NOVARTIS

Clinical Development and Medical Affairs

AMN107 Tasigna® (nilotinib)

Protocol No.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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Component name / number **AMN107 Tasigna® (nilotinib)**

Protocol no. **CAMN107ETR02**

Approved by:

Signature of Novartis staff:

Please write/print name (Oncology Medical Director)	Signature	Date
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Chief Investigator's Signature

Please write/print name (Chief Investigator)	Signature	Date

Signature page for the investigator

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I have read this protocol and I commit to conducting this study in accordance with all the conditions of the protocol and as per the principles outlined in Helsinki Declaration.

Write/print name
(Investigator) Signature Date

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List of abbreviations

ABL	Abelson proto-oncogene
AP	Accelerated phase
AE	Adverse event
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
BP	Blastic phase
BID	*bis in diem*/two times daily
BC	Blast crisis
WBC	White blood cell
CT	Computed tomography
BUN	Blood urea nitrogen
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
FISH	Fluorescent *in situ* hybridization
GI	Gastrointestinal
CTC	Common Toxicity Criteria
HDL	High-density lipoprotein
HLA	Human Leukocyte Antigen
IFN-α	Interferon-α
GCP	Good Clinical Practice
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
MedDRA	Medical Dictionary for Regulatory Activities
MMR	Major molecular response
mCR	Minor cytogenetic response
MCR	Major cytogenetic response
LLN	Lower limit of normal
ULN	Upper limit of normal
CRF	Case Report Form
PCR	Polymerase chain reaction
Ph+	Philadelphia chromosome-positive
PP	*Per* Protocol
QD	*Quoque die* / once daily
CRO	Contract Research Organization
CR	Cytogenetic response
CNS	Central nervous system
LVEF	Left ventricular ejection fraction
CHR	Complete hematologic response
CCyR	Complete cytogenetic response
ICH	International Conference on Harmonization
VLDL	Very low-density lipoprotein
DQF	Data Questioning Form

Definition of terms

Assessment	A procedure used to generate data required by the study
Enrollment	Point/time of subject entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol).
Investigational drug	The study drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with "investigational new drug."
Subject number	A number assigned to each subject who enrolls in the study. When combined with the center number, a unique identifier is created for each subject in the study.
Period	A minor subdivision of the study timeline; divides phases into smaller functional segments such as screening, baseline, titration, washout, etc.
Premature subject withdrawal	Point/time when the subject exits from the study prior to the planned completion of all study drug administration and assessments; at this time all study drug administration is discontinued and no further assessments are planned.
Stop study participation	Point/time at which the subject comes in for a final evaluation visit or when study drug is discontinued, whichever is later.
Study drug	Any drug administered to the subject as part of the required study procedures; includes investigational drug and any control drugs.
Study drug discontinuation	Point/time when subject permanently stops taking study drug for any reason; may or may not also be the point/time of premature subject withdrawal.
Variable	Information used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified time points.

Protocol synopsis

Title of the study: 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)
Purpose of the study: This study is designed to investigate molecular and cytogenetic efficacy and safety profile of nilotinib in the treatment of early chronic phase of Ph+ CML in patients from different risk groups

Objectives:
Primary objective:

- To investigate the efficacy of nilotinib in the treatment of early phase Ph+ CML (cumulative major molecular response [MMR] during the first 12 months)

Secondary objectives:

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

Population: All eligible adult Ph + CML-CP patients who have been newly diagnosed cytogenetically during the past six months and who have not received treatment for CML other than anagrelide and hydroxyurea will be enrolled in the study.

A total of 110 subjects will be enrolled despite risk stratification.

Inclusion / exclusion criteria:
The patients must fulfill all inclusion criteria during the 4 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.

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 smear and bone marrow
  - <30% blast in peripheral blood smear 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
- 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 any study-related procedure may be initiated.

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 > 450msn 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 history 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 patients 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 treatment starts.
- 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 subjects who are not willing to take contraceptive measures throughout the study (in order to confirm that menopausal a woman does not have childbearing potential, she should have been amenorrheic for at least 12 months).

Study and reference treatment: All enrolled subjects will be treated with nilotinib (AMN107 Tasigna®) 300 mg BID (600 mg/day) for 24 months. The study drug will be dispensed in open-label vials containing 150 mg strength capsules. Nilotinib should be taken at least 2 hours before breakfast and dinner with a glass of water. No oral intake, except water, is permitted within 1 hour following the dose.

This study does not involve a reference treatment.

Study 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-week 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 for 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.

Efficacy assessments:
Primary

- MMR rate during 12 months is defined as BCR-ABL/control gene ratio of ≤ 0.1% as measured by RQ-PCR on an international scale (in %).

Secondary

- CCyR rate is defined as the ratio of patients with 0% Ph+ metaphases.
- MMR rate is defined as BCR-ABL/control gene ratio of ≤0.1% as measured by RQ-PCR on the international scale (%)
- WBC <10 x 10^9/L, platelet <450 x 10^9/L, blood myelocyte + metamyelocyte <5%, absence of blast and promyelocyte in blood, basophiles <5%, absence of extramedullary involvement (defined as complete hematologic response)
- Time to MMR is defined as time to first documented MMR following treatment with the first dose
- MMR duration defined as the duration from the first documented MMR to the first date when MMR is lost, or to progression or death (whichever is first)

Safety assessments:
Primary

- Rate, severity, seriousness and relationship to the study drug of adverse events

Secondary

- Laboratory profiles (hematology/biochemistry)
- ECG
- Physical examinations

Data analysis: The primary efficacy variable in this study is the best cumulative MMR rate 12 months after the administration of the first dose of the study treatment. Patients who withdraw prematurely or those who fail to provide data for the study will be considered as unfit for analysis and will be included in the ITT analysis as non-responders. Criteria to consider a subject as non-responder will be presented in another table. Only those subjects who achieve MMR within 12 months will be considered as responders. Analysis of secondary variables will be performed on ITT population.

Efficacy variables for the primary and secondary objectives will be analyzed by descriptive statistics 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 will not be replaced for secondary end points. All values 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.

