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Protocol CAMN107A US37 / NCT01744665

A phase II randomized, multicenter study of treatment-free remission in chronic myeloid leukemia in chronic phase (CML-CP) patients who achieve and sustain MR4.5 after switching to nilotinib

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List of abbreviations

ABL	Abelson proto-oncogene
AE	Adverse Event
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
ANC	Absolute Neutrophil Count
AP	Accelerated Phase
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
b.i.d	*bis in diem*/twice a day
BC	Blast crisis
BCR	Breakpoint Cluster Region gene/BCR gene product
BCR-ABL	Fusion gene from BCR and ABL
CCG	Case Report Form Completion Guidelines
CCyR	Complete cytogenetic Response
CD	Consolidation Day
[redacted]	[redacted]
CHR	Complete hematologic response
CML	Chronic myeloid leukemia
CP	Chronic phase
CRO	Contract Research Organization
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
[redacted]	[redacted]
DNA	Deoxyribonucleic acid
DS&E	Drug Safety and Epidemiology
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report/Record Form
EDC	Electronic Data Capture
EMA	European Medicines Agency
ENESTcmr	Evaluation nilotinib efficacy and safety in clinical trials complete molecular response study
ENESTnd	Evaluating nilotinib efficacy and safety in clinical trials newly diagnosed study
EOC	End of Cycle
FAS	Full Analysis Set
FDA	Food and Drug Administration
[redacted]	[redacted]
GCP	Good Clinical Practice
G-CSF	Colony Stimulating Growth Factors
GI	Gastrointestinal
GIMEMA	Gruppo Italiano Malattie EMatologiche dell'Adulto (Italian Group for Hematological Diseases in Adults
GM-CSF	Granulocyte-macrophage colony-stimulating factor
H2	Histamine receptor H2

[redacted]

HBV	Hepatitis B Virus
HBcAb	Hepatitis B Core Antibody
HBsAb	Antibodies to Hepatitis B Surface Antigen
HBsAg	Hepatitis B Surface Antigen
HDL	High Density Lipoprotein
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IN	Investigator Notification
IRB	Institutional Review Board
IRIS	International Randomized Interferon versus STI571 study
IRT	Interactive Response Technology
IS	International Scale
LDH	Lactate dehydrogenase
LDL	Low Density Lipoprotein
LLN	Lower limit of normal
[redacted]	[redacted]
MD	Monitoring Day
MDASI-CML	M.D. Anderson Symptom Inventory – Chronic Myeloid Leukemia
MMR	Major molecular response
NCI	National Cancer Institute
NTRI	Nilotinib Treatment Re-Initiation
OS	Overall Survival
p.o.	*per os*/by mouth/orally
PCR	Polymerase Chain Reaction
Ph+	Philadelphia chromosome positive
PHI	Protected Health Information
PI-3	Phosphoinositide-3
PK	pharmacokinetics
PLT	Platelets
pt/pts	Patient / Patients
q.d.	Quaque die/ once a day
QoL	Quality of Life
QTcF	Frederica corrected QT interval
RD	Re-Initiation Day
REB	Research Ethics Board
RFR	Relapse-free rate
RNA	Ribonucleic acid
RQ-PCR	Quantitative real-time polymerase chain reaction
RR	Relative Risk (Sokal score)
RR	Respiratory Rate
SAE	Serious Adverse Event
SGOT	Serum Glutamic Oxaloacetic Transaminase

[redacted]

SGPT	Serum Glutamate Pyruvate Transaminase
SI	International System of Units
SMC	Study Management Committee
SmPC	Summary of Product Characteristics
SOC	Standard of Care
SOP	Standard Operating Procedure
STAT5	Signal Transducer and Activator of Transcription 5
TC	Total Cholesterol
TFR	Treatment Free Remission
TG	Triglycerides
TKI	Tyrosine kinase inhibitor
ULN	Upper Limit of Normal
VAS	Visual analogue scale
VES	Visit Evaluation Schedule
WBC	White Blood Cell
WHO	World Health Organization
WNL	Within Normal Limits

Glossary of terms

Assessment	A procedure used to generate data required by the study
Accelerated Phase (AP)	Accelerated Phase is defined as any of the following: • ≥ 15% blasts in the peripheral blood or bone marrow, but < 30% blasts in both the peripheral blood and bone marrow • ≥ 30% blasts plus promyelocytes in peripheral blood or bone marrow • ≥ 20% basophils in the peripheral blood • Thrombocytopenia (<100 x 10^9/L) that is unrelated to therapy
Blast Crisis (BC)	Blast crisis as defined by any of the following: • ≥ 30% blasts in peripheral blood or bone marrow • Appearance of extramedullary involvement other than hepatosplenomegaly proven by biopsy
Confirmed loss of MR4.0	Two consecutive BCR-ABL results taken 4-8 weeks apart that are greater than 0.01%IS
Cycles	Number and timing or recommended repetitions of therapy are usually expressed as number of days. In this study, one cycle = 30 days
Cytogenetic response	• Complete (CCyR) - 0% Ph+ metaphases • Partial (PCyR) - 1 to 35% Ph+ metaphases • Minor (mCyR) - 36 to 65% Ph+ metaphases • Minimal - 66 to 95% Ph+ metaphases • None - 96 to 100% Ph+ metaphases
Disease Progression	The following events are considered disease progression: • Accelerated phase • Blast crisis • CML-related death
Enrollment	Point/time of patient 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 treatment	Drug whose properties are being tested in the study as well as their associated placebo and active treatment controls (when applicable). This also includes approved drugs used outside of their indication/approved dosage, or that are tested in a fixed combination. Investigational treatment generally does not include other study treatments administered as concomitant background therapy required or allowed by the protocol when used in within approved indication/dosage.
Loss of CCyR	Loss of complete cytogenetic response is defined as any increase from 0% in the Ph+ bone marrow cells.

[redacted]

Loss of CHR	Loss of CHR is defined as the appearance of any of the following, confirmed by a second evaluation ≥4 weeks later (unless associated with progression to AP/BC or CML-related death): • WBC count >20 x 10^9/L • Platelet count ≥600 x10^9/L • Progressing hepatosplenomegaly to a size ≥5 cm below the left intercostal margin • Appearance of ≥ 5% myelocytes + metamyelocytes in the peripheral blood • Appearance of blasts or promyelocytes in the peripheral blood
Molecular Response	MMR (major molecular response, MR3.0) = BCR-ABL ≤ 0.1%IS MR4.0 = BCR-ABL ≤ 0.01%IS MR4.5 = BCR-ABL ≤0.0032%IS
Subject Number	A unique identifying number assigned to each patient/subject/healthy volunteer who enrolls in the study.
Premature patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study treatment administration and/or assessments; at this time all study treatment administration is discontinued and no further assessments are planned, unless the patient will be followed for progression and/or survival.
Study treatment	Includes any drug or combination of drugs in any study arm administered to the patient (subject) as part of the required study procedures, including placebo and active drug run-ins. In specific examples, it is important to judge investigational treatment component relationship relative to a study treatment combination; study treatment in this case refers to the investigational and non-investigational treatments in combination.
Study treatment discontinuation	Point/time when patient permanently stops taking study treatment for any reason; may or may not also be the point/time of premature patient withdrawal.
Treatment-free Remission Phase	The phase of the study where patients stop nilotinib treatment.
Variable	Identifier used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified time points

[redacted]

Amendment 4

Primary purpose for this amendment is the following:

- To include hepatitis B virus testing as one of the study procedures, to identify study patients who may be at risk of hepatitis B reactivation. Reactivation of hepatitis B virus can occur in patients who are chronic carriers of this virus and are receiving a drug of the BCR-ABL TKI class such as nilotinib. Some cases involving BCR-ABL TKI resulted in acute hepatic failure or fulminant hepatitis leading to liver transplantation or a fatal outcome.

Changes to protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

The following changes were implemented in the protocol synopsis as well as within the protocol sections below as applicable:

- Added Section 6.3.2.11 Hepatitis B reactivation language
- Section 7.1 added language on HBV testing
- Table 7-4 corrected the HbA1 and lipid panel visit schedule.
- Table 7-8 added language on HBV testing, addition to the collection plan
- Added Section 7.2.2.5.5 on Hepatitis B testing
- Correct minor discrepancies and add clarifications within the protocol.

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs) and Health Authorities.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

Amendment 3

Primary purposes for the amendment are the following:

- Redefine Molecular Relapse as confirmed loss of MMR (2 consecutive BCR-ABL levels > 0.1% IS taken approximately 4 weeks apart). Molecular relapse was defined as having a confirmed BCR-ABL ratio above MR4.0 (2 consecutive BCR-ABL levels >0.01%IS) in the original protocol, however per amendment 2 the criterion was changed to confirmed BCR-ABL level above MR 3.0, to be consistent with the other TFR ongoing trials. The definition of relapse will be changed to be consistent throughout the protocol and to align with the definition of relapse.
- In the TFR phase, a confirmed loss of MMR rather than an unconfirmed loss of MMR (BCR-ABL>0.1%IS) will trigger restarting nilotinib due to the variability of the testing.

[redacted]

- As per the original protocol, any loss of cytogenetic response would lead to early termination from the study. During the conduct of the study, the SMC has suggested that it would be important to maintain these patients on study so that their subsequent course could be monitored. The patients will resume nilotinib at a dose of 300 mg b.i.d. If a patient re-starts nilotinib and does not achieve CCyR within 3 months, then the patient should come off study. Re-achievement of CCyR must be confirmed through PCR testing (PCR<1%IS); repeat bone marrow aspirate is not mandated.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

The following changes were implemented in the protocol synopsis as well as within the protocol sections below as applicable.

- Table 3-1 – Updated the molecular relapse definition for [redacted] primary [redacted]. Molecular relapse free rate at 6 months after discontinuation from nilotinib therapy in patients with MR4.5. Molecular relapse is defined as having a confirmed BCR-ABL ratio above MMR (2 consecutive BCR-ABL levels >0.1%IS taken approximately 4 weeks apart).
- Section 4.1.4 Treatment Free Remission (TFR) Phase. Added confirmation of loss of MMR prior to re-starting nilotinib.
- Section 4.1.5 Nilotinib Treatment Reinitiation (NTRI) Phase updated the language on patients in TFR who lose any cytogenetic response; the patient will start nilotinib at an unscheduled visit. If the patient does not achieve CCyR after restarting nilotinib within 3 months, then the patient must come off of the study. Once a patient enters the re-initiation phase, the patient will not be eligible to re-enter the TFR phase again.
- Section 6.1.2 Treatment duration. Added re-confirmation of loss of MMR
- Table 7-6 for the TFR phase section added loss of CCyR will re-trigger nilotinib re-initiation.

[redacted]

- Section 10.4 Updated the molecular relapse definition on the Primary Objective section
- Section 10.5.2 Updated the molecular relapse definition for the secondary efficacy objectives
- Correct discrepancies and add clarifications within the protocol.

Amendment 2

Amendment rationale

Due to low enrollment, the sample size of the study has been reduced to a total of 59 patients, all of which were enrolled by January 9, 2015. Of these 59 patients, approximately 20 are

[redacted]

expected to enroll into the Treatment Free Remission (TFR) Phase. Based on this small sample size the decision was made to no longer have two Consolidation arms (1 year vs. 2 year), and instead have all patients enter into one Consolidation arm (2 years). The 2 year Consolidation Arm was chosen as the more conservative approach. Patients who were randomized to Arm A, a total of 1 year Consolidation, and entered into the TFR Phase prior to protocol Amendment 2 will continue in the TFR Phase. Patients who were randomized to Arm A and are the in Consolidation Phase at the time protocol Amendment 2 was finalized will remain in the Consolidation Phase for two years.

Primary purpose for the amendment is:

- Reduce the sample size
- Change the trial design to a 2 year Consolidation Phase for all patients
- Reduce the TFR Phase from 3 years to 2 years in duration
- To clarify how patients that are randomized prior to Amendment 2 will be handled
- To clarify that the loss of MR3.0, within the variability of the testing used, during Monitoring Phase must be confirmed by a subsequent PCR sample before the patient is discontinued.
- To update the criterion for coming off study during the Consolidation Phase to a confirmed loss of MR4.0, rather than a confirmed loss of MR4.5 due to the ±0.5 log variability in PCR testing.
- To update the criterion for Nilotinib Treatment Re-initiation to a loss of MR3.0 rather than a loss of MR3.0 or a confirmed loss of MR4.0 in an effort to align with other ongoing Novartis TFR studies.
- To update endpoints and statistics in alignment with the aforementioned changes
- To update clinical efficacy parameters in the background section to be consistent with the label update for nilotinib.
- Correct discrepancies and add clarifications within the protocol.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

The following changes were implemented in the protocol synopsis as well as within the protocol sections below as applicable.

- Section 1.2.2.1 Updated to be consistent with the 60-month label update for nilotinib.
  - Addition of Clinical Pharmacokinetics information on the moderate inhibitory effects of nilotinib on CYP3A4.
  - Addition of 60-month Clinical Efficacy and safety information
- Section 2.1, Section 2.2, Section 4.1.3, Section 6.1.2 and Section 6.5.2 Removed 1 year consolidation phase arm, randomization and stratification. Reduced the TFR Phase from 3 years to 2 years.
- Table 3-1Revised other secondary endpoint to evaluate molecular relapse free rates at 12 and 24 months after treatment discontinuation and removed the 36 month time point.

[redacted]

- Section 4.1 Added figure of new study design, with a 2 years consolidation phase. Removed 1 year consolidation phase arm.
- Section 4.1.2 Updated the total number of patients enrolled. Clarified that the loss of MR 3.0, within the variability of the testing used, during monitoring phase must be confirmed by a subsequent PCR sample.
- Section 4.1.5 Added new section header for Nilotinib Treatment Re-initiation (NTRI) Phase and reduced the TFR Phase from 3 years to 2 years.
- Section 4.2 Clarification in timing of data cuts for annual abstracts.
- Section 4.3 Updated the length of the study was updated from 7 years to 6 years
- Section 4.4 Clarification of the early stopping rules to reinforce that they are related to the 48 weeks following the start of the TFR Phase. Updated the stopping rule number of cases of failure to achieve MR3.0 after 12 months of re-initiating nilotinib to 5 from 7 due to the overall smaller sample size expected to reach the TFR Phase.
- Section 5 the total number of patients enrolled.
- Section 6.1 Updated to include dose reduction administration instructions.
- Section 6.4 Removed in-vitro data stating that nilotinib is a competitive inhibitor of CYP3A4, CYP2C8, CYP2C9, CYP2D6 and UGT1A1 and instructions regarding the co-administration when co-administering nilotinib with substrates of these enzymes to be consistent with the 60-month label update for nilotnib.
- Section 6.6 Updated to specify 200mg nilotinib for dose reductions.
- Table 7-2 Visit Evaluation Schedule-Consolidation Phase was updated to Removed 1 year consolidation phase arm, randomization and stratification.
- Table 7-3 Visit Evaluation Schedule-Treatment-free Remission Phase was updated to reduce the TFR Phase from 3 years to 2 years.
- Table 7-4 Visit Evaluation Schedule-Treatment Re-initiation was updated to reduce the TFR Phase from 3 years to 2 years.
- Section 7.1.2 Removed 1 year consolidation phase arm, randomization and stratification and clarified how patients that are randomized prior to Amendment 2 will be handled.
- Table 7-6 clarification in the variability of the PCR testing done by the central lab, Genoptix, as ± .5log. and to limit the Efficacy Milestone Lost during the Consolidation Phase to a confirmed loss of MR4.0, resulting in patient terminating from the study early.
- Section 9.4 Removed reference to randomization and stratification. Updated the authorization terms of database changes to locked data.
- Section 10 and Section 10.1.1 Removed 1 year consolidation phase arm, randomization and clarified how patients that are randomized prior to Amendment 2 will be handled.
- Section 10.2, Section 10.3, Section 10.5.2, Section 10.5.3.1, Section 10.5.3.3 and 10.5.3.5 Removed reference to treatment two arms
- Section 10.4.2 Clarify that statistical hypothesis will not be tested on the primary efficacy variable.
- Section 10.4.4. Removed reference to randomization and stratification from supportive analysis.

[redacted]

- Section 10.7 Removed sample size calculation by statistical methods. Update the number of patients enrolled, and the number expected to reach the TFR Phase.
- Other minor corrections and clarifications were also made in the protocol.

Amendment 1

Amendment rationale

Primary purposes for the amendment are:

- To include additional safety monitoring parameters as recommended by the Investigator Brochure version 9.0, version 10, and the 48-month label update for nilotinib.
- To address feedback from investigators received during the study startup.
- To include cholesterol testing in the assessment schedule. Elevations in total serum cholesterol and low density lipoprotein cholesterol have been observed very commonly (more than 10%) in patients treated with nilotinib and commonly (between 1 to 10%) in patients treated with imatinib. Most of the cholesterol elevations were Grade 1 (> ULN - 300 mg/dL; > ULN - 7.75 mmol/L) or 2 (> 300 - 400 mg/dL; > 7.75 - 10.34 mmol/L), and some elevations were present prior to initiation of CML therapy. Lipid profiles including total cholesterol, LDL-C and HDL-C will be assessed at baseline and during the conduct of this study. If test results warrant intervention, investigators should follow their local standards of practice or treatment guidelines, which may recommend treatment even for grade 1 cholesterol elevation. Before prescribing a lipid lowering medication, the possibility of drug-drug interactions should be considered due to the moderate inhibitory effect of nilotinib on CYP3A4 isoenzyme that is involved in the metabolic pathway of some statins (HMG-CoA reductase inhibitors).
- To include glucose testing in the assessment schedule. Elevations of blood glucose levels have been observed very commonly (more than 10%) in CML patients treated with nilotinib. Blood glucose will be assessed at baseline and during the conduct of this study. If test results warrant intervention, investigators should follow their local standards of practice and treatment guidelines.
- To provide a harmonization on dose reductions guidelines across Novartis-sponsored Tasigna study protocols. Hence the dose reduction guidelines for the non-hematologic toxicities have been updated.
- To incorporate guidance for the management of:
  - Serum cholesterol increases
  - Blood glucose increases
  - Other cardiac risk factors
  - Ischemic vascular or ischemic cardiovascular events occurring in patients treated with nilotinib.
- To incorporate precaution of use for antacid drugs to be aligned with Tasigna® FDA Prescribing Information and EMA SmPC.
- To define ischemic vascular and ischemic cardiovascular events as Adverse Events of special interest, and their reporting.

