NOVARTIS

Clinical Development

Nilotinib/AMN107/Tasigna®

Protocol CAMN107I2201 / NCT01784068

A single-arm, multicenter, nilotinib treatment-free remission study in patients with BCR-ABL1 positive Chronic Myelogenous Leukemia in chronic phase who have achieved durable minimal residual disease (MRD) status on first line nilotinib treatment

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List of abbreviations

ABL	Abelson leukemia virus
AE	Adverse Event
AESI	Adverse Events of Special Interest
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
ANC	Absolute Neutrophil Count
Anti HBc	Hepatitis B Core Antibody
AP	Accelerated Phase
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
ATP	Adenosine Triphosphate
AUC	Area Under Curve
BC	Blast Crisis
BCR	Break point Cluster Region
BCR-ABL	BCR-ABL oncoprotein product of BCR-ABL fusion gene
BID	*bis in diem*/twice a day
CCyR	Complete Cytogenetic Response
CHR	Complete Hematologic Response
CI	Confidence Interval
Cmin,ss	Lowest steady-state concentration observed
CML	Chronic Myeloid Leukemia
CMO&PS	Chief Medical Office and Patient Safety
CMR	Complete Molecular Response
CP	Chronic Phase
CRF	Case Report/Record Form; the term CRF can be applied to either EDC or Paper
CRO	Contract Research Organization
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CT	Computed Tomography
CTCAE	NCI Common Terminology Criteria for Adverse Events
CV	Coefficient of Variation
CVE	Cardiovascular Event
CYP3A4	Cytochrome P450 3A4
DDI	Drug-Drug Interaction
DRID	Dose Reference ID
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture
EDTA	Ethylenediaminetetraacetic acid
EEA	European Economic Area
ELN	European LeukemiaNet
ENEST	Evaluating Nilotinib Efficacy and Safety in Clinical Trials
EOS	End of Study
EOT	End of Treatment
CCI	[redacted]
ER	Emergency room
eSAE	Electronic Serious Adverse Event

FAS	Full Analysis Set
FDA	Food and Drug Administration (USA)
FISH	Fluorescent In-situ Hybridization
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony Stimulating Growth Factors
GDPR	General Data Protection Regulation
GI	Gastrointestinal
GM-CSF	Granulocyte-Macrophage Colony-Stimulating Factors
GP	General Practitioner
H2	Histamine H2-receptor antagonists
HBc Ab	Hepatitis B Core Antibody
HBs Ag	Hepatitis B Surface Antigen
HDL-C	High Density Lipoprotein-Cholesterol (i.e. HDL)
HMG-CoA	Hydroxy-Methyl-Glutaryl-Coenzyme A
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICVE	Ischemic Cerebrovascular Events
IEC	Independent Ethic Committee
IFN	Interferon
IHD	Ischemic Heart Disease
IN	Investigator Notification
IRB	Institutional Review Board
IRT	Interactive Response Technology
IS	International scale
IUD	Intrauterine Device
IUS	Intrauterine System
KIR	Killer Inhibitory Receptor
KM	Kaplan-Meier
LC-MS/MS	Liquid Chromatography-tandem mass spectrometry
LDL-C	Low Density Lipoprotein-Cholesterol (i.e. LDL)
LFTs	Liver Function Tests
LLN	Lower Limit of Normal
LLOQ	Lower Limit Of Quantification
LPFV	Last Patient First Visit
LPLV	Last Patient Last Visit
mCyR	minor Cytogenetic Response
MCyR	Major Cytogenetic Response
CCI	[redacted]
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MMR	Major Molecular Response
MR	Molecular Response
MR3.0	Molecular Response 3.0 log reduction from baseline
MR4.0	Molecular Response 4.0 log reduction from baseline
MR4.5	Molecular Response 4.5 log reduction from baseline
MR5.0	Molecular Response 5.0 log reduction from baseline
MRD	Minimal Residual Disease

N	Sample size
NCCN	National Comprehensive Cancer Network
NTCS	Nilotinib Treatment Consolidation phase
NTCT	Nilotinib Treatment Continuation phase
NTCT-P	Nilotinib Treatment Continuation Prolonged phase
NTRI	Nilotinib Treatment Re-Initiation phase
OS	Overall Survival
PAOD	Peripheral Artery Occlusive Disease
PCR	Polymerase Chain Reaction
PCyR	Partial Cytogenetic Response
PD	Pharmakodynamics
PFS	Progression Free Survival
Ph	Philadelphia chromosome
Ph+ CML	Philadelphia chromosome positive Chronic Myeloid Leukemia
PHI	Protected Health Information
PI	Principal Investigator
PI-3 kinase	Phosphatidylinositol 3-kinases
PK	Pharmacokinetic
PPS	Per-Protocol Set
PRO	Patient Reported Outcome
PSUR	Periodic Safety Update Report
QD	Once a day
QTc	Q-T Corrected
QTcF	Q-T interval in the ECG (corrected according to the formula of Fridericia)
RAP	The Report and Analysis Plan
REB	Research Ethics Board
RoW	Rest of World
RR	Relative Risk
RU	Resource Utilization
SAE	Serious Adverse Event
SC	Steering Committee
SD	Standard Deviation
SGOT	Serum Glutamic Oxaloacetic Transaminase/AST
SGPT	Serum Glutamic Pyruvic Transaminase/ALT
SMC	Study Management Committee
SS	Safety Set
SST	Serum Separator
STAT5	Signal transducer and activator of transcription 5
SUSAR	Suspected Unexpected Serious Adverse Reaction
TFR	Treatment-Free Remission
TFS	Treatment Free Survival
TKI	Tyrosine Kinase Inhibitor
UC	Urgent Care
ULN	Upper Limit of Normal
VAP	Validation and Planning
VAS	Visual Analogue Scale
VES	Visit Evaluation Schedule

WBC	White Blood Cell

Glossary of terms

Assessment	A procedure used to generate data required by the study
Accelerated phase (AP)	● ≥ 15% blasts in the peripheral blood or bone marrow aspirate, but < 30% blasts in both the peripheral blood and bone marrow aspirate ● ≥ 30% blasts plus promyelocytes in peripheral blood or bone marrow aspirate ● ≥ 20% basophils in the peripheral blood ● Thrombocytopenia (<100 x 10^9/L) that is unrelated to therapy
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study subject or study patient
Blast crisis (BC)	● ≥ 30% blasts in peripheral blood or bone marrow aspirate ● Appearance of extramedullary involvement other than hepatosplenomegaly proven by biopsy (i.e., chloroma)
Complete Molecular Response	Undetectable BCR-ABL levels with high sample sensitivity (10^{-5} or greater) for a minimum of two years
Cytogenetic response	● Complete (CCyR) - 0% Ph+ metaphases ● Partial (PCyR) - >0 to 35% Ph+ metaphases ● Major (MCyR) - 0 to 35% Ph+ metaphases ● Minor (mCyR) - >35 to 65% Ph+ metaphases ● Minimal - >65 to 95% Ph+ metaphases ● None - >95 to 100% Ph+ metaphases
Disease progression	The following events are considered disease progression: ● CML-related death ● Accelerated Phase (AP) ● Blast Crisis (BC)
Durable Minimal Residual Disease (MRD)	The 4 last quarterly performed PCR assessments must fulfill the following criteria: ● Last assessment is MR4.5 ● No assessment worse than MR4.0 (BCR-ABL > 0.01% IS) and ● No more than two assessments between MR4.0 and MR4.5 (0.0032% IS < BCR-ABL ≤ 0.01% IS)
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)

Full Analysis Set	The Full Analysis Set (FAS) comprises all patients who enter the TFR phase.
Investigational drug	The study treatment whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with "investigational new drug."
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
Molecular response	MMR – BCR-ABL ≤ 0.1% (IS); MR4.0 – BCR-ABL ≤ 0.01% (IS); MR4.5 – BCR-ABL ≤ 0.0032% (IS)
Overall survival	The time from the date of starting TFR phase to the date of death, where the "failure" event is the occurrence of death from any cause.
Per-protocol set	A subset of the FAS who are compliant with clinical study protocol.
Personal Data	Patient information collected by the Investigator that is transferred to Novartis for the purpose of the clinical trial. This data includes patient identifier information, study information and biological samples.
Progression free survival	Progression to AP/BC or death where the "failure" event is the earliest occurrence of the following event: progression to AP/BC or death from any cause.
Treatment-Free Survival	Time from the start of the TFR phase to the earliest occurrence of the following events: loss of MMR, re-initiation of treatment due to any cause, progression to AP/BC or death due to any cause.
Safety Set	All patients who received at least one dose of study medication.
Study treatment	Includes any drug or combination of drugs in any study arm administered to the patient 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;
Subject Number (Subject No.)	A unique identifying number assigned to each subject who enrolls in the study.
Variable	Identifier used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified time points
Withdrawal of Study Consent	Withdrawal of consent from the study occurs only when a patient does not want to participate in the study any longer, and does not allow any further collection of personal data.

Amendment 6 (27-Apr-2018)

Amendment rationale

The recruitment of this study has been completed (LPFV 22-Nov-2013) and 215 patients have been enrolled. As of 26-Apr-2018, 160 patients are ongoing in the study.

The primary purposes of the amendment are:

- To extend the study duration by a further period of 5 years to a minimum of 528 weeks (10 calendar years) after last patient entered the treatment-free remission (TFR) phase in order to confirm stability of the rate of patients remaining in the TFR phase and to evaluate the long-term safety and potential risk of resistance to treatment after nilotinib discontinuation, by collecting information on late relapses, loss of response and occurrence of mutations (risk of developing resistance).
- To evaluate the percentage of patients who are in stable response (MMR and MR4.5) after achievement of that response in nilotinib re-initiation phase for 48 weeks, 96 weeks, 144 weeks, 192 weeks, 240 weeks, 288 weeks, 336 weeks, 384 weeks and 432 weeks, based on availability of appropriate data.

Changes to the protocol



CCI

IRBs/IECs

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.

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 5 (15-Nov-2016)

Amendment rationale

The recruitment of this study has been completed (LPFV 22-Nov-2013) and 215 patients have been enrolled. As of 03-Nov-2016, 175 patients are ongoing in the study.

The primary purposes of the amendment are:

- To extend the study duration to a minimum of 5 calendar years (264 weeks) after last patient entered the TFR phase and to include the corresponding analysis of data after nilotinib discontinuation, to confirm stability of the rate of patients staying in the TFR phase.
- To add a Treatment Free Survival (TFS) sensitivity analysis to consider discontinuation from the TFR phase due to any reason as a TFS event, in addition to the TFS events already defined in Section 10.5.1.
- To clarify that the testing of LDL-C, which is currently restricted to the calculated LDL-C parameter in the protocol, may also include the direct LDL-C parameter. Since protocol amendment 2, direct LDL-C is automatically measured and reported to sites for blood samples with a triglycerides value above 400mg/dL or 4.52mmol/L, for which the central laboratory cannot provide a calculated LDL-C value.
- To update Section 6.4.3 Prohibited concomitant therapy to bring clarity on action to be performed when QT prolonging drugs are taken depending on the risk category of Torsades de Pointe.

Changes to the protocol

CCI


CCI



IRBs/IECs

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.

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 4

Amendment rationale

The recruitment of this study has been completed (LPFV 22-Nov-2013) and 215 patients have been enrolled. Currently 182 patients are ongoing in the study.

The primary purpose for the amendment is:

- 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



IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) 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

Amendment rationale

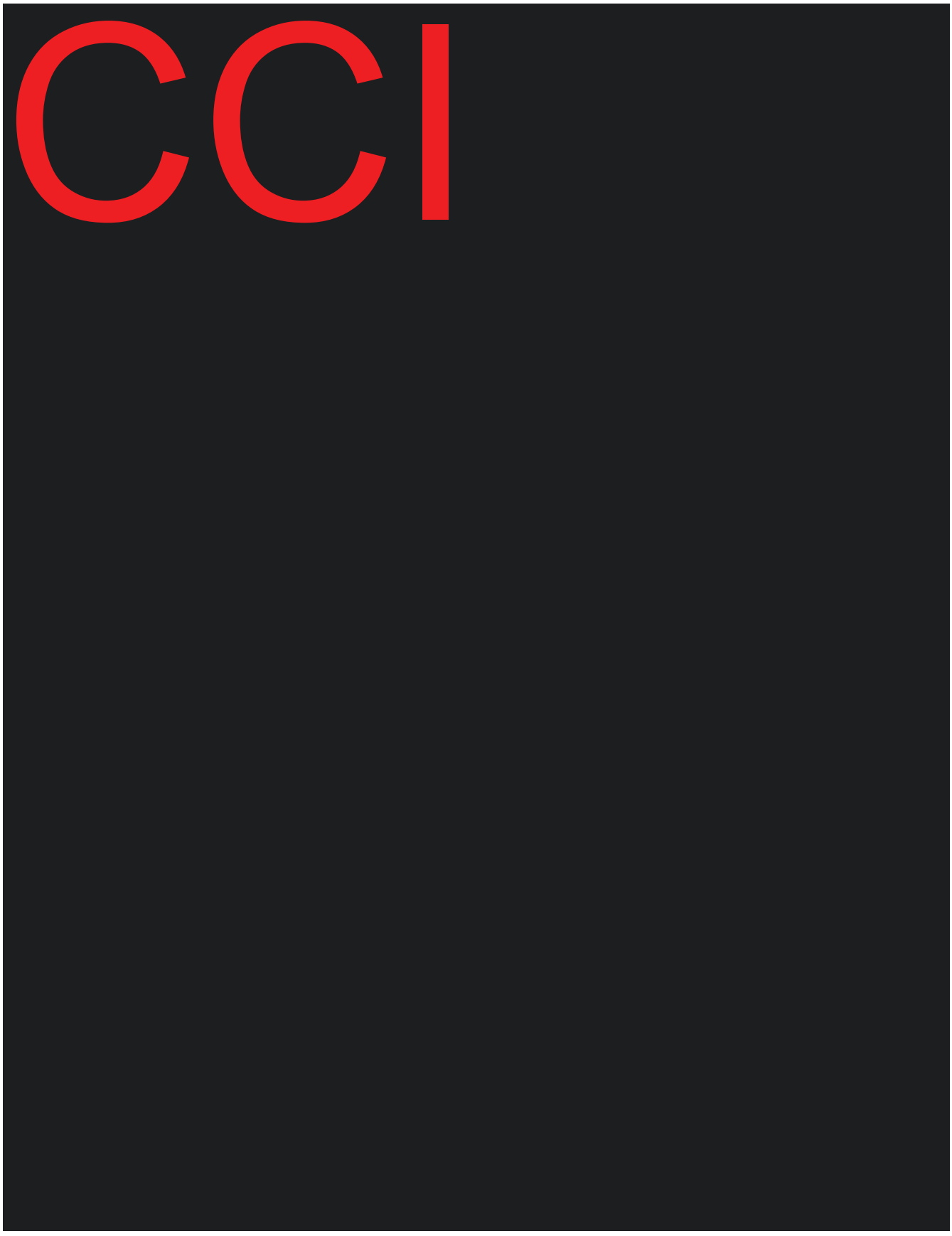
The recruitment of the study has been completed (LPFV 22 Nov 2013) and 216 patients have been enrolled. All eligible patients (190) have entered the TFR phase of the study which is currently ongoing.