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.

An interim analysis is planned when 30% of the targeted number of patients is reached and these patients received six-month treatment with nilotinib.

1. Background

1.1 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).

1.2 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.

2 Purpose and rationale

Efficacy and safety of imatinib treatment in newly-diagnosed patients with chronic phase CML patients have been shown in several studies, including the landmark IRIS study.

Although imatinib is very effective in chronic phase Ph + CML, leukemia persists in many of responders and there is always the risk of disease progression molecularly, cytogenetically and clinically.

Nilotinib is a novel oral tyrosine kinase inhibitor with improved potency and selectivity compared to imatinib, since it fits better to ATP-binding pocket of imatinib. It seems reasonable to evaluate high potency and selectivity of nilotinib in patients with high Sokal risk in the high Sokal risk population to meet the unmet needs of these patients.

GIMEMA (Rosti 2008) and MDACC (Cortes 2008) studies independently investigated the efficacy of nilotinib in newly diagnosed, treatment-naïve patients with Ph+-CML. Faster and more profound responses were demonstrated when the results reported from ASH 2008 were compared to published data of imatinib. CCR rates of evaluable patients at months 3 and 6 were 78 and 96% in the GIMEMA study and 93 and 100% in the MDACC study, respectively. Major molecular response rates at month 6 in the GIMEMA and MDACC studies were 74 and 45%, respectively. These results are more impressive than those reported from IRIS study, which demonstrated 69% CCyR and 40% MMR at month 12.

Further clinical data are required to demonstrate efficacy in different risk groups in order to evaluate the efficacy of nilotinib in newly diagnosed (*de novo*) patients regardless of Sokal scores.

The present study was designed to investigate the efficacy of nilotinib (cumulative major molecular response [MMR] in 12 months)

3 Study Objectives

3.1 Primary Objective(s)

- To investigate the efficacy of nilotinib (cumulative major molecular response [MMR] in 12 months).

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 Investigational 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]

[redacted]

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

[redacted]

5 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 [redacted] will be enrolled in the study.

A total of 110 patients will be enrolled.

[redacted] and should not meet any of the exclusion criteria.

5.1 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.

5.2 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).

6 Treatment

6.1 Investigational treatment and control drugs

The investigational drug is nilotinib (AMN107 Tasigna®) 150 mg strength capsules in open-label vials.

This study does not involve a reference treatment.

6.2 Treatment arms

All enrolled subjects will be treated with nilotinib (AMN107 Tasigna®) 300 mg BID (600 mg/day) for 24 months.

6.3 Treatment assignment

Since this is an open-label study with one treatment arm, all subjects will be treated with the given regime.

6.4 Treatment blinding

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

6.5 Treating the subject

6.5.1 Subject numbering

Each subject in the study will be identified by unique nine-digit number, which is a combination of four-digit the center number and five-digit patient number. Center number will be assigned to study centers by Novartis. After signing the informed consent form, each subject will be given a patient number by the investigator. At each center, the first enrolled subject will be given [redacted] and the following subjects will be assigned the subsequent numbers (e.g., [redacted] to the second subject and [redacted] to the third subject). Once a subject number is assigned to a subject, it will not be used for any other subjects. If the subject fails to start treatment for any reason, the reason will be stated on the Screening Log.

6.5.2 Dispensing the study treatment

The study drug nilotinib will be supplied by Novartis to each center.

The study personnel will identify the study drug to be dispensed to patients to be used at the dose levels indicated on labels. The study personnel will record the subject number at both sections of the label before dispensing to the subject and will remove the outer part of the label and stick it on the source documents (Drug Label Form) containing the unique subject number.

6.5.3 Supply, storage and tracking of study treatment

Study drugs must be received at the study site by a designated person, handled and stored safely and properly, and kept in a secured location to which only the Investigator and designated staff have access. Upon receipt, the study drugs should be stored according to the instructions specified on the drug labels. Clinical materials should only be dispensed according to the protocol.

Drub labels will be in Turkish and will be in accordance with regulatory requirements of each country. They will contain information on storage conditions of the drug but will include no patient information other than the drug number.

The Investigator must maintain an accurate record of the shipment and dispensing of study drug in a drug accountability ledger. Drug accountability will be noted by the Monitor during site visits and/or at the completion of the trial. Subjects will be asked to return all unused study drugs and packaging at the end of the study or at the time of study drug discontinuation.

At the conclusion of the study or during course of the study, if applicable, the investigator will send all the used and unused study drug supplies as well as the empty containers and a copy of the completed drug accountability ledger to the Novartis monitor or Novartis address provided in the investigator filed given to each center.

6.5.4 Instructions for prescribing and taking study treatment

All patients will undergo a preliminary assessment (screening visit) and will return within 2 weeks following the screening for Baseline assessments if considered appropriate.

Beginning on the after the baseline visit, all eligible subjects will receive 300 mg (600 mg/day) nilotinib BID (AMN107 Tasigna®) for 24 months.

Nilotinib must not be taken with food. Subjects must take nilotinib on empty stomach. They should not consume food during the 2 hours following treatment and they should take anything orally except water during the 1 hour following treatment. Subjects must be reminded to take the capsules as a whole and with a full glass of water and not to chew the capsules. All subjects must avoid grapefruit juice, starfruit and Seville orange throughout the study. Juices of these fruits should also be avoided. Doses eliminated with vomit must not be compensated with a new dose. Missed doses must not be taken. Nilotinib doses must be taken in 12-hour intervals.

The investigator must promote compliance by instructing the subject to take the study drug exactly as prescribed and by stating that compliance is necessary for the subject's safety and the validity of the study. The subject should be instructed to contact the investigator if he/she is unable for any reason to take the study drug as prescribed.

All dosages prescribed and dispensed to the subject and any dosage changes during the study must be recorded on the Dosage Administration Record on CRF.

If nilotinib is authorized and included in the reimbursement list following completion of the active treatment period, the subjects who are still on treatment will be switched to the commercial drug in one month.