[redacted]

The main points addressed are:

- According to the Novartis "Guideline on Prevention of Pregnancies in Clinical Trials" for highly effective contraception, monthly urine pregnancy testing was included in the assessments schedule. The requirement of using highly effective contraception was clarified to include 14 days after the final study visit. Additionally the acceptable method of highly effective contraception was corrected for periodic abstinence
- Dose reduction guidelines for study-drug related non-hematologic toxicity and suggested management of selected adverse events have been updated to reflect the latest version of the nilotinib [Investigator Brochure] on Management of Ischemic vascular or Cardiovascular Events.
- Correct discrepancies and add clarifications within the protocol.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

Modifications were implemented in Protocol summary, Section 5.2 Exclusion criteria #18, Section 7.1 Visit Evaluation Schedule (VES) and Section 7.2.2.5.3 Pregnancy and assessments of fertility to update the pregnancy language in the protocol according to the Novartis "Guideline on Prevention of Pregnancies in Clinical Trials" for highly effective contraception.

Table 6-2 Summary of dose reduction guidelines for study-drug related non-hematologic toxicity and Section 6.3.2 Suggested management of selected adverse events have been amended to reflect the changes done in the latest version of the nilotinib [Investigator Brochure] on Ischemic vascular or cardiovascular events.

Other key changes were implemented for correction of discrepancies and clarifications and are listed in the sections of the protocol below:

- Section 4.1.1. Clarification that it is under the investigator's discretion how many times a patient can be re-screened
- Section 4.1.2. Addition of a 4-6 week window for the confirmatory PCR after MR4.5 is reached in the Monitoring Phase
- Section 4.1.3. Deletion of PCR window of variability language
- Section 4.3. Clarification of the approximate length of the study
- Section 4.4. Addition of study stopping rules
- Section 5.1 Correction and clarification of molecular milestones: MMR (MR3.0), MR4.5
- Section 5.2 Clarification for inclusion criteria 6, updated website links for inclusion criteria 12 and 13, clarified inclusion criteria 13, and updated pregnancy/contraception language in inclusion criteria 15
- Section 6.3.1. Clarification of version of the CTCAE that is being used for the study
- Table 6-3 Updated guidelines for nilotinib dose adjustments for non-hematologic adverse events

[redacted]

- Section 6.3.2.1 – 6.3.2.4. Addition of Management of cholesterol increases, glucose increases, other cardiac risk factors, and ischemic vascular or cardiovascular events recommendations.
- Section 6.3.2.7. Addition of Management of ischemic vascular or cardiovascular events
- Section 6.4.1. Updated CRF page name and addition of language for blood glucose management
- Section 6.4.2. Added permitted concomitant therapy requiring caution and/or action and antacid precaution
- Section 6.4.3. Updated website links
- Section 6.5.1. and Section 6.5.2. Clarification of IRT usage
- Section 6.6.3.1. Addition of option for sites to implement a pill diary
- Section 7.1. Clarification of visit windows
- Table 7-1 Visit Evaluation Schedule updated to include new evaluations, corrected visit numbers, and clarified visit schedule
- Section 7.1.1.1. Deletion of screen failure information that will not be collected via eCRF but instead through IRT.
- Section 7.1.1.2.3. Addition of history of tobacco use will be collected on a eCRF
- Section 7.1.3. Clarification of Early Termination and End of Study visit definitions
- Table 7-5 Updated Sokal score calculator website link
- Table 7-8 Clarification of lab parameters, including addition of HbA1c, total cholesterol, triglycerides, LDL, and HDL
- Section 7.2.2.5.3. Addition of monthly home urine pregnancy test and pregnancy test diary requirement
- Table 7-9 Correction of ECG timing for Cycle 1 Day 8
- Section 7.2.4. Correction of typo for patient reported outcome tool, should be EQ-5D-3L
- Section 8.2.2. Clarification of SAE reporting during TFR Phase and addition of language for SAE causality assessment
- Section 8.4.Clarified that pregnancies that occur during the TFR Phase must also be reported
- Section 8.7 Clarification of Study Management Committee description
- Section 9.3. Deletion of coagulation since this field is not a required assessment

Other minor corrections and clarifications were also made in the protocol.

IRB/IEC

A copy of this amended protocol will be sent to the Institutional Review Board

(IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation. In addition, if the changes herein affect the Informed Consent, sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this amended protocol.

[redacted]

Protocol summary:

Protocol number	CAMN107AUS37
Title	A phase II randomized, multicenter study of treatment-free remission in chronic myeloid leukemia in chronic phase (CML-CP) patients who achieve a MR4.5 after switching to nilotinib
Brief title	A study switching patients from imatinib to nilotinib then followed by treatment cessation.
Sponsor and Clinical Phase	II
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The current clinical practice for CML drug therapy is to treat patients indefinitely with tyrosine kinase inhibitors (TKIs). With the finding that a number of patients treated with imatinib achieved deep responses with TKI therapy, investigators have explored the possibility of discontinuing TKI treatment once an undetectable BCR-ABL level is achieved and sustained over a period of time. Based on these findings, the Stop Imatinib (STIM) study evaluated imatinib discontinuation in 100 CML patients who achieved undetectable BCR-ABL levels for at least 2 years. Patients must have had 5 undetectable data points of BCR-ABL analyses by RT-PCR over 2 consecutive years and the 6th data point was confirmed by a central PCR lab which assay had a 5 log reduction sensitivity. After discontinuation, approximately 60% of patients had a molecular relapse in 4-6 months. All relapsed patients were re-started on imatinib and responded to treatment. Although only a minority of patients were able to sustain MR4.5 after discontinuation (~40% at 24 and 36 months), this study demonstrates that there is a population that may be considered “cured” from TKI therapy. Although sustaining MR4.5 is a key factor in becoming a candidate for TKI discontinuation, the STIM study revealed there may be other factors (i.e. Sokal score and TKI treatment duration) which may affect the outcomes (Mahon 2010). With the development of second generation TKIs, molecular responses have been shown to occur at earlier time points and deeper in quality compared to imatinib. Limited data is available regarding discontinuation of TKI therapy after treatment with 2nd generation TKIs, however, the French CML Group has reported on discontinuation data for second generation TKIs. Twenty-five patients were enrolled in the study and data for 16 patients were presented at American Society of Hematology meeting in 2011, 9 were treated with dasatinib and 7 with nilotinib. After discontinuing the TKI for a median of 4 months, 31% (5/16) patients lost MMR (MR3.0). Molecular response was regained once the TKI was restarted. (Rea 2012). Current discontinuation study designs typically begin discontinuation strategies after patients have achieved at least 2 years of sustained MR4.5.
Primary Objective(s) and Key Secondary Objective	**Primary Objective**: To evaluate molecular relapse free rates 6 months after discontinuation from nilotinib therapy in patients who have achieved a MR4.5 **Key Secondary Objective**: Estimated Relapse-Free Survival

[redacted]

Secondary Objectives	• To evaluate molecular relapse free rates at 12 and 24 months after nilotinib treatment discontinuation • To evaluate the proportion of patients who regain MR4.5 after restarting nilotinib following molecular relapse • To describe the impact of nilotinib treatment discontinuation on progression to AP/BC and CML-related deaths • Overall survival
Study design	This is an open-label study of imatinib treated patients who are switched to nilotinib and their ability to discontinue TKI treatment once MR4.5 is achieved and sustained MR4.0 or better for 2 years. **Screening (Day -28 to 0)** • Patients who have had at least one year of imatinib therapy and achieved MMR (MR3.0) but not MR4.5 are eligible for screening. Written informed consent must be obtained prior to any screening evaluations. If a patient is unable to read, an impartial witness should be present during the entire informed consent discussion. • During screening, a peripheral blood sample for RQ-PCR must be drawn and sent to the Novartis designated central lab. Eligible patients must have achieved MMR (MR3.0) (BCR-ABL level ≤0.1%IS), but still have detectable disease defined as not having achieved MR4.5 (or having a BCR-ABL level >0.0032%IS). All other inclusion and exclusion criteria should be assessed and screening evaluations performed. • Re-screening of a patient will be permitted for this study. As long as the patient meets all inclusion and none of the exclusion criteria, the patient may be enrolled after re-screening. Patients who did not meet the molecular BCR-ABL criteria may be re-screened at least 4 weeks from the most recent BCR-ABL assessment. **Monitoring Phase (Years 1 and 2)** • Fifty-nine patients were enrolled and switched from imatinib to nilotinib 300 mg b.i.d. upon study entry. Patients will be monitored every 3 months for molecular response for up to 2 years. • If during the Monitoring Phase, a patient has a PCR result demonstrating a confirmed loss of MR3.0 the patient will not be eligible for subsequent phases and will early terminate from the study. • Patients who achieve MR4.5 will have the result confirmed by another sample drawn 4 weeks later. Once MR4.5 is confirmed, patients will enter the Consolidation Phase. **Consolidation Phase** • Patients can enter the Consolidation Phase anytime during and up to the first 2 years on study, as soon as MR4.5 is confirmed. After confirmation of MR4.5, the date of the initial MR4.5 results will be counted as the start of the Consolidation Phase. Patients will continue to be treated with nilotinib during the Consolidation Phase. • If MR4.0 or better is sustained during the 2 year the Consolidation Phase, patients will be eligible for discontinuing nilotinib therapy in the TFR Phase. • If during the Consolidation Phase, a patient has one PCR result above MR4.0, within the variability of the testing used or a sample is missing, a subsequent unscheduled visit peripheral blood sample for PCR must be collected within 4 weeks of the most recent sample. If loss of

[redacted]

	MR4.0 is confirmed in the subsequent sample, this patient will not be eligible for nilotinib discontinuation and will early terminate from the study. • Patients who were randomized to Arm A and entered into TFR prior to protocol Amendment 2 will follow the TFR visit schedule. Patients who were randomized to Arm A and are the in Consolidation Phase at the time protocol Amendment 2 was finalized will remain in the Consolidation Phase for two years. **Treatment-Free Remission (TFR) Phase** • Once nilotinib treatment is stopped in the TFR Phase, patients will be followed by PCR every month for the first 6 months, then every 2 months for the next 18 months. Confirmed loss of MMR (MR3.0) (BCR-ABL >0.1%IS) will trigger restarting nilotinib. **Nilotinib Treatment Reinitiation (NTRI) Phase** • Patients who re-initiate nilotinib during the TFR Phase will be monitored by PCR once a month for the first 3 months, and then every 3 months until they reach 2 years from the start date of their TFR Phase. For patients who need to re-initiate nilotinib with less than a year left of their TFR Phase, they will be followed for one year in the Nilotinib Treatment Re-initiation Phase.
Population	• The study has enrolled 59 adult patients who have been treated with at least 1 year of imatinib, and have achieved MMR (MR3.0) but not MR4.5. • Patients treated with up to 2 weeks of nilotinib may enter the study. With sponsor approval, patients may have been treated with other FDA approved TKIs for up to 4 weeks prior to study entry. Other previous CML non-TKI treatment (e.g. hydrea, ara-C, interferon) are permitted.
Key Inclusion criteria	• Male or female patients ≥ 18 years of age • ECOG Performance Status of 0, 1, or 2 • Diagnosis of Ph+ CML • At least 1 year of imatinib treatment prior to study entry. Dose interruptions due to adverse events while on imatinib are permitted. Patients must have an imatinib washout of at least 1 day prior to the first dose of nilotinib. Patients may have been switched and treated with other FDA approved TKIs for up to 4 weeks prior to study entry. Other previous CML non-TKI treatment (e.g. Hydrea, Ara-C, interferon) are permitted. • BCR-ABL level will be assessed by a central lab at screening and must be less than or equal to 0.1% IS and greater than 0.0032% IS. • Adequate end organ function
Key Exclusion criteria	• Prior imatinib failure, AP, BC or allo-transplant • Previously documented T315I mutation • Patient ever attempted to permanently discontinue imatinib or nilotinib treatment • Known impaired cardiac function • Pregnant or lactating women
Investigational therapy	AMN107, nilotinib

[redacted]

Efficacy assessments	RQ-PCR, [redacted]
Safety assessments	Physical Exam, Vital Signs, Height and Weight, Hematology and Clinical chemistry labs, Electrocardiogram, ECOG Performance status, Hepatitis B serology
Other assessments	• An assessment of patient reported outcomes is planned in this trial using the MDASI-CML, EQ-5D-3L, and SF-8. [redacted]
Data analysis	• No statistical testing of the relapse-free rate will be performed due to the small number of patients that are anticipated to enter into the TFR Phase. • The primary efficacy variable molecular relapse free rate at 6 months after stopping nilotinib will be summarized descriptively by frequencies and percentages. The relapse free rate will also be summarized at Months 12 and 24 of stopping nilotinib as a secondary objective. An exact 95% confidence interval for the relapse free rate at 6, 12, and 24 months will also be provided. • The FAS will be used for the analysis.
Key words	CML, nilotinib, discontinuation, imatinib, tyrosine kinase inhibitor (TKI), MR4.5, treatment-free remission

[redacted]

1 Background

1.1 Overview of disease pathogenesis, epidemiology and current treatment

Chronic myeloid leukemia (CML) is a hematological stem cell disorder associated with a specific chromosomal translocation known as the Philadelphia (Ph) chromosome detected in 95% of patients (Nowell and Hungerford 1960, Rowley 1973). The molecular consequence of the translocation is the fusion of the ABL proto-oncogene to the BCR gene resulting in the production of an activated form of the ABL protein-tyrosine kinase (Bartram 1983, Bartram 1983, Heisterkamp 1983). Expression of the BCR-ABL protein is capable of inducing leukemia in mice, implicating the protein as the cause of these diseases (Daley 1990, Kelliher 1990).

Clinically, prior to the availability of tyrosine kinase inhibition (TKI) therapy, CML typically progressed through three distinct phases of increasing refractoriness to therapy: chronic phase (CP) (median duration 3-4 years; median survival up to 10 years with allogeneic bone marrow transplant and 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 months) (Enright and McGlave 2000). Most patients however present in the chronic phase, characterized by splenomegaly and leukocytosis with generally few symptoms.

The National Comprehensive Cancer Network (NCCN) guideline on CML [NCCN guidelines v 2.2013] recommends TKI treatment in all responding patients. The guidelines also summarize data available from TKI discontinuation trials and TKI discontinuation is not recommended outside of a clinical trial.

1.2 Introduction to investigational treatment

1.2.1 Overview of nilotinib

Nilotinib is a novel aminopyrimidine, available as an oral formulation that is an Adenosine triphosphate (ATP)-competitive inhibitor of the protein tyrosine kinase activity of BCR-ABL. It prevents the activation of BCR-ABL dependent mitogenic and anti-apoptotic pathways (e.g. PI-3 kinase and STAT5), leading to the death of the BCR-ABLBCR-ABL phenotype. Following oral administration to animals, nilotinib is moderately absorbed with approximately 30% bioavailability, and is well tolerated.

1.2.2 Non-clinical experience

Data from preclinical studies demonstrate that nilotinib achieves higher intracellular concentrations than imatinib, and that nilotinib inhibits BCR-ABL tyrosine kinase activity and induces apoptosis at lower concentrations than imatinib. (Le Coutre 2004, White 2005). Therefore, based on the preclinical data, and observed efficacy of nilotinib in imatinib-resistant and intolerant patients, nilotinib is predicted to have significant efficacy in newly diagnosed chronic phase CML patients. For more details on non-clinical experience, please refer to [AMN107 Investigator's Brochure].

1.2.2.1 Clinical experience

Clinical safety and tolerability

Overall, nilotinib has been found to be effective and well tolerated in patients with Ph+ CML-CP, and AP who were resistant to imatinib or intolerant of imatinib as well as in patients with newly diagnosed Ph+ CML-CP.

For detailed nilotinib clinical safety and tolerability, please refer to [AMN107 Investigator's Brochure].

Ischemic Vascular and Ischemic Cardiovascular Events Reported for CAMN107A2303 (ENESTnd Study)

Newly-diagnosed or worsened Ischemic Vascular and Ischemic Cardiovascular Events such as Ischemic Heart Disease (IHD), Ischemic Cerebrovascular Events (ICVE) or Peripheral Artery Occlusive Disease (PAOD) have occurred in a relatively small number of CML-CP patients while on study medication. However, such events have been reported with higher frequency on the nilotinib treatment arms compared with the imatinib treatment arm. Up to the data cut-off for the 60 Month analysis (30-Sep-2013), the number of patients reported with these events is as follows:

- Nilotinib 300 mg b.i.d.: IHD, 11 (3.9%); ICVE, 4 (1.4%); PAOD, 7 (2.5%)
- Nilotinib 400 mg b.i.d.: IHD, 24 (8.7%); ICVE, 9 (3.2%); PAOD, 7 (2.5%)
- Imatinib 400 mg q.d.: IHD, 5 (1.8%); ICVE, 1 (0.4%); PAOD, 0 (0.0%)

The majority of reported ischemic vascular and ischemic cardiovascular events were in patients with associated risks (e.g., advanced age, hypertension, hyperlipidemia, hypercholesterolemia, smoking, diabetes mellitus, pre-existing peripheral vascular disease). The background incidence of these events has not been established for the CML patient population.

TKI withdrawal

Some patients who have discontinued imatinib in a clinical trial have experienced musculoskeletal pain. This may represent a tyrosine kinase withdrawal syndrome. To date there is no published TKI withdrawal syndrome data reported with nilotinib.

In the multinational trial of TKI discontinuation, Europe Stop Tyrosine Kinase Inhibitors (EURO-SKI, NCT01596114), fifteen out of fifty (15/50) patients treated with imatinib subsequently reported musculoskeletal pain that began or worsened within weeks after stopping therapy. The pain occurred to various parts of the body, including the shoulder and hip regions, extremities, and/or hands and feet. The 15 patients consisted of nine women and six men with a median age at TKI discontinuation of 62 years (range, 49 to 74 years). In eight patients the symptoms were graded as 2 on the Common Terminology Criteria for Adverse Events scale (version 4.0), and in seven patients as grade 1. Four had a previous medical history that included musculoskeletal system symptoms. Although these adverse events were mild in seven individuals, only leading to use of nonprescription drugs (paracetamol or nonsteroidal anti-inflammatory drugs), eight patients were more severely afflicted, with manifestations that interfered with everyday activities. In five of these patients, corticosteroids

[redacted]

were given (10 to 20 mg prednisolone per day), with tapering within weeks. All five patients demonstrated clear improvement within days, but in one patient, prednisolone could not be tapered without the reappearance of symptoms (Richter et al 2014).

The information above is intended to inform you of the possibility that the patients in TFR may experience a TKI withdrawal syndrome.