The main purposes of the amendment are:

- To clarify instructions on when intensified PCR bi-weekly monitoring will be ended if loss of MR4.0 happened after the first 48 weeks of the TFR phase.
- To more precisely define "immediate" treatment re-initiation after loss of MMR.
- To further clarify the early study termination rules during the first 48 weeks of the TFR phase.
- To add a section "General non-hematological laboratory toxicity" to allow for a distinction from "General non-hematology toxicity", for which the described rules must be strictly applied without any possibility of modification by the investigator. It was necessary to introduce the section "General non-hematological laboratory toxicity" to accommodate an individual assessment by the investigator in some clinical situations such as serum glucose increase ≥G2 or bilirubin increase ≥G2 in Gilbert's patients lasting longer than 28 days even upon dose reduction of study drug, which are not harmful to the patient or typical can be transient during the management of concomitant disease (e.g. diabetes mellitus). In such situations, stopping of study medication might not be appropriate and this new section would avoid that such patients have to be withdrawn from study for medically unjustifiable reasons.
- To clarify that strong CYP3A4 inhibitors and QT interval prolonging agents are considered as prohibited concomitant medications during the whole duration of the study.
- To include retrospective collection of Sokal risk category at diagnosis parameters.
- To introduce additional guidance for investigators to differentiate between patients who discontinue certain clinical trial protocol elements (e.g., discontinue study treatment, or some or all visits etc), who withdraw consent or who are lost to follow-up.

Changes to the protocol




CCI



IRB/IEC/HA

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.

Amendment 2

Amendment rationale

The main purposes of the amendment are:

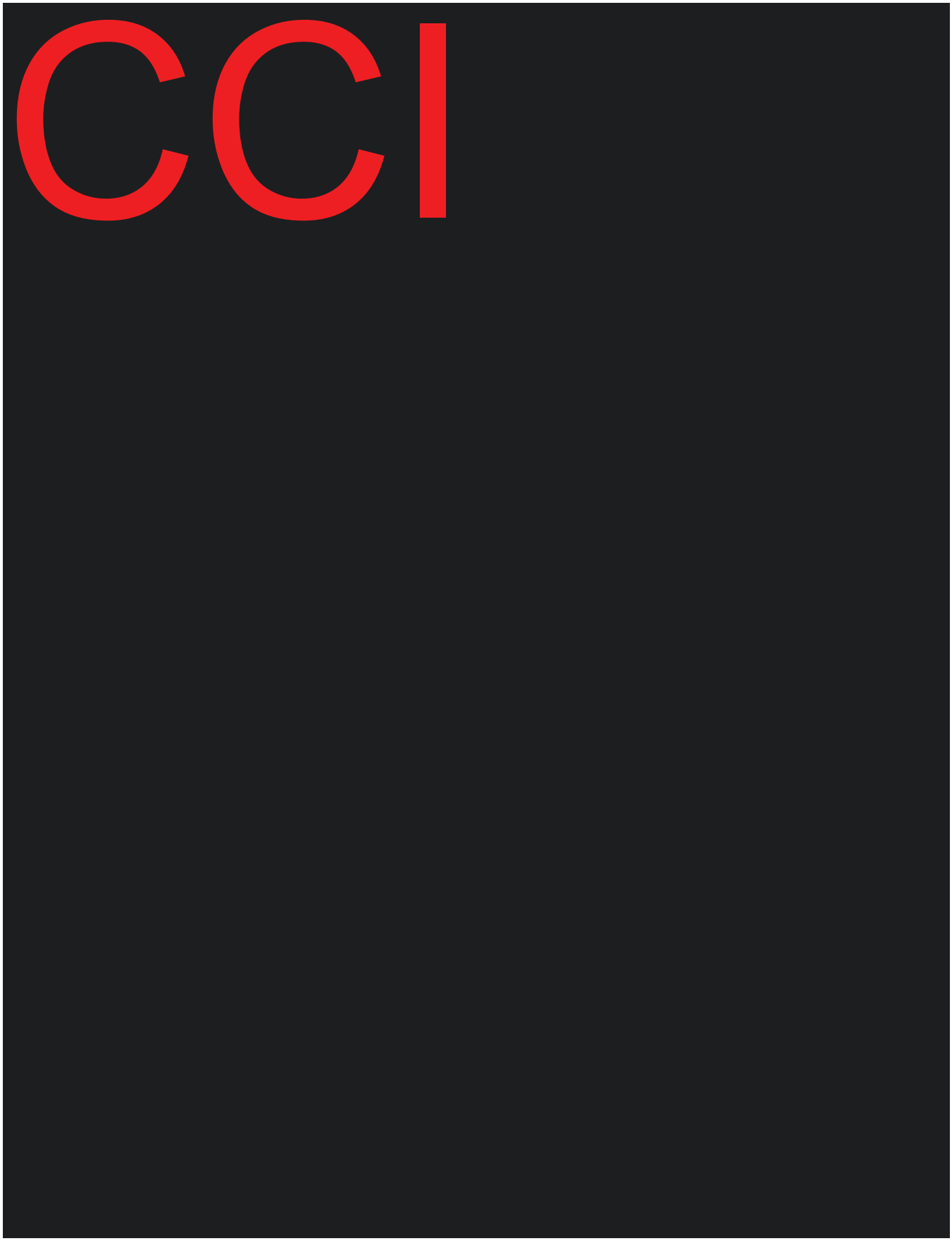
- To include cholesterol testing in the assessment schedule. Elevations in total serum cholesterol and low density lipoprotein cholesterol have been observed very commonly (more than 10 %) in patients treated with nilotinib and commonly (between 1 to 10 %) in

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 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 moderate inhibitory effect of nilotinib on CYP3A4 isoenzyme that is involved in the metabolic pathway of some statins (HMG-CoA reductase inhibitors). The Appendix 14.1.1 reflects these interactions and provides guidance.

- To provide a harmonization on dose reductions guidelines across Novartis-sponsored Tasigna study protocols. Hence the dose reduction guidelines for the following non-hematologic toxicities have been updated:
  - Pancreatitis Grade 4: change from “Hold therapy” to “Stop therapy”
  - QTcF prolongation > 480 msec toxicity
  - Cardiac “Other”: change from “Hold therapy” to “Stop therapy”
- 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.
- To include serum phosphate testing in the assessment schedule to ensure consistency with the dose reduction guidelines provided in Table 6-2 in case of serum hypophosphatemia.
- To clarify the specification of the statistical alternative hypothesis H_1 in Section10.
- To inform the IRBs/IECs/REBs and HAs about over-recruitment and its impact on the stopping rules applied to the first 48 weeks after start of TFR and on the sample size calculation in Section 10.8.
- To correct discrepancies and add clarifications within the protocol.

Changes to the protocol




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Amendment 1

Amendment rationale

This study is currently in the startup phase; 16 patients have been enrolled as of 20-June-2013.

Primary purpose for the amendment is:

- To implement modifications as requested from different Health Authorities (HAs) and Ethic Committees/Institutional Review Boards (ECs/IRBs) during review of the original protocol.
- To address feedback from Investigators received during the study startup.

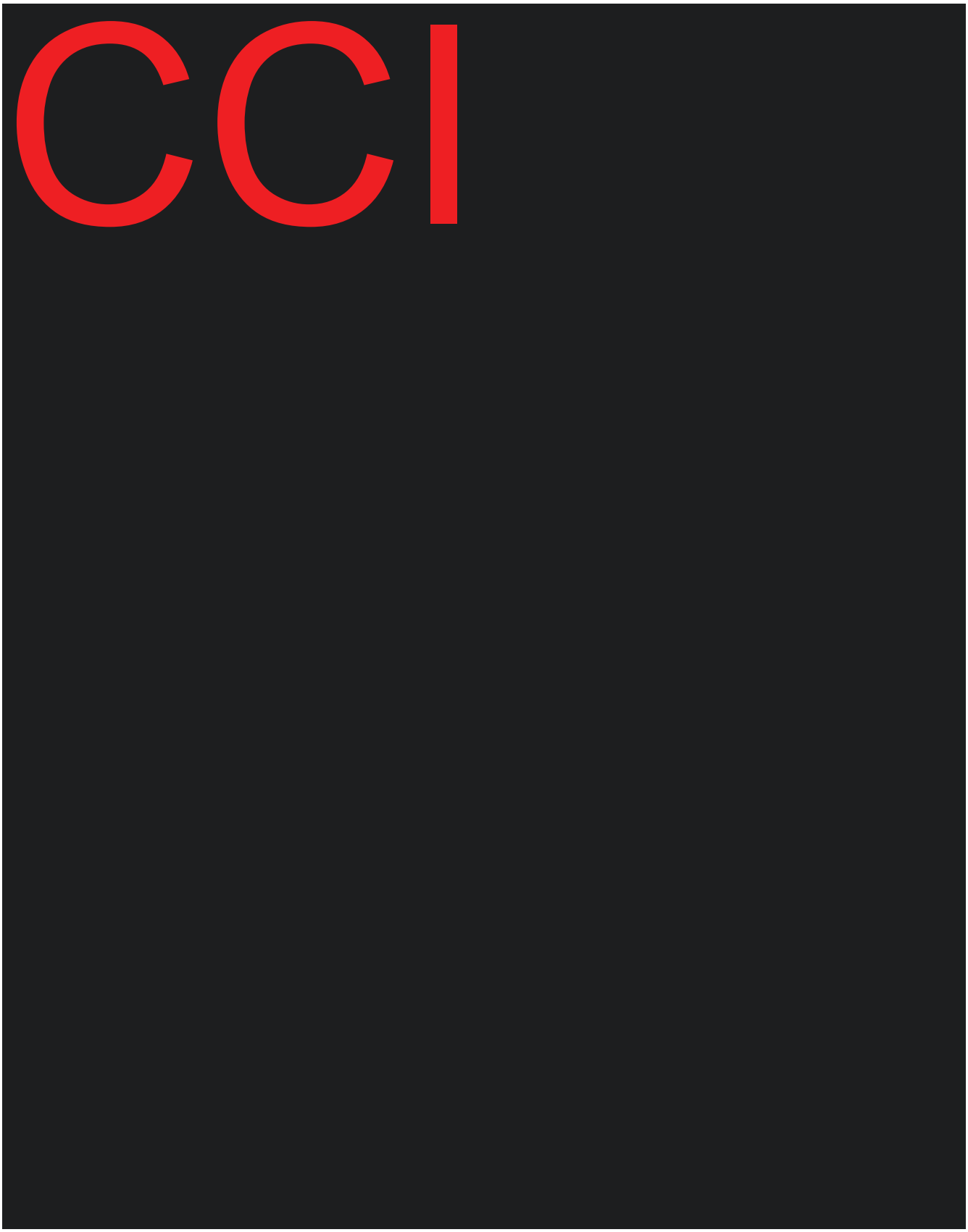
The main points addressed are:

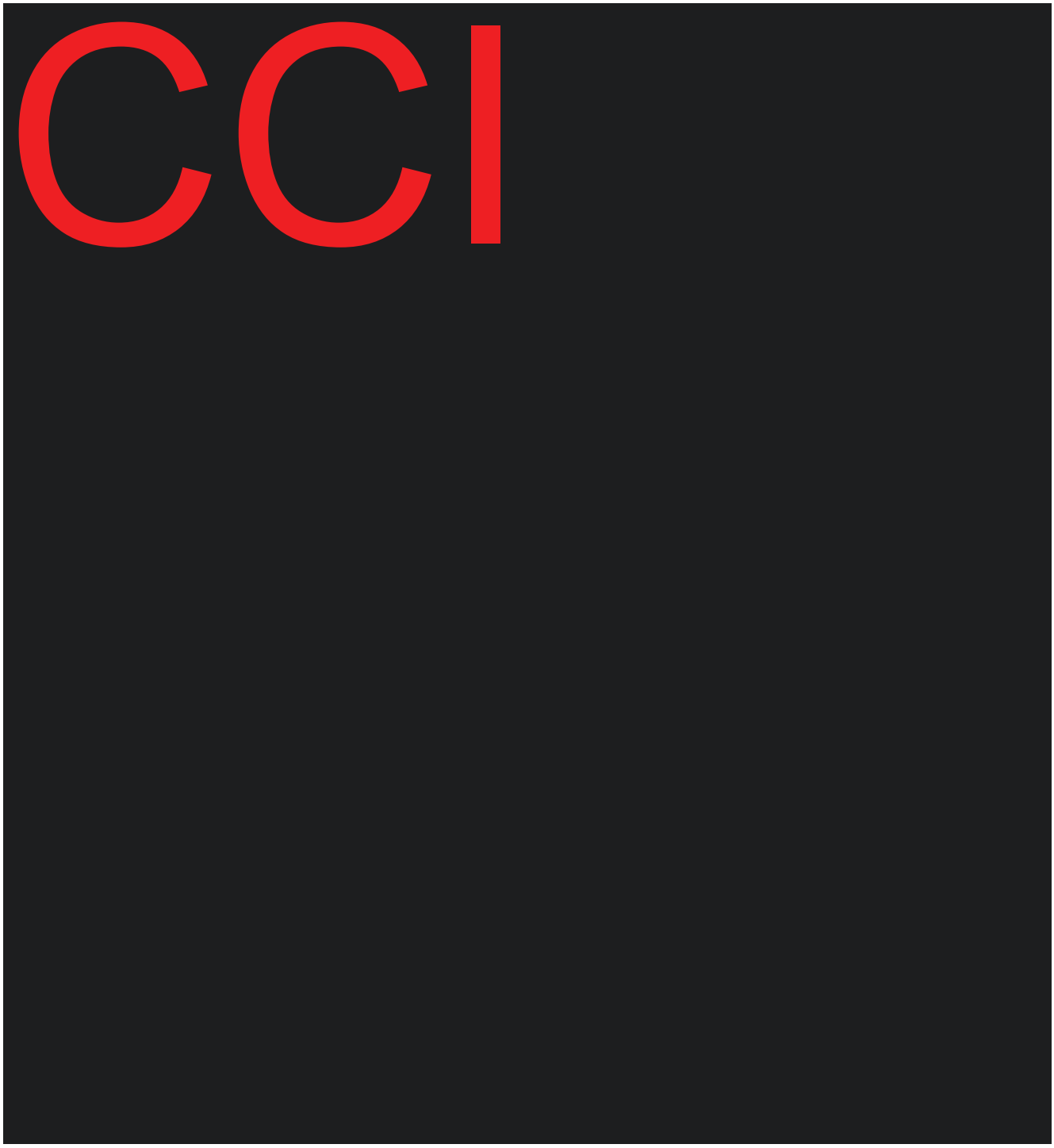
- Allow repeated pre-screenings for BCR-ABL transcript level as soon as possible when MR4.5 cannot be assessed at pre-screening due to logistical or quality issues (e.g. sample lost, sample not arrived frozen, insufficient ABL copy numbers). This modification is considered to increase the chance of enrolling patients who are actually eligible for screening/enrollment.
- 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 changed from 30 to 14 days after the final dose of nilotinib based on the half-life of Tasigna® and the individual variability of metabolism. Additionally the acceptable method of highly effective contraception was corrected for periodic abstinence.
- Clarify the criteria for premature withdrawal and how to proceed if a pregnancy occurred during TFR.
- Inclusion and exclusion criteria have been amended to better reflect the patient population to be included in the CAMN107I2201 study.
    - Patients must have been treated for a minimum of 2 calendar years with at least the last 12 months prior to pre-screening at the approved total daily dose of 600 mg nilotinib (or at a reduced dose level of 400 mg QD if required from the perspective of tolerance).
    - Patients with both types of typical BCR-ABL transcripts (b3a2 and b2a2) at the time of CML-CP diagnosis are now as well eligible.
    - Exceptions are granted for patients with Gilbert's syndrome and asymptomatic hyperbilirubinemia.
    - Guidance was included in case QT interval cannot be determined on the ECG.
- Allow screening patients from the CAMN107EIC01 (ENEST1st) study for participation to this CAMN107I2201 study without having first to discontinue CAMN107EIC01. Patients will discontinue CAMN107EIC01 only if they are confirmed eligible for CAMN107I2201. This practice is in compliance with the ICH Topic E8 guidelines as it constitutes a "justified exception" for the following reasons:
    - Subjects are treated in the CAMN107EIC01 study and will be treated in this CAMN107I2201 study with the same drug (Tasigna®) at the same dose/same formulation in the approved indication.