6.5.5 Permitted dose adjustments and interruptions of study treatment

In order to main the subject safely on the study treatment, dose adjustments are permitted for patients who fail to tolerate the dose scheme described in the protocol, provided that the toxic symptoms disappear within 28 days in non-hematologic toxicities and in 42 days in hematologic toxicities (Day limits are considered for each discontinuation). Please refer to

the following tables for dose adjustments. Any changes in the dose should be recorded on the Dosage Administration Record on CRF.

CTCAE (NCI Common Terminology Criteria for Adverse Events) version 3.0 will be used for toxicity and adverse event reporting for this study. If there are multiple toxicities leading to dose reduction, then the highest dose reduction scheme will be used.

6.5.5.1 Dose reduction guidance for study treatment-related non-hematologic toxicity

Guidance for dose reduction in study treatment-related non-hematologic toxicity is summarized in Table 6-1. No dose reduction below 400 mg/day nilotinib will be permitted. If a subject is unable to tolerate the minimum dose of 400 mg/day nilotinib, he/she should not continue to the study. Any non-hematologic toxicity should be resolved within 28 days for the subject to resume the study treatment at the reduced dose. If a non-hematologic toxicity is not resolved after 28 days, the subject must be withdrawn from the study.

Table 6-1 Summary of dose reduction guideline for non-hematologic toxicity

Grade	Occurrence	Dose modification
1	At any time	No dose reduction
2 or 3	First or second incidence	Discontinue nilotinib Weekly monitoring of laboratory values until < grade 2 Resume with nilotinib 600 mg/day
	Third incidence	Discontinue nilotinib Weekly monitoring of laboratory values until < grade 2 Start with 400 mg/day nilotinib Increase nilotinib 600 mg/day one week later
	Fourth incidence	Discontinue nilotinib Weekly monitoring of laboratory values until < grade 2 Start with 400 mg/day nilotinib Contact with study steering committee, discuss whether nilotinib 600 mg/day may be administered
4	At any time	Discontinue nilotinib Contact with the study steering committee – discuss whether to resume nilotinib or discontinue permanently

Cardiac AEs – Dose Reduction

- QTc prolongation > 480 msn: discontinue nilotinib, perform serum electrolyte analysis (including potassium and magnesium) and, if below normal limits, correct with supplements. Concomitant medication should be considered.
- If QTcF < 450 msn and returns to 20 msn limit of the baseline: resume nilotinib at the previous dose within 2 weeks.
- If QTcF is 450-480 msn after two weeks, reduce the dose to 400 mg once daily.
- If following 400 mg once daily dose QTcF returns to >480 msn, nilotinib should be discontinued.

6.5.5.2 Dose reduction guidance for study treatment-related hematologic toxicity

Guidance for dose reduction in study treatment-related ≥ grade 3 non-hematologic toxicity is summarized in Table 6-2. No dose reduction should be made for Grade 1 and Grade 2 hematologic toxicities. Any hematologic toxicity should be resolved within 42 days for the subject to resume the study treatment at the reduced dose. If a hematologic toxicity is not resolved after 42 days, please consult the study steering committee.

Table 6-2 Summary of dose reduction guideline for hematologic toxicity

Grade	Occurrence	Dose modification
1 or 2	At any time	No dose reduction
3 or 4	First or second incidence	Discontinue nilotinib Weekly monitoring of laboratory values until < grade 3 Resume with nilotinib 600 mg/day
	Third incidence	Discontinue nilotinib Weekly monitoring of laboratory values until < grade 3 Resume with 400 mg/day nilotinib Increase nilotinib 600 mg/day one week later
	Fourth incidence	Discontinue nilotinib Weekly monitoring of laboratory values until < grade 3 Resume with 400 mg/day nilotinib Increase nilotinib 600 mg/day one month later
	Fifth incidence	Discontinue nilotinib Contact with the study steering committee – discuss whether to resume nilotinib or discontinue permanently

6.5.5.3 Guidance to re-increase the dose

All efforts must be made to increase the nilotinib dose back to the previous dose (i.e., the dose before dose reduction). This applies to both hematologic and non-hematologic toxicities.

6.5.5.4 Recommended treatment for some specific adverse events observed with nilotinib

Dose reduction guidance provided in Table 6-1 and Table 6-2 should be followed. Additional guidance for treatment of the subject is listed below.

6.5.5.4.1 Treatment of bone marrow suppression

Bone marrow suppression may develop at any time during treatment with nilotinib. Colony-stimulating factors (G-CSF and GM-CSF) including sargramostim and pegfilgrastim may develop in recurrent Stage 3 neutropenia. Treatment with recombinant erythropoietin is permitted.

6.5.5.4.2 Treatment of rash/itch

Rash is mild and self-limited in most of the cases and may be treated with antihistaminics or topical steroids. In more severe cases, short-term treatment with an oral steroid may be initiated. Prednisone 25 mg is recommended for one week or until rash is resolved.

6.5.5.4.3 Treatment of edema

Subjects should be monitored closely for peripheral edema and fast increases in body weight. Treatment with diuretics may be started for edema. Patients who develop ≥ Stage 3 edema with cardio-respiratory symptoms must undergo relevant medical assessments such as echocardiography and chest radiography for underlying cardiac or respiratory conditions. Further tests may be indicated for optimum treatment of the condition.

6.5.5.4.4 Treatment of hepatic toxicity

Routine hepatic function tests as outlined in the visit schedule should be performed throughout the study. Dose reduction may be necessary and the decision to continue or discontinue nilotinib should be based on the individual clinical status.

6.5.5.5 Monitoring toxicities

Subjects who are permanently withdrawn from the study treatment due to an adverse event or abnormal laboratory finding associated with the study treatment should be monitored for once a week for 4 weeks or until the event is resolved or the subject is stabilized, whichever comes first. All subjects will be monitored for adverse events for 30 days after the administration of the last dose of the study treatment. Each subject prematurely withdrawing from the study will be monitored for survival every 3 months up to 2 years after the study start.

6.5.6 Concomitant treatment

In general, supportive treatments and concomitant medications and treatments necessary for subject safety are permitted provided that their use and the period of treatment (start and stop dates or that the treatment was ongoing at the time of most recent examination) are documented in subject records and relevant case report forms. This includes blood and platelet transfusions in subjects with anemia and thrombocytopenia.