Clinical pharmacokinetics

Nilotinib is metabolized by the liver, primarily via CYP3A4. Therefore strong inhibitors or inducers of CYP3A4 can significantly alter the pharmacokinetics and systemic exposure of nilotinib in humans. In addition, nilotinib exhibits moderate inhibitory effect on CYP3A4 substrates. Unchanged nilotinib represents the predominant systemic circulating component (approximately 88% of the total drug-related serum exposure). The terminal elimination half-life of nilotinib was estimated to be approximately 17 hours.

Exposure-response analysis in study ENESTnd [CAMN107A2303], suggested a weakly positive, but statistically insignificant association between the degree of exposure and BCR-ABL transcript reduction at 12 months. There was no clear association between the degree of exposure and major molecular response (MMR (MR3.0)) at 12 months.

Patient demographics are not a clinically significant factor contributing to the inter-patient variability of nilotinib PK. Race was assessed as a covariate on the bioavailability or clearance of nilotinib in the population pharmacokinetic analysis which included a total of 550 patients. No significant differences were observed in nilotinib PK across various race groups, e.g. Caucasian (n=348 patients), Black (n=23 patients), Asian (n=138 patients) and other races (n=41 patients) [Modeling report CAMN107A2303]. These findings are consistent with the previous observations in patients with imatinib resistant or intolerant CML [Study CAMN107A2101 PopPK] and the ethnic insensitivity analysis conducted for the original Tasigna submission. Other demographic variables, such as age, body weight, and gender, do not significantly affect nilotinib PK.

For additional nilotinib clinical PK information, please refer to [AMN107 Investigator's Brochure].

Clinical efficacy

Nilotinib is approved by US Food and Drug Administration and European Commission to treat newly diagnosed adult patients with Ph+ CML-CP, or to treat Ph+ CML-CP and CML-AP in adult patients resistant to or intolerant to prior therapy that included imatinib. The recommended adult dosage of nilotinib is 300 mg orally twice daily for newly diagnosed Ph+ CML-CP and 400 mg orally twice daily for resistant or intolerant Ph+ CML-CP and CML-AP.

The results of study ENESTnd [CAMN107A2303] demonstrated superiority of nilotinib vs. imatinib in the CML-CP frontline setting (Saglio et al 2010, Larson et al 2012). More patients treated with nilotinib achieved deeper molecular responses and the differences were significantly superior at each of the analyzed time points to date. The rate of major molecular response (MMR (MR3.0)) at 12 months was 43% in the nilotinib 400 mg b.i.d. treatment arm, 44% in the nilotinib 300 mg b.i.d. treatment arm, and 22% in the imatinib treatment arm $p<0.001$ (primary endpoint). The cumulative incidence of molecular response 4.5 log

[redacted]

reduction from standardized baseline (MR4.5) was 7%, 19%, 28%, 39.7% and 52.5% by 12, 24, 36, 48 and 60 months in the nilotinib 400 mg b.i.d. arm, and was 11%, 25%, 32%, 37% and 53.5% in the nilotinib 300 mg b.i.d. arm. In the imatinib arm the rates were 1%, 9%, 15%, 22.6% and 31.4% at the same time points. The differences between the rates of MR4.5 in nilotinib and imatinib arms increased over time (6%, 10%, 13%, 17.1% and 21.1% difference by month 12, 24, 36, 48 and 60 for the 400 mg b.i.d. arm and 10%, 16%, 17%, 14.4% and 22.1% difference for the 300 mg b.i.d. arm by the same time points respectively). These results demonstrated that more patients starting CML-CP therapy with nilotinib vs. imatinib can achieve levels of molecular response (MR) necessary to allow for a future treatment discontinuation.

In ENESTcmr study [CAMN107A2405] patients with persistent residual disease after two or more years on imatinib were randomized to either continuing imatinib or switching to nilotinib 400 mg b.i.d. This study showed by 12 months that a higher proportion of patients treated with nilotinib achieved undetectable BCR-ABL levels (23.1% vs. 10.7%; p=0.02) and confirmed undetectable BCR-ABL levels - primary endpoint (12.5% vs. 5.8%; p=0.108). Among patients with no MR4.5 at study entry, 33% of patients randomized to nilotinib achieved MR4.5 vs. 16.5% of patients who remained on imatinib; p=0.008 (Lipton et al 2012; Cervantes et al 2012). This study demonstrated that patients on chronic imatinib therapy after switching to nilotinib can also achieve molecular response necessary to allow for a future treatment discontinuation.

For additional nilotinib clinical efficacy information, please refer to [AMN107 Investigator's Brochure].

2 Rationale

2.1 Study rationale and purpose

The current clinical practice for CML drug therapy is to treat patients indefinitely with tyrosine kinase inhibitors (TKIs). With the finding that a number of patients treated with imatinib achieved deep responses with TKI therapy, investigators have explored the possibility of discontinuing TKI treatment once an undetectable BCR-ABL level is achieved and sustained over a period of time.

A pilot discontinuation study was conducted at five centers in France which evaluated discontinuing imatinib treatment in patients with CML who were in complete cytogenetic remission (CCyR) and had undetectable BCR-ABL transcripts for longer than 2 years on imatinib therapy. Twelve patients were enrolled with the median duration of prior imatinib therapy of 45 months. Six patients developed a molecular relapse, all within the first five months of discontinuing therapy. The remaining six patients (50%) maintained an undetectable level of BCR-ABL transcript after a median follow-up of 18 months (Rousselot 2007).

Based on these findings, the Stop Imatinib (STIM) study evaluated imatinib discontinuation in 100 CML patients who achieved undetectable BCR-ABL levels for at least 2 years. Patients must have had 5 undetectable data points of BCR-ABL analyses by RT-PCR over 2 consecutive years and the 6th data point was confirmed by a central PCR lab which assay had

a 5 log reduction sensitivity. After discontinuation, approximately 60% of patients had a molecular relapse in 4-6 months. All relapsed patients were re-started on imatinib and responded to treatment. Although only a minority of patients were able to sustain MR4.5 after discontinuation (~40% at 24 and 36 months), this study demonstrates that there is a population that may be considered "cured" from TKI therapy. Although sustaining MR4.5 is a key factor in becoming a candidate for TKI discontinuation, the STIM study revealed there may be other factors (i.e. Sokal score and TKI treatment duration) which may affect the outcomes (Mahon 2010).

With the development of second generation TKIs, molecular responses have been shown to occur at earlier time points and deeper in quality compared to imatinib. Limited data is available regarding discontinuation of TKI therapy after treatment with the newer and more potent TKIs (nilotinib or dasatinib), however, the French CML Group has reported on discontinuation data for both of these TKIs. Twenty-five patients were enrolled in the study and data for 16 patients were presented at American Society of Hematology meeting in 2011, 9 were treated with dasatinib and 7 with nilotinib. After discontinuing the TKI for a median of 4 months, 31% (5/16) patients lost MMR (MR3.0). Molecular response was regained once the TKI was restarted (Rea 2012).

Current TKI treatment discontinuation study designs typically begin discontinuation strategies after patients have achieved at least 2 years of sustained MR4.5.

2.2 Rationale for the study design

The rates of molecular recurrence following discontinuation of imatinib therapy in patients who had achieved and maintained deep molecular responses on imatinib have been described in previous clinical trials (Mahon 2010; Ross 2012). In contrast, patients who did not achieve deep molecular responses after two or more years on imatinib and required a switch to nilotinib to achieve MR4.5 may have a disease with distinct biological characteristics. Feasibility of TKI treatment discontinuation in this group of patients has not been evaluated in any of the previous clinical trials.

This is an open label study with the goal of establishing the rate of successful discontinuation of TKI therapy in patients who were previously treated with at least 1 year of imatinib and subsequently treated with nilotinib. Patients must have achieved MMR (MR3.0), but still have detectable disease and not yet achieved MR4.5 prior to study entry. Eligible patients will be enrolled, switched from imatinib to nilotinib and then monitored every 3 months to see if they can achieve a deeper response of MR4.5 within 2 years of starting nilotinib therapy (Monitoring Phase). Those who achieve a confirmed MR4.5 will enter into the Consolidation Phase. Those who sustain MR4.0 or better for 2 years during the Consolidation Phase will be eligible for discontinuing nilotinib in the Treatment Free Remission Phase (TFR). Patients in the TFR Phase will be followed every month for the first 6 months and then every 2 months for the next 18 months, and then every 3 months until the end of the study. In the STIM trial, it was observed that that relapses occurred mainly in the first 6 months of the study; therefore more frequent monitoring is required during the first six months following nilotinib treatment discontinuation. [redacted]

[redacted]

2.3 Rationale for dose and regimen selection

As per the approved dosage for CML-CP patients, nilotinib 300 mg b.i.d. will be used on study. The results of the study ENESTnd [CAMN107A2303] demonstrated numerically higher response rates in nilotinib 300 mg b.i.d. vs. 400 mg b.i.d. at every time point and every depth of molecular response. The cumulative incidence of MR4.5 by 12 months is 11% and 7% and by 36 months 32% and 28% in nilotinib 300 mg b.i.d. and 400 mg b.i.d., respectively. Patients treated with nilotinib 300 mg b.i.d. experienced fewer adverse events and fewer patients discontinued the study due to adverse events (10% vs. 14% in nilotinib 300 mg b.i.d. vs. 400 mg b.i.d., respectively.) It is anticipated that with better tolerability of nilotinib 300 mg b.i.d. dose, more patients will adhere to therapy which may result in further BCR-ABL transcript reduction.

3 Objectives and endpoints

Objectives and related endpoints are described in Table 3-1 below.

[redacted]

Table 3-1 Objectives and related endpoints

Objective	Endpoint	Analysis
Primary		
To evaluate molecular relapse free rates 6 months after discontinuation from nilotinib therapy in patients who have achieved a MR4.5	Molecular relapse free rate at 6 months after discontinuation from nilotinib therapy in patients with MR4.5. Molecular relapse is defined as having a confirmed BCR-ABL ratio above MMR (2 consecutive BCR-ABL levels >0.1%IS taken at least 4 weeks apart).	Refer to Section 10.4.
Key secondary		
Estimated Relapse-Free Survival	Relapse-free survival	Refer to Section 10.5.1.
Other secondary		
To evaluate molecular relapse free rates at 12 and 24 months after nilotinib treatment discontinuation	Molecular relapse free rates at 12, and 24 months after nilotinib treatment discontinuation	Refer to Section 10.5.2.
To evaluate proportion of patients who regain MR4.5 after restarting nilotinib after molecular relapse	Proportion of patients who achieve MR4.5 after restarting nilotinib after relapse	Refer to Section 10.5.2.
Describe impact of discontinuation of nilotinib attempts on progression to AP/BC and CML-related deaths	Proportion of patients who progress to CML-AP/BC and number of CML-related deaths	Refer to Section 10.5.2.
To estimate overall survival (OS)	Time from date of discontinuation of nilotinib therapy to the date of death from any cause	Refer to Section 10.5.2.
To assess the impact of nilotinib discontinuation on patient symptom burden	Change in symptom burden from baseline to the time when MR4.5 is confirmed, and also from the end of the Consolidation Phase to 6 and 12 months into the TFR Phase.	Refer to Section 10.5.3.5.
To assess the impact of nilotinib discontinuation on patient health utility	Change in health utility from baseline to the time when MR4.5 is confirmed, and also from the end of the Consolidation Phase to 6 and 12 months into the TFR Phase.	Refer to Section 10.5.3.5.

[redacted]

Objective	Endpoint	Analysis
To assess the impact of nilotinib discontinuation on patient quality of life	Change in patient quality of life from baseline to the time when MR4.5 is confirmed, and also from the end of the Consolidation Phase to 6 and 12 months into the TFR Phase.	Refer to Section 10.5.3.5.

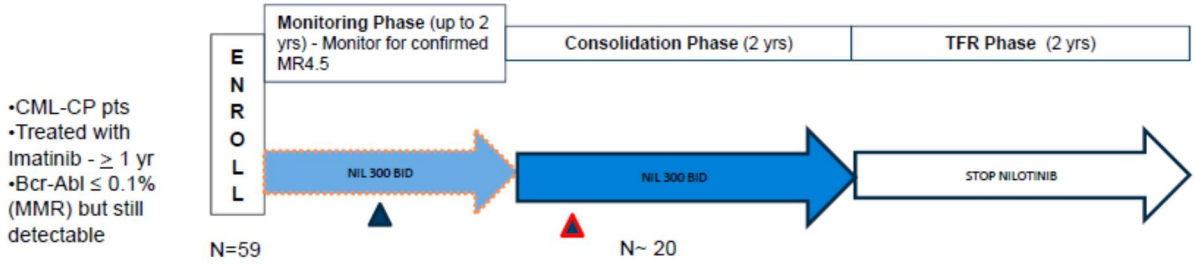
[redacted]

[redacted]

4 Study design

4.1 Description of study design

This is an open-label study of imatinib treated patients who are switched to nilotinib and their ability to discontinue TKI treatment once a confirmed MR4.5 is achieved and sustained MR4.0 or better for 2 years.



4.1.1 Screening (Day -28-0)

Patients who have had at least one year of imatinib therapy and achieved MMR (MR3.0) but not MR4.5 are eligible for screening. Written informed consent must be obtained prior to any screening evaluations. If a patient is unable to read, an impartial witness should be present during the entire informed consent discussion.

During screening, a peripheral blood sample for RQ-PCR must be drawn and sent to the Novartis designated central lab. Eligible patients must have achieved MMR (MR3.0)(BCR-ABL level ≤0.1%IS), but still have detectable disease defined as not having achieved MR4.5 (or having a BCR-ABL level >0.0032%IS). All other inclusion and exclusion criteria should be assessed and screening evaluations performed.

Re-screening of a patient will be permitted for this study. As long as the patient meets all inclusion and none of the exclusion criteria, the patient may be enrolled after re-screening. Patients who did not meet the molecular BCR-ABL criteria may be re-screened at least 4 weeks from the most recent BCR-ABL assessment. It is under the discretion of the investigator how many times a patient can be re-screened.

4.1.2 Monitoring Phase (Years 1 and 2)

Fifty-nine patients have been enrolled and were switched from imatinib to nilotinib 300 mg b.i.d. upon study entry. Patients will be monitored every 3 months for molecular response for up to 2 years.

If during the Monitoring Phase, a patient has a PCR result demonstrating a loss of MR3.0, a subsequent unscheduled visit peripheral blood sample for PCR must be collected within 4 weeks of the most recent sample. If loss of MR3.0 is confirmed, the patient will not be eligible for subsequent phases and will early terminate from the study.

Patients who achieve a MR4.5 will have the result confirmed by another sample drawn 4-6 weeks later. Once MR4.5 is confirmed, patients will then enter the Consolidation Phase.

[redacted]

Refer to Table 7-6 for guidance on reasons for early termination.

4.1.3 Consolidation Phase

Patients can enter the Consolidation Phase anytime during and up to the first 2 years on study, as soon as MR4.5 is confirmed. After confirmation of MR4.5, the date of the initial MR4.5 results will be counted as the start of the Consolidation Phase. Patients will continue to be treated with nilotinib for 2 years during the Consolidation Phase.

If during the Consolidation Phase, a patient has one PCR result above MR4.0 or a sample is missing, a subsequent unscheduled visit peripheral blood sample for PCR must be collected within 4 weeks of the most recent sample. If loss of MR4.0 is confirmed by the subsequent sample, the patient will not be eligible for nilotinib discontinuation and will early terminate from the study.

Refer to Table 7-6 for guidance on reasons for early termination.

4.1.4 Treatment-Free Remission (TFR) Phase

The Treatment-Free Remission Phase will begin after the last scheduled PCR sample collected in the Consolidation Phase confirms the patient remains in MR4.0 or better. During the TFR phase patients will be monitored for two years. Once nilotinib treatment is stopped in the TFR Phase, patients will be followed by PCR every month for the first 6 months, then every 2 months for the next 18 months. Confirmed loss of MMR (BCR-ABL>0.1%IS) will trigger restarting nilotinib.

Refer to Table 7-6 for guidance on reasons for early termination.

4.1.5 Nilotinib Treatment Reinitiation (NTRI) Phase

Patients who re-initiate nilotinib during the TFR Phase will be monitored by PCR once a month for the first 3 months, and then every 3 months until they reach 2 years from the start date of their TFR Phase. For patients who need to re-initiate nilotinib with less than a year left of their TFR Phase, they will be followed for one year in the Nilotinib Treatment Re-initiation Phase.

Refer to Table 7-6 for guidance on reasons for early termination.

4.2 Timing of data cuts

No formal interim analyses will be performed. Data cuts for abstracts are planned at least annually once enrollment has commenced.

4.3 Definition of end of the study

The end of study is defined as last patient last visit which occurs when the last patient completes the TFR Phase, which includes patients who must be followed into the Nilotinib Treatment Re-Initiation Phase. The approximate maximum length of the study for a patient is six years. It may be longer if the patient requires re-initiation of nilotinib during the end of their TFR Phase. Patients who require re-initiation of nilotinib will be followed for a minimum of one year.

[redacted]

4.4 Early study termination

Should this study show that a pre-determined number of patients who ceased nilotinib therapy do not regain MMR (MR3.0) (among patients who lost MMR (MR3.0) during TFR Phase, and within 12 months of resuming treatment), or show confirmed loss of CCyR or progress to AP/BC, the study will be stopped.

The stopping rules are based upon the frequency of these events occurring on study ENESTnd [CAMN107A2303]. It is considered crucial that patients treated on this study have outcomes during the TFR phase at least as good as those patients who were treated on study [CAMN107A2303] with continuous nilotinib therapy (300 mg b.i.d. or 400 mg b.i.d.). Therefore, the following stopping rules for this study will apply to the first 48 weeks after the start of the TFR Phase:

1. More than 2 cases of progression to AP/BC despite BCR-ABL monitoring during the TFR Phase according to protocol, or
2. More than 2 cases of confirmed loss of CCyR despite BCR-ABL monitoring during the TFR Phase according to protocol, or
3. More than 5 cases of failure to achieve MMR (MR3.0) (among patients who lost MMR (MR3.0)) after 12 months of reinitiation of nilotinib in the NTRI Phase according to protocol.

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the patient should be seen as soon as possible according to the timelines provided and the same assessments should be performed as described in Section 7 for a prematurely withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing IRBs of the early termination of the trial.

5 Population

5.1 Patient population

The target population of this study includes adult patients with diagnosis of Ph+ CML-CP. Patients must have received at least 1 year of imatinib therapy, and have a RQ-PCR result that is between ≤ 0.1% (MMR, MR3.0) and > 0.0032% (MR4.5) by IS standardized testing. The study enrolled 59 patients.