  - Therefore, Tasigna® cannot be considered as an investigational agent.
  - As a consequence of the above:
    - No new toxicities are expected in context of this CAMN107I2201 study.
    - No carry-over effect is expected between both studies.
    - Based on the two points above a wash-out period is neither nor advisable.
  - Subjects will only participate transiently in the two studies; in particular only during the time (4 weeks) needed to assess eligibility for this CAMN107I2201 study.
- 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.
- Pharmacogenetics study was added to identify factors (i.e. pt. demography, genetic polymorphisms as well as genomic biomarkers) associated with successful TFR of nilotinib therapy. Polymorphisms known to be associated with sub-optimal response to treatment with imatinib, nilotinib or other TKI as well as polymorphisms proposed in the literature as criteria for discontinuing treatment will be tested for their association with successful TFR. These may include polymorphisms in NKp30, members of the KIR family and members of the BCL2 family (such as BIM).
- Correct discrepancies and add clarifications within the protocol.

Changes to the protocol




CCI



IRB/IEC/HA

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.

Protocol summary:

Protocol number	CAMN107I2201
Title	A single-arm, multicenter, nilotinib treatment-free remission study in patients with BCR-ABL1 positive Chronic Myelogenous Leukemia in chronic phase who have achieved durable minimal residual disease (MRD) status on first line nilotinib treatment
Brief title	Nilotinib treatment suspension study
Sponsor and Clinical Phase	Novartis Phase II
Investigation type	Drug
Study type	Interventional
Purpose and rationale	**Purpose**: The main purpose of this study is to determine the rate of treatment-free molecular remission (molecular remission is defined as MMR=MR3.0 (BCR-ABL level ≤ 0.1 % IS) or better) after 48 weeks following start of the TFR phase in a selected population of CML-CP patients (TFR phase is often referred to as discontinuation phase in other studies). Eligible patients must have achieved a very deep level of molecular response (MR4.5) after a minimum of two years of first line nilotinib treatment before entering this study. MR4.5 is defined as BCR-ABL level ≤ 0.0032% IS or undetectable BCR-ABL level with assay sensitivity of at least 4.5 log. The study further seeks to provide evidence that suspending nilotinib therapy in these eligible patients does not cause short- or long-term harm to them. **Rationale**: Stop imatinib study (STIM) (Mahon et al 2010) investigated feasibility of imatinib suspension in a highly selected group of patients who achieved and maintained complete molecular response (CMR) defined as undetectable BCR-ABL levels with high sample sensitivity (10^{-5} or greater) for a minimum of 2 years. With a median follow up of 34 months (Mahon et al 2011), 39% of patients have successfully remained in treatment-free remission. This provided the first evidence that achieving and maintaining deep molecular responses can lead to successful therapy suspension. In terms of regaining molecular response, 61 patients had a molecular recurrence and 56 regained undetectable BCR-ABL transcript level after median of 4 months on imatinib (range 0-21 months). Five patients did not return to undetectable transcript level: four remained treatment-free with detectable transcript (range 0.05% to 0.3%) and one patient was switched to dasatinib due to loss of CCyR (Mahon et al 2011). No loss of hematological response or progression to advanced phase was noted after stopping imatinib. Similar results were observed in another study conducted by an Australian group (Ross et al 2012). In this study with median 33 months of follow-up, 55% of patients met the protocol definition of molecular relapse (BCR-ABL detected by RQ-PCR in two consecutive tests). Twenty one of 22 patients who restarted imatinib regained undetectable BCR-ABL level and one patient remains in MMR at 14 month follow-up. In a pilot study of patients switched to nilotinib or dasatinib for imatinib intolerance, Rea et al (Rea et al 2011) reported successful suspension without a loss of MMR in 11 out of 16 patients following achievement and maintenance of undetectable minimal residual disease (MRD) (defined as undetectable BCR-ABL with a minimum of 20,000 copies of ABL amplified) on nilotinib (n=7) or dasatinib (n=9) in 6 month follow-up. However, the results were reported as combined data for both TKIs and the rate of successful suspension from nilotinib remained unknown. Based on results of ENESTnd [CAMN107A2303], nilotinib enables a higher proportion of newly diagnosed patients to achieve deep levels (MR4.0 (molecular response 4.0 log reduction from standardized baseline) or MR4.5) of MR vs. imatinib and potentially to be eligible for treatment suspension.

	The study intends to generate data on the safety, feasibility and success of TFR phase in a rigorously controlled manner. These data will provide critical guidance to physicians with respect to which patients may be appropriate candidates for starting the TFR phase, monitoring patients off-treatment, and when patients should have nilotinib treatment re-initiation.
Primary Objective	**Primary Objective**: To determine the percentage of patients who are in MMR (BCR-ABL ≤ 0.1% IS (MR3.0) at 48 weeks after starting the Treatment-Free Remission (TFR) phase (patients who required re-initiation of treatment will be considered as non-responders)
Secondary Objectives	- To determine the percentage of patients who are in MR4.5 (BCR-ABL ≤ 0.0032% IS) at 48 weeks after starting the TFR phase (patients who required re-initiation of treatment will be considered as non-responders) - To determine the percentage of patients who are in MMR at 96, 144, 192, 264 weeks and, at the end of 6, 7, 8, 9 and 10 years after starting the TFR phase (patients who required re-initiation of treatment will be considered as non-responders) - To determine the percentage of patients who are in MR4.5 at 96, 144, 192, 264 weeks and, at the end of 6, 7, 8, 9 and 10 years after starting the TFR phase (patients who required re-initiation of treatment will be considered as non-responders) - To determine the percentage of patients in MMR at 48, 96, 144, 192, 264 weeks and, at the end of 6, 7, 8, 9 and 10 years after starting the TFR phase of nilotinib irrespective of whether or not patients required re-initiation of treatment - To determine the percentage of patients in MR4.5 at 48, 96, 144, 192, 264 weeks and, at the end of 6, 7, 8, 9 and 10 years after starting the TFR phase of nilotinib irrespective of whether or not patients required re-initiation of treatment - To determine the percentage of patients who achieve MMR within 12 weeks of re-treatment with nilotinib -To determine the percentage of patients who are in stable MMR after achievement of that response in the nilotinib re-initiation phase for 48 weeks, 96 weeks, 144 weeks, 192 weeks, 240 weeks, 288 weeks, 336 weeks, 384 weeks and 432 weeks, based on availability of appropriate data. -To determine the percentage of patients who are in stable MR4.5 after achievement of that response in the nilotinib re-initiation phase for 48 weeks, 96 weeks, 144 weeks, 192 weeks, 240 weeks, 288 weeks, 336 weeks, 384 weeks and 432 weeks, based on availability of appropriate data. - To characterize the kinetics of BCR-ABL transcripts after re-start of nilotinib therapy - To estimate the duration of re-initiated treatment required to regain MMR after loss of MMR - To estimate the duration of re-initiated treatment required to regain MR4.5 after loss of MMR - To estimate the treatment-free survival (TFS) after the start of the TFR phase - To estimate progression-free survival (PFS) after the start of the TFR phase - To estimate overall survival (OS) after the start of the TFR phase - To assess the safety profile during the nilotinib treatment consolidation phase, during the TFR phase and during re-initiation treatment with nilotinib

	- To assess the occurrence of BCR-ABL mutations highly resistant to nilotinib (T315I, E255K/V, Y253H, F359V/C/I) or any other BCR-ABL mutations in patients who lost MMR
Study design	This is a single-arm, open label study. This study has 2 main phases: nilotinib consolidation phase (52 weeks), and nilotinib treatment-free remission (TFR) phase (week 04 – up to 528 weeks after the last patient enters the nilotinib TFR phase). All patients who have received a minimum of 2 years of first-line nilotinib treatment can be pre-screened. Patients with pre-screen PCR results in ≥ MR4.5 (BCR-ABL ≤0.0032% IS) will be screened for eligibility prior to Study Day 1. During the first 52 weeks of the study, all patients will be treated with the planned dose 300 mg BID nilotinib (or at a reduced dose level of 400 mg QD if required from the perspective of tolerance). Each patient will have PCR assessments every 12 weeks by a Novartis designated laboratory. If a patient fulfills the protocol specific definition of durable Minimal Residual Disease (the 4 last quarterly performed PCR assessments must fulfill the following criteria: the last assessment is MR4.5, no assessment worse than MR4.0 (BCR-ABL > 0.01% IS) and no more than two assessments between MR4.0 and MR4.5 (0.0032% < BCR-ABL ≤ 0.01% IS) he/she will be eligible to start the nilotinib TFR phase. Duration of the nilotinib TFR phase is up to 528 weeks after the last patient enters the nilotinib TFR phase. Patients will suspend the nilotinib treatment on the day they enter this phase. During this phase, BCR-ABL levels will be monitored every 4 weeks during the first 48 weeks, every 6 weeks for the following 48 weeks, and every 12 weeks during the last period up to 528 weeks after the last patient enters TFR phase. All PCR assessments will be performed by a Novartis designated laboratory. Loss of MR4.0 will trigger an intensified biweekly (every two weeks) BCR-ABL levels monitoring to identify loss of MMR early as to further minimize the risk of overlooking molecularly recurring disease in the TFR study patients. Biweekly monitoring will begin upon loss of MR4.0 and will end at one of the following time points: ● When the patient loses MMR (and therefore re-initiates nilotinib treatment), ● When the BCR-ABL transcript levels return to a range between MR4.0 and MR4.5. ● When the BCR-ABL transcript levels remain lower than MMR for 4 consecutive measurements (8 weeks from initial loss of MR4.0). At this point, the patient may proceed to monthly BCR-ABL monitoring. If after additional 12 consecutive measurements on a monthly monitoring the BCR-ABL transcript levels remain lower than MMR (56 weeks from initial loss of MR4.0) the patient may proceed to 6 weeks BCR-ABL monitoring. If after additional 8 consecutive measurements on a 6 weeks monitoring the BCR-ABL transcript levels remain lower than MMR (104 weeks from initial loss of MR4.0) the patient may proceed to 12 weeks BCR-ABL monitoring. Loss of MMR defined as BCR-ABL >0.1% IS assessed in a single blood sample (confirmation of loss of MMR is not required) will mandate re-initiation of nilotinib treatment at 300 mg BID or at a reduced dose level of 400 mg QD if required from the perspective of tolerance within 5 weeks after the collection date of the blood sample demonstrating loss of MMR. Patients not eligible for the TFR phase will continue nilotinib treatment for 52 weeks in the nilotinib continuation phase. During this phase PCR assessments will be performed every 12 weeks. Patients will be eligible to enter the TFR-2 phase after the consolidation phase if they fulfill the protocol specific definition of durable MRD. Patients who do not qualify to start TFR-2 may continue to receive nilotinib treatment in the nilotinib prolonged continuation phase for up to 528 weeks after the last patient enters the nilotinib TFR phase. Patients who discontinue the study will be followed for Post-Treatment follow-up up to 528 weeks after last patient enters the nilotinib TFR phase.

Population	The targeted population of this study includes adult patients who are treated with nilotinib as a first line treatment for newly diagnosed CML-CP. Patients must have been treated for a minimum of 2 calendar years with at least the last 12 months prior to pre-screening at the approved total daily dose of 600 mg nilotinib (or at a reduced dose level of 400 mg QD if requested from the perspective of tolerance) Patients must have achieved MR4.5 (BCR-ABL ≤ 0.0032% IS) at the time of the pre-screening.
Inclusion criteria	1. Male or female patients ≥ 18 years of age 2. Minimum of 2 calendar years of nilotinib treatment with at least the last 12 months of nilotinib treatment prior to pre-screening at the approved total daily dose of 600 mg or at a reduced dose level of 400 mg QD if required from the perspective of tolerance) for BCR-ABL positive CML in documented chronic phase at the time of diagnosis 3. Documented chronic phase CML must meet all the criteria defined by: ● < 15% blasts in peripheral blood and bone marrow, ● < 30% blasts plus promyelocytes in peripheral blood and bone marrow, ● < 20% basophils in the peripheral blood, ● ≥ 100 x 10^9/L (≥ 100,000/mm3) platelets, ● No evidence of extramedullary leukemic involvement, with the exception of hepatosplenomegaly. 4. Patients must tolerate a minimum total daily dose of nilotinib of 400 mg 5. Evidence of typical BCR-ABL transcripts [b3a2 (e14a2) and/or b2a2 (e13a2)] at the time of CML-CP diagnosis i.e. prior to first start of TKI treatment which are amenable to standardized RT-PCR quantification" 6. Patient in MR4.5 at prescreening at Novartis designated lab 7. ECOG performance status 0-2 8. Adequate end organ function as defined by: ● Direct bilirubin ≤ 1.5 x ULN, 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) ≤ 3 x ULN i.e. equivalent to ≤ Grade 1 NCI-CTCAE v.4.03 ● Serum lipase ≤ 2 x ULN i.e. equivalent to ≤ Grade 2 NCI-CTCAE v.4.03 ● Alkaline phosphatase ≤ 2.5 x ULN ● Serum creatinine < 1.5 x ULN 9. Patients must have the following electrolyte values within normal limits or corrected to be within normal limits with supplements prior to first dose of study medication: ● Potassium (suggested keep to prevent issues with QT and/or rhythm abnormalities) ● Magnesium (suggested keep to prevent issues with QT and/or rhythm abnormalities) ● Total calcium (corrected for serum albumin) 10. Patients must have normal marrow function as defined: ● Absolute Neutrophil Count (ANC) ≥ 1.5 x 10^9/L ● Hemoglobin ≥ 9.0 g/dL ● Platelets ≥ 100 x 10^9/L 11. Willingness and ability to comply with scheduled visits, treatment plans, laboratory tests and other study procedures
Exclusion criteria	1. Previous treatment with BCR-ABL inhibitors other than nilotinib for more than a total cumulative duration of 4 weeks 2. Previous treatment with alpha-interferon of any duration 3. Previous anticancer agents for CML other than nilotinib except for cytoreduction after CML diagnosis until up to 4 weeks after first dose of nilotinib 4. Known second chronic phase of CML after previous progression to AP/BC 5. Poorly controlled diabetes mellitus (defined as HbA1c > 9%)