Treatment with other investigational drugs except nilotinib is not permitted. Other anti-cancer agents including chemotherapy and biologic agents are not permitted.

6.5.7 Discontinuation of study treatment

Subjects who discontinue treatment with the study drug will be considered as withdrawals after the final visit assessments or it they are lost to follow up.

6.5.7.1 Progression

The following are recognized as disease progression and such subjects must not continue to the study:

1. Death
2. Accelerated phase (AP) defined as any of the following:
    - ≥15% blast in peripheral blood or bone marrow but <30% blast in both peripheral blood and bone marrow
    - ≥30% blast in peripheral blood and bone marrow plus promyelocytes
    - ≥20% basophil in peripheral blood

- Thrombocytopenia not associated with the treatment (>100 x 10^9/L)

3. Blast crisis defined as any of the following:
   - ≥30% blast in peripheral blood
   - Development of extramedullary involvement, except for hepatosplenomegaly (i.e., chloroma)

6.5.7.2 Identifying intolerance

Subjects may be withdrawn from the study due to intolerance. Intolerance is defined as follows:

- Persisting or recurring Stage 3 and 4 adverse events or those that require treatment cessation despite optimum supportive care,
- Nilotinib-associated Stage 2 adverse events which last ≥ one month and recur > 3 times despite dose reduction or treatment cessation.

6.5.7.3 SOKAL risk identification

For risk identification, the following criteria should be met at the time of diagnosis, prior to any treatment:

- Age
- Spleen size (below the rib margin, in cm – maximum distance)
- Platelet count
- Blasts (%) in peripheral blood

As demonstrated in the table below, the risk is calculated according to the international prognostic formula.

Table 6-3 SOKAL risk estimation and definition

Age (years)	0.0016 (age – 43.4)
Spleen (below the rib margin, in cm – maximum distance)	0.0345 (spleen – 7.51)
Platelet count (x10^9/L)	0.188 [(Platelet^2:700) – 0.563]
Myeloblasts in peripheral blood (%)	0.0887 (myeloblasts – 2.10)
Basophils in peripheral blood (%)	/
Eosinophils in peripheral blood (%)	/
RELATIVE RISK	Exponential of total
LOW	<0.8
MODERATE	0.8-1.2
HIGH	>1.2

6.5.7.4 End of Treatment

Subjects may withdraw at any time of their own accord or may be withdrawn by the investigator. If premature withdrawal occurs for any reason, the investigator must make every effort to determine the primary reason for a subject's premature withdrawal from the study and record this information on the Study Completion on CRF.

Subjects may withdraw from the study at any time in case of progression or treatment failure. They may also withdraw due to treatment intolerance.

6.5.7.5 Withdrawal

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

A complete end-of-study visit assessment should be performed within 7 days following the administration of the last study treatment for each subject who prematurely withdraw from the study (before the two years of study period is complete). End-of-study assessments will include adverse events, concomitant drugs and treatments, physical examination, vital findings, ECOG performance status, biochemistry, hematology findings, extramedullary involvement, PCT analyses and bone marrow assessments. Whenever a subject withdraws from the study, Study Completion page of CRF should be completed. If an end-of-study assessment is performed within 7 days after withdrawal, it is not necessary to repeat this assessment.

Any information on the event that leads to withdrawal, including cofactors, should be included on CRF.

Subjects who are permanently withdrawn from the study treatment due to an adverse event associated with the study treatment will be monitored for once a week for 4 weeks or until the event is resolved or the patient is stabilized, whichever comes first. All subjects prematurely withdrawing from the study will be monitored for survival every 3 months up to 2 years after the study start.

Mutation analysis will be performed for patients who withdraw due to inefficacy of treatment with nilotinib and in whom progression occurs during treatment with nilotinib.

6.5.8 Emergency unblinding of study treatment
Not applicable. This is an open-label study.

6.5.9 Study steering committee
The coordinator and three investigators of the trial, one independent international physician and one Novartis member will form the study's steering committee.

The steering committee was created for three purposes:

- to recommend treatment in case of SAEs. The committee should be consulted to in the following defined cases: recurrent Stage 3/4 hematologic AE, recurrent Stage 2/3 non-hematologic AE and Stage 4 non-hematologic AE.
- to monitor SAEs and to recommend treatment cessation or continuation following SAEs
- to recommend treatment cessation due to inefficacy

Novartis member will only be responsible of communicating the decisions of the study steering committee to relevant center(s).

7 Visit schedule and assessments
Table 7-1 lists all assessments and the visits at which these assessments will be performed are marked with an "X". At all visits, the subjects should be seen on the designated day or at the earliest time possible.

Patients, who prematurely withdraw from the study for any reason, should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit will be performed.

At minimum, they should be contacted to perform safety assessments within the 30 days following the last treatment with the study drug. Proof of efforts to contact with the subject should be documented in patient records.

All data listed in Table 7.1 and obtained with the assessments described below in detail should be supported by subject's source information.

7.1 Screening and baseline
Informed consent in written should be obtained before any study-related procedure may be initiated.

Screening assessments to confirm eligibility should be performed before administration of the first study treatment. Bone marrow aspiration should have been performed by 8 weeks before the first dose and the results should have been obtained before administration of the first dose of the study treatment.

At least 20 bone marrow cell metaphases are required for all cytogenetic assessments. FISH analysis is acceptable if bone marrow analysis is not possible. In addition, a peripheral blood sample will be analyzed with PCR.

A complete physical examination including baseline laboratory analyses (including hematology, chemistry, serum potassium, calcium and magnesium), performance status and body weight should be performed prior to the first dose of study treatment. Potassium and/or magnesium levels of subjects whose potassium and/or magnesium levels were <LLN at the screening should be corrected with supplements and their levels should be within normal limits before administration of the first dose of the study treatment.

If an assessment has already been made within the 48 hours before administration of the first dose of the study treatment as a part of screening assessments, this assessment need not be repeated on day 1.