The investigator or designee must ensure that only patients who meet all the following inclusion and none of the exclusion criteria are offered treatment in the study.

5.2 Inclusion criteria

Patients eligible for inclusion in this study have to meet **all** of the following criteria.

1. Male or female patient ≥ 18 years of age
2. ECOG Performance Status of 0, 1, or 2
3. Diagnosis of Ph+ CML

[redacted]

4. At least 1 year of imatinib treatment prior to study entry. Dose interruptions due to adverse events while on imatinib are permitted. Patients must have an imatinib washout of at least 1 day prior to the first dose of nilotinib. With sponsor approval, patients may have been treated with other FDA approved TKIs for up to 4 weeks prior to study entry. Other previous CML non-TKI treatment (e.g. hydrea, ara-C, interferon) are permitted.
5. BCR-ABL level will be assessed by a central lab at screening and must be less than or equal to 0.1% IS and greater than 0.0032% IS.
6. Adequate end organ function as defined by:
   - Total bilirubin < 1.5 x ULN (upper limit of normal) except for i) patients with documented Gilbert's syndrome for whom any bilirubin value is allowed and ii) for patients with asymptomatic hyperbilirubinemia (liver transaminases and alkaline phosphatase within normal range)
   - SGOT(AST) and SGPT(ALT) < 2.5 x ULN
   - Serum lipase ≤ 1.5 x ULN
   - Alkaline phosphatase ≤ 2.5 x ULN
   - Serum creatinine < 1.5 x ULN
7. Patients must have the following electrolyte values ≥ LLN limits or corrected to within normal limits with supplements prior to the first dose of study medication:
   - Potassium
   - Magnesium
   - Total calcium (corrected for serum albumin)
8. Patients must have normal marrow function as defined below:
   - Absolute Neutrophil Count (ANC) ≥ 1.5 x 10^9/L
   - Platelets ≥ 100 x 10^9/L
9. Written informed consent obtained prior to any screening procedures

5.3 Exclusion criteria

Patients eligible for this study must not meet any of the following criteria:

1. Prior imatinib failure, AP, BC or allo-transplant
2. Previously documented T315I mutation
3. Patient ever attempted to permanently discontinue imatinib or nilotinib treatment
4. Known impaired cardiac function including any one of the following:
   - Inability to determine the QT interval on ECG
   - Complete left bundle branch block
   - Long QT syndrome or a known family history of long QT syndrome
   - History of or presence of clinically significant ventricular or atrial tachyarrhythmias
   - Clinically significant resting bradycardia (< 50 beats per minute)
   - QTcF > 450 msec. If QTcF > 450 msec and electrolytes are not within normal ranges, electrolytes should be corrected and then the patient re-screened for QTcF
   - History or clinical signs of myocardial infarction within 1 year of study entry

[redacted]

- History of unstable angina within 1 year of study entry
- Other clinically significant heart disease (e.g. uncontrolled congestive heart failure or uncontrolled hypertension)

5. Severe and/or uncontrolled concurrent medical disease that in the opinion of the investigator could cause unacceptable safety risks or compromise compliance with the protocol (e.g. uncontrolled diabetes, uncontrolled infection)
6. History of acute pancreatitis within 1 year prior to study entry or past medical history of chronic pancreatitis
7. Acute or chronic liver, pancreatic, or severe renal disease considered unrelated to study disease
8. History of significant congenital or acquired bleeding disorder unrelated to cancer
9. History of other active malignancy within 2 years prior to study entry with the exception of previous or concomitant basal cell skin cancer, previous cervical carcinoma in situ. Consult with sponsor prior to screening.
10. Major surgery within 4 weeks prior to Day 1 on study or those who have not recovered from prior surgery
11. Treatment with other investigational agents (defined as not used in accordance with the approved indication) within 4 weeks of Day 1 on study
12. Patients actively receiving therapy with strong CYP3A4 inhibitors and/or inducers, and the treatment cannot be either discontinued or switched to a different medication prior to study entry. Refer to medicine.iupui.edu/clinpharm/ddis/.aspx for a list of agents.
13. Patients who are currently receiving treatment with any medications that are categorized as “Drugs with known Torsades de Pointes risk” and the treatment cannot be either safely discontinued or switched to a different medication prior to study entry. Refer to crediblemeds.org/ for a list of agents. If a patient needs treatment with an agent listed under the category of “Possible Risk” or “Conditional Risk”, Novartis must be contacted and the decision documented on the eCRF.
14. Impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of study drug
15. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during the study and for 14 days after the final study visit. Highly effective contraception is defined as either:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed and documented by follow up hormone level assessment
    - Male sterilization (at least 6 months prior to screening). For female patients on the study, study participation assumes the vasectomized male partner is the sole partner for that patient

[redacted]

Use of a combination of any two of the following:

a. Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/ vaginal suppository
b. Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception
c. Placement of an intrauterine device (IUD) or intrauterine system (IUS)

In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment

Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks prior to enrolling. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

6 Treatment

6.1 Study treatment

Study treatment: nilotinib (AMN107, Tasigna)

Study drugs: nilotinib (AMN107, Tasigna)

Nilotinib will be labeled as AMN107 and supplied as 150mg and 200mg hard gelatin capsules. Nilotinib will not be dosed by weight or body surface area.

For detailed safety information refer to the [Investigator's Brochure] and the approved product labeling.

6.1.1 Dosing regimen

Table 6-1 Dose and treatment schedule

Study treatments	Pharmaceutical form and route of administration	Dose	Frequency and/or Regimen
AMN107 (nilotinib)	Capsule for oral use	300mg	Twice Daily

Nilotinib will be administered orally at 300 mg twice daily (b.i.d.), at approximately 12 hour intervals, and must not be taken with food. In the event of a dose reduction, Nilotinib will be administered orally at 400mg once daily, and must not be taken with food. The capsules should be swallowed whole with water. No food should be consumed for at least 2 hours before the dose is taken and no additional food should be consumed for at least one hour after the dose is taken.

[redacted]

6.1.2 Treatment duration

Patients will be treated on study in the Monitoring Phase for a maximum duration of 2 years and, an additional 2 years in the Consolidation Phase. All patients will be treated with nilotinib 300mg b.i.d. during the Monitoring and Consolidation Phase, unless the patient experiences unacceptable toxicity, disease progression and/or treatment is discontinued at the discretion of the investigator or withdrawal of consent.

Once enrolled, patients will have 2 years during the Monitoring Phase to achieve MR4.5. Anytime within these first 2 years on study, when MR4.5 is achieved the patient will enter into a Consolidation Phase. Patients will continue to receive nilotinib 300mg b.i.d. during the Consolidation Phase. Patients who sustain MR4.0 or better for 2 years during the Consolidation Phase will be eligible for discontinuing nilotinib in the TFR Phase. If during the TFR Phase, patients have a confirmed loss of MR3.0 they will restart nilotinib 300 mg b.i.d. and may stay on study drug up to 2 years from the start date of their TFR Phase. Patients who lose confirmed MMR (MR3.0) during the TFR Phase will restart nilotinib 300mg b.i.d. and will be followed for a total of 2 years from the start date of their TFR Phase. For patients who need to re-initiate nilotinib with less than a year left of their TFR Phase, they will be followed for one year in the Nilotinib Treatment Re-initiation Phase.

6.2 Dose escalation

Dose escalation beyond 300mg b.i.d. is not allowed for this study.

6.3 Dose modifications

6.3.1 Dose modification and dose delay

For patients who do not tolerate the protocol-specified dosing schedule, dose adjustments are permitted in order to allow the patient to continue the study treatment. Please refer to the dose modification guidelines in Table 6-2 and Table 6-3 for details.

According to International Conference on Harmonization (ICH) E6 the investigator is responsible for all trial-related medical decisions. During and following a patient's participation in a trial, the investigator should ensure that adequate medical care is provided to a patient for any adverse events, including clinically significant laboratory values, related to the study drug. If multiple dose-reducing toxicities are present, the greatest dose reduction schedule must be used.

For the purpose of these dose reduction guidelines, toxicity is defined as any adverse event (AE) which is, with reasonable likelihood according to investigator's judgment, caused by study drug. Dose reduction is required in cases of grade 3 or 4 hematologic AEs and in cases of grade 2, 3 or 4 non-hematologic AEs. The dose reduction schedule used in this study has been successfully pioneered by the GIMEMA study group in a nilotinib trial (Rosti 2008), which included similar population of patients (1st line CML-CP). If a nilotinib related toxicity does not resolve after 28 days, the patient must be early terminated from the study.

These changes must be recorded on the Dosage Administration Record page.

[redacted]

This study will use the CTCAE (NCI Common Terminology Criteria for Adverse Events) version 4.03 for toxicity and adverse event reporting. CTCAE version 4.03 can be found at the following website: evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

Table 6-2 Nilotinib dose adjustments for hematologic AE (WBC or PLT)

For patients receiving oral anticoagulants, refer to Section 6.3.2.5 to manage thrombocytopenia.

Note: 400mg q.d. must be taken at one time (two 200mg capsules), do not split the dose

Grade	Occurrence	Dose modification
1 or 2	Any time	No dose reduction
3 or 4	1st and 2nd time	• Stop nilotinib • Check labs weekly until Grade 2 or 1. • Resume nilotinib at 300mg b.i.d. if recovery to Grade 1/2 occurs within 2 weeks. • Resume nilotinib at 400mg q.d. if recovery to Grade 1/2 takes longer than 2 weeks. Dose re-escalation to 300mg b.i.d. is permitted if no recurrent Grade 3 or 4 hematological toxicities occur over the 4 weeks while on the reduced dose.
	3rd and 4th time	• Stop nilotinib • Check labs weekly until Grade 2 or 1. • Resume nilotinib at 400mg q.d. • Dose re-escalation to 300mg b.i.d. is permitted if no recurrent Grade 3 or 4 hematological toxicities occur over the 4 weeks while on the reduced dose.
	5th time	Stop nilotinib. Contact Novartis (for review with the SMC) to discuss if nilotinib can be resumed at 400mg q.d. or if the patient should be early terminated from the study

If nilotinib is stopped and re-initiated, an ECG should be repeated prior to re-starting nilotinib and approximately 7 days after.

If nilotinib is dose escalated (i.e. from 400mg q.d. to 300mg b.i.d.), an ECG should be repeated approximately 7 days after the dose adjustment.

Myelosuppression can occur at any time during imatinib or nilotinib therapy. Use of colony-stimulating growth factors (G-CSF and GM-CSF) such as sargramostim, filgrastim, and pegfilgrastim may be initiated with recurrent grade 3 neutropenia. The use of recombinant erythropoietin is permitted.

A summary of dose reduction guidelines for study drug-related non-hematological toxicity and for ischemic vascular and cardiovascular events regardless of study drug relationship is presented in Table 6-3.

These guidelines provide general principles and recommendations intended to support the investigator's judgment and decisions about appropriate management of toxicity in the individual patient.

[redacted]

However, for those toxicities detailed in Table 6-3, the following rules (as detailed in the bullet points below) must be strictly followed:

- Any non-hematological toxicity Grade 3 or 4 must be resolved within 28 days to ≤ Grade 2 in order to resume study drug at the reduced dose. If a non-hematological toxicity Grade 3 or 4 does not resolve after 28 days, the patient must be discontinued from the study.
- If Grade 4 toxicity of the same type recurs despite nilotinib dose reduction to 400 mg q.d. the patient must be discontinued from the study.
- In case of Grade 3 pancreatitis, study drug treatment must be hold and Novartis must be consulted immediately.
- In case of Grade 4 pancreatitis, study drug treatment must be permanently stopped and the patient must be discontinued from study.
- In case of Grade 4 liver toxicity, study drug treatment must be hold and Novartis must be consulted immediately.
- In case of Grade 4 cardiac toxicity, study drug treatment must be permanently stopped and the patient must be discontinued from study.
- In case of recurrent QTcF prolongation to > 480 msec despite dose reduction the patient must be discontinued unless the reason for QTcF prolongation can be corrected (such as discontinuing or replacing of QT-prolonging concomitant drugs)

Table 6-3 Summary of nilotinib dose reduction guidelines for study drug-related non-hematologic toxicity and for ischemic vascular and cardiovascular events regardless of study drug relationship

Study drug and dose	**Nilotinib 600 mg daily (as 300 mg b.i.d.) or Nilotinib 400 mg daily (must be taken as two 200mg caps at one time)**
General non-hematological toxicity	
Grade 2 (persisting > 7 days with optimal supportive care)	The dose of nilotinib may be reduced to 400 mg q.d. at the discretion of the investigator if clinically appropriate and in the best overall interest of the patient
≥ Grade 3	Hold study drug and resume nilotinib at next lower dose level after recovery to ≤ Grade 2 is seen l→ 400 mg q.d. If recovery to ≤ Grade 2 is greater than 28 days, the patient must be discontinued from the study. If Grade 4 toxicity recurs despite dose reduction to 400mg q.d. l→ discontinue from study.
Serum hypophosphatemia	
Grade 2-3	Continue nilotinib at the full dose and start phosphate supplementation.
Grade 4	Hold study drug and consult Novartis.
Serum creatinine	
Grade 2 > 1.5 -3.0 x ULN	The dose of nilotinib may be reduced to 400mg q.d. at the discretion of the investigator if clinically appropriate and in the best overall interest of the patient.

[redacted]

Study drug and dose	**Nilotinib 600 mg daily (as 300 mg b.i.d.) or Nilotinib 400 mg daily (must be taken as two 200mg caps at one time)**
≥ Grade 3 ≥ 3.0 x ULN	Hold study drug and resume nilotinib at next lower dose level after recovery to ≤ Grade 2 is seen I→ 400mg q.d. If recovery to ≤ Grade 2 is greater than 28 days, the patient must be discontinued from the study. If Grade 4 toxicity recurs despite dose reduction to 400mg q.d. I→ discontinue from study
Hepato-biliary [bilirubin, SGPT(AST), SGOT (ALT)] Note: If hyperbilirubinemia is primarily due to the indirect bilirubin (with indirect bilirubin > direct bilirubin and direct bilirubin ≤ 15 µmol/L) and ALT ≤ Grade 1, AST ≤ Grade 1, ALP ≤ Grade 1, and hemolysis has been ruled out as per institutional guidelines (e.g. by determination of hepatoglobin), nilotinib may be continued at the same dose, at the discretion of the investigator.	
Grade 2	The dose of nilotinib may be reduced to 400mg q.d. at the discretion of the investigator if clinically appropriate and in the best overall interest of the patient
≥ Grade 3	Hold study drug and resume nilotinib at next lower dose level after recovery to ≤ Grade 2 is seen I→ 400mg q.d. If recovery to ≤ Grade 2 is greater than 28 days, the patient must be discontinued from the study If Grade 4 toxicity recurs despite dose reduction to 400mg q.d. I→ discontinue from study
Pancreatitis (with abdominal symptoms plus lipase elevation)	
Grade 2	Hold study drug and perform abdominal CT with contrast to exclude pancreatic pathology. If CT is positive, continue to hold therapy and repeat CT, at investigator's discretion. If CT is negative, re-start nilotinib at 400mg q.d. after recovery to ≤ Grade 1 is seen. If recovery to ≤ Grade 1 is greater than 28 days, the patient must be discontinued from the study. If toxicity recurs I→ discontinue from study
Grade 3	Hold study drug and consult Novartis
Grade 4	Stop study drug. The patient must be discontinued from study
Elevated lipase without symptoms	
≥ Grade 3	Hold study drug Re-start nilotinib at 400mg q.d. after recovery to ≤ Grade 2 is seen. If recovery to ≤ Grade 2 is greater than 28 days, the patient must be discontinued from the study. If toxicity recurs without symptoms consider appropriate diagnostic procedures such as abdominal CT or ultrasound to exclude pancreatitis. After recovery to ≤ Grade 2, I→ continue dosing at 400mg q.d. based on investigator's discretion.

[redacted]

Study drug and dose	**Nilotinib 600 mg daily (as 300 mg b.i.d.) or Nilotinib 400 mg daily (must be taken as two 200mg caps at one time)**
Diarrhea Note: Anti-diarrheal medication is recommended at the first sign of loose stools or overt diarrhea. If diarrhea cannot be controlled with optimal anti-diarrheal treatments, take the following actions:	
≥ Grade 3	Hold study drug and resume nilotinib at next lower dose level after recovery to ≤ Grade 2 is seen l→ 400mg q.d. If recovery to ≤ Grade 2 is greater than 28 days, the patient must be discontinued from the study.
Vomiting Note: Antiemetic medication should be withheld until the patient experiences ≥ grade 1 vomiting then institute symptomatic therapy as appropriate. Antiemetics with the potential to prolong QT such as domperidone must be avoided. If nausea and vomiting cannot be controlled with optimal antiemetic treatment take the following actions:	
≥ Grade 3	Hold study drug and resume nilotinib at next lower dose level after recovery to ≤ Grade 2 is seen l→ 400mg q.d. If recovery to ≤ Grade 2 is greater than 28 days, the patient must be discontinued from the study.
Skin rash Note: Institute symptomatic therapy as appropriate. If skin rash does not resolve with optimal treatments, take the following actions:	
Grade 2	The dose of nilotinib may be reduced to 400mg q.d. at the discretion of the investigator if clinically appropriate and in the best overall interest of the patient.
≥ Grade 3	Hold study drug and resume nilotinib at next lower dose level after recovery to ≤ Grade 2 is seen l→ 400mg q.d. If recovery to ≤ Grade 2 is greater than 28 days, the patient must be discontinued from the study. If Grade 4 toxicity recurs despite dose reduction to 400mg q.d. l→ discontinue from study

[redacted]

Study drug and dose	**Nilotinib 600 mg daily (as 300 mg b.i.d.) or Nilotinib 400 mg daily (must be taken as two 200mg caps at one time)**
Cardiac QTc prolongation	
QTcF > 480 msec	Hold study drug when an ECG with a QTcF > 480 msec. • Perform an analysis of serum potassium and magnesium, and if below lower limit of normal, correct with supplements to within normal limits. • Concomitant medication usage must be reviewed for their potential to inhibit CYP3A4 and/or to prolong the QT-interval. • Perform a repeat ECG within one hour of the first QTcF of > 480 msec • If QTcF remains > 480 msec, repeat ECG as clinically indicated, but at least once a day until the QTcF returns to < 480 msec. Study drug may be restarted, at same dose, if reason for elevation of QTcF is identified and corrected so that QTcF returns to < 450 msec and to within 20 msec of baseline within 2 weeks. If the QTcF is repeated and is more than 20 msec greater than baseline or between 450 msec and 480 msec, the dose of study drug should be reduced to 400mg q.d. ECGs must be repeated 7 days after dose re-start for all patients who had therapy held due to QTcF > 480 msec. If QTcF of > 480 msec recurs, the patient is to be discontinued from study The investigator should contact Novartis regarding any questions that arise if a patient with QTcF prolongation should be maintained on study.
Ischemic cardiovascular events	
Grade 2*	Hold study drug and refer patient for assessment by a vascular or cardiovascular specialist. Resume nilotinib at next lower dose level after recovery to ≤ Grade 1 is seen l→ 400mg q.d. If another recurrence l→ discontinue from study If recovery to ≤ Grade 1 is greater than 28 days, the patient must be discontinued from the study.
Grade 3* or 4*	Hold study drug and refer patient for assessment by a vascular or cardiovascular specialist. Consideration should be given for discontinuation from the study.
* Patient should be assessed for potential risk factors for the event including causality secondary to CML therapy	
Cardiac "other"	
Grade 2 or Grade 3	Hold study drug and resume nilotinib at next lower dose level after recovery to ≤ Grade 1 is seen l→ 400mg q.d. If recovery to ≤ Grade 1 is greater than 28 days, the patient must be discontinued from the study. If Grade 3 toxicity recurs despite dose reduction to 400mg q.d. l→ discontinue from study
Grade 4	Stop study drug. The patient must be discontinued from study

If nilotinib is stopped and re-initiated, an ECG should be repeated prior to re-starting nilotinib and approximately 7 days after.