	6. Impaired cardiac function including any one of the following: ● LVEF < 45% or below the institutional lower limit of the normal range (whichever is higher) ● Inability to determine the QT interval on ECG, except for patients with measurable QT interval at the time of CML diagnosis (e.g. prior to first start of TKI treatment) and who have no documented clinical signs of cardiovascular disease and/or conduction abnormality.-- Complete left bundle branch block ● Right bundle branch block plus left anterior or posterior hemiblock ● Use of a ventricular-paced pacemaker ● Congenital 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 ● QTc > 450 msec on the average of three serial baseline ECG (using the QTcF formula). If QTcF > 450 msec and electrolytes are not within normal ranges, electrolytes should be corrected and then the patient re-tested for QTc. This exclusion criterion is not applicable for patients with non-measurable QT interval who have evidence of measurable QT interval at the time of CML diagnosis (e.g prior to first start of TKI treatment) and who have no documented clinical signs of cardiovascular disease and/or conduction abnormality. ● History or clinical signs of myocardial infarction within 1 year of study entry ● History of unstable angina within 1 year of study entry ● Other clinically significant heart disease (e.g., congestive heart failure, cardiomyopathy, or uncontrolled hypertension) 7. 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) 8. History of acute pancreatitis within 1 year of study entry or past medical history of chronic pancreatitis 9. Known presence of significant congenital or acquired bleeding disorder unrelated to cancer 10. History of another active malignancy within 5 years prior to study entry with the exception of previous or concomitant basal cell skin cancer and previous carcinoma in situ treated curatively 11. Patients who have not recovered from prior surgery 12. Treatment with other investigational agents (defined as not used in accordance with the approved indication) within 4 weeks of Day 1 13. 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 starting study drug. See Appendix 14.1.1 for a list of these medications. This list may not be exhaustive. 14. Patients actively receiving therapy with herbal medicines that are strong CYP3A4 inhibitors and/or inducers, and the treatment cannot be either discontinued or switched to a different medication prior to starting study drug. These herbal medicines may include Echinacea, (including E. purpurea, E. angustifolia and E. pallida), Piperine, Artemisinin, St. John's Wort, and Ginkgo. 15. Patients who are currently receiving treatment with any medications that have the potential to prolong the QT interval and the treatment cannot be either safely discontinued or switched to a different medication prior to starting study drug. (Please see http://crediblemeds.org/everyone/composite-list-all-qtdrugs/ for a list of agents that prolong the QT interval). 16. Impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of study drug (e.g. ulcerative disease, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, small bowel resection, or gastric bypass surgery). 17. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive

	hCG laboratory test. 18. 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 dose of nilotinib. 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 by follow up hormone level assessment. ● Male sterilization (at least 6 months prior to enrolling). For female patients on the study the vasectomized male partner should be the sole partner for that patient. ● Use of a combination of any two of the following: a. 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. b. Placement of an intrauterine device (IUD) or intrauterine system (IUS) c. Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository. 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. If a study patient becomes pregnant or suspects being pregnant during the study or within 30 days after the final dose of nilotinib, the Study Doctor needs to be informed immediately and ongoing study treatment with nilotinib has to be stopped immediately.
Investigational and reference therapy	N/A
Efficacy assessments	● Molecular Response (RQ-PCR, optional mutation analysis) ● Bone marrow assessments (optional)
Safety assessments	● Physical examination ● Vital Sign ● Height and weight ● ECOG performance status ● Laboratory chemistry and hematology ● Serology ● Electrocardiogram (ECG)
Other assessments	One blood sample for the assessment of nilotinib PK trough level will be collected from all patients at week 48 of the consolidation phase. CCI

	[redacted] Parameters for the assessment Sokal risk category at the time of the initial diagnosis of CML will be collected retrospectively at any time point during the study.
Data analysis	Demonstration of successful treatment-free remission will be evaluated using the following hypothesis: H_0: $p \leq 0.50$, where p is the rate of patients who are in MMR at 48 weeks after starting the TFR phase. H_1: $p>0.50$, where p is the rate of patients who are in MMR at 48 weeks after starting the TFR phase. The rate of patients who are in MMR at 48 weeks after starting the TFR phase will be presented together with an exact 95% Clopper-Pearson confidence interval. Primary efficacy analysis will be performed on the FAS. For primary efficacy variable, the analysis time point is when all patients who entered the TFR phase completed 48 weeks of the TFR phase or discontinued the study earlier.
Key words	Phase II, single arm, open label, nilotinib, treatment-free remission, MR4.5, loss of MR4.0, loss of MMR, Ph+ CML-CP.

1 Background

1.1 Overview of chronic myelogenous leukemia

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 et al 1983; Heisterkamp et al 1983). Expression of the BCR-ABL protein is capable of inducing leukemia in mice, implicating the protein as the cause of these diseases (Daley et al 1990; Kelliher et al 1990).

Clinically, CML progresses 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, 5-6 years with interferon (IFN) and beyond 10 years with imatinib), 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 CP, characterized by splenomegaly and leukocytosis with generally few symptoms.

National Comprehensive Cancer Network (NCCN) guideline on CML (NCCN guideline v 2.2012) and European Leukemia Net (ELN) (Baccarani et al 2009) recommend continuing tyrosine kinase inhibitor (TKI) treatment indefinitely in all responding patients. There are currently no recommendations or provisions for temporary or permanent Treatment-Free Remission (TFR) phase of TKI treatment.

1.2 Introduction to investigational treatment(s) and other study treatment(s)

1.2.1 Overview of Nilotinib (AMN107, Tasigna®)

Nilotinib is a aminopyrimidine, available as an oral formulation that is an Adenosine triphosphate (ATP)-competitive inhibitor of the protein tyrosine kinase activity of BCR-ABL, which prevents the activation of BCR-ABL dependent mitogenic and anti-apoptotic pathways (e.g. Phosphatidylinositol 3-kinases (PI-3 kinase) and signal transducer and activator of transcription 5 (STAT5)), leading to the death of the BCR-ABL phenotype. Following oral administration to animals, nilotinib is moderately absorbed with approximately 30% bioavailability, and is well tolerated.

1.2.1.1 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 et al 2004, White et al 2005). Therefore, based on the preclinical data, and observed efficacy of nilotinib in imatinib-resistant and intolerant patients, nilotinib was predicted to have significant

efficacy in newly diagnosed CML-CP patients. For more details on non-clinical experience, please refer to the latest nilotinib [Investigator's Brochure].

1.2.1.2 Clinical experience

Clinical safety and tolerability

Overall, nilotinib has been found to be effective and well tolerated in patients with Philadelphia chromosome positive chronic myeloid leukemia (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 the latest nilotinib [Investigator's Brochure]. Safety data in newly diagnosed Ph+ CML-CP have been acquired from the Phase III ENESTnd (Evaluating Nilotinib Efficacy and Safety in Clinical Trials - newly diagnosed CML-CP), [CAMN107A2303] study. Additional safety data have been acquired from a Phase I/II open-label study [CAMN107A2101] in CML patients, and a Phase III study in gastrointestinal stromal tumor (GIST) patients, as well as from further clinical studies and post-marketing experience. The most commonly reported (>5%) all grade non-hematologic adverse reactions in patients with CML were rash, headache, nausea, pruritus, alopecia, myalgia, fatigue, dry skin, arthralgia, vomiting, abdominal pain upper, muscle spasms, diarrhea, constipation, peripheral oedema, dyspepsia, erythema, abdominal pain, and asthenia. Hematologic adverse drug reactions included myelosuppression (thrombocytopenia, neutropenia and anemia). Clinically relevant biochemical abnormalities included hyperglycemia, hyperbilirubinemia, hypophosphatemia, and increases in lipase, ALT, and AST. There are insufficient safety data for using nilotinib during pregnancy.

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 events is as follows:

- Nilotinib 300 mg BID: IHD, 11 (3.9%); ICVE, 4 (1.4%); PAOD, 7 (2.5%)
- Nilotinib 400 mg BID: IHD, 24 (8.7%); ICVE, 9 (3.2%); PAOD, 7 (2.5%)
- Imatinib 400 mg QD: 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.

Clinical Pharmacokinetics

Nilotinib is metabolized by the liver, primarily via CYP3A4. Thus 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, which may increase the exposure of sensitive 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.

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 pharmacokinetics 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. Population pharmacokinetics (PK) analysis also suggested that male patients had an approximately 10% lower bioavailability or 10% lower systemic exposure than female Patients. However, since the observed extent of the difference is relatively small, such a sex effect is unlikely to be clinically meaningful for nilotinib therapy. Other demographic variables, such as age and body weight did not significantly affect nilotinib PK. Thus, patient demographics are not a clinically important factor contributing to interpatient variability in nilotinib PK and exposure.

For additional nilotinib clinical pharmacokinetics information, please refer to the latest nilotinib [Investigator's Brochure].

Clinical efficacy

Nilotinib is approved by US Food and Drug Administration (FDA) and European Commission (EC) to treat newly diagnosed adult patients with Ph+ CML in CP, and to treat CP and AP Ph+ CML 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). This study was designed to compare the efficacy and safety of nilotinib 400 mg twice daily (BID) and nilotinib 300 mg BID with imatinib 400 mg once daily (QD) treatment. The primary efficacy endpoint is the rate of major molecular response (MMR) at 12 months after the start of first study medication. The data cut-off for this first analysis of study [CAMN107A2303] was 02-Sep-2009, at which time the last patient had completed 12 cycles of treatment. 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) at 12 months was 43% in the nilotinib 400 mg BID treatment arm, 44% in the nilotinib 300 mg BID treatment arm, and 22% in the imatinib treatment arm $p<0.001$

(primary endpoint). The cumulative incidence of molecular response 4.5 log 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 BID arm, and was 11%, 25%, 32%, 37% and 53.5% in the nilotinib 300 mg BID 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 BID arm and 10%, 16%, 17%, 14.4% and 22.1% difference for the 300 mg BID 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. For additional nilotinib clinical efficacy information, please refer to the latest nilotinib [Investigator's Brochure].

2 Rationale

2.1 Study rationale and purpose

The main purpose of this study is to determine the rate of treatment-free molecular remission (molecular remission is defined as MMR=MR3.0 (BCR-ABL level ≤ 0.1 % IS) or better) after 12 months following start of the TFR phase in a selected population of CML-CP patients (TFR phase is often referred to as discontinuation phase in other studies). Eligible patients must have achieved a very deep level of molecular response (MR4.5) after a minimum of two years of first line nilotinib treatment before entering this study. MR4.5 is defined as BCR-ABL level ≤ 0.0032% IS or undetectable BCR-ABL level with assay sensitivity of at least 4.5 log.

The study further seeks to provide evidence that suspending nilotinib therapy in these eligible patients does not cause short or long term harm to them.

BCR-ABL inhibitors, first imatinib and subsequently nilotinib, have changed the course of CML. Although, CML is now a chronic disease and many patients can anticipate a normal life expectancy, physicians and patients have shown a strong interest to explore TFR strategies for BCR-ABL inhibitors. The potential medical benefits of successful TFR Phase include elimination of chronic and/or acute side effects, minimization of drug-drug interactions, and the possibility of a pregnancy without exposure to TKIs.

Stop imatinib study (STIM) (Mahon et al 2010) investigated feasibility of imatinib suspension in a highly selected group of patients who achieved and maintained complete molecular response (CMR) defined as undetectable BCR-ABL levels with high sample sensitivity (10^{-5} or greater) for a minimum of 2 years. With a median follow up of 34 months (Mahon et al 2011), 39% of patients have successfully remained in treatment-free remission. This provided the first evidence that achieving and maintaining deep molecular responses can lead to successful therapy suspension. In terms of regaining molecular response, 61 patients had a molecular recurrence and 56 regained undetectable BCR-ABL transcript level after median of 4 months on imatinib (range 0-21 months). Five patients did not return to undetectable transcript level: four remained treatment-free with detectable transcript (range 0.05% to 0.3%)

and one patient was switched to dasatinib due to loss of CCyR (Mahon et al 2011). No loss of hematological response or progression to advanced phase was noted after stopping imatinib.

Similar results were observed in another study conducted by an Australian group (Ross et al 2012). In this study with median 33 months of follow-up, 55% of patients met the protocol definition of molecular relapse (BCR-ABL detected by RQ-PCR in two consecutive tests). Twenty one of 22 patients who restarted imatinib regained undetectable BCR-ABL level and one patient remains in MMR at 14 month follow-up.

In a pilot study of patients switched to nilotinib or dasatinib for imatinib intolerance, Rea et al (Rea et al 2011) reported successful suspension without a loss of MMR in 11 out of 16 patients following achievement and maintenance of undetectable minimal residual disease (MRD) (defined as undetectable BCR-ABL with a minimum of 20,000 copies of ABL amplified) on nilotinib (n=7) or dasatinib (n=9) in 6 month follow-up. However, the results were reported as combined data for both TKIs and the rate of successful suspension from nilotinib remained unknown.

Based on results of ENESTnd [CAMN107A2303], nilotinib enables a higher proportion of newly diagnosed patients to achieve deep levels (MR4.0 (molecular response 4.0 log reduction from standardized baseline) or MR4.5) of MR vs. imatinib and potentially to be eligible for treatment suspension.

The study intends to generate data on the safety, feasibility and success of the TFR phase in a rigorously controlled manner. These data will provide critical guidance to physicians with respect to which patients may be appropriate candidates for starting the TFR phase, monitoring patients off-treatment, and when patients should have nilotinib treatment re-initiation.

2.2 Rationale for the study design

The rates of successful discontinuations in patients who achieved and maintained deep molecular responses (defined as MR4.5, MR5.0 or undetectable BCR-ABL level with sensitivity of MR4.5) on imatinib have been reported from several clinical trials (Mahon et al 2010; Ross et al 2012; Goh et al 2011; Matsuki et al 2011; Rousselot et al 2011; Lee et al 2012; Rousselot et al 2012). All of these patients achieved and maintained deep molecular responses on the initial TKI regimen (imatinib). In STIM study (Mahon et al 2010) the median time to achieve undetectable BCR-ABL was 19 months (range: 2-56 months).

This is an open label, multicenter, single-arm study with the goal of establishing the percentage of patients who are in MMR (MMR or MR3 or BCR-ABL $\leq$ 0.1% IS) at 48 weeks after starting the Treatment-Free Remission phase of the study.

Eligible patients must have achieved a very deep molecular response (i.e. MR4.5 or better at any time point before screening). In addition, a minimum of two years of nilotinib therapy is required prior to study entry.