During the first 3 months of treatment, all routine assessments should be performed within ± 1 day of the date specified in the assessment schedule. All routine assessments after Visit 8 (until month 12 is completed) should be performed within ± 3 days of the dates specified in the assessment schedule. ± 7 day deviations will be acceptable for the visit scheme between months 12 and 24. One cycle (one month) is considered as 4 weeks (i.e. 28 days).

Table 7-1 Assessment schedule

Period	**Screening**	**Treatment and monitoring**																			
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**	**M7**	**M8**	**M9**	**M10**	**M11**	**M12**	**M15**	**M18**	**M21**	**M24**
Screening info																					
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 [a]	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 [b]																					X
Study completion form																					X

[a] Bone marrow analyses will be performed at scheduled visits or until the subject achieves CCR or MMR.
b Mutation analysis will be performed for patients who withdraw because nilotinib is not effective and in whom if progression occurs during treatment with nilotinib.

7.2 Information to be collected on screen failures

In case of screen failure, patient's demographic information as well as the primary reason why he/she was not eligible for this study will be recorded on the relevant section of the CRF (ineligible screened patients).

7.3 Subject demographics/other baseline characteristics

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 Treatment exposure and compliance

All doses of study drug prescribed and taken by the subject, start date and end date of treatment, dose and dose adjustments, if applicable, will be recorded in Dose Administration Record.

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 must be recorded on source documents at every visit.

The date and time nilotinib dose is dispensed (morning or evening doses, as appropriate) will be recorded in the relevant Dose Administration Record of the CRF.

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.

Information on whether the patient completed or withdrawn from the study, reasons for withdrawal and the last dose of study treatment will be entered in the Study Completion CRF.

For each patient who prematurely withdraws from the study, survival information as well as information on the patient's the disease state will be collected every three months for a period

of 2 years. [redacted]

All comments on the conduct of the trial will be entered in the comments section of the CRF.

If repeat assessments are necessary (e.g., ECG, laboratory tests, vital findings, etc.) the reason for the repeat assessment should be entered in the additional visits section of the CRF.

7.5 Efficacy

7.5.1 Molecular response

Molecular response (MR) will be evaluated in all patients. BCR-ABL transcript level will be determined by a RQ-PCR test using peripheral blood and will be analyzed in a central laboratory. This central laboratory is standardized as a national laboratory as a part of the EUTOS molecular monitoring project and its conversion factor was set. For each sample, the ratio of BCR-ABL transcripts to control gene transcript and a reference standard will be calculated as percentage concerted to the international scale (Hughes and Branford 2006).

Major molecular response is defined as follows:

- MMR rate is defined as BCR-ABL/control gene ratio of ≤ 0.1% as measured by RQ-PCR with two repeat analyses on an international scale (in %).
- Time to MMR is defined as the time from the administration of the first dose to the first documented MMR
- MMR duration is defined as the duration from the first documented MMR to the first date when MMR is lost, or to progression or death (whichever is first)

MMR loss is defined as % BCR-ABL/control gene ≤0.1% on the international scale

7.5.1.1 Sampling for molecular response

20 ml peripheral blood will be collected from each subject at all visits scheduled for blood sampling to monitor molecular response under study treatment. PCR sample collected on day 1 before dose administration will be used for all subsequent PCR comparisons. The samples will be forwarded to the central laboratory for baseline BCR-ABL transcript level measurements. Samples will be collected from all patients at the end of months 1, 3, 6, 9 and 12, and then at the end of every three months for 2 years. The blood will be analyzed by quantitative PQ-PCR for presence of BCR-ABL transcripts. If a ≥ 5-fold increase in BCR-ABL transcripts compared to the lowest level measured in the study is obtained, this should be confirmed by a second analysis. If ≥ 4-fold reduction is measured in MMR or BCR-ABL transcripts levels compared to standard baseline levels, the response will be confirmed by a second analysis.

Each center will be provided with the kits for PCR sampling. At each sampling point, 20 ml of peripheral will be collected in four 10 ml sterile EDTA tubes contained in the kits. Following sampling, the tubes should be inverted gently 8-10 times to prevent clotting. The tubes must be stored at 4-8ºC. The samples are to be transferred to the reference laboratory in cold boxes.

RNA extraction and reverse transcriptase (RT) - polymerase chain reaction (PCR)
Total cellular RNA trizol extraction will be obtained by izopropanol precipitation and ethanol 70% wash. RNA will be measured by spectrophotometer at 260 nm and its integrity will be studied by agarose 2% gel electrophoresis. 1 μg of the total cellular RNA will be reverse transcribed to xDNA by random hexamer primer and 200 U M-MLV reverse transcripts.

Real-time quantitative RT-PCR
Real time RT-PCR will be performed using the LightCycler480 system. ABL will be used as the control gene to compensate RNA quality differences and the absolute contents of BCR-ABL mRNAs will be normalized to ABL mRNA content. Primers and probes for BCR-ABL, ABL were determined through collaboration of 25 individual centers from 10 European countries (European Concerted Action, SANCO), as reported by Gabert et al. (Leukemia (2003) 17, 2318–2357). Plasmids containing sequences of the same genes in plasmid pME-2 will be used. Quantitative real-time RT-PCR (RQ-PCR) will be performed three times for BCR-ABL, total ABL transcripts for cDNAs of all samples. Seven series of dilutions will be used for 4_106 copies of pME-2 for each reaction to provide an external control in each PCR study. Preliminary runs were performed to optimize the real-time PT-PCR equipment. Integrity and quality of the RNA will be checked by gel electrophoresis. In addition, ABL CT higher than 28 will be considered functionally damaged and no further analyses will be performed. Finally, if BCR-ABL Ct is higher than the cut-off value on the relative standard curve of the study (VT corresponds to a copy), the sample will be considered negative (below the limit detectable by the MRD technique). Average of each triple measurement will be calculated; BCR-ABL/ total ABL ratios will be estimated and will be presented in percentages. Single outliers will be excluded from the calculation of mean values: e.g. to consider BCR-ABL positive, at least 2 out of 3 samples should be positive.