[redacted]

If nilotinib is dose escalated (i.e. from 400mg q.d. to 300mg b.i.d.), an ECG should be repeated approximately 7 days after the dose adjustment.

6.3.2 Suggested management of selected adverse events for nilotinib

Dose reduction guidelines listed in Table 6-2 and Table 6-3 should be followed. Additional guidelines for management of patients are listed below.

6.3.2.1 Management of cholesterol increases

Blood lipid panel tests should be performed at baseline and throughout the study as indicated in the visit schedule. If test results warrant intervention, investigators should follow their local standards of practice or treatment guidelines, which may recommend treatment even for grade 1 cholesterol elevation. Before prescribing a lipid lowering medication, the possibility of drug-drug interactions should be considered due to the moderate inhibitory effect of nilotinib on CYP3A4 isoenzyme that is involved in the metabolic pathway of some statins (HMG-CoA reductase inhibitors).

6.3.2.2 Management of glucose increases

Blood glucose tests should be performed at baseline and throughout the study as indicated in the visit schedule. If blood glucose results warrant intervention, investigators should follow their local standards of practice and treatment guidelines in order to normalize blood glucose levels.

6.3.2.3 Management of other cardiac risk factors

Patients should be assessed or monitored for any other cardiac risk factors such as family history, cardiovascular events in the past medical history, smoking, hypertension, and obesity. If the assessment for presence of any other cardiovascular risk factors warrants intervention, investigators should follow their local standards of practice or treatment guidelines.

6.3.2.4 Management of ischemic vascular or cardiovascular events

Newly-diagnosed or worsened ischemic vascular or cardiovascular events have occurred in a relatively small number of CML-CP patients while on study medication. If a patient experiences such an adverse event the Investigator should ensure that the patient is assessed by a vascular or cardiovascular specialist. Further recommendations for the management of ischemic vascular or cardiovascular-related events are outlined in Table 6-3.

6.3.2.5 Management of myelosuppression

Myelosuppression can occur at any time during nilotinib therapy. Use of granulocyte colony stimulating growth factors and granulocyte-macrophage colony-stimulating factors (G-CSF and GM-CSF) such as sargramostim, filgrastim, and pegfilgrastim may be initiated with recurrent grade 3 neutropenia. The use of recombinant erythropoietin is also permitted as per local clinical practice. In case of late onset of severe peripheral blood cytopenia underlying progression of CML and other alternative etiologies may need to be considered and ruled out.

[redacted]

6.3.2.6 Management of skin rash/pruritus

In most cases, rash is mild, self-limiting, and manageable with antihistamines or topical steroids. A short course of oral steroids may be initiated for the management of more severe cases. Prednisone 25 mg is recommended for one week or until rash has resolved.

6.3.2.7 Management of edema

Patients should be monitored closely for peripheral edema and rapid weight gain. The use of diuretics may be initiated for the management of edema. Patients who develop ≥ Grade 3 edema associated with cardio-respiratory symptoms should receive immediate medical evaluations for the development of concomitant cardiac or respiratory diagnoses as indicated, such as an echocardiogram and a chest X-ray. Other medical tests may also be necessary to best manage the medical condition.

6.3.2.8 Management of liver toxicity

Routine Liver Function Tests (LFTs) should be performed throughout the study as indicated in the visit schedule. Dose reduction may be warranted and the decision to continue nilotinib needs to be made in light of the clinical situation (see dose reduction table). Alternative etiologies for LFT abnormalities such as viral hepatitis should be considered as clinically indicated.

6.3.2.9 Dose modification for patients nilotinib and oral anticoagulants other than coumarin derivatives

For patients on treatment with oral anticoagulants other than coumarin derivatives, the following guidelines will apply for thrombocytopenia: If platelets ≤ 100 x 10^9/L, withhold treatment with study drug until recovery to at least > 100 x 10^9/L and resume treatment at same dose. If recurrence of platelets ≤ 100 x 10^9/L, then withhold treatment until recovery to at least > 100 x 10^9/L and resume treatment at the same dose or may be reduced to a minimum dose of 400mg/day. If the platelet count remains below 100 x 10^9/L, then nilotinib should be ceased or management with anticoagulation therapy re-evaluated at the discretion of the Investigator.

See Section 6.4.1 for patient taking coumarin derivatives.

6.3.2.10 Platelet aggregation inhibitors

For patients on treatment with platelet aggregation inhibitors and platelets ≤ 100 x 10^9/L, modification of platelet aggregation inhibitor therapy and/or study drug interruption/dose reduction should be considered by the investigator as clinically appropriate. Advice from SMC may be requested via Novartis.

6.3.2.11 Hepatitis B reactivation

Hepatitis B virus testing should be performed during the study as indicated in Section 7.1 to identify patients who may be at risk for Hepatitis B reactivation. Experts in liver disease and in the treatment of hepatitis B should be consulted for patients who test positive for hepatitis B virus during nilotinib treatment or for TFR patients who test positive for hepatitis B virus

before treatment is re-initiated. Carriers of hepatitis B virus who require treatment with nilotinib should be closely monitored for signs and symptoms of active hepatitis B infection throughout therapy and for several months following termination of therapy

6.3.3 Follow-up for toxicities

Patients whose treatment is interrupted or permanently discontinued due to an adverse event or clinically significant laboratory value, must be followed up at least once a week (or more frequently if required by institutional practices, or if clinically indicated) for 4 weeks, and subsequently at approximately 4-week intervals, until resolution or stabilization of the event, whichever comes first. All patients must be followed up for adverse events and serious adverse events for 30 days following the last dose of nilotinib or the last day in the TFR Phase.

6.3.4 Anticipated risks and safety concerns of the study drug

Appropriate eligibility criteria, as well as specific dose modification and stopping rules are included in this protocol. Recommended guidelines for prophylactic or supportive treatment for expected toxicities are provided in Section 6.3.2. Refer to preclinical toxicity and or clinical data found in the [Investigator's Brochure].

6.4 Concomitant medications

In general, concomitant medications and therapies deemed necessary for the supportive care and safety of the patient are allowed, provided their use is documented in the patient records and on the appropriate case report form. These include blood and platelet transfusions for patients with anemia and with thrombocytopenia.

Nilotinib is a competitive inhibitor of CYP3A4, CYP2C8, CYP2C9, CYP2D6, and UGT1A1 in vitro, potentially increasing the concentrations of drugs eliminated by these enzymes. In addition, single-dose administration of nilotinib with midazolam to healthy subjects increased midazolam exposure by 30%. Caution should be exercised when co-administering nilotinib with substrates of these enzymes having a narrow therapeutic index.

6.4.1 Permitted concomitant therapy

The patient must be told to notify the investigational site about any new medications he/she takes after the start of the study drug. All medications (other than study drug) and significant non-drug therapies (including physical therapy, herbal/natural medications and blood transfusions) administered during the study must be listed on the Prior/Concomitant Medications/Significant Non-Drug Therapies eCRF.

Note that previously the use of therapeutic coumarin derivatives (i.e. warfarin, acenocoumarol, phenprocoumon) was not permitted while taking nilotinib but it is now allowed. There is data demonstrating the lack of effect of nilotinib on PK and pharmacodynamics (PD) of warfarin, suggesting nilotinib does not inhibit CYP2C9 activity in human subjects. These findings suggest that warfarin may be used with nilotinib concurrently if needed (Yin et al 2011). Low molecular weight heparin and heparin may be substituted for coumarin and other medications for anticoagulation may also be considered at the physicians discretion.

[redacted]

Patients on anticonvulsants should have regular monitoring of plasma concentration of these agents.

The routine use of systemic corticosteroid therapy is permitted. Note glucocorticoids are CYP3A4 inducers, please refer to Section 6.4.3.

Anti-emetics may be allowed if the patient has experienced > Grade 1 nausea or vomiting.

The use of loperamide may be initiated for patients experiencing ≥ Grade 2 diarrhea, before dose interruption (e.g. Imodium®, with suggested dosing to start as 4 mg p.o. x 1, than 2 mg p.o. after each loose stool, up to a max of 16mg/day).

Nilotinib is known to be associated with an increase of blood glucose in some patients who might need to be optimally managed for hyperglycemia according to current clinical standards. However, when a patient enters TFR, management of previously elevated blood glucose might need to be adapted.

6.4.2 Permitted concomitant therapy requiring caution and/or action

Cytochrome P450 3A4 substrates

Nilotinib is a moderate CYP3A4 inhibitor *in vivo*. Because of the potential risk for drug-drug interactions, the systemic exposure of other drugs known to be sensitive substrates of CYP3A4 and also to have a narrow therapeutic index should be used with caution.

Antacid drugs:

Nilotinib has a pH-dependent solubility; therefore, in order not to impact nilotinib pharmacokinetics, administration of the following antacid drugs (if necessary) should be as follows:

- H2 blocker (famotidine) may be administered approximately 10 hours before or approximately 2 hours after the dose of nilotinib,
- Antacid (hydroxide/magnesium hydroxide/simethicone) may be administered approximately 2 hours before or approximately 2 hours after the dose of nilotinib.

6.4.3 Prohibited concomitant therapy

The concomitant administration of investigational drugs other than nilotinib is not allowed.

The administration of any other anticancer agents including chemotherapy and biologic agents is not permitted.

All patients must avoid grapefruit, star fruit, and Seville oranges during the study. The juices and products containing these fruits must also be avoided.

Cardiac monitoring (ECG) is required upon re-initiation of nilotinib at any point during the study. See Section 7.2.2.5.4.

CYP3A4 inhibitors

Every effort should be made NOT to administer strong CYP3A4 inhibitors. CYP3A4 inhibitors may decrease the metabolism of nilotinib and thereby increase serum

concentrations and increase exposure to nilotinib. If administration of a strong CYP3A4 inhibitor cannot be avoided during the study and cannot be switched to an alternative therapy, nilotinib must be STOPPED. If a patient requires long term therapy with a strong CYP3A4 inhibitor which requires study drug (nilotinib) interruption for > 28 days, then the investigator must notify the sponsor to discuss further treatment options.

A comprehensive list of cytochrome P450 isoenzymes and CYP3A4 inhibitors may be found at medicine.iupui.edu/clinpharm/ddis/ Novartis must be contacted if a patient needs to be started on any of these drugs during study treatment.

QT prolonging agents

Every effort should be made NOT to administer a QT prolonging agent. Please see crediblemeds.org/ for a comprehensive list of agents that prolong QT interval. If during the course of the study, concomitant administration of an agent listed under the category of "Drugs with Known Risk of Torsades de Pointes" on the above link is required and cannot be switched to an alternative therapy, nilotinib must be STOPPED. If a patient requires long term therapy with a QT prolonging agent which requires nilotinib study drug interruption for > 28 days, the investigator must notify the sponsor to discuss further treatment options

If a patient needs treatment with an agent listed under the category of "Possible Risk" or "Conditional Risk", Novartis must be contacted and the decision documented on the eCRF. In such cases an ECG must be obtained both 24 to 48 hours and 7 days after initiating the concomitant therapy.

CYP3A4 inducers

Every effort should be made NOT to administer CYP3A4 inducers however, if administration of a CYP3A4 inducer cannot be avoided during the study, temporary stopping of study drug is NOT required. Please see medicine.iupui.edu/clinpharm/ddis/table.aspx for a list of CYP3A4 inducers. Novartis must be contacted if a patient needs to be started on any of these drugs during study treatment.

6.5 Patient numbering, treatment assignment or randomization

6.5.1 Patient numbering

Each patient is identified in the study by a Subject Number (Subject No.), that is assigned when the patient is first enrolled for screening and is retained as the primary identifier for the patient throughout his/her entire participation in the trial. The Subject No. consists of the Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential patient number suffixed to it, so that each subject is numbered uniquely across the entire database. Upon signing the informed consent form, the patient is assigned to the next sequential Subject No. available to the investigator through the Interactive Response Technology (IRT) system.

The investigator or designated staff will use IRT and provide the requested identifying information for the patient to register them into the IRT. Once assigned, the Subject No. must not be reused for any other subject and the Subject No. for that individual must not be

changed, even if the patient is re-screened. If the patient fails to enroll or start treatment for any reason, the reason will be entered IRT.

6.5.2 Treatment assignment or randomization

Sites will register their patients who sign consent at screening with IRT and subsequently at Enrollment (C1D1).

6.6 Study drug preparation and dispensation

The investigator or responsible site personnel must instruct the patient or caregiver to take the study drugs as per protocol. Study drug(s) will be dispensed to the patient by authorized site personnel only. All dosages prescribed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record eCRF.

Patients will be provided with an adequate supply of nilotinib study drug supply until their next scheduled visit. Patients will be dispensed 150mg capsules (or 200mg capsules in the event of a dose reduction), including instructions for self-administration.

6.6.1 Study drug packaging and labeling

Medication labels will be in English and comply with the legal requirements of the U.S. They will include storage conditions for the drug and the medication number but no information about the patient.

6.6.2 Drug supply and storage

Nilotinib study drug will be centrally supplied by Novartis. The study drug must be received by designated personnel at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, nilotinib should be stored according to the instructions specified on the drug labels and in the [Investigator's Brochure].

6.6.3 Study drug compliance and accountability

6.6.3.1 Study drug compliance

Compliance will be assessed by the investigator and/or study personnel at each patient visit and information provided by the patient and/or caregiver will be captured in the Drug Accountability Form. This information must be captured in the source document at each patient visit. Total daily dose of nilotinib administered with start and end date will be collected on the dose administration eCRF. Sites may ask patients to keep a pill diary for compliance purposes, but it is not required for the study.

6.6.3.2 Study drug accountability

The investigator or designee must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Drug accountability will be noted by the field monitor during site visits and at the completion of the study. Patients will be asked to return

all unused study treatment and packaging on a regular basis, at the end of the study/early termination or at the time of study treatment discontinuation.

At study close-out, and, as appropriate during the course of the study, the investigator will return all used and unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the study monitor (or to the Novartis address provided in the investigator folder at each site), or destroy study treatment on site if approved by the sponsor.

6.6.3.3 Handling of other study treatment

Not applicable.

6.6.3.4 Disposal and destruction

The study drug supply can be destroyed by a Novartis contracted third party or on site provided that Novartis grants approval after reviewing the site drug destruction SOP.

7 Visit schedule and assessments

7.1 Study flow and visit schedule

Table 7-1 lists all of the assessments and indicates with an "X", the visits when they are performed. All data obtained from these assessments must be supported in the patient's source documentation. No eCRF will be used as a source document. The table indicates which assessments produce data to be entered into the clinical database (D) or remain in source documents only (S) ("Category" column).

Hepatitis B testing will be performed once and only once, at the next possible visit. The hepatitis serology will include: Hepatitis B surface antigen (HbsAG), antibodies to hepatitis B surface antigen (HBsAb), antibodies to hepatitis B core antigen (HbcAb).

Visit windows

One cycle is equal to 30 days.

In the event that an evaluation is performed within 2 days of the next study visit, the evaluations will not be required to be repeated.

Assessments must be performed within 2 days of the day indicated on the visit schedules for the following:

- Monitoring Phase Cycle 1
- Re-Initiation Phase Cycle 1
- First 6 months of the TFR Phase

Screening evaluations may be performed on Monitoring Phase C1D1 as long as all the results are reviewed to confirm inclusion/exclusion criteria prior to dosing the patient with study drug.

During the TFR Phase EOC 24 and Re-Initiation Phase EOC 24, assessments must be performed within 15 days of the day indicated on the visit schedules.

[redacted]

The confirmatory MR4.5 PCR blood sample may be drawn 4-6 weeks after the previous draw.

All other assessments during the various phases must be performed within 10 days of the day indicated on the visit evaluation schedule.

