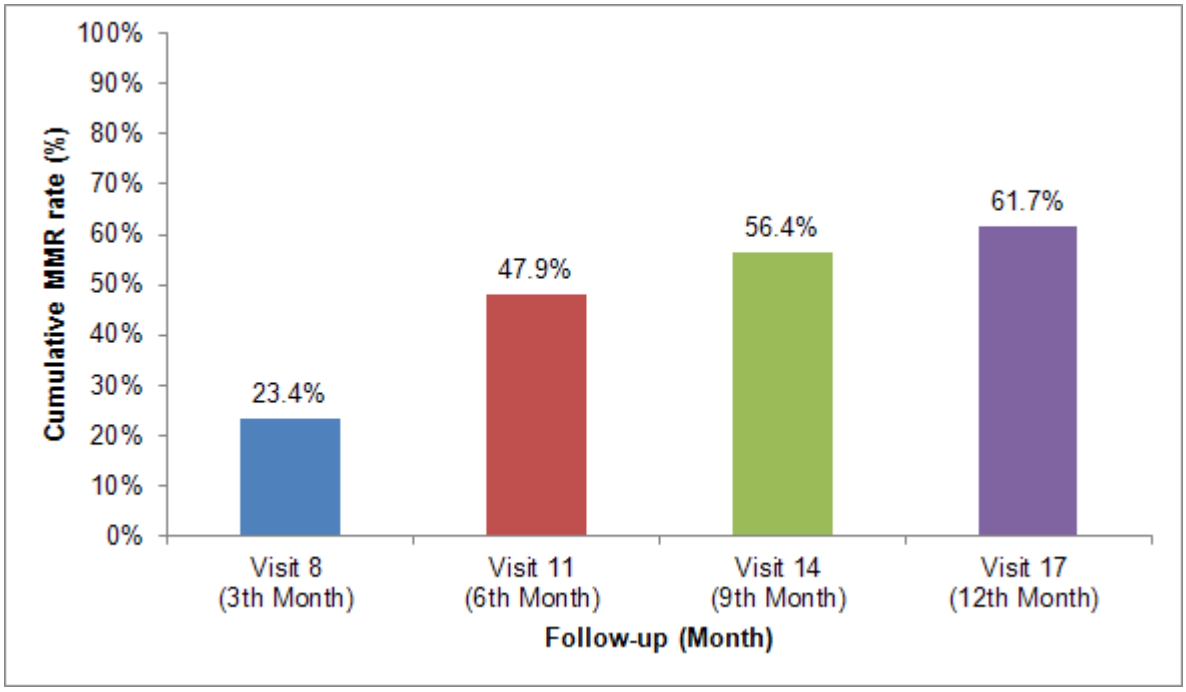
CCyR by socal risk groups.

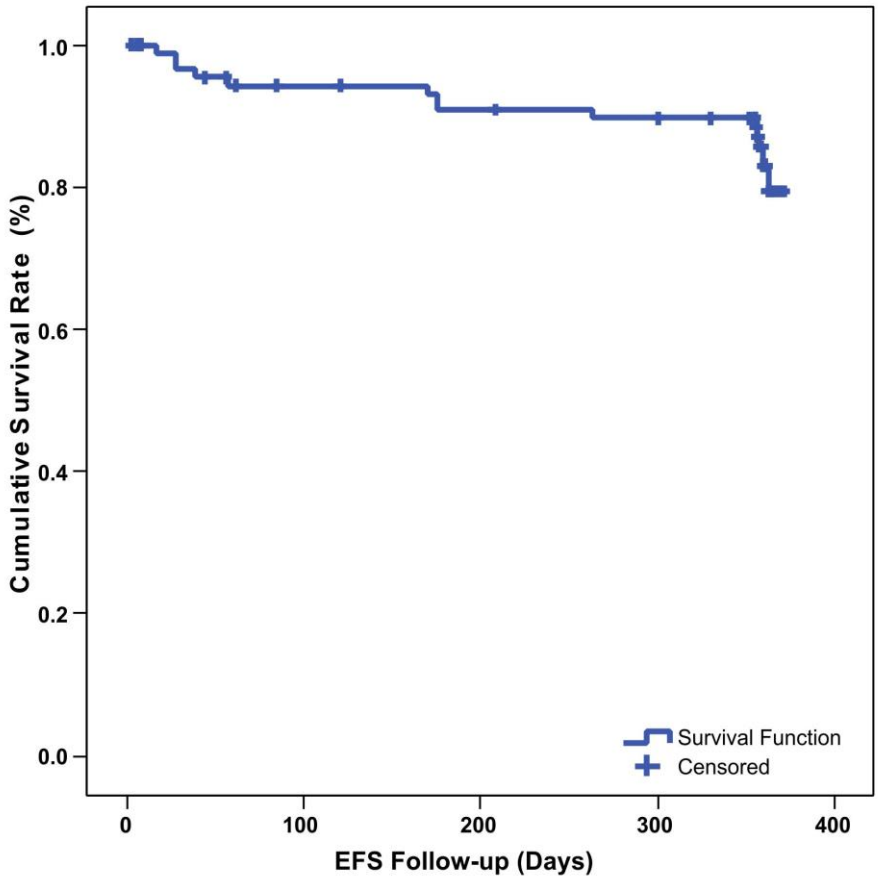
MMR by socal risk groups.

[redacted]

12 Figures

Bar charts for categorical data and Kaplan-Meier survival curves will be used in this study. Examples for these graph are shown below:




1.0
0.8
0.6
0.4
0.2
0.0
Cumulative Survival Rate (%)
0
100
200
300
400
EFS Follow-up (Days)
Survival Function
Censored

13 Reporting Conventions

P-values ≥0.001 will be reported to 3 decimal places; p-values less than 0.001 will be reported as "<0.001". The mean, standard deviation, and any other statistics other than quantiles, will be reported to one decimal place greater than the original data. Quantiles, such as median, or minimum and maximum will use the same number of decimal places as the original data. Estimated parameters, not on the same scale as raw observations (e.g. regression coefficients) will be reported to 3 significant figures.

14 Technical Details

Statistical analyses will be performed by an expert statistician employed by an independent CRO, and by using PASW Statistics 18 and Stata 11.

15 Summary of Changes to the Protocol

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC/REB. Only amendments that are required for patient safety may be implemented prior to IRB/IEC/REB approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC/REB at the study site should be informed within 10 working days.

16 References

Not applicable.