The reason for these requirements relate to the historical experience. The STIM study (Mahon et al 2010; Mahon et al 2011) enrolled patients with minimum of 3 years of imatinib therapy and demonstrated higher successful rate of discontinuation among patients with longer

imatinib therapy (more vs. less than 60 months p=0.047). Duration of nilotinib treatment prior to attempt treatment suspension will be three years: two years prior to study entry plus one year of consolidation. In the STIM study, duration of CMR was not identified as a significant prognostic factor associated with successful discontinuation (33% vs. 36% vs. 55% for duration of CMR <31 months vs. 31-47 months vs. >47 months, respectively; p=0.362). Based on the results of this analysis, there will be no minimal duration of MR4.5 requirement prior to study entry:

MR4.5 will be determined by a Novartis designated laboratory with validated PCR technology that has a sensitivity of at least 4.5 logs at screening prior to study entry. During the "consolidation" phase of 52 weeks when all patients continue to receive nilotinib therapy, BCR-ABL levels will be monitored every 12 weeks (week 12, 24, 36 and 48). In order for patients to be eligible to start the TFR phase, they will have to fulfill the study protocol specific definition of durable Minimal Residual Disease (MRD)

The 4 last quarterly performed PCR assessments must fulfill the following criteria:

- Last assessment is MR4.5 (BCR-ABL ≤ 0.0032% IS)
- No assessment worse than MR4.0 (BCR-ABL > 0.01% IS) and
- No more than two assessments between MR4.0 and MR4.5 (0.0032 % IS < BCR-ABL ≤ 0.01% IS)

The PCR methodology used shows minimal fluctuations at the very deep level of sensibility. Therefore the protocol specific definition of durable MRD allows for minimal fluctuations between MR4.0 and MR4.5 during the consolidation phase. To guarantee that the patient is not losing his/her deep molecular response the last BCR-ABL level prior to entering the TFR phase must be MR4.5 or better.

Duration of TFR phase will be up to 528 weeks after the last patient enters the nilotinib TFR phase. In the imatinib discontinuation study (STIM), with median follow-up of 34 months, 61 recurrences were observed. Fifty-eight of the recurrences were observed in the first 7 months following the suspension of imatinib. Three additional recurrences were observed, one in each of the following months: 19, 20 and 22. The 528 weeks (at least) of TFR will provide adequate observation to ensure all losses of molecular responses are captured. BCR-ABL levels will be closely monitored via PCR assessments by a Novartis designated laboratory. Frequency of PCR during the TFR will be every 4 weeks during the first 48 weeks, every 6 weeks for the second period of 48 weeks and every 12 weeks during the last period of 432 weeks. The median doubling time of BCR-ABL transcript among patients who stop imatinib is approximately 9 days (Branford et al 2012) and corresponds to approximately 1 log in 4 weeks. PCR monitoring performed every 4 weeks should identify all patients who are potential candidates for re-initiating nilotinib. More frequent monitoring is not necessary. Every 12 week monitoring in the last period of the TFR is consistent with the recommended frequency of monitoring in clinical practice for patients in MMR or better response (Baccarani et al 2009). Monitoring every 6 weeks represents an intermediate frequency in the second period of 48 weeks.

One BCR-ABL result > 0.01% on the international scale (IS) will trigger an intensified biweekly (every two weeks) BCR-ABL levels monitoring to identify loss of MMR early and thereby further minimize the risk to patients in case of impending molecular recurrence.

Biweekly monitoring will begin upon loss of MR4.0 and will end at one of the following time points:

1. When the patient loses MMR (and therefore re-initiates nilotinib treatment)
2. When the BCR-ABL levels return to a range between MR4.0 and MR4.5
3. When the BCR-ABL levels remain lower than MMR for 4 consecutive measurements (8 weeks after initial loss of MR4.0). At this point, the patient may return to monthly BCR-ABL monitoring

   If after additional 12 consecutive measurements on a monthly monitoring the BCR-ABL transcript levels remain lower than MMR (56 weeks from initial loss of MR4.0) the patient may proceed to 6 weeks- BCR-ABL monitoring.
   If after additional 8 consecutive measurements on a 6 weeks monitoring the BCR-ABL transcript levels remain lower than MMR (104 weeks from initial loss of MR4.0) the patient may proceed to 12 weeks BCR-ABL monitoring.

Loss of MMR (BCR-ABL results > 0.1% IS) will trigger re-initiation of nilotinib treatment immediately and will not require confirmation. These triggers were selected based on published data suggesting that loss of MMR may be a more robust criterion of re-initiating treatment (Rousselot et al 2012). In the Rousselot study, a second attempt at nilotinib treatment suspension after a patient fails the TFR phase is not allowed.

175 eligible patients will be enrolled in the study, and 122 eligible patients will undergo nilotinib suspension. For detailed patient sample size calculation, please refer to Section 10.8.

Novartis had an End of Phase II Type B meeting with the FDA (29 June 2012) and a Scientific Advice Meeting with the EMA Rapporteur (05 July 2012). Both Health Agencies agreed with the overall study design, the patient population, the eligibility criteria, the monitoring plan, the primary endpoint and the clinical events that would require re-initiating nilotinib therapy.

2.3 Rationale for dose and regimen selection

Patients on treatment with nilotinib for newly diagnosed CML-CP will be enrolled into this study. Accordingly, the planned dose of nilotinib will be 300 mg BID which is the approved dose and regimen for this indication in many countries world-wide. Patients who do not tolerate this standard dose but still achieved and/or maintained MR4.5 on a minimum dose of 400 mg QD may continue to be treated at this lower dose of 400 mg QD at the discretion of the investigator. Dose re-escalation to the standard dose of 300 mg BID while on study will be allowed in these patients after sufficient recovery from side effects as stipulated in the Section 6.3.4 of this protocol. Patients who require re-initiation of nilotinib therapy because of loss of MMR (MR3.0 or BCR-ABL level ≤ 0.1% IS) should resume their previously-tolerated nilotinib dose.

2.4 Rationale for choice of combination drugs

Not applicable.

2.5 Rationale for choice of comparators drugs

Not applicable.

2.6 Risks and benefits

Appropriate eligibility criteria, as well as specific dose modification and stopping rules, are included in this protocol. Recommended guidelines for prophylactic or supportive management of study-drug induced adverse events are provided in Section 6.3. The risk to subjects in this trial may be minimized by compliance with the eligibility criteria and study procedures as well as, close clinical monitoring. There may be unforeseen risks with nilotinib which could be serious (refer to the latest [Investigator's Brochure]).

3 Objectives and endpoints

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

Table 3-1 Objectives and related endpoints

Objective	Endpoint	Analysis
Primary		Refer to Section 10.4
To determine the percentage of patients who are in MMR at 48 weeks after starting the treatment-free remission (TFR) phase (patients who required re-initiation of treatment will be considered as non-responders)	BCR-ABL ≤ 0.1% IS (MMR or MR3.0) at 48 weeks after starting the TFR phase with no loss of MMR **and** no re-initiation of nilotinib therapy in the first 48 weeks after starting the TFR phase. In case of missing PCR assessment at 48 weeks after starting the TFR phase, if both 44 and 54 weeks PCR assessments are available and if both show MMR, 48 weeks assessment will be imputed as "response", otherwise "non-response"	Proportion of patients who are in MMR at 48 weeks after starting the TFR phase is calculated by dividing the number of patients with MMR at 48 weeks after starting the TFR phase with no loss of MMR **and** no re-initiation of nilotinib therapy in the first 48 weeks after starting the TFR phase by the number of patients entered the TFR phase
Secondary		Refer to Section 10.5.1
To determine the percentage of patients who are in MR4.5 (BCR-ABL ≤ 0.0032% IS) at 48 weeks after starting the TFR phase (patients who required re-initiation of treatment will be considered as non-responders)	BCR-ABL ≤ 0.0032% IS (MR4.5) at 48 weeks after starting the TFR phase with no loss of MR4.5 **and** no re-initiation of nilotinib therapy in the first 48 weeks after starting the TFR phase. In case of missing PCR assessment at 48 weeks after starting the TFR phase, if both 44 and 54 weeks PCR assessments are available and if both show MR4.5, the 48 weeks assessment will be imputed as "response", otherwise "non-response"	Proportion of patients who are in MR4.5 at 48 weeks after starting the TFR phase is calculated by dividing the number of patients with MR4.5 at 48 weeks after starting the TFR phase with no loss of MR4.5 **and** no re-initiation of nilotinib therapy in the first 48 weeks after starting the TFR phase by the number of patients who entered the TFR phase
To determine the percentage of patients who are in MMR at 96, 144, 192, 264 weeks, and at the end of 6, 7, 8, 9 and 10 years after starting the TFR phase (patients who required re-initiation of treatment will be considered as non-responders)	BCR-ABL ≤ 0.1% IS (MMR) at 96, 144, 192, 264 weeks, and at the end of 6, 7, 8, 9 and 10 years after starting the TFR phase with no loss of MMR **and** no re-initiation of nilotinib therapy in the first 96, 144, 192, 264 weeks, and in the first 6, 7, 8, 9 and 10 years after starting the TFR phase	Proportion of patients who are in MMR at 96, 144, 192, 264 weeks, and at the end of 6, 7, 8, 9 and 10 years after starting the TFR phase is calculated by dividing the number of patients with MMR at 96, 144, 192, 264 weeks, and at the end of 6, 7, 8, 9 and 10 years after starting the TFR phase with no loss of MMR **and** no re-initiation of nilotinib therapy during those intervals by the number of patients who entered the TFR phase

Objective	Endpoint	Analysis
Secondary (cont'd)		Refer to Section 10.5.1
To determine the percentage of patients who are in MR4.5 at 96, 144, 192, 264 weeks, and at the end of 6, 7, 8, 9 and 10 years after starting the TFR phase (patients who required re-initiation of treatment will be considered as non-responders)	BCR-ABL ≤ 0.0032% IS (MR4.5) at 96, 144, 192, 264 weeks, and at the end of 6, 7, 8, 9 and 10 years after starting the TFR phase with no loss of MR4.5 **and** no re-initiation of nilotinib therapy in the first 96, 144, 192, 264 weeks, and in the first 6, 7, 8, 9 and 10 years after starting the TFR phase	Proportion of patients who are in MR4.5 at 96, 144, 192, 264 weeks, and at the end of 6, 7, 8, 9 and 10 years after starting the TFR phase is calculated by dividing the number of patients with MR4.5 at 96, 144, 192, 264 weeks, and at the end of 6, 7, 8, 9 and 10 years after starting the TFR phase with no loss of MR4.5 **and** no re-initiation of nilotinib therapy during those intervals by the number of patients who entered the TFR phase
To determine the percentage of patients in MMR at 48, 96, 144, 192, 264 weeks, and at the end of 6, 7, 8, 9 and 10 years after starting the TFR phase of nilotinib irrespective of whether or not patients required re-initiation of treatment	BCR-ABL ≤ 0.1% IS (MMR) at 48, 96, 144, 192, 264 weeks, and at the end of 6, 7, 8, 9 and 10 years after starting the TFR phase	Proportion of patients who are in MMR at 48, 96, 144, 192, 264 weeks, and at the end of 6, 7, 8, 9 and 10 years after starting the TFR phase is calculated by dividing the number of patients with MMR at 48, 96, 144, 192, 264 weeks, and at the end of 6, 7, 8, 9 and 10 years after starting the TFR phase by the number of patients who entered the TFR phase. Patients who are re-initiated with nilotinib but have less than 12 weeks of re-initiation of treatment will be excluded from the analysis
To determine the percentage of patients in MR4.5 at 48, 96, 144, 192, 264 weeks, and at the end of 6, 7, 8, 9 and 10 years after starting the TFR phase of nilotinib irrespective of whether or not patients required re-initiation of treatment	BCR-ABL ≤ 0.0032% IS (MR4.5) at 48, 96, 144, 192, 264 weeks, and at the end of 6, 7, 8, 9 and 10 years after starting the TFR phase	Proportion of patients who are in MR4.5 at 48, 96, 144, 192, 264 weeks, and at the end of 6, 7, 8, 9 and 10 years after starting the TFR phase is calculated by dividing the number of patients with MR4.5 at 48, 96, 144, 192, 264 weeks, and at the end of 6, 7, 8, 9 and 10 years after starting the TFR phase by the number of patients who entered the TFR phase. Patients who are re-initiated with nilotinib but have less than 12 weeks of re-initiation of treatment will be excluded from the analysis
To determine the percentage of patients who achieve MMR within 12 weeks of re-treatment with nilotinib	BCR-ABL < 0.1% at least at one assessment within 12 weeks after re-start of nilotinib treatment	Proportion of patients who achieve MMR within 12 weeks of re-initiation of nilotinib is calculated by dividing the number of patients who are in MMR at least at one assessment within 12 weeks after re-start of nilotinib treatment by the number of patients who are re-initiated for at least 12 weeks

Objective	Endpoint	Analysis
To determine the percentage of patients who are in stable MMR after achievement of that response in the nilotinib re-initiation phase for 48 weeks, 96 weeks, 144 weeks, 192 weeks, 240 weeks, 288 weeks, 336 weeks, 384 weeks and 432 weeks, based on availability of appropriate data.	BCR-ABL ≤ 0.1% IS (MMR) at 48 weeks, 96 weeks, 144 weeks, 192 weeks, 240 weeks, 288 weeks, 336 weeks, 384 weeks and 432 weeks, based on availability of appropriate data, since first achievement of MMR during the nilotinib re-initiation phase	Proportion of patients who are in stable MMR after achievement of that response in the nilotinib re-initiation phase for 48 weeks, 96 Weeks, 144 weeks, 192 weeks, 240 weeks, 288 weeks, 336 weeks, 384 weeks and 432 weeks, based on availability of appropriate data, is calculated by dividing the number of patients achieving MMR any time during the nilotinib re-initiation phase and having the same response 48 weeks, 96 weeks, 144 weeks, 192 weeks, 240 weeks, 288 weeks, 336 weeks, 384 weeks and 432 weeks after the first achievement of MMR, irrespective of whether there is loss of MMR in between, by the number of patients who achieved MMR at any time during the nilotinib re-initiation phase
To determine the percentage of patients who are in stable MR4.5 after achievement of that response in the nilotinib re-initiation phase for 48 weeks, 96 weeks, 144 weeks, 192 weeks, 240 weeks, 288 weeks, 336 weeks, 384 weeks and 432 weeks, based on availability of appropriate data.	BCR-ABL ≤ 0.0032% IS (MR4.5) at 48 weeks, 96 weeks, 144 weeks, 192 weeks, 240 weeks, 288 weeks, 336 weeks, 384 weeks and 432 weeks, based on availability of appropriate data, since first achievement of MR4.5 during the nilotinib re-initiation phase	Proportion of patients who are in stable MR4.5 after achievement of that response in the nilotinib re-initiation phase for 48 weeks, 96 weeks, 144 weeks, 192 weeks, 240 weeks, 288 weeks, 336 weeks, 384 weeks and 432 weeks, based on availability of appropriate data, is calculated by dividing the number of patients achieving MR4.5 any time during the nilotinib re-initiation phase and having the same response 48 weeks, 96 weeks, 144 weeks, 192 weeks, 240 weeks, 288 weeks, 336 weeks, 384 weeks and 432 weeks after the first achievement of MR4.5, irrespective of whether there is loss of MR4.5 in between, by the number of patients who achieved MR4.5 at any time during the nilotinib re-initiation phase