[redacted]

Table 7-1 Visit evaluation schedule – Monitoring Phase

Follow this schedule until confirmed MR4.5 is achieved (* MD = Monitoring Day)

	Category	Protocol Section	Screening	Cycle 1 Day 1 (baseline, prior to dosing)	Cycle 1 Day 8	End of Cycle (EOC) 1	EOC 3, 6, 9, 12, 15, 18, 21, 24	Early Termination	30 Day Safety Follow-up
Visit Number			**1**	**2**	**3**	**4**	**5,6,7,8,9,10,11,12**	**777**	**501**
Day of cycle			**-28 to-0**	**MD*1**	**MD8**	**MD30**	**MD90,180,270,360, 450,540, 630, 720, --**		**--**
Obtain Informed Consent	(S)		X						
[redacted]									
IVRS Registration	(D)		X	X				X	
Patient history									
Inclusion/exclusion criteria	(S)	7.1.1.2.1.	X						
Demography	(D)	7.1.1.2.2.	X						
Relevant medical history/current medical conditions	(D)	7.1.1.2.3.	X						
Disease History/Sokal risk score	(D)	7.1.1.2.4. 7.1.1.2.5.	X						
Prior antineoplastic therapy	(D)	7.1.1.2.6.	X						
Prior/concomitant medications	(D)	7.1.1.2.7.	X						
Prior RQ-PCR, [redacted] result	(D)	7.1.1.2.8. [redacted]	X						
Physical examination, Extramedullary involvement	(D)	7.2.2.1.	X				X	X	
Vital signs	(D)	7.2.2.2.	X				X	X	
Height	(D)	7.2.2.3.	X						
Weight	(D)	7.2.2.3.	X				X	X	
Performance status	(D)	7.2.2.4.	X				X	X	

[redacted]

	Category	Protocol Section	Screening	Cycle 1 Day 1 (baseline, prior to dosing)	Cycle 1 Day 8	End of Cycle (EOC) 1	EOC 3, 6, 9, 12, 15, 18, 21, 24	Early Termination	30 Day Safety Follow-up
Visit Number			**1**	**2**	**3**	**4**	**5,6,7,8,9,10,11,12**	**777**	**501**
Day of cycle			**-28 to-0**	**MD*1**	**MD8**	**MD30**	**MD90,180,270,360, 450,540, 630, 720, --**		**--**
Laboratory assessments		7.2.2.5.							
Hematology (local)	(D)	7.2.2.5.1.	X				X	X	
Chemistry (local)	(D)	7.2.2.5.2.	X				X	X	
HbA1c and Lipid Panel (local) – LDL, HDL, TC, TG	(D)	7.2.2.5.	X				X – Visit 5, 6, 8, 12	X	
Serum Pregnancy test (local), if applicable	(D)	7.2.2.5.3.	X					X	
Urine Pregnancy test and diary, if applicable	(D)	7.2.2.5.3.		X	X- Monthly (every 30 days)				
ECG (local)	(D)	7.2.2.5.4.	X	X	X	Required for dose changes			
RQ-PCR (central)	(D)	7.2.1.1.	X			X	X	X	
[redacted]									
Safety									
Adverse events	(D)	8.	Continuous						X
[redacted]									
Patient reported Outcomes									
MDASI-CML	(D)	7.2.4.	X						
EQ-5D-3L	(D)	7.2.4.	X						
SF-8	(D)	7.2.4.	X						
Study Drug administration	(D)	6.1.1.		Continuous					

[redacted]

	Category	Protocol Section	Screening	Cycle 1 Day 1 (baseline, prior to dosing)	Cycle 1 Day 8	End of Cycle (EOC) 1	EOC 3, 6, 9, 12, 15, 18, 21, 24	Early Termination	30 Day Safety Follow-up
Visit Number			**1**	**2**	**3**	**4**	**5,6,7,8,9,10,11,12**	**777**	**501**
Day of cycle			**-28 to-0**	**MD*1**	**MD8**	**MD30**	**MD90,180,270,360, 450,540, 630, 720, --**		**--**
End of Treatment (eCRF)	(D)	7.1.3.					X – at visit 12 for patient ineligible for the Consolidation Phase	X	
Study Evaluation Completion (eCRF)	(D)	7.1.3.					X – only at visit 12	X	

[redacted]

Table 7-2 Visit evaluation schedule – Consolidation Phase

* CD = Consolidation Day

	Category	Protocol Section	Consolidation EOC 3	Consolidation EOC 6	Consolidation EOC 9	Consolidation EOC 12, 15, 18, 21, 24)	Early Termination	30 Day Safety Follow-up
Visit Number			**13**	**14**	**15**	**16,17,18,19,20**	**778**	**501**
Day of cycle			**CD90**	**CD180**	**CD270**	**CD360, 450, 540, 630, 720**	**--**	**--**
IVRS Registration	(D)						X	
Physical examination, Extramedullary involvement	(D)	7.2.2.1.	X	X	X	X		
Vital signs	(D)	7.2.2.2.	X	X	X	X	X	
Weight	(D)	7.2.2.3.	X	X	X	X	X	
Performance status		7.2.2.4.	X	X	X	X	X	
Laboratory assessments		7.2.2.5.						
Hematology (local)	(D)	7.2.2.5.1.	X	X	X	X	X	
Chemistry (local)	(D)	7.2.2.5.2.	X	X	X	X	X	
HbA1c and Lipid Panel (local) – LDL, HDL, TC, TG	(D)	7.2.2.5.	The lipid panel and HbA1c level must be done at the end of every 3 cycles until the patient has been on nilotinib for 1 year regardless of phase.			X – only at Visit 16 and Visit 20	X	
Serum Pregnancy test (local), if applicable	(D)	7.2.2.5.3.					X	
Urine Pregnancy test and diary, if applicable	(D)	7.2.2.5.3.	X - Monthly (every 30 days)					
ECG (local)	(D)	7.2.2.5.4.	Required for dose changes					
PCR (central)	(D)	7.2.1.1.	X	X	X	X	X	
[redacted]								
Safety								

[redacted]

	Category	Protocol Section	Consolidation EOC 3	Consolidation EOC 6	Consolidation EOC 9	Consolidation EOC 12, 15, 18, 21, 24)	Early Termination	30 Day Safety Follow-up
Visit Number			**13**	**14**	**15**	**16,17,18,19,20**	**778**	**501**
Day of cycle			**CD90**	**CD180**	**CD270**	**CD360, 450, 540, 630, 720**	**--**	**--**
Adverse events	(D)	8.	Continuous					X
[redacted]								
Patient reported Outcomes								
MDASI-CML	(D)	7.2.4.	X			At Visit 16 and 20	X	
EQ-5D-3L	(D)	7.2.4.	X				X	
SF-8	(D)	7.2.4.	X				X	
Study Drug administration	(D)	6.1.1.	Continuous					
End of Treatment (eCRF)	(D)	7.1.3.				X – when last dose of study drug is taken	X	
Study Evaluation Completion (eCRF)	(D)	7.1.3.					X	

[redacted]

Table 7-3 Visit evaluation schedule – Treatment-free Remission Phase

* TFR = TFR Day

	Category	Protocol Section	TFR EOC 1,2,3,4,5,6	TFR EOC 8,10, 12, 14, 16, 18, 20, 22, 24	Early Termination	30 Day Safety Follow-up
Visit Number			**21,22,23,24,25,26**	**27, 28, 29 30, 31, 32, 33, 34,35**	**779**	**501**
Day of cycle			**TFRD*30, 60, 90, 120, 150, 180**	**TFRD240, 300, 360, 420, 480, 540, 600, 660, 720**	**--**	**--**
IVRS Registration	(D)				X	
Physical examination, Extramedullary involvement	(D)	7.2.2.1.	X (Visit 23, 26)	X (Visit 29,32,35)	X	
Vital signs	(D)	7.2.2.2.	X (Visit 23,26)	X (Visit 29,32,35)	X	
Weight	(D)	7.2.2.3.	X (Visit 23, 26)	X (Visit 29,32,35)	X	
Performance status	(D)	7.2.2.4.	X (Visit 23, 26)	X (Visit 29,32,35)	X	
Laboratory assessments		7.2.2.5.				
Hematology (local)	(D)	7.2.2.5.1.	X (Visit 23, 26)	X (Visit 29,32,35)	X	
Chemistry (local)	(D)	7.2.2.5.2.	X (Visit 23, 26)	X (Visit 29, 32,35)	X	
HbA1c and Lipid Panel (local) – LDL, HDL, TC, TG	(D)	7.2.2.5.		X – at Visit 29 and 35	X	
Serum Pregnancy test (local), if applicable	(D)	7.2.2.5.3.			X	
Urine Pregnancy test and diary, if applicable	(D)	7.2.2.5.3.	X - Monthly (every 30 days)			
ECG (local)	(D)	7.2.2.5.4.	Required for dose changes			
PCR (central)	(D)	7.2.1.1.	X	X	X	
[redacted]						
Safety						
Adverse events	(D)	8.	Continuous			X (patients must be followed for AEs 30 days after stopping nilotinib)

[redacted]

	Category	Protocol Section	TFR EOC 1,2,3,4,5,6	TFR EOC 8,10, 12, 14, 16, 18, 20, 22, 24	Early Termination	30 Day Safety Follow-up
Visit Number			**21,22,23,24,25,26**	**27, 28, 29 30, 31, 32, 33, 34,35**	**779**	**501**
Day of cycle			**TFRD*30, 60, 90, 120, 150, 180**	**TFRD240, 300, 360, 420, 480, 540, 600, 660, 720**	**--**	**--**
[redacted]						
MDASI-CML	(D)	7.2.4.	At Visit 26, for those with MR4.5	At Visit 29, for those with MR4.5		
EQ-5D-3L	(D)	7.2.4.				
SF-8	(D)	7.2.4.				
Study Evaluation Completion (eCRF)	(D)	7.1.3.		X – only at Visit 39	X	

[redacted]

Table 7-4 Visit evaluation schedule – Nilotinib Treatment Re-initiation

Follow this schedule if a patient in TFR phase must be restarted on nilotinib (* RD = Re-initiation Day)

	Category	Protocol Section	Re-Initiation Cycle 1 Day 1 (baseline, prior to dosing)	Re-initiation Cycle 1 Day 8	Re-initiation End of Cycle (EOC) 1,2,3	End of every 3 cycles until 2 yrs from D/C phase start date	Early Termination	30 Day Safety Follow-up
Visit Number			**40**	**41**	**42,43,44**	**45,46,47,48,49, 50,51**	**780**	**501**
Day of cycle			**RD*1**	**RD8**	**RD30, 60, 90**	**RD180,270,360,450,540,630,720**		**--**
IVRS Registration	(D)						X	
Physical examination, Extramedullary involvement	(D)	7.2.2.1.	X		X	X	X	
Vital signs	(D)	7.2.2.2.	X		X	X	X	
Weight	(D)	7.2.2.3.	X		X	X	X	
Performance status	(D)	7.2.2.4.	X		X	X	X	
Laboratory assessments		7.2.2.5.						
Hematology (local)	(D)	7.2.2.5.1.	X		X	X	X	
HbA1c and Lipid Panel (local) – LDL, HDL, TC, TG	(D)	7.2.2.5.			X – Visit 44	X – Visit 45, 46, 47, and 51	X	
Chemistry (local)	(D)	7.2.2.5.2.	X		X	X	X	
Urine Pregnancy test and diary (local), if applicable	(D)	7.2.2.5.3.	X		X – Monthly (every 30 days)			
Serum Pregnancy test, if applicable	(D)	7.2.2.5.3.					X	
ECG (local)	(D)	7.2.2.5.4.	X	X	Required for dose changes			
RQ-PCR (central)	(D)	7.2.1.1.			X	X	X	
[redacted]								

[redacted]

	Category	Protocol Section	Re-Initiation Cycle 1 Day 1 (baseline, prior to dosing)	Re-initiation Cycle 1 Day 8	Re-initiation End of Cycle (EOC) 1,2,3	End of every 3 cycles until 2 yrs from D/C phase start date	Early Termination	30 Day Safety Follow-up
Visit Number			**40**	**41**	**42,43,44**	**45,46,47,48,49, 50,51**	**780**	**501**
Day of cycle			**RD*1**	**RD8**	**RD30, 60, 90**	**RD180,270,360,450,540,630,720**		**--**
[redacted]								
Safety								
Adverse events	(D)	8.	Continuous					X
Study Drug Administration	(D)	6.1.1.	Continuous					
End of Treatment (eCRF)	(D)	7.1.3.	X – at the last study visit				X	
Study Evaluation Completion (eCRF)	(D)	7.1.3.					X	

[redacted]

7.1.1 Screening (Day -28 to 0)

Written informed consent must be obtained prior to having any study evaluations performed. It is recommended that the first evaluation to be done as part of screening is the peripheral blood draw for RQ-PCR testing. Once the result confirms that the patient meets the molecular criteria for entry, the rest of the screening visit evaluations may be performed which are listed in Table 7-1.

7.1.1.1 Information to be collected on screening failures

Patients who sign an informed consent but fail to be started on treatment for any reason will be considered a screen failure. The reason for not being started on treatment will be entered on in IRT. No other data will be entered into the clinical database for patients who are screen failures, unless the patient experienced a Serious Adverse Event during the Screening Phase (see Section 8 for SAE reporting details). If the patient fails to be enrolled, the IRT must be notified within 2 days of the screen fail that the patient was not enrolled.

7.1.1.2 Patient demographics and other baseline characteristics

7.1.1.2.1 Inclusion/exclusion criteria

Patient eligibility is to be established by confirming all inclusion/exclusion criteria. A relevant record (e.g. checklist) must be stored with the source documentation at the study site. Deviation of any entry criterion excludes a subject from enrollment into the study.

7.1.1.2.2 Demographics

The patient's date of birth, gender, and predominant race will be collected.

7.1.1.2.3 Relevant medical history / current medical conditions

Relevant medical history and current medical conditions, including condition and symptoms related to CML will be collected until the start of the study drug. History of tobacco use will also be collected on an eCRF.

7.1.1.2.4 Disease history

Date of initial diagnosis of CML and the initial disease classification (CML-CP, CML-AP, CML-BC) will be reported on the eCRF. Information on CML disease response will also be collected ([redacted]).

7.1.1.2.5 Sokal score

Sokal risk score at time of diagnosis will be collected if available. If a Sokal Risk score has not been assigned in the medical record, the components required to calculate the Sokal risk score will be collected (i.e. Age, spleen size, platelet count and % peripheral blood myeloblasts).

[redacted]

Table 7-5 Sokal formulation

Sokal's variables	
Age (years)	0.0116 (age – 43.4)
*Spleen (cm)	0.0345 (spleen – 7.51)
Platelets (x10^9/L)	0.188[(platelets/700)^2 – 0.563]
^ Myeloblasts (%)	0.0887 (myeloblasts – 2.10)
Relative Risk (RR)	Exponential of the total
* Maximum distance from costal region ^ Percent in peripheral blood Reference: (Sokal et al 1984) Sokal score calculator at leukemia-net.org/content/leukemias/cml/cml_score/index_eng.html	

In the Sokal formulation, all four variables are continuous. High, intermediate, and low Sokal risk scores are defined as the following:

- Low risk patients have a Relative Risk (RR) < 0.8
- Intermediate risk patients have a RR ≥0.8 and ≤1.2
- High risk patients have a RR > 1.2

The Sokal risk score at diagnosis will be recorded on an eCRF page.

7.1.1.2.6 Prior antineoplastic therapy

Prior antineoplastic medications, radiotherapy, and surgeries will be collected on the appropriate Prior Antineoplastic Therapy eCRF.

7.1.1.2.7 Prior/concomitant medications

All prescription medications and over-the-counter drugs including vitamins and blood transfusions taken within 30 days prior to the start of and throughout the study must be recorded on the Concomitant Medications/Significant Non-Drug Therapies eCRFs. Medication entries should include the name, start and end dates, and the reason for therapy.

7.1.1.2.8 Prior RQ-PCR results

Prior RQ-PCR and laboratory information will be collected if available. The information to be collected will be outlined in the case report form completion guidelines.

7.1.2 Treatment period

Patients will be treated with nilotinib and monitored for MR4.5 for up to 2 years. After Cycle 1 Day 8, patients will have study visits every 3 months during the Monitoring Phase. Those who achieve a confirmed MR4.5 and sustain MR4.0 or better for 2 years during the Consolidation Phase will be eligible for discontinuing nilotinib during the Treatment Free Remission Phase (TFR). Patients who achieve a confirmed MR4.5 will enter the Consolidation Phase and continue to receive nilotinib and be monitored every 3 months for 2 years. Patients who are able to sustain MR4.0 or better during the 2 years of consolidation therapy with nilotinib will be eligible for stopping nilotinib therapy during the TFR Phase.

[redacted]

Patients will receive no study drug treatment during the TFR Phase and will have study visits every month for the first 6 months, and every other month for the next 18 months.

7.1.2.1 TFR visit schedule. Dose administration record

The Dosage Administration Record eCRF will capture the nilotinib dosing regimen information. Reasons for dose changes as well as start and end dates are recorded in the entries.

Patients should be reminded to bring in their study drug containers (blister packs/bottles) at each study visit. Compliance will be assessed by the investigator and/or study personnel at each visit using pill counts.

7.1.2.2 Additional assessments

If it is necessary to perform an additional unscheduled assessment (i.e. laboratory test, ECG, RQ-PCR), the results of the evaluation should be entered in the appropriate additional assessment eCRF page.

7.1.3 Study completion and early termination from study

At the time patients complete the study, there will be a study visit for either Early Termination (Visit 777, 778, 779, or 780) or at the end of the study (which is either Visit 12 for those not eligible to continue on to the Consolidation Phase or Visit 39 for those who complete the TFR Phase). Refer to the visit schedules for evaluations required. An End of Treatment and Study Evaluation Completion eCRF pages should be completed according to the visit schedule. At a minimum, all patients who stop treatment, including those who refuse to return for a final visit, will be contacted for safety evaluations during the 30 days following the last dose of study treatment.

Patients who stop study treatment prematurely during the treatment phases should be considered withdrawn from the study after the final visit assessments are performed or when it is clear that the patient will not return for these assessments. If a study withdrawal occurs, or if the patient fails to return for visits, the investigator must determine the primary reason for a patient's premature withdrawal from the study and record this information on the End of Treatment eCRF page.

7.1.3.1 Criteria for early termination from study

Patients may voluntarily withdraw from the study or be dropped from it at the discretion of the investigator at any time.

Patients may be withdrawn from the study if any of the following

1. Pregnancy
2. Discovery of patient ineligibility/ Protocol deviation
3. Non-compliance
4. Adverse event(s)
5. Abnormal laboratory value(s)
6. Abnormal test procedure result(s)

[redacted]

7. Lost to follow-up
8. Unsatisfactory therapeutic effect – Refer to Table 7-6.

Table 7-6 Loss of efficacy milestones requiring early termination

Phase	**Efficacy Milestone Lost** within the variability of the testing used (±.5log)	Action Required	Follow-up Required
Monitoring Phase	Confirmed loss of MMR (MR3.0)	Patient terminates from study early	AEs 30 days after stopping nilotinib
Consolidation Phase	Confirmed loss of MR4.0	Patient terminates from study early	AEs 30 days after stopping nilotinib
TFR Phase	Confirmed loss of MMR (MR3.0) Loss of CCyR	Patient re-starts nilotinib and continues on study	See Table 7-4.
Nilotinib Treatment Re-Initiation (NTRI)	Failure to achieve MMR(MR3.0) after 12 months of re-initiation	Contact Sponsor and the case will be reviewed with SMC	
	Failure to achieve CCyR within 3 months of nilotinib re-initiation (confirm loss - PCR<1%IS)	Patient terminates from study early	AEs 30 days after stopping nilotinib

9. Subject's condition no longer require study drug (i.e. bone marrow transplantation)
10. Treatment duration completed as per protocol
11. Administrative problems
12. Disease progression
    a. **Accelerated phase** as defined by any of the following (Kantarjian 1993):
        i. ≥ 15% blasts in the peripheral blood or bone marrow, but < 30% blasts in both the peripheral blood and bone marrow
        ii. ≥ 30% blasts plus promyelocytes in peripheral blood or bone marrow
        iii. ≥ 20% basophils in the peripheral blood
        iv. Thrombocytopenia (<100 x 10^9/L) that is unrelated to therapy
    b. **Blast crisis as defined by any of the following** (Druker 2007):
        i. ≥ 30% blasts in peripheral blood or bone marrow
        ii. Appearance of extramedullary involvement other than hepatosplenomegaly proven by biopsy
    c. CML-related death (any death during treatment or follow-up if the principal cause of death is marked as "study indication" in the CRF by the investigator, or if the death occurred subsequent to documented progression to AP/BC and the cause of death is reported as "unknown" or not reported by the investigator)

Refer to the visit schedules for the list of evaluations required at Early Termination/End of Study.