7.5.2 Cytogenetic response
Cytogenetic response will be taken as the percentage of bone marrow Ph+ metaphases and will be defined as follows (at least 20 metaphases should be reviewed):

- Complete (CCyR) – 0% Ph+ metaphase
- Partial (PCyR) - 1 to 35% Ph+ metaphase
- Major (MCyR) – 0 to 35% Ph+ metaphase
- Minor (mCyR) - 36 to 65% Ph+ metaphase
- Minimal - 66 to 95% Ph+ metaphase
- No response - 96 to 100% Ph+ metaphase

Major response (0 to 35% Ph+ metaphase) combines both the complete and partial responses.

Loss of complete cytogenetic response: Any increase from 0% in Ph+ bone marrow. This should be regarded as disease progression.

Loss of partial cytogenetic response: Any increase from 1 to >35% in Ph+ bone marrow. This should be regarded as disease progression.

7.5.2.1 Bone marrow and cytogenetic analyses

Bone marrow aspiration and/or biopsy and bone marrow cytogenetic analysis to evaluate Ph+ metaphases should be performed within 8 week before the administration of the first dose of study treatment. Bone marrow aspiration and/or biopsies for cytogenetic analysis to assess response will be performed at the end of months 6 and 12 or until the patient achieves CCyR or MMR. Bone marrow cytogenetic analyses will also be performed at the end of study visits or in the event of premature subject withdrawal. These evaluations can be performed within 14 days of the scheduled visit or within 21 of the study end.

Cytogenetic analysis should be performed centrally by standardized methods. For cytogenetic response evaluation, FISH analysis is only acceptable if bone marrow aspiration is not possible. Twenty metaphases should be studied for each bone marrow aspiration sample. Percentage of Ph+ chromosome metaphases, metaphase count, number of those positive for Ph chromosome, cellularity and percentage of blasts and promyelocytes will be recorded in Bone marrow CRF. These assessments will be performed and analyzed locally.

No further CR assessment will be performed for the subjects who achieve CCyR or MMR.

Bone marrow (BM) analyses should be performed at least once a year, and in case of CHR or MCyR loss and to confirm MMR loss.

If additional bone marrow assessments are made, their results should be recorded in the CRF as unscheduled visit.

Bone marrow samples will be transferred to the reference laboratory for cytogenetic analysis in cold boxes.

7.5.3 Hematologic response

Hematologic response includes any of the following:

1. Complete hematologic response (CHR)

2. Absence of leukemia evidences in the peripheral blood, without a complete peripheral blood recovery

CHR is defined as all of the following for ≥ 4 weeks:

1. Normalization of peripheral blood count
   - WBC count < 10 x 10^9/L
   - Platelets < 450 x 10^9/L
2. Normal WBC subgroups distribution
   - No blast(<1%) and promyelocyte in circulating peripheral blood

- A total level of myelocytes plus metamyelocytes of <5% will be allowed in peripheral blood; higher level of immature granulocyte will not be permitted.
- Less than 5% basophiles.

3. Absence of any disease-related symptoms and evidence of an extramedullary disease including disorders of the liver and spleen.

CHR loss: Any of the following, provided that the findings is confirmed by a second analysis after ≥1 month:

- Increased WBC count up to >20.0 x 10^9/L
- Increased platelet count up to ≥600 x 10^9/L
- Gradually increasing splenomegaly extending ≥5 cm below the inferior intercostals margin. This should be confirmed after 4 weeks. No extramedullary disease.
- Presence of ≥5% myelocyte + meta myelocyte in peripheral blood
- Presence of blast or promyelocyte in peripheral blood

Increased WBC count, which is defined as a two-fold increase in WBC count at least one month apart being at least >20.0 x 10^9/L during the second month in subjects who did not achieve CHR, indicating progression. Subjects must be maintained on the maximum tolerated dose of nilotinib. The condition where there is no evidence of leukemia but peripheral blood did not recover completely is defined as follows:

- No circulation blood blasts
- ANC ≥1.0 x 10^9/L
- Platelet count ≥ 20 x 10^9/L (independent of platelet transfusion and no evidence of bleeding)
- No evidence of extramedullary involvement

7.5.4 Treatment failure

Treatment failure with nilotinib is defined as follows in this study:

- Response less than complete hematologic response at month 6 is below CHR or absence of any cytogenetic response (CR) (Ph+ > 95%)
- Response less than partial cytogenetic response at month 12 (Ph+ > 35%)
- Response less than complete cytogenetic response at month 18 (Ph+ > 0%)
- Loss of CHR, PCyR or CCyR, progression to AP/BP and increased WBC count at any time

[redacted]

[redacted]

7.6 Safety

Safety assessments will include adverse events and serious advers events, concomitant medication/treatments for their treatment, laboratory parameters including hematology and blood chemistry, body weight, physical examination and ECG monitoring.

7.6.1 Adverse events

In line with the objectives of this protocol, an adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after informed consents are signed, even if the event is not considered to be related to study drug.

CTCAE version 3.0 common toxicity criteria will be used for adverse events in this study. If no CTCAE grading is available for an adverse event, then the terms mild, moderate, severe and life-threatening or Grades 1-4 will be used. CTCAE grade 5 (death) will not be used in this study. This information will be entered in the Study End Survival Information CRF instead.

Adverse events occurring before the study start but after informed consent forms are signed will be recorded in the Medical History/Current Medical Status Case Report form. Abnormal laboratory values or test results will constitute adverse events only if they induce clinically significant clinical signs or symptoms (i.e., if a value or result results in discontinuation or represents a Serious Adverse Reaction by itself) or require therapy (i.e., all hematologic anomalies requiring transfusion or cytokine treatment). These should be recorded in the Adverse Event CRF together with findings, symptoms and relevant diagnoses. Adverse events that occur after start of treatment with study drug will be recorded in Adverse Events CRF.