Objective	Endpoint	Analysis
Secondary (cont'd)		Refer to Section 10.5.1
To characterize the kinetics of BCR-ABL transcript after re-start of nilotinib therapy	BCR-ABL transcript levels (IS) after re-start of nilotinib therapy	Descriptive statistics of BCR-ABL levels (IS) over time after re-start of nilotinib therapy
To estimate the duration of re-initiated treatment required to regain MMR after loss of MMR	Duration of re-initiated treatment required to regain MMR is defined as time from date of start of re-initiation of treatment after loss of MMR to the date of first achievement of MMR	Kaplan-Meier (KM) estimation of duration of re-initiated treatment required to regain MMR which is measured from the time from date of start of re-initiation of treatment after loss of MMR to the date of first achievement of MMR. Patients who do not regain MMR after re-initiation of treatment on or before the cut-off date, duration will be censored at the date of last PCR assessment
To estimate the duration of re-initiated treatment required to regain MR4.5 after loss of MMR	Duration of re-initiated treatment required to regain MR4.5 (BCR-ABL ≤ 0.0032% IS) is defined as the time from start of re-initiation of treatment after loss of MMR to the first achievement of MR4.5	Kaplan-Meier (KM) estimation of duration of re-initiated treatment required to regain MR4.5 which is measured from the time from date of start of re-initiation treatment after loss of MMR to the date of first achievement of MR4.5. Patients who do not regain MR4.5 after re-initiation of treatment on or before the cut-off date, duration will be censored at the date of last PCR assessment
To estimate the treatment-free survival (TFS) after the start of the TFR phase	TFS is defined as the time from the start of the TFR phase to the earliest occurrence of the following events: loss of MMR, re-initiation of treatment due to any cause, progression to AP/BC or death due to any cause	Kaplan-Meier (KM) estimation of TFS which is measured from the date of the start of the TFR phase to the date of the earliest of the following events: loss of MMR, re-initiation of treatment due to any cause, progression to AP/BC or death due to any cause. For patients without any event on or before the cut-off date, survival time will be censored at the date of their last assessment (PCR, cytogenetic, hematologic or extramedullary) A TFS sensitivity analysis will be conducted to consider discontinuation from TFR phase due to any reason as a TFS event, in addition to the TFS events as defined above

Objective	Endpoint	Analysis
Secondary (cont'd)		Refer to Section 10.5.1
To estimate progression-free survival (PFS) after the start of the TFR phase	PFS is defined as the time from the start of the TFR phase to the earliest occurrence of the following events: progression to AP/BC or death due to any cause	Kaplan-Meier (KM) estimation of PFS which is measured from the date of the start of the TFR phase to the date of the earliest of the following events: progression to AP/BC or death due to any cause. For patients without any event on or before the cut-off date, survival time will be censored at the date of their last assessment (cytogenetic, hematologic or extramedullary) for patients who are still on study and at the date of last contact for patients who are in follow-up
To estimate overall survival (OS) after the start of the TFR phase	OS is defined as the time from start of the TFR phase to death due to any cause	Kaplan-Meier (KM) estimation of OS which is measured from the date of the start of the TFR phase to the date of death due to any cause. For patients without any event on or before the cut-off date, survival time will be censored at the date of their last assessment for patients who are still on study and at the date of last contact for patients who are in follow-up
To assess the safety profile during the nilotinib treatment consolidation phase, during the TFR phase and during re-initiation treatment with nilotinib	Type, frequency and severity of adverse events, laboratory values that fall outside the pre-determined ranges and clinically notable ECG and other safety data	Descriptive statistics on adverse events, laboratory abnormalities and clinically notable ECG and other safety parameters during the nilotinib treatment consolidation phase, during the TFR phase and during re-initiation of treatment with nilotinib
To assess the occurrence of BCR-ABL mutations highly resistant to nilotinib (T315I, E255K/V, Y253H, F359V/C/I) or any other BCR-ABL mutations in patients who lost MMR	Proportion of patients who develop T315I, E255K/V, Y253H, F359V/C/I mutations on study or any other BCR-ABL mutations in patients who lost MMR after nilotinib suspension.	Proportion will be calculated by dividing the number of patients who developT315I, E255K/V, Y253H, F359V/C/I mutations after nilotinib suspension by the number of patients who lost MMR

Objective	Endpoint	Analysis
Exploratory		Refer to Section 10.6



4 Study design

4.1 Description of study design

This is a single-arm, open label, multicenter, nilotinib TFR study in patients with BCR-ABL positive Chronic Myelogenous Leukemia in chronic phase who have achieved durable MRD status on first line nilotinib treatment. Approximately 175 patients will be enrolled into this study. However, if the proportion of patients ineligible for discontinuation appears to be higher than expected, additional patients will be enrolled in order to get the required number of patients to discontinue.

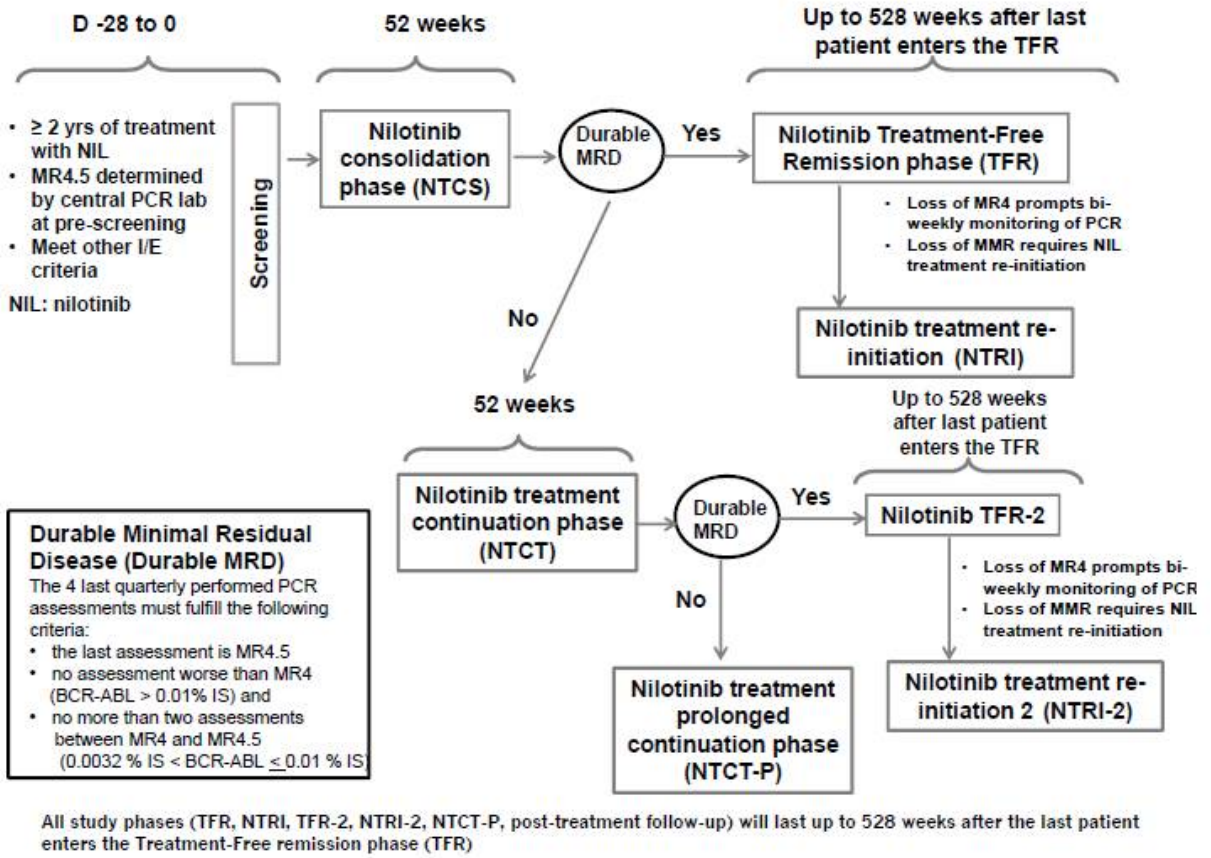
During the course of this study, patients can also participate in an observational trial as appropriate.

This study has 2 main phases: nilotinib consolidation, and nilotinib Treatment-Free Remission phases. Please see Figure 4-1 for study design.

Study design:

The study schema is presented in Figure 4-1:

Figure 4-1 Study design



4.1.1 Screening

All study patients must be thoroughly informed about all aspects of the study, including the study visit schedule and required assessments for informed consent. The written informed consent must be obtained prior to the performance of pre-screening PCR assessment and any screening evaluations. All screening procedures have to be performed between study Day -28 and Day 0. If the patient is unable to read, an impartial witness should be present during the entire informed consent discussion.

All patients who have received a minimum of 2 years of first-line nilotinib treatment can be pre-screened with one PCR sample using a Novartis designated laboratory with validated PCR technology that has a sensitivity of at least MR4.5.

Patients with pre-screen PCR results in ≥ MR4.5 (BCR-ABL ≤ 0.0032% IS) will be evaluated for eligibility. The inclusion and exclusion criteria will be assessed and all screening laboratory assessments and procedures will be carried out. Results of all screening evaluations must be reviewed by the Principal Investigator or his/her designee prior to enrollment of the patient into the study to assure that all inclusion and exclusion criteria have been satisfied.

When MR4.5 cannot be assessed due to logistical or quality issues (e.g. sample lost, sample not arrived frozen, insufficient ABL copy numbers) repeated pre-screenings for the BCR-ABL transcript level are allowed as soon as possible.

When a patient has not achieved MR4.5 at pre-screening, repeated pre-screening for the BCR-ABL transcript level is allowed after a minimum additional period of 12 weeks of nilotinib. This pre-screening can be repeated until the end of the recruitment. It is under the discretion of the investigator how many times a patient will be re-screened. As long as a patient meets all inclusion criteria and none of the exclusion criteria, he/she will be enrolled in this study after re-screening.

In exceptional cases (after discussion with and agreement by Novartis) the pre-screening and screening visits can be combined.

Patients, who are currently enrolled in the Novartis [CAMN107EIC01] study, are allowed to be consented and screened for the CAMN107I2201 study without discontinuing from their current enrollment. This is to ensure that patients receive continuous nilotinib treatment. If a patient is eligible for the CAMN107I2201 study after screening procedures and assessments, he/she must discontinue participation from [CAMN107EIC01], and complete all end of study assessments before enrolling into study CAMN107I2201.

4.1.2 Nilotinib consolidation phase

During the first 52 weeks of the study, all patients will be treated with the planned dose 300 mg nilotinib BID (or at a reduced dose level of 400 mg QD if required from the perspective of toxicity). The treatment will continue until the patient experiences unacceptable toxicity, disease progression, death, lost to follow-up (refer to Section 7.1.5 and Section 7.1.6) and/or treatment is discontinued at the discretion of the investigator or withdrawal of consent. Patients will be monitored every 12 weeks for BCR-ABL levels with a highly standardized and validated RT-PCR assay by a Novartis designated laboratory. Monitoring BCR-ABL levels every 12 weeks during the consolidation phase is consistent with the recommended

frequency of monitoring in clinical practice for patients in MMR or better response (Baccarani et al 2009). Details of the assay characteristics and testing logistics will be provided in a dedicated PCR charter and PCR Lab manual for this study.

In order for patients to be eligible to start the TFR phase, they have to fulfill the protocol specific definition of durable MRD. The 4 last quarterly performed PCR assessments must fulfill the following criteria:

- The last assessment is MR4.5 (BCR-ABL ≤ 0.0032% IS)
- No assessment worse than MR4.0 (BCR-ABL > 0.01% IS) and
- No more than two assessments between MR4.0 and MR4.5 (0.0032 % IS < BCR-ABL ≤ 0.01% IS)

The PCR methodology used shows minimal fluctuations at the very deep level of sensibility. Therefore the protocol specific definition of durable MRD allows for minimal fluctuations between MR4.0 and MR4.5 during the consolidation phase. To guarantee that the patient is not losing his/her deep molecular response the last BCR-ABL level prior to entering the TFR phase must be MR4.5 or better.

4.1.3 Nilotinib continuation phase and prolonged continuation phase

If a patient is not eligible to start TFR phase, he/she will continue the nilotinib treatment in the continuation phase. The treatment will continue until the patient experiences unacceptable toxicity, disease progression, death, lost to follow-up (refer to Section 7.1.5 and Section 7.1.6) and/or treatment is discontinued at the discretion of the investigator or withdrawal of consent. During the continuation phase (52 weeks), PCR assessments will be performed every 12 weeks. Patients will be eligible to enter the TFR-2 phase after the continuation phase if they fulfill the protocol specific definition of durable MRD. Patients who do not qualify to start TFR-2 may continue to receive nilotinib treatment in the nilotinib prolonged continuation phase for up to 528 weeks after the last patient enters the nilotinib TFR phase, or until the patient experiences unacceptable toxicity, disease progression, death, lost to follow-up and/or the treatment is discontinued at the discretion of the investigator or withdrawal of consent. As mentioned in Table 7-7, the patients in the prolonged continuation phase will keep being followed for safety and efficacy (PCR data).

4.1.4 Nilotinib Treatment-Free Remission phase (TFR)

Duration of the nilotinib TFR phase is up to 528 weeks after the last patient enters the nilotinib TFR phase. Patients will suspend nilotinib therapy on the day they enter this phase. During this phase, BCR-ABL levels will be monitored every 4 weeks during the first 48 weeks, every 6 weeks for the following 48 weeks and every 12 weeks during the last period. The median doubling time of BCR-ABL transcripts is approximately 9 days for patients who stop imatinib (Branford et al 2012) corresponding to approximately 1 log increase in BCR-ABL transcripts in 4 weeks. PCR monitoring performed every 4 weeks should therefore be sufficient to identify all patients who are potential candidates for re-initiation of nilotinib. More frequent monitoring is unlikely to improve the identification of patients in need for re-initiation of nilotinib. Every 12 week monitoring in the last period of the TFR is consistent

with the recommended frequency of monitoring in clinical practice for patients in MMR or better response (Baccarani et al 2009).

Monitoring every 6 weeks represents an intermediate frequency in the second period of 48 weeks. All PCR assessments will be performed by a Novartis designated laboratory with validated PCR technology that has a sensitivity of at least 4.5 logs.

Loss of MR4.0 will trigger an intensified biweekly (every two weeks) BCR-ABL levels monitoring to identify loss of MMR early as to further minimize the risk of overlooking molecular recurring disease in the TFR study patients. Biweekly monitoring will begin upon loss of MR4.0 and will end at one of the following time points:

- When the patient loses MMR (and therefore re-initiates nilotinib treatment)
- When the BCR-ABL levels return to a range between MR4.0 and MR4.5
- When the BCR-ABL levels remain lower than MMR for 4 consecutive measurements (8 weeks from initial loss of MR4.0). At this point, the patient may proceed to monthly BCR-ABL monitoring.