[redacted]

7.1.4 Safety follow up

All patients must have safety evaluations for 30 days after the last dose of study treatment or the last day of the TFR Phase. This follow-up period for safety does not require a visit and can be conducted over the phone.

Patients lost to follow up should be recorded as such on the eCRF. For patients who are lost to follow-up, the investigator should show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc.

7.2 Assessment types

7.2.1 Efficacy assessments

7.2.1.1 Molecular response

Levels of BCR-ABL transcripts will be determined by quantitative RQ-PCR testing of peripheral blood. Samples will be analyzed at a central testing laboratory and reported on the International Scale (IS). Log reduction in BCR-ABL transcripts levels from the standardized baseline value will be calculated for each sample from the reported percent ratio of BCR-ABL transcripts versus control gene transcripts converted to a reference standard. Samples for RQ-PCR analysis will be collected according to the visit schedules.

RQ-PCR laboratory and supplies

The BCR-ABL RQ-PCR test quantitatively measures the RNA blood level of BCR-ABL. For this test total RNA from whole leukocytes is reverse transcribed with random primers and the cDNA product is quantitated by fluorescent real-time RQ-PCR. The BCR-ABL RQ-PCR contains primers from bcr exons b2 & b3 and abl exon 2, such that the major (p210) translocation breakpoint is detected. Abl cDNA copy numbers are used to control for the quality and quantity of sample RNA. Therefore, the result of this test is expressed in % as a fraction of BCR-ABL expression to that of the control gene ABL (% BCR-ABL/ABL).

Major Molecular Response (MMR) (MR3.0)) is equivalent to a 3-log reduction from a standardized baseline value from the International Randomized Interferon versus STI571 (IRIS) study or 0.1% per IS. A standardized baseline value was established in the IRIS trial by calculating the median BCR-ABL transcript value of 30 patient samples collected from newly diagnosed CML-CP patients prior to commencing study drug. The same set of patient samples were tested in the three IRIS trial RQ-PCR laboratories. The standardized baseline, instead of the baseline transcript level of an individual patient, was then used to calculate subsequent molecular response. A correction factor is applied to all BCR-ABL/ABL ratios to obtain the International Scale value and MMR (MR3.0) is reported when a patient shows a BCR-ABL/Abl% less than or equal to 0.1% IS. A result of MR4.5 indicates a greater than or equal to 4.5-log reduction of Bcr- Abl copy number from a standardized baseline value on the international scale.

The central RQ-PCR laboratory used in this study has a validated assay and values of BCR-ABL/control gene% will be reported on the International Scale and also calculated as a log

reduction from the standardized baseline value. RQ-PCR kits from the central RQ-PCR lab will be provided to each site. Each kit will have accession numbers that are specific to each patient and to each sample. Peripheral blood samples will be couriered to the central RQ-PCR laboratory. The results of the central RQ-PCR laboratory will be communicated to the sites to guide patient treatment.

Sample collection for molecular response

In order to monitor molecular response under study treatment, 10 ml of peripheral blood will be collected at each sampling time point for RQ-PCR analysis. The blood will be analyzed for the presence and quantity of BCR-ABL transcripts by RQ-PCR.

Sample collection kits for RQ-PCR [redacted] will be provided to each site by the central lab. Please refer to the central PCR lab manual for collection and shipping instructions. Refer to the visit schedules for PCR evaluation time points.

[redacted]

[redacted]

[redacted]

7.2.2 Safety and tolerability assessments

Safety will be monitored by assessing hematology and biochemistry laboratory results, physical exam results, and ECG monitoring as well as collecting of the adverse events and concomitant medications at every visit. For details on AE collection and reporting, refer to Section 8.

7.2.2.1 Physical examination and extra-medullary involvement

A physical examination will be performed according to the visit schedules. A complete physical examination should include examination of general appearance, eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular, and neurological systems.

Information about the physical examination must be present 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 eCRF. Significant findings made after the start of study drug, which meets the definition of an Adverse Event, must be recorded on the Adverse Events eCRF. There are no eCRF pages to capture routine

[redacted]

normal findings from physical examinations; however these findings must be present in the patient's source documents.

Presence of extra-medullary leukemic involvement will be checked with each physical exam as outlined above. Findings on physical examination consistent with extra-medullary involvement will be recorded on the eCRF (i.e. lymph nodes, liver, and spleen size).

7.2.2.2 Vital signs

Pulse rate, blood pressure, body temperature data will be collected on the eCRFs at the specified visits in the visit schedules must be present in the patient's chart.

7.2.2.3 Height and weight

Height (in centimeters) will be measured only at baseline and recorded on the eCRF.

Body weight (in kilograms) will be measured. To detect early signs of fluid retention, patients should be weighed according to the visit schedules. Patients should be counseled to measure their body weight regularly and report to the study investigator any body weight change of more than 2 kg as compared to their pre-study body weight. Rapid weight gain of ≥ 2 kg should be carefully investigated and managed as appropriate Except for the body weight measurements performed during study visits, other body weight measurements will not be captured on eCRFs nor entered into the clinical database

7.2.2.4 Performance status

Performance status will be recorded in the eCRF according to the visit schedules and as defined by the Eastern Cooperative Oncology Group (ECOG) criteria in Table 7-7.

Table 7-7 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

7.2.2.5 Laboratory evaluations

Each institution will perform hematology and clinical chemistry using their local laboratory according to the visit schedules. The normal ranges and units for each parameter will be collected. If at any time a patient has laboratory parameters obtained from a different laboratory, the certification, tabulation of the normal ranges and units for that laboratory must be provided.

When abnormal laboratory values or test results constitute an adverse event (i.e. induces clinical signs/symptoms or requires therapy) they must be recorded on the Adverse Events

[redacted]

eCRF. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant (e.g. cause study discontinuation or constitutes in and of itself a Serious Adverse Event) or require therapy (e.g., any hematologic abnormality that requires transfusion or cytokine treatment); and should be recorded on the Adverse Events eCRF under the signs, symptoms or diagnosis associated with them. Refer to the visit schedule for the collection frequency.

Table 7-8 Clinical laboratory parameters collection plan

Test Category	Test Name
Hematology	Hemoglobin, total WBC count, platelet count, and a differential count (neutrophils, bands, lymphocytes, monocytes, eosinophils, basophils, promyelocytes, myelocytes, metamyelocytes, blasts, atypical cells)
Chemistry	Creatinine, uric acid, albumin, total protein, total bilirubin, direct bilirubin and/or indirect bilirubin, alkaline phosphatase, AST (SGOT), ALT (SGPT), LDH, sodium, chloride, fasting glucose, HbA1c, calcium, lipase, potassium, magnesium, phosphorus, total cholesterol, triglycerides, LDL, HDL
Serology	Hepatitis B surface antigen (HBs Ag), hepatitis B core antibodies (HBc Ab), antibodies to hepatitis B surface antigen (HBsAb)

7.2.2.5.1 Hematology

Hematology labs are to be done locally at the site. The hematology parameters required to be evaluated are listed in Table 7-8.

Automated differential counts are permitted, however manual differential counts are mandatory in the following situations:

- if loss of CHR is suspected
- if progression to accelerated phase/blast crisis is suspected
- whenever automated differential counts indicate the presence of blasts, promyelocytes, myelocytes, metamyelocytes or atypical cells which cannot be automatically counted

7.2.2.5.2 Clinical chemistry

Blood chemistry labs, including the lipid profile, are to be done locally at the site and the parameters required are listed in Table 7-8. Patients should fast for the biochemistry labs. The routine biochemistry evaluations identified on the visit schedule will be captured on the eCRF.

In addition to the routine biochemistry assessments identified on the visit schedule, patients must have their serum potassium and magnesium levels checked when there is QTcF prolongation and also at the investigator's discretion throughout the study. Additional electrolyte results (i.e. potassium and magnesium) will not be captured on eCRFs nor entered into the clinical database unless supplementation or replacement is required. If supplementation or replacement is required, the lab abnormality should be documented on an unscheduled or scheduled lab result eCRF page, and also as an adverse event. If a supplement or replacement is given, these are to be identified as a concomitant medication. Otherwise, these additional results must be only present in the source documentation at the study site.

[redacted]

7.2.2.5.3 Pregnancy and assessments of fertility

At screening, a serum pregnancy test is required and a urine pregnancy test is required at baseline prior to dosing at Visits 777, 778, 779, and 780. Pregnancy testing is not required for patients who are determined to be post-menopausal as defined in the Exclusion criteria. The serum pregnancy tests will be performed by the local lab.

In addition, monthly urine pregnancy test is also mandatory for all women of child bearing potential throughout the duration of this study. Urine pregnancy tests should be performed at home by the patient throughout the duration of this study. All urine pregnancy test results should be recorded in patient diaries and brought to each scheduled visit for the site to review. Sites are to document the results of the home urine pregnancy test recorded in the diary to an eCRF page. If a positive urine pregnancy test result is discovered at home, the patient should contact the investigator immediately. All pregnancies should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the oncology Novartis Drug Safety and Epidemiology Department (DS&E).

7.2.2.5.4 Electrocardiogram (ECG)

A standard 12 lead ECG will be performed locally according to the schedule below.

Table 7-9 Local ECG collection plan

Cycle	Day	Time	ECG Type
Screening	D-28 to 0	Anytime	12 Lead
1	1	Pre-dose	12 Lead
1	8	Anytime	12 Lead
Unscheduled sample		Anytime	12 Lead

An ECG must be performed at screening, Day 1, and Day 8. QTcF values must be documented in the CRFs. The ECG performed on Day 1 should be done prior to dosing. The ECG obtained at screening and Day 8 can be done at any time. The QT interval should be corrected using the Fridericia formula which is $QTcF = QT/(RR)^{1/3}$. If the ECG machine is preprogrammed with the Bazett formula, $QTcB = QT/(RR)^{1/2}$, the value of QTcF can be manually calculated by using the formula $QTcF = QT/(RR)^{1/3}$, or $QTcF = QT/[(QT/QTcB)^2]^{1/3}$ since $RR = (QT/(QTcB)^2)$. A study tool will also be provided to help with this conversion. If the QTcB value is converted to QTcF, provide both values on the eCRF page. (Bazett 1920) (Fridericia 1920)

After a dose interruption or after any dose changes, additional (unscheduled) ECGs are required. For example, if nilotinib is stopped due to administration of any agents known to prolong the QT interval or strong CYP3A4 inhibitors, additional ECGs are required prior to re-initiation of nilotinib and approximately 7 days after. If a patient is dose reduced to 400mg q.d. for an adverse event, an ECG is required 7 days after re-escalating the dose to 300mg b.i.d.

Interpretation of the tracing must be made by a qualified physician and documented on the ECG eCRF page. Each ECG tracing should be labeled with the study number, patient number, date, and kept in the source documents at the study site. Clinically significant abnormalities present when the patient signed informed consent should be reported on the Medical History

[redacted]

eCRF page. Clinically significant findings must be discussed with Novartis prior to enrolling the patient in the study. New or worsened clinically significant findings occurring after informed consent must be recorded on the Adverse Events eCRF page.

7.2.2.5.5 Hepatitis B testing

Patients will be tested once for the following hepatitis B serologic markers: hepatitis B surface antigen (HBsAg), antibodies to hepatitis B surface antigen (HBsAb) and antibodies to hepatitis B core antigen (HBcAb).

[redacted]

7.2.4 Patient reported outcomes

Patients will be asked to complete the M.D. Anderson Symptom Inventory – Chronic Myeloid Leukemia (MDASI-CML), the EuroQol- Five Dimension Three -level (EQ-5D-3L), and SF-8 questionnaires. The MDASI-CML is a symptom-burden questionnaire, the EQ-5D-3L and the SF-8 are health related quality of life questionnaire.

The patient should be given the questionnaire(s) to be completed at the scheduled visit before any clinical assessments are conducted. Patient's refusal to complete all or any part of a questionnaire should be documented in the study data capture system and should not be captured as a protocol deviation. Patient questionnaires should be completed in the language most familiar to the patient.

The patient should be given sufficient space and time to complete the questionnaire. The site personnel should check the questionnaire for completeness and ask the patient to complete any missing responses. The original questionnaire will be kept with the patient's file as the source document.

Completed questionnaire(s) and any unsolicited comments written by the patient should be reviewed and assessed by the investigator for responses which may indicate potential AEs or SAEs before any clinical study examinations. This assessment should be documented in study source records. If AEs or SAEs are confirmed, study investigators should not encourage the patient to change responses reported in the completed questionnaires. Study investigators must follow reporting instructions outlined in Section 8 (e.g. reference "Adverse Events" section) of the study protocol.

MDASI-CML

The M.D. Anderson Symptom Inventory (MDASI) tool will be utilized to measure symptom burden during the first year on study (Cleeland et al 2000). The 13 core symptom items of the MDASI have been tested in a sample of 527 cancer patients that included CML patients and were found to have discriminant and construct validity. Principle factor analysis showed two underlying constructs of general symptom severity and gastrointestinal symptom severity for the MDASI. The reliability, measured by coefficient a values, for the general symptom

[redacted]

severity factor, the GI symptom severity factor, and the symptom interference in the validation sample were 0.85, 0.82, and 0.91, respectively, and in the cross-validation sample were 0.87, 0.87, and 0.94, respectively, which demonstrates a high level of reliability (Cleeland et al 2000). The MDASI is scored by calculating a mean symptom severity score of symptom ratings and a mean interference score of interference item ratings.

A CML specific MDASI has been developed and patients will be asked to complete this questionnaire. The MDASI-CML consists of 13 validated core symptom items and 6 validated core interference items. Six additional symptom items specific to patients undergoing treatment for CML are being investigated. The items are assessed utilized an 11 point scale. Patients will be asked to rate their symptom severity and interference within the last 24 hours.

The MDASI-CML questionnaire will be given to patients to complete upon the patient's arrival at the clinic. This is to ensure that the patients' recordings are not influenced by any discussions with the physicians during the visit. The data collector will remain with the patient while the questionnaires are completed to ensure that it is the patient who completes the forms and that no one else influences the patient's answers. Patients should be instructed to read the instructions before completing the questionnaire. Patients should be encouraged to answer every item. Patients should be instructed to indicate the response they think best represents how they are feeling. If for whatever reason the patient does not complete the questionnaire at the scheduled assessment, time and reason should be recorded. The study personnel is responsible for collecting the form from the patient at each of the visits when indicated. Translated versions of the MDASI-CML will be available as CRFs. Refer to the eCRF Completion Guidelines (CCGs) on how to administer the questionnaire.

EQ-5D-3L

The EQ-5D-3L questionnaire is a standardized measure of health status developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal. The EQ-5D-3L is applicable to a wide range of health conditions and treatments; it provides a simple descriptive profile and a single index value for health status that can be used in the clinical and economic evaluation of health care as well as in population health surveys.

The EQ-5D-3L is designed for self-completion by respondents and is ideally suited for use in postal surveys, in clinics, and in face-to-face interviews. It is cognitively undemanding, taking only a few minutes to complete.

Instructions to respondents are included in the questionnaire. The EQ-5D-3L measures 5 items on mobility, self-care, usual activities, pain/discomfort, anxiety/depression, measured on 3 levels: no problems, some problems, and extreme problems. The EQ-5D-3L also includes a 20 cm vertical, VAS (visual analogue scale) with on a scale of 0-100, with endpoints labeled 'the best health you can imagine' and 'the worst health you can imagine'. A single index value is analyzed for the EQ-5D-3L and VAS score.

Patients must be asked to complete each questionnaire prior to clinical assessments being undertaken, and these must be completed in accordance with the schedules listed in the visit schedule.

[redacted]

SF-8

SF-8 is an 8-item questionnaire designed to provide a HRQL profile, developed by QualityMetric, Incorporated (QMI). It measures health profile in eight scales (i.e., domains) with a single item in each scale: general health (SF8GH), physical functioning (SF8PF), role physical (SF8RP), bodily pain (SF8BP), vitality (SF8VT), social functioning (SF8SF), mental health (SF8MH), emotional roles (SF8RE). The profile is summarized into physical component (PCS) and mental component (MCS) continuous summary scores, with higher scores indicating better self-reported HRQL. The PCS and MCS have been normalized in the United States population. These norms are useful for comparing the health of participants to the general US population. SF-8 is sensitive to change, and can therefore be used to assess change in HRQL over time.

SF-8 belongs to short form (SF) family, which also include SF-36 (based on 36 questions) and SF-12 (based on 12 questions). SF-8 measures the same eight health domains as the SF-36 and SF-12. It has the advantage of being brief, while yielding scores that are directly comparable to that produced by the standard SF-36 and SF-12 questionnaires.

8 Safety monitoring and reporting

8.1 Adverse events

8.1.1 Definitions and reporting

An adverse event is defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) that occur after patient's signed informed consent has been obtained.

Abnormal laboratory values or test results occurring after informed consent constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, require therapy (e.g., hematologic abnormality that requires transfusion or hematological stem cell support), or require changes in study medication(s).

Adverse events that begin or worsen after informed consent should be recorded in the Adverse Events eCRF. This includes any adverse events that occur in the TFR Phase

Conditions that were already present at the time of informed consent should be recorded in the Medical History page of the patient's eCRF. Adverse event monitoring should be continued for at least 30 days (or 5 half-lives, whichever is longer) following the last dose of study treatment. Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate Adverse Event.

Adverse events will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, corresponding to Grades 1 - 4, will be used. CTCAE Grade 5 (death) will

[redacted]

not be used in this study; rather, information about deaths will be collected though a Death form.