The occurrence of adverse events should be sought by non-directive questioning of the subject at each visit during the study. Adverse events also may be detected when they are voluntarily reported by the subject during or between visits or through physical examination, laboratory tests, or other assessments. All adverse events must be investigated to determine the following:

1. Grade (CTCAE Grade 1-4)
2. Its relationship to the study drug (suspected/not suspected)
3. Its duration (start and end dates or if continuing at final exam)
4. Actions taken (no action taken; study drug dosage adjusted/temporarily interrupted; study drug permanently discontinued due to this adverse event; concomitant medication given; non-drug therapy given; patient hospitalized/patient's hospitalization prolonged).
5. Whether it constitutes a serious adverse event (SAE) (**please see Section 9.2 for definition and reporting SAEs**)

All adverse events should be treated appropriately. These treatments may include possible temporary interruptions or permanent discontinuation of the study drug, starting or stopping concomitant medication, changes in the frequency and content of examinations, hospitalizations or other medically indicated interventions. Once an adverse event is detected, it should be followed until its resolution and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug(s), the interventions required to treat it, and the outcome.

Information about common side effects already known about the investigational drug can be found in the Investigator Brochure (IB) or will be communicated between IB updates in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

7.6.2 Physical examination

A physical examination will be performed according to the visit schedule (see Table 7-1). Information for all physical examinations must be included in the source documentation at the study site. Significant findings that are present prior to the start of study drug must be included in the Relevant Medical History/Current Medical Conditions CRF. Significant findings after the start of study drug which meet the definition of an Adverse Event must be recorded on the Adverse Event CRF.

No case report form to enter normal findings of physical examinations is available. However, these findings must be included in subject's source documentation.

7.6.2.1 Extramedullary involvement

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.

7.6.3 Vital findings and body weight

Heart rate, blood pressure, body temperature and body weight as shown in Table 7-1 should be noted in patient chart and recorded in the CRF. Height will only be measured at screening and will be recorded in the CRF.

Subjects should be weighed according to the visit schedule to detect early signs of liquid retention (see Table 7-1) and they should also be instructed to check their weights regularly at home (i.e., three times a week). Additional body weight checks other than those performed during visits to evaluate performance status will not be recorded in the CRF but they must be included in source documentation of the study center.

The subjects will be encouraged to check their body weight and to inform the investigator in case of any increases >2 kg from their previous weight. Weight increases ≥ 2 kg must be carefully investigated and appropriate measures must be taken.

7.6.4 Performance status

Performance status will be recorded in the CRF according to the ECOG criteria described in Table 7-1 and Table 7-2.

Table 7-2 ECOG Performance Status

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

7.6.5 Laboratory Assessments

Laboratory assessments will be performed by a certified central laboratory according to the visit schedule (see Table 7-1). If a subject has parameters from another laboratory at any time, the sponsor must obtain the certificate and normal ranges and unit tables of this laboratory.

Clinically relevant abnormal laboratory parameters (e.g., those that require dose adjustment and/or interruption of the study drug, those that result in clinical symptoms or sings or require treatment) occurring at any time throughout the study must be recorded in the relevant CRF laboratory page as well as relevant comment page of the CRF, whether or not required by the protocol.

When abnormal laboratory values or test results constitute adverse events (i.e., when they trigger clinical signs/symptoms or require treatment) these should be recorded in the Adverse event CRF. If abnormal laboratory values or test results induce clinically significant signs or symptoms (i.e., if a value or result necessitates discontinuation or represents a Serious Adverse Reaction by itself) or require treatment (i.e., all hematologic anomalies requiring transfusion or cytokine treatment), these should be recorded in the Adverse Event CRF together with findings, symptoms and relevant diagnoses.

7.6.5.1 Hematology

Hematology laboratory assessments will be performed by a certified central laboratory. Hematologic assessments will include hemoglobin, hematocrit, total WBC count, platelet count and differentials (neutrophil, band, lymphocyte, monocyte, eosinophil, basophil,

promyelocyte, myelocyte, metamyelocyte and blast percentage) and will be performed according to the visit schedule (Table 7-1).

7.6.5.2 Biochemistry

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. These will be performed according to the visit schedule (Table 7-1).

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.

7.6.5.3 Pregnancy test

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.

7.6.5.4 Electrocardiography (ECG)

12-lead electrocardiography will be performed according to the scheme presented in Table 7-1.

8 Safety monitoring

8.1 Adverse events

Any serious adverse events in this clinical study will be reported immediately by the Investigator to Novartis on Novartis Serious Adverse Event Report Form and faxed to Novartis Turkey Drug Safety Department within 24 hours.

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

Every SAE, regardless of suspected causality, occurring after the subject has provided informed consent and until 4 weeks after the subject has stopped study participation must be reported. This includes the study protocol period overlapping with the standard treatment given.

A serious adverse event, recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode, regardless of when the event occurs. An SAE that is considered completely unrelated to a previously reported one should be reported separately as a new event.

Pregnancies in subjects on study drug must be reported by completing Novartis Clinical Trial Pregnancy Form. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements; see Section 9.2.

8.2 Serious adverse event reporting

Every SAE, regardless of suspected causality, should be reported by the investigator to Novartis within **24 hours** after learning of its occurrence. Previously reported serious adverse events should be reported with relevant follow-up information within 24 hours by the investigator within **24 hours** after learning of its occurrence. The investigator must complete a Serious Adverse Event Report form and fax the completed and signed form to Novartis Turkey Drug Safety Department within **24 hours**.

Follow-up information is sent to Novartis Turkey Drug Safety Department, 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. Each recurrence, complication and worsening of the original event should be reported as follow-up to that event. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was

broken or not, and whether the subject continued or withdrew from study participation. Please refer to Novartis guidelines for directions on completing the Serious Adverse Event Report Form.

Contact information: Investigators are required to report any serious adverse events by completing the serious adverse event report form **within 24 hours** to Ms. [redacted] from Novartis Turkey Drug Safety Department using the contact information below:
Tel: [redacted] or [redacted]
Fax: [redacted]

8.3 Pregnancies

To ensure patient safety, each pregnancy in a patient on study drug must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the local Novartis Drug Safety & Epidemiology Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the Novartis study drug of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

Investigators are required to report any pregnancies during the study by completing the pregnancy report form **within 24 hours** to Ms. [redacted] from Novartis Turkey Drug Safety Department using the contact information below:
Tel: [redacted] or [redacted]
Fax: [redacted]

Follow-up information of pregnancies must also be reported to Novartis within 24 hours of learning of its occurrence.