  If after additional 12 consecutive measurements on a monthly monitoring the BCR-ABL transcript levels remain lower than MMR (56 weeks from initial loss of MR4.0) the patient may proceed to 6 weeks BCR-ABL monitoring.
  If after additional 8 consecutive measurements on a 6 weeks monitoring the BCR-ABL transcript levels remain lower than MMR (104 weeks from initial loss of MR4.0) the patient may proceed to 12 weeks BCR-ABL monitoring.

Loss of MMR defined as BCR-ABL > 0.1% IS assessed in a single blood sample (confirmation of loss of MMR is not required) will mandate re-initiation of nilotinib treatment at 300 mg BID or at a reduced dose level of 400 mg QD if required from the perspective of tolerance within 5 weeks after the collection date of the blood sample demonstrating loss of MMR.

Patients who require re-initiation of nilotinib treatment will be monitored for BCR-ABL level every 4 weeks for the first 24 weeks and then every 12 weeks thereafter in patients who regained MMR. The frequency of BCR-ABL monitoring in patients not regaining MMR within the first 24 weeks after re-initiation of treatment will be at least every 12 weeks or more frequently as clinically indicated. The nilotinib re-initiation phase will last up to 528 weeks after the last patient enters the TFR phase.

4.1.4.1 Nilotinib TFR-2 phase

Duration of the nilotinib TFR-2 phase will last up to 528 weeks after the last patient enters the TFR. Patients will suspend nilotinib therapy on the day they enter this phase. During this phase, BCR-ABL levels will be monitored every 4 weeks during the first 48 weeks, every 6 weeks for the following 48 weeks and every 12 weeks during the last period. All PCR assessments will be performed by a Novartis designated laboratory with validated PCR technology that has a sensitivity of at least 4.5 logs.

During the TFR-2 phase the same rules in case of loss of MR4.0 or of MMR will be applied as during the TFR phase.

Patients who require re-initiation of nilotinib treatment will be monitored for BCR-ABL level every 4 weeks for the first 24 weeks and then every 12 weeks thereafter in patients who regained MMR. The frequency of BCR-ABL monitoring in patients not regaining MMR within the first 24 weeks after re-initiation of treatment will be at least every 12 weeks or more frequently as clinically indicated. The nilotinib re-initiation phase-2 will last up to 528 weeks after the last patient enters the TFR phase.

The out-come of TFR-2 phase in these patients will be analyzed separately in an exploratory manner.

4.1.5 End of Treatment Phase / End of TFR Phase

This visit will occur within 7 days after the decision has been made to discontinue the patient from any study phases or at the end of participation as per protocol.

4.1.6 Safety follow-up

A safety follow-up should be performed 30 days after a patient ends his/her participation in the study (see Section 7.1.7).

4.1.7 Post-treatment follow up

Survival information, stem cell transplant, antineoplastic therapies as well as information on the status of the patient‘s disease (i.e. disease progression to AP/BC according to protocol definition) will be collected from all patients who discontinue the study.

The post-treatment follow-up will be done every 12 weeks up to 528 weeks after the last patient enters the nilotinib TFR phase (see Section 7.1.9).

4.2 Timing of interim analyses and design adaptations

There are no formal interim analyses planned. Please refer to Section 10.6 for details. Please refer to Section 10.7 for details on data monitoring and reporting.

4.3 Definition of end of study

End of study occurs (EOS) occurs 528 weeks after the last patient enters the nilotinib TFR phase. At which point all patients will have completed the TFR phases, or completed nilotinib treatment, or discontinued the study early.

All patients still on study treatment at the time of End of Study, or if the study is stopped early, will be transitioned to prescribed nilotinib. Should nilotinib not be commercially available to patients due to local regulations, Novartis will have a transition plan in place to ensure that patients continue to have access to nilotinib without any interruption in treatment.

4.4 Early study termination

Should within 48 weeks after the start of the TFR phase a pre-determined number of patients not regain MMR (MR3.0 or BCR-ABL $\leq$ 0.1% IS among patients who lost MMR, and within 12 weeks of re-initiating nilotinib treatment), or show confirmed loss of CCyR, or progress to AP/BC, the study will be stopped. This is expected to be unlikely to happen due to the

frequency and reliability of BCR-ABL monitoring methodology proposed in this study, since molecular recurrence should be identified quickly and will mandate re-initiation of therapy.

The stopping rules are based upon the frequency of these events occurring on study ENESTnd [CAMN107A2303]. It is considered crucial that patients treated on the proposed study have outcomes during the treatment-free remission phase at least as good as those patients who were treated on study [CAMN107A2303] with continuous nilotinib 300 mg BID after a median follow-up of approximately 3 years. Therefore, the following stopping rules for this study will apply to the first 48 weeks after start of TFR:

1. More than 3 cases of progression to AP/BC despite BCR-ABL monitoring and re-initiation of nilotinib treatment according to protocol or
2. More than 3 cases of loss of CCyR despite BCR-ABL monitoring according to protocol or
3. More than 11 cases of failure to regain MMR (among patients who lost MMR) after 12 weeks of nilotinib re-treatment, within 48 weeks after start of TFR phase.

During the TFR-2 the following stopping rules will apply if at least 20 patients are entering the TFR-2 phase. Should one of the rules apply, the strategy of entering TFR-2 after 52 weeks of consolidation phase plus 52 weeks of continuation phase would no longer be granted. Abandoning of the TFR-2 strategy will lead to a careful review of events in the TFR phase, but may not lead to the abandoning of TFR phase if the stopping rules applied to TFR phase are not met.

1. More than 5% cases of progression to AP/BC despite BCR-ABL monitoring according to protocol
2. More than 5% cases of loss of CCyR despite BCR-ABL monitoring according to the protocol
3. More than 10% cases of failure to regain MMR (MR3.0 or BCR-ABL < 0.1% IS) after 12 weeks of nilotinib re-treatment within 48 weeks after start of TFR-2 phase.

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 and the same assessments should be performed as described in Section 7 for a discontinued or 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 sponsor or the investigator (based on local regulations) will be responsible for informing Institutional Review Board (IRBs) and/or Ethics committee of the early termination of the trial.

5 Population

5.1 Patient population

The targeted population of this study includes adult patients who are treated with nilotinib as a first line treatment for newly diagnosed CML-CP. Patients must have been treated for a minimum of 2 calendar years with at least the last 12 months prior to pre-screening at the approved total daily dose of 600 mg nilotinib (or at a reduced dose level of 400 mg QD if required from the perspective of tolerance). All patients must have achieved MR4.5 (BCR-ABL $\leq$ 0.0032% IS) at any time point before being enrolled in the study (this time point can

be the pre-screening assessment). MR4.5 must have been determined by a Novartis designated laboratory with validated PCR technology that has a sensitivity of at least 4.5 logs. Evidence of typical BCR-ABL transcripts which are amenable to standardized RT-PCR measurements is required.

Patients, who are currently enrolled in Novartis study [CAMN107EIC01], are allowed to be consented and screened for the CAMN107I2201 study without discontinuing from their current enrollment. This is to ensure that patients receive continuous nilotinib treatment. If a patient is eligible for the CAMN107I2201 study after screening procedures and assessments, he/she must discontinue participation from [CAMN107EIC01], and complete all end of study assessments before enrolling into study CAMN107I2201.

Approximately 175 patients will be enrolled into this study. However, if the proportion of patients' ineligible for discontinuation appears to be higher than expected, additional patients will be enrolled in order to get the required number of patients to discontinue.

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 patients ≥ 18 years of age
2. Minimum of 2 calendar years of nilotinib treatment with at least the last 12 months of nilotinib treatment prior to pre-screening at approved total daily dose of 600 mg or at a reduced dose of 400 mg QD if required from the perspective of tolerance) for BCR-ABL positive CML in documented chronic phase at the time of diagnosis
3. Documented chronic phase CML must meet all the criteria defined by:
   - < 15% blasts in peripheral blood and bone marrow,
   - < 30% blasts plus promyelocytes in peripheral blood and bone marrow,
   - < 20% basophils in the peripheral blood,
   - ≥ 100 x 10^9/L (≥ 100,000/mm^3) platelets,
   - No evidence of extramedullary leukemic involvement, with the exception of hepatosplenomegaly.
4. Patients must tolerate a minimum total daily dose of nilotinib of 400 mg
5. Evidence of typical BCR-ABL transcripts [b3a2 (e14a2) and/or b2a2 (e13a2)] at the time of CML-CP diagnosis i.e. prior to first start of TKI treatment which are amenable to standardized RT-PCR quantification"
6. Patient in MR4.5 at prescreening at Novartis designated lab
7. ECOG performance status of 0-2
8. Adequate end organ function as defined by:
   - Direct bilirubin ≤ 1.5 x ULN, 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) ≤ 3 x ULN i.e. equivalent to ≤ Grade 1 NCI-CTCAE v.4.03
- Serum lipase ≤ 2 x ULN i.e. equivalent to ≤ Grade 2 NCI-CTCAE v.4.03
- Alkaline phosphatase ≤ 2.5 x ULN
- Serum creatinine < 1.5 x ULN

9. Patients must have the following electrolyte values within normal limits or corrected to be within normal limits with supplements prior to first dose of study medication:
   - Potassium (suggested keep to prevent issues with QT and/or rhythm abnormalities)
   - Magnesium (suggested keep to prevent issues with QT and/or rhythm abnormalities)
   - Total calcium (corrected for serum albumin)
10. Patients must have normal marrow function as defined:
    - Absolute Neutrophil Count (ANC) ≥ 1.5 x 10^9/L
    - Hemoglobin ≥ 9.0 g/dL
    - Platelets ≥ 100 x 10^9/L
11. Willingness and ability to comply with scheduled visits, treatment plans, laboratory tests and other study procedures

Written informed consent must be obtained prior to any screening procedures.

5.3 Exclusion criteria

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

1. Previous treatment with BCR-ABL inhibitors other than nilotinib for more than a total cumulative duration of 4 weeks
2. Previous treatment with alpha-interferon of any duration
3. Previous anticancer agents for CML other than nilotinib except for cytoreduction after CML diagnosis until up to 4 weeks after first dose of nilotinib
4. Known second chronic phase of CML after previous progression to AP/BC
5. Poorly controlled diabetes mellitus (defined as HbA1c > 9%)
6. Impaired cardiac function including any one of the following:
   - LVEF < 45% or below the institutional lower limit of the normal range (whichever is higher)
   - Inability to determine the QT interval on ECG, except for patients with evidence of measurable QT interval at the time of CML diagnosis (e.g. prior to first start of TKI treatment) and who have no documented clinical signs of cardiovascular disease and / or clinical signs of conduction abnormality
   - Complete left bundle branch block
   - Right bundle branch block plus left anterior or posterior hemiblock
   - Use of a ventricular-paced pacemaker
   - Congenital 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

- QTc > 450 msec on the average of three serial baseline ECG (using the QTcF formula). If QTcF > 450 msec and electrolytes are not within normal ranges, electrolytes should be corrected and then the patient re-tested for QTc. This exclusion criterion is not applicable for patients with non-measurable QT interval who have evidence of measurable QT interval at the time of CML diagnosis (e.g. prior to first start of TKI treatment) and who have no documented clinical signs of cardiovascular disease and / or clinical signs of conduction abnormality
- History or clinical signs of myocardial infarction within 1 year of study entry
- History of unstable angina within 1 year of study entry
- Other clinically significant heart disease (e.g. congestive heart failure, cardiomyopathy or uncontrolled hypertension)

7. 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)
8. History of acute pancreatitis within 1 year of study entry or past medical history of chronic pancreatitis
9. Known presence of significant congenital or acquired bleeding disorder unrelated to cancer
10. History of another active malignancy within 5 years prior to study entry with the exception of previous or concomitant basal cell skin cancer and previous carcinoma in situ treated curatively
11. Patients who have not recovered from prior surgery
12. Treatment with other investigational agents (defined as not used in accordance with the approved indication) within 4 weeks of Day 1
13. 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 starting study drug. See Appendix 14.1.1 for a list of these medications. This list may not be exhaustive.
14. Patients actively receiving therapy with herbal medicines that are strong CYP3A4 inhibitors and/or inducers, and the treatment cannot be either discontinued or switched to a different medication prior to starting study drug. These herbal medicines may include Echinacea, (including E. purpurea, E. angustifolia and E. pallida), Piperine, Artemisinin, St. John's Wort, and Ginkgo.
15. Patients who are currently receiving treatment with any medications that have the potential to prolong the QT interval and the treatment cannot be either safely discontinued or switched to a different medication prior to starting study drug. (Please see http://crediblemeds.org/everyone/composite-list-all-qtdrugs/ for a list of agents that prolong the QT interval)
16. Impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of study drug (e.g. ulcerative disease, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, small bowel resection, or gastric bypass surgery)

17. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test.
18. 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 dose of nilotinib. 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 by follow up hormone level assessment.
    - Male sterilization (at least 6 months prior to enrolling). For female patients on the study the vasectomized male partner should be the sole partner for that patient.
    - Use of a combination of any two of the following:
        a. 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.
        b. Placement of an intrauterine device (IUD) or intrauterine system (IUS)
        c. Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository

        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.

If a study patient becomes pregnant or suspects being pregnant during the study or within 30 days after the final dose of nilotinib, the Study Doctor needs to be informed immediately and ongoing study treatment with nilotinib has to be stopped immediately.

6 Treatment

6.1 Study treatment

Study treatment: nilotinib (AMN107, Tasigna®)

Nilotinib will be provided as commercial packs and sourced in the country or where not available / not allowed as clinical packs. Clinical packs will be labeled as AMN107 and

supplied as 150 mg and 200 mg hard gelatin capsules in bottles. Commercial packs will be labeled as Tasigna® and supplied as 150 mg and 200 mg hard gelatin capsules in blisters. Nilotinib will not be dosed by weight or body surface area.

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

6.1.1 Dosing regimen

Nilotinib will be administered orally at 300 mg twice daily (BID), at approximately 12 hour intervals, 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.

Dose regimen can be decreased to 400 mg QD in case of study-drug related hematological and non-hematological toxicities. Refer to Section 6.3.1.1 and Section 6.3.1.2.

Table 6-1 Dose and treatment schedule

Study treatments	Pharmaceutical form and route of administration	Dose	Frequency and/or Regimen
Nilotinib	Capsule for oral use	300 mg BID (2x150 mg)	Daily
Nilotinib	Capsule for oral use	400 mg QD (2x200 mg)	Daily

Note: the above packaging applies to centrally supplied study medication. If nilotinib is sourced and labeled in country, the commercial package will be provided

6.1.2 Ancillary treatments

Not Applicable.

6.1.3 Rescue medication

Not Applicable.

6.1.4 Guidelines for continuation of treatment

If a patient is not eligible to start TFR phase, he/she will continue the nilotinib treatment in the continuation phase for 52 weeks. The treatment will continue until the patient experiences unacceptable toxicity, disease progression, death, lost to follow-up (refer to Section 7.1.5 and Section 7.1.6) and/or treatment is discontinued at the discretion of the investigator or withdrawal of consent.