The occurrence of adverse events should be sought by non-directive questioning of the patient during the screening process after signing informed consent and at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during the screening process or between visits, or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

1. The severity grade (CTCAE Grade 1-4)
2. Its duration (Start and end dates or Ongoing at End of Study)
3. Its relationship to the study treatment
4. Action taken with respect to study or investigational treatment
5. Whether medication or therapy was given
6. Whether it is serious, where a serious adverse event (SAE) is defined as in Section 8.2.1.

All adverse events should be treated appropriately. If a concomitant medication or non-drug therapy is given, this action should be recorded on the Adverse Event eCRF.

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome.

8.1.2 Laboratory test abnormalities

8.1.2.1 Definitions and reporting

Laboratory abnormalities that constitute an Adverse event in their own right (are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy or require changes in study treatment), should be recorded on the Adverse Events eCRF. Whenever possible, a diagnosis, rather than a symptom should be provided (e.g. anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for Adverse Events should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported adverse event, it is not necessary to separately record the lab/test result as an additional event.

Laboratory abnormalities, that do not meet the definition of an adverse event, should not be reported as adverse events. A Grade 3 or 4 event (severe) as per CTCAE does not automatically indicate a SAE unless it meets the definition of serious as defined below and/or as per investigator's discretion. A dose hold or medication for the lab abnormality may be required by the protocol in which case the lab abnormality would still, by definition, be an adverse event and must be reported as such.

[redacted]

8.1.3 Adverse events of special interest

Ischemic vascular and ischemic cardiovascular events include (but are not limited to) the events listed below. Patients should be educated on the clinical symptoms of such events to ensure accurate reporting to the Investigator.

- Ischemic Heart Disease (IHD): angina pectoris, coronary artery disease, acute myocardial infarction and coronary artery stenosis
- Ischemic Cerebrovascular Events (ICVE): ischemic cerebrovascular accident, and transient ischemic attack
- Peripheral Artery Occlusive Disease (PAOD): intermittent claudication, arterial stenosis of a limb

If patients experience ischemic vascular or ischemic cardiovascular events (i.e. ischemic, cardiac, cerebrovascular or peripheral artery-related), carefully consider protocol guidance for dose reduction or study drug discontinuation (Protocol Table 6-3).

The Investigator should ensure that the patient is assessed by a vascular or cardiovascular specialist.

8.1.3.1 Reporting of AE of special interest

Ischemic vascular or ischemic cardiovascular events in patients should be documented and reported as any other AE (please refer to Section 8.1.1 for further details).

8.2 Serious adverse events

8.2.1 Definitions

Serious adverse event (SAE) is defined as one of the following:

- Is fatal or life-threatening
- 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
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Note that hospitalizations for the following reasons should not be reported as serious adverse events:
  - Routine treatment or monitoring of the studied indication (CML), not associated with any deterioration in condition
  - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
  - Social reasons and respite care in the absence of any deterioration in the patient's general condition
- Note that treatment on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of a SAE given above is not a serious adverse event

[redacted]

8.2.2 Reporting

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided the main informed consent and until at least 30 days after the patient has stopped study treatment or last day in the TFR Phase must be reported to Novartis (using the SAE Report Form) within 24 hours of learning of its occurrence. SAEs will be followed until resolution or until clinically relevant improvement or stabilization.

Any SAEs experienced after this 30 days period (or 5 half-lives, whichever is longer) should only be reported to Novartis if the investigator suspects a causal relationship to the study treatment. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form in English, and send the completed, signed form by fax within 24 hours to the oncology Novartis Drug Safety and Epidemiology (DS&E) department. Causality for each reported serious event on the SAE report form must be assessed as either as "Suspected" or "Not Suspected" to the study drug. No other term such as "Probable", "Plausible", "May be" or "Could be" etc. should be used for causality assessment.

The telephone and telefax number of the contact persons in the local department of DS&E, specific to the site, are listed in the investigator folder provided to each site. The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the case report form documentation at the study site.

Follow-up information is sent to the same contact(s) to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. 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 patient continued or withdrew from study participation.

If the SAE is not previously documented in the [Investigator's Brochure] or Package Insert (new occurrence) and is thought to be related to the Novartis study treatment, an oncology DS&E department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN), to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

[redacted]

8.3 Emergency unblinding of treatment assignment

Not applicable

8.4 Pregnancies

To ensure patient safety, each pregnancy occurring while the patient is on study treatment and/or in the TFR Phase 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 oncology Novartis Drug Safety and Epidemiology Department (DS&E). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment and pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

8.5 Warnings and precautions

No evidence available at the time of the approval of this study protocol indicated that special warnings or precautions were appropriate, other than those noted in the provided [Investigator Brochure]. Additional safety information collected between IB updates will be communicated 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.

8.6 Data Monitoring Committee

Not applicable

8.7 Study Management Committee (SMC)

A Study Management Committee (SMC) will be established comprising 5 external investigators who are clinical experts in CML and 3 Novartis team members.

The SMC will ensure transparent management of the study according to the protocol through recommending and approving modifications as circumstances require; to interpret/clarify RQ-PCR and mutation analysis results as appropriate. The SMC will review protocol amendments as appropriate. Together with the clinical trial team, the SMC will also develop recommendations for abstracts and publications of study results including authorship rules.

9 Data collection and management

9.1 Data confidentiality

Information about study subjects will be kept confidential and managed under the applicable laws and regulations. Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study

[redacted]

- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect follow-up safety information (e.g. has the subject experienced any new or worsened AEs) at the end of their scheduled study period.

The data collection system for this study uses built-in security features to encrypt all data for transmission in both directions, preventing unauthorized access to confidential participant information. Access to the system will be controlled by a sequence of individually assigned user identification codes and passwords, made available only to authorized personnel who have completed prerequisite training.

9.2 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, Novartis personnel and the designated CRO will review the protocol and Electronic Case Report Forms (eCRFs) 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 eCRFs, the adherence to the protocol to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment 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 recorded on eCRFs must be traceable to source documents in the patient's file. The investigator must also keep the original signed informed consent form (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 eCRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria and documentation of SAEs. Additional checks of the consistency of the source data with the eCRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the patients will be disclosed.

9.3 Data collection

This study will use Electronic Data Capture (EDC) and the designated investigator staff will enter the data required by the protocol into the eCRFs using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements. Designated investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs and, allow modification or verification of the entered data by the investigator staff.

[redacted]

The Principal Investigator is responsible for assuring that the data entered into eCRF is complete, accurate, and that entry and updates are performed in a timely manner.

PCR [redacted] will be collected and analyzed by 3rd party vendors. Results will be sent to the designated CRO, who will export the data to SAS datasets.

Laboratory assessments for hematology, chemistry, and ECGs will be collected locally and entered directly onto the eCRFs.

9.4 Database management and quality control

This study will be using eCRFs and the designated CRO will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior 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.

[redacted] data will be processed centrally and the results will be sent electronically to the designated CRO.

PCR samples and/or data will be processed centrally and the results will be sent electronically to the designated CRO.

Patient status during the study will be tracked using an Interactive Response Technology. The system will be supplied by a vendor(s), who will also manage the database. The data will be sent electronically to the designated CRO.

At the conclusion of the study, the occurrence of any protocol violations will be determined. After this action has been completed and the data has been verified to be complete and accurate, the database will be declared locked and the data made available for data analysis. Authorization is required prior to making any database changes to locked data.

For EDC studies, after database lock, the investigator will receive a CD-ROM or paper copies of the patient data for archiving at the investigational site.

10 Statistical methods and data analysis

A designated Clinical Research Organization (CRO) will perform the statistical analysis.

It is planned that the data from all centers that participate in this protocol will be used, so that an adequate number of patients will be available for analysis.

The primary analyses of all efficacy and safety variables will be performed when all patients enrolled have completed 6 months of the TFR Phase, follow-up or discontinued from the study. All analyses will include patients who entered the TFR Phase following a 12 month

[redacted]

Consolidation Phase (Arm A) prior to protocol amendment 2 and a 24 month Consolidation Phase (formerly Arm B).

After all patients enrolled have completed 12 and 24 months of follow-up, analyses of all efficacy and safety will be performed including the same patients as in the primary analyses. These analyses performed after the primary analyses will be considered secondary. No formal testing of any kind will be performed at these analyses.

Since the study collects data in 3 phases (monitoring, consolidation and treatment-free remission phases), all safety (dosing, AEs, vitals signs and laboratory) and patient reported outcomes data will also be summarized overall in the Consolidation Phase.

10.1 Analysis sets

10.1.1 Full Analysis Set

The Full Analysis Set (FAS) for the primary analyses comprises all patients who entered the TFR Phase.

The FAS will be the primary set for all efficacy analyses and safety analyses in the TFR Phase only.

10.1.2 Safety set

The safety set consists of all patients who received at least one dose of study drug and had at least one post-baseline safety assessment after enrollment.

Please note: the statement that a patient had no adverse events (on the Adverse Event eCRF) constitutes a safety assessment. Patients who have received at least one dose of study drug but who have no post-treatment safety data of any kind would be excluded from the safety set.

The safety set will be used for the summary of all safety and patient reported outcomes in the monitoring and Consolidation Phase.

10.1.3 Per-protocol set

No per-protocol set will be defined for this study.

10.2 Patient demographics/other baseline characteristics

Demographic and other baseline data including age, gender, height, weight, ECOG status, disease history, medical conditions etc. will be summarized overall for all enrolled patients. Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, 25^{th} and 75^{th} percentiles, minimum and maximum will be presented.

10.3 Treatments (study treatment, concomitant therapies, compliance)

The actual daily dose and duration of study drug will be summarized overall using descriptive statistics in the monitoring and Consolidation Phase respectively.

[redacted]

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be summarized overall in both monitoring and Consolidation Phases.

10.4 Primary objective

The primary objective of the study is to evaluate molecular relapse-free rates 6 months after discontinuation from nilotinib therapy in patients who have achieved a MR4.5.

10.4.1 Molecular relapse is defined as having a confirmed BCR-ABL ratio above MMR (2 consecutive BCR-ABL levels >0.1%IS taken approximately 4 weeks apart) variable

Molecular relapse free rate (RFR) at 6 months after discontinuation from nilotinib therapy in patients with MR4.5

10.4.2 Statistical hypothesis, model, and method of analysis

No statistical hypothesis will be tested on the primary efficacy variable.

The primary efficacy variable will be summarized by frequencies and percentages overall. An exact 95% confidence interval for the relapse free rate at 6 months will also be provided overall.

The FAS will be used for the summary.

10.4.3 Handling of missing values/censoring/discontinuations

No imputation of missing values will be performed.

10.4.4 Supportive analyses

An exploratory analysis of the relapse free rate will be performed using a logistic regression model to evaluate the dependence of relapse (Yes or No) on important prognostic variables (e.g., duration on nilotinib, duration of sustained MR4.5, and selected baseline characteristics).

10.5 Secondary objectives

10.5.1 Key secondary objective(s)

The key secondary objective of the study is to evaluate relapse-free survival.

10.5.2 Other secondary efficacy objectives

The other secondary objectives of the study are:

- To evaluate molecular relapse free rates at 12 and 24 months after nilotinib treatment discontinuation
- To evaluate the proportion of patients who regain MR4.5 after restarting nilotinib following molecular relapse
- To describe the impact of nilotinib treatment discontinuation on progression to AP/BC and CML-related deaths
- Overall survival

[redacted]

Relapse free survival is defined as time from the date of nilotinib treatment discontinuation to the first documented molecular relapse (confirmed loss of MR4.0, confirmed loss of MMR are 2 consecutive BCR-ABL levels > 0.1% IS taken approximately 4 weeks apart).The relapse-free survival will be summarized and graphed using the product-limit (Kaplan-Meier) overall. Patients who drop out without relapse will be treated as censored observations. The estimates of the 25^{th}, median, 75^{th} percentiles for the relapse-free survival and its 95% confidence intervals will be provided, if applicable.

The molecular relapse free rates at 12 and 24 months and the proportion of patients who regain MR4.5 after restarting nilotinib will summarized overall by frequencies and percentages. An exact 95% confidence interval for each will also be provided using binomial distribution.

Overall survival is defined as the time from the date of nilotinib treatment discontinuation to the date of death from any cause.

Overall survival will be summarized and graphed using the product-limit (Kaplan-Meier) method as described above. Patients who are alive at the date of last contact will be treated as censored observations.

The FAS for the primary analysis as described above will be used for these analyses.

10.5.3 Safety objectives

10.5.3.1 Analysis set and grouping for the analyses

The assessment of safety will be based primarily on the frequency of adverse events and on the number of laboratory values that fall outside of pre-determined ranges. Other safety data (e.g., electrocardiogram, vital signs, etc.) will be also be summarized. All safety data will be summarized overall in the 3 different phases as appropriate. All safety listings will be done overall.

The safety set will be used for all safety summaries.

10.5.3.2 Adverse events (AEs)

All adverse events recorded during the study will be summarized. The incidence of treatment-emergent adverse events (new or worsening from baseline) will be summarized by system organ class, severity (based on CTC grades), type of adverse event, relation to the study drug. The adverse events which result in death, early termination of the treatment or are otherwise classified as dose limiting will be presented separately.

10.5.3.3 Laboratory abnormalities

All laboratory values will be converted into SI units and the severity grade calculated using appropriate common toxicity criteria (CTC).

A listing of laboratory values will be provided by laboratory variable, patient, and dose level. A separate listing will display notable laboratory abnormalities (i.e., newly occurring CTC grade 3 or grade 4 laboratory toxicities). The frequency of laboratory abnormalities will be displayed by variable andcycle. Laboratory data will be summarized by presenting shift tables.

[redacted]

10.5.3.4 Other safety data

Data from other tests (e.g., electrocardiogram or vital signs) will be summarized and listed, notable values will be flagged, and any other information collected will be listed as appropriate. Any statistical tests performed to explore the data will be used only to highlight any interesting comparisons that may warrant further consideration.

10.5.3.5 Supportive analyses for secondary objectives

The M.D. Anderson Symptom Inventory for CML patients (MDASI-CML) will be used to assess the nature and impact of symptom burden on life. The MDASI-CML consists of 19 validated symptom items and 6 validated core interference items. Each item is assessed on an 11 point scale.

The symptom, interference subscale total scores and the overall total score in MDASI-CML with their change from baseline will be summarized descriptively at all post-baseline time points by mean, median, standard deviation, 25^{th} and 75^{th} percentiles and the range.

The EQ-5D-3L will be used to assess the impact of nilotinib treatment discontinuation on patient utility. The questionnaire comprises 5 items: mobility, self-care, usual activities, pain/discomfort and anxiety/depression and the EQ visual analog scale. Each item has 3 levels (no problems, some problems and extreme problems) and visual analog has a scale 0 to 100 (0=worst imaginable health state, 100=best imaginable health state).

The percentages of patients at each level of the five items of the EQ-5D-3L will be summarized overall as appropriate at baseline and all post-baseline time points.

Mean and standard deviation of the visual analog scale be provided.

The SF-8 Questionnaire consisting of 8 items (general health, physical functioning, role-physical, bodily pain, vitality, social functioning, role-emotional and mental health) will be used to assess the impact of nilotinib treatment discontinuation on the quality of life. Each item has a 5 or 6 point response range. Physical and mental component summary measures (calculated using a norm-based scoring method given in the instrument guidelines) and each item score will be summarized at baseline and all post-baseline time points using mean and standard deviation.

[redacted]

10.6 Interim analysis

No interim analysis will be performed for this study.

10.7 Sample size calculation

The sample size of the study is not based on statistical considerations, it is based on feasibility. Due to slow enrollment, the sample size of the study has been reduced to 59 patients, all of which were enrolled by January 9, 2015. Of these 59 patients, approximately 20 are expected to enter into the TFR Phase. It is assumed that the study will show an improvement of 20% RFR rate over the historical control rate of 40% RFR observed in the STIM study.

11 Ethical considerations and administrative procedures

11.1 Regulatory and ethical compliance

This clinical study was designed, shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC and US Code of Federal Regulations Title 21), and with the ethical principles laid down in the Declaration of Helsinki.

11.2 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. 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.

11.3 Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC/REB-approved informed consent.

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 patient source documents. The date when a subject's Informed Consent was actually obtained will be captured in their eCRFs.

Novartis will provide to investigators, in a separate document, a proposed informed consent form (ICF) that is considered appropriate for this study and complies with the ICH GCP

[redacted]

guideline and regulatory requirements. Any changes to this ICF 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 child bearing potential should be informed that taking the study medication may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they should not be entered in the study.

[redacted]

11.4 Discontinuation of the study

Novartis reserves the right to discontinue this study under the conditions specified in the clinical study agreement. Specific conditions for terminating the study are outlined in Section 4.4.

11.5 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 study will be either submitted for publication and/or posted in a publicly accessible database of clinical study results.

11.6 Study documentation, record keeping and retention of documents

Each participating site will maintain appropriate medical and research records for this trial, in compliance with Section 4.9 of the ICH E6 GCP, and regulatory and institutional requirements for the protection of confidentiality of subjects. As part of participating in a Novartis-sponsored study, each site will permit authorized representatives of the sponsor(s) and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete,

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microfiches, photographic negatives, microfilm or magnetic media, x-rays, and subject files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site Principal Investigator. The study case report form (eCRF) is the primary data collection instrument for the study. The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported in the CRFs and all other required reports. Data reported on the eCRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. All data requested on the eCRF must be recorded. Any missing data must be explained. Any change or correction to a paper eCRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry. For electronic CRFs an audit trail will be maintained by the system. The investigator should retain records of the changes and corrections to paper CRFs.

The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (ICH E6 Section 8) and as required by applicable regulations and/or guidelines. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

Essential documents (written and electronic) should be retained for a period of not less than fifteen (15) years from the completion of the Clinical Trial unless Sponsor provides written permission to dispose of them or, requires their retention for an additional period of time because of applicable laws, regulations and/or guidelines

11.7 Confidentiality of study documents and patient records

The investigator must ensure anonymity of the patients; patients must not be identified by names in any documents submitted to Novartis. Signed informed consent forms and patient enrollment log must be kept strictly confidential to enable patient identification at the site.

11.8 Audits and inspections

Source data/documents must be available to inspections by Novartis or designee or Health Authorities.

11.9 Financial disclosures

Financial disclosures should be provided by study personnel who are directly involved in the treatment or evaluation of patients at the site - prior to study start.

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, if any, monitoring the study to request approval of a protocol deviation, as no authorized deviations are permitted. 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 Amendments to the protocol

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC/REB. Only amendments that are required for patient safety may be implemented prior to IRB/IEC/REB approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations (e.g. UK requires the notification of urgent safety measures within 3 days) but not later than 10 working days.

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