8.4 Data monitoring committee

No data monitoring committee has been assigned for this study.

9 Data review and database management

9.1 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and CRFs with the investigators and their staff. During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the CRFs, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study drug is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the patient's file. Data not requiring a separate written record will be defined before study start and will be recorded directly on the CRFs. The investigator must also keep the original informed consent form signed by the patient (a signed copy is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the CRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and the recording of data that will be used for all primary and safety variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the patients will be disclosed.

9.2 Data collection

Designated investigator staff will enter the data required by the protocol to Novartis CRFs printed on three-layer paper not requiring carbon paper. Field monitors will visit the site regularly to check the completeness of patient records and the accuracy of entries on the CRFs and will instruct the site personnel to perform necessary corrections and additions. CRFs will be transferred to the Date management and a copy will be stored at the site. When CRFs are received by the Data Management, proofs of receipt will be documented and will be reviewed again before data entry.

9.3 Database management and quality control

Very 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.

The entered data will then be checked systematically by the data management personnel using verification software and error messages printed out from database lists. Obvious mistakes will be corrected by the data management personnel. Other errors and missing information will be entered to Data Query Forms and will be forwarded back to the investigational site for correction. Signed original and corrected Data Query Forms together with CRFs will be maintained at the investigational site and a copy will be sent to Novartis, enabling entry of the corrected data to the database. All important safety and efficacy data should undergo a quality control check before the database lock.

Concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Any protocol violation that may have occurred will be determined at the end of the study. The database will be locked after this process is completed and the completeness and accuracy of

the database is confirmed. Any changes to the database after this time will require written confirmation of the Study Statistician and Statistics Reporter and the Steering Committee of the study.

10 Data analysis

10.1 Populations for analysis

Safety population 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.

ITT population will consist of all subjects who provided informed consent form.

Per protocol population 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.

10.2 Subject demographics/other baseline characteristics

Historical data and demographical characteristics will be presented 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.

10.3 Treatments (rescue medication, other concomitant therapies, compliance)

Exposure to study drug and administered doses of the study treatment will be presented 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.

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.

10.4 Analysis of primary variable(s)

10.4.1 Variable

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.

10.4.2 Statistical model, hypothesis and method of analysis

The primary objective is to determine the best cumulative MMR ratio obtained with nilotinib 300 mg BID treatment of 12 months

The IRIS study reported major molecular responses obtained by 40% of patients with newly-diagnosed chronic phase CML after treatment with imatinib 400 mg.

Compared to IRIS data, nilotinib is expected to produce a 15% improvement in MMR rates with a significance level at 5%.

Cumulative MMR rate at 12 months will be presented with 80% confidence interval. Primary analyses will be performed on the ITT population.

10.4.3 Handling of missing values/censoring/discontinuations

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.

10.4.4 Supportive analyses

In addition, per protocol population will also be analyzed for the primary endpoint.

10.5 Analysis of secondary variables

10.5.1 Efficacy (secondary)

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.

10.5.2 Safety

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.

Adverse events will be coded by primary system organ class and by preferred terms in accordance with the Medical Dictionary for Regulatory Activities (MedDRA). A study drug-related adverse event is defined as an adverse event which the investigator suspects to be related with the study treatment. Adverse events will be summarized by presenting the number and percentage of subject having any adverse event according to each primary system

organ class and preferred terms. The most severe event of a preferred term will be used for an individual patient in summaries presented by event severity. Summary tables presenting treatment-emergent adverse events and their severity will be prepared.

If an AE or SAE is observed more than once in an individual patient, then this AE or SAE will be counted once by presenting the most severe instance and its relation to the study treatment.

Data listing on adverse events will list the severity of an AE, whether it is related to the study treatment and whether it is serious.

Other information collected will be listed as appropriate. All statistical tests to analyze the data will be performed to elucidate interesting comparisons which are to be discussed in the future.

10.6 Sample size calculation
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.

10.7 Power for analysis of key secondary variables
This study will not be powered for secondary efficacy endpoints.

[redacted]

11 Ethical considerations

11.1 Regulatory and ethical compliance
This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations and with the ethical principles laid down in the Declaration of Helsinki.

11.2 Informed consent procedures
Eligible subjects may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC/REB-approved informed consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the subject. In cases where the subject's representative gives consent, the subject should be informed about the study to the extent possible given his/her understanding. If the subject is capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent document or a separate assent form. Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the

protocol). The process of obtaining informed consent should be documented in the subject source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC/REB, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC/REB approval.

Women of childbearing potential should be informed that taking the study drug may involve unknown risks to the fetus in case pregnancy occurs during the study and they should agree to practice contraception throughout the study in order to be able to participate in the study. If there is a doubt that the subject will actually comply with this requirement, then she should not be included in the study.

11.3 Responsibilities of the investigator and IRB/IEC/REB

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB) before study start. As per local regulations, the protocol and the proposed informed consent form must be reviewed and approved by Independent Ethics Committees of each study site and then the central ethics committee at the Ministry of Health before the study start. A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC/REB must be given to Novartis before study initiation. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/IECs/REBs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

11.4 Publication of study protocol and results

Novartis assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report, the results of this trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

Final results based on the final analysis of the study will be written by the study steering committee. The draft paper will be communicated to the local Novartis medical team for review.

Authors of the paper will be the investigators who will be responsible of more than 10% of the eligible subjects (as per the inclusion criteria) and will be acting on behalf of Novartis Pharma-Turkey. All other contributors to the study will be mentioned in the acknowledgements section, unless specified otherwise by the Study Steering Committee.

12 Protocol adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact Novartis or its agents. However, he/she may contact the study monitor to request approval of a protocol amendment which cannot be introduced since the competent authorities did not authorize. If the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC/REB it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

12.1 Protocol amendments

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.

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