If a patient does not qualify to start TFR-2 after 52 weeks of nilotinib in the continuation phase, he/she will continue to receive nilotinib treatment in the nilotinib prolonged continuation phase for up to 528 weeks after the last patient enters the nilotinib TFR phase, or until the patient experiences unacceptable toxicity, disease progression, death, lost to follow-up and/or the treatment is discontinued at the discretion of the investigator or withdrawal of consent.

If a patient does not tolerate the 300 mg BID dose, dose modification guidelines specified in Table 6-2 and Table 6-3 should be followed.

6.1.5 Treatment duration

Patients will remain on study for at least 580 weeks (52 weeks of nilotinib consolidation and up to 528 weeks after the last patient enters the nilotinib TFR phase).

During the consolidation phase, all patients will receive 52 weeks of the planned dose of 300 mg BID nilotinib (or at a reduced dose level of 400 mg if required from the perspective of toxicity) treatment until patient experiences unacceptable toxicity, disease progression, death, lost to follow-up and/or treatment is discontinued at the discretion of the investigator or withdrawal of consent during the first 52 weeks.

Patients not fulfilling the protocol specific definition of durable MRD at the end of the nilotinib consolidation phase will continue the nilotinib treatment in the continuation phase (52 weeks). The treatment will continue until the patient experiences unacceptable toxicity, disease progression, death, lost to follow-up (refer to Section 7.1.5 and Section 7.1.6) and/or treatment is discontinued at the discretion of the investigator or withdrawal of consent.

Patients who do not qualify to start TFR-2 after the nilotinib continuation phase may continue to receive nilotinib treatment in the nilotinib prolonged continuation phase for up to 528 weeks after the last patient enters the nilotinib TFR phase, or until the patient experiences unacceptable toxicity, disease progression, death, lost to follow-up and/or the treatment is discontinued at the discretion of the investigator or withdrawal of consent. The patients will be followed for efficacy and safety.

During the TFR phases, patients with loss of MMR will immediately re-initiate nilotinib treatment for the remainder of the study or until the patient experiences unacceptable toxicity, disease progression, death, lost to follow-up and/or the treatment is discontinued at the discretion of the investigator or withdrawal of consent.

6.2 Dose escalation guidelines

Dose escalation 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 guideline in Table 6-2, Table 6-3 for details.

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.

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.

Dose changes must be recorded on the Dosage Administration Record eCRF.

Drug adjustment should take place as soon as possible, as clinically indicated. Patients do not need to wait for a scheduled visit once clinical need has been determined.

This study will use the CTCAE (NCI Common Terminology Criteria for Adverse Events) versions 4.03 for toxicity and adverse event reporting. CTCAE version 4.03 can be downloaded as a PDF file from the following website: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40

If multiple dose-reducing toxicities are present, the greatest dose reduction schedule must be used.

6.3.1.1 Dose reduction guidelines for study drug-related non-hematologic toxicity and for ischemic vascular and cardiovascular events regardless of study drug relationship

A summary of dose reduction guidelines for study drug-related non-hematologic toxicity and for ischemic vascular and cardiovascular events regardless of the study drug relationship for the 300 mg BID dosage is presented in Table 6-2. 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.

However for those toxicities detailed in Table 6-2, the following rules (as detailed in the bullet points) 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.
- Any non-hematological laboratory 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 laboratory toxicity Grade 3 or 4 does not resolve after 28 days, the patient must be considered for discontinuation from the study by the investigator.
- If Grade 4 toxicity of the same type recurs despite nilotinib dose reduction to 400mg QD the patient must be discontinued from the study.
- In case of Grade 3 pancreatitis, study drug treatment must be held 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 held 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 6-2 Summary of 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 BID)
General non-hematological toxicity	
Grade 2 (persisting > 7 days with optimal supportive care)	The dose of nilotinib may be reduced to 400 mg QD at the discretion of the investigator if clinically appropriate and in the best overall interest of the patient.
≥ Grade 3	Hold therapy and resume nilotinib at next lower dose level after recovery to ≤ Grade 2 is seen I→ 400 mg QD. 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 QD I→ discontinue from the study.
General non-hematological laboratory toxicity (not mentioned below in the table)	
Grade 2 (persisting > 7 days with optimal supportive care)	The dose of nilotinib may be reduced to 400 mg QD at the discretion of the investigator if clinically appropriate and in the best overall interest of the patient.
≥ Grade 3	Hold therapy and resume nilotinib at next lower dose level after recovery to ≤ Grade 2 is seen I→ 400 mg QD. If recovery to ≤ Grade 2 is greater than 28 days, the patient should be considered for discontinuation from the study by the investigator. If Grade 4 toxicity recurs despite dose reduction to 400mg QD I→ discontinue from the study.
Serum hypophosphatemia	
Grade 2-3	Continue nilotinib at 300 mg BID and start phosphate supplementation.
Grade 4	Hold therapy and consult Novartis.
Serum creatinine	
Grade 2 > 1.5 -3.0 x ULN	The dose of nilotinib may be reduced to 400 mg QD at the discretion of the investigator if clinically appropriate and in the best overall interest of the patient.
≥ Grade 3 ≥ 3.0 x ULN	Hold therapy and resume nilotinib at next lower dose level after recovery to ≤ Grade 2 is seen I→ 400 mg QD. 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 QD I→ discontinue.
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 ≤ 1.5 x ULN 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 400 mg QD at the discretion of the investigator if clinically appropriate and in the best overall interest of the patient.

Study drug and dose	**Nilotinib 600 mg daily (as 300 mg BID)**
≥ Grade 3	Hold therapy and resume nilotinib at next lower dose level after recovery to ≤ Grade 2 is seen I→ 400 mg QD. 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 QD I→ discontinue.
Pancreatitis (with abdominal symptoms plus lipase elevation)	
Grade 2	Hold therapy 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 400 mg QD 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.
Grade 3	Hold therapy and consult Novartis.
Grade 4	Stop therapy. The patient must be discontinued from study.
Elevated lipase without symptoms	
≥ Grade 3	Hold therapy. Re-start nilotinib at 400 mg QD 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 400 mg QD based on investigator's discretion.
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 therapy and resume nilotinib at next lower dose level after recovery to ≤ Grade 2 is seen I→ 400 mg QD. 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 therapy and resume nilotinib at next lower dose level after recovery to ≤ Grade 2 is seen I→ 400 mg QD. If recovery to ≤ Grade 2 is greater than 28 days, the patient must be discontinued from the study.

Study drug and dose	Nilotinib 600 mg daily (as 300 mg BID)
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 400 mg QD at the discretion of the investigator if clinically appropriate and in the best overall interest of the patient.
≥ Grade 3	Hold therapy and resume nilotinib at next lower dose level after recovery to ≤ Grade 2 is seen I→ 400 mg QD. 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 QD I→ discontinue.
Cardiac QTc prolongation	
QTcF > 480 msec	Hold dosing when an ECG with a QTcF > 480 msec. In addition to the procedures below, the investigator should follow their local standards of practice and treatment guidelines for treating prolonged QT intervals. For example in France, this would include consultation with a cardiologist and close cardiac monitoring. • 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 400 mg QD. 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. The investigator should contact Novartis regarding any questions that arise if a patient with QTcF prolongation should be maintained on study. **Note**: QTcB can be used in centers that do not have the ability to automatically measure QTcF for QTc prolongation. In patients with a heart rate lower than 60 per minute decisions are always based on QTcF because QTcB underestimates QT-prolongation at heart rates below 60 per minute.
Ischemic vascular or cardiovascular events	

Study drug and dose	Nilotinib 600 mg daily (as 300 mg BID)
Grade 2*	Hold therapy 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 I→ 400 mg QD. If another recurrence I→ discontinue. If recovery to ≤ Grade 1 is greater than 28 days, the patient must be discontinued from the study.
Grade 3* or 4*	Hold therapy and refer patient for assessment by a vascular or cardiovascular specialist. Consideration should be given for discontinuation from the study. The patient must be discontinued from the study if recovery to < Grade 2 is greater than 28 days.
* 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 therapy and resume nilotinib at next lower dose level after recovery to ≤ Grade 1 is seen I→ 400 mg QD. 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 QD I→ discontinue.
Grade 4	Stop therapy. The patient must be discontinued from study

When a patient on 400 mg QD dosage experiences study drug-related non-hematologic toxicity, study dose will be held until the toxicity is resolved. If the toxicity does not resolve after 28 days of dose interruption, the patient must be discontinued from the study.

6.3.1.2 Dose reduction guidelines for study drug-related hematological toxicity

A summary of dose reduction guidelines for ≥ Grade 3 study drug-related hematological toxicity for 300 mg BID dose is presented in Table 6-3. No dose adjustments should be made for Grade 1 or 2 hematologic toxicities. These guidelines provide some general principles as well as recommendations which are intended to support the investigator's judgment and decision about the appropriate management of toxicity in the individual patient. However, if a hematological toxicity does not resolve to ≤ Grade 2 within 28 days, Novartis must be consulted.

Table 6-3 Summary of dose reduction guidelines for study drug-related hematological toxicity

Study drug and dose	Nilotinib 600 mg daily (as 300 mg BID)
≥ Grade 3	Hold therapy and resume at nilotinib 300 mg BID after recovery to ≤ Grade 2, if recovery occurs within 14 days If ≥ Grade 3 toxicity persists for 15-28 days or recurs, hold therapy and resume at next lower dose level after recovery to ≤ Grade 2: I→ 400 mg QD

	If recovery to ≤ Grade 2 is greater than 28 days, consult Novartis. If another recurrence is seen I→ discontinue.
Note: Dose of study drug need not be reduced or interrupted for hematological toxicity of Grade 2 or lower.	

When a patient on 400 mg QD dosage experiences study drug-related Grade 3 or 4 hematologic toxicity, study dose will be held until the toxicity is resolved. If the toxicity does not resolve after 28 days of dose interruption, the patient must be discontinued from the study.

6.3.2 Suggested management of selected adverse events for nilotinib

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

6.3.2.1 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, alternative etiologies may need to be considered and ruled out.

6.3.2.2 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.

6.3.2.3 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.

6.3.2.4 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.

6.3.2.5 Management of cholesterol increases

Blood lipid panel tests should be performed 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 moderate inhibitory effect of nilotinib on CYP3A4 isoenzyme that is involved in the metabolic pathway of some statins (HMG-CoA reductase inhibitors). Please refer to Appendix 14.1.1 for additional information.

6.3.2.6 Management of glucose increases

Blood glucose tests should be performed 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.

6.3.2.7 Management of glucose and/or lipids during TFR

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

6.3.2.8 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 and treatment guidelines.

6.3.2.9 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 6-2.

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

For patients on treatment with oral anticoagulants other than coumarin derivatives (see Section 6.4.1), the following guidelines will apply for thrombocytopenia: If platelets $\leq 100 \times 10^9$/L, withhold treatment with study drug until recovery to at least $> 100 \times 10^9$/L and resume treatment at same dose. If recurrence of platelets $\leq 100 \times 10^9$/L, then withhold treatment until recovery to at least $> 100 \times 10^9$/L and resume treatment at the minimum dose of 400 mg/day for nilotinib. If the platelet count remains below 100×10^9/L, then nilotinib should be ceased or management with anticoagulation therapy re-evaluated at the discretion of the Investigator.

6.3.2.11 Platelet aggregation inhibitors

For patients on treatment with platelet aggregation inhibitors and platelets $\leq 100 \times 10^9$/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 SC may be requested via Novartis.

6.3.2.12 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

All patients who permanently terminate the study at any time due to a study drug related AE or abnormal laboratory value must be followed at least once a week for 4 weeks, until resolution or stabilization of the event, whichever comes first. All patients will be followed for serious adverse events (SAEs) for 30 days following premature discontinuation from any phases of the study or following end of participation as per protocol.

6.3.4 Guidelines for dose-re-escalation

Re-escalation of the dose of nilotinib to the 300 mg BID is permitted at the discretion of the investigator. This applies to either dose reductions due to hematological or non-hematological toxicities if the following criterion is met at least one month on treatment on the reduced dose.

- All $\geq$ Grade 3 toxicities have resolved to $\leq$ Grade 2

6.4 Concomitant medications

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 Concomitant Medications or the Procedures and Significant Non-Drug Therapies CRF.

The routine use of systemic corticosteroid except strong CYP3A4 inducers is permitted.

Antiemetic medication can be used as clinically indicated. However, the use of prophylactic medication for vomiting is not recommended. Antiemetic medications that prolong the QT-time such as domperidone must be avoided.

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 new

data demonstrating the lack of effect of nilotinib on PK and pharmacodynamics (PD) of warfarin, suggesting nilotinib does not inhibit CYP2C9 activity in human patients. 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 investigator's discretion.

6.4.2 Permitted concomitant therapy requiring caution and/or action (if applicable)

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. A list of these drugs is listed in Appendix 14.1.1.

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 except for anti-cancer treatments of newly diagnosed solid cancers (e.g. prostate cancer) that would not impact the level of minimal residual disease of patients. These patients may remain in study after consultation with Novartis. The administration of other tyrosine kinase inhibitors indicated for treatment of Ph+ CML is **not** allowed.

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. If administration of a strong CYP3A4 inhibitor cannot be avoided during the study and cannot be switched to an alternative therapy, study treatment must be STOPPED. Furthermore, increased awareness should be exercised when administering moderate inhibitors and/or multiple weak inhibitors. A list of these medications and inhibitor classifications can be found in Appendix 14.1.2, however this list may not be comprehensive.

Every effort should be made NOT to administer strong CYP3A4 inducers **however, if** administration of a CYP3A4 inducer cannot be avoided during the study, temporary discontinuation of study treatment is NOT required. A list of these medications and inducer classifications can be found in Appendix 14.1.1, however this list may not be comprehensive.

As far as possible avoid co-administering drugs with a "Known", "Possible" or "Conditional" risk of Torsades de Pointe (per www.qtdrugs.org) during the course of the study:

- If concomitant administration of drugs with a "Known risk of Torsades de Pointe" is required and cannot be avoided, study drug must be interrupted. If, based on the investigator assessment and clinical need, study treatment is resumed, close ECG monitoring is advised.
- If during the course of the study, concomitant administration of a drug with "Possible risk" or "Conditional risk of Torsades de Pointe" is required, based on the investigator assessment and clinical need, study treatment may be continued under close ECG monitoring to ensure patient safety.

A list of drugs associated with QT prolongation and/or Torsades de Pointe is available online at www.qtdrugs.org.

Cardiac monitoring is required upon re-initiation of nilotinib therapy at any point. Triplicate ECGs must be obtained before the treatment re-initiation, and four weeks after re-initiation of nilotinib therapy.

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

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 study. 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 Oracle Clinical RDC interface.

The investigator or designated staff will contact the 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 patient and the Subject No. for that individual must not be changed, even if the patient is re-screened. If the patient fails to be randomized or start treatment for any reason, the reason will be entered into the Screening Disposition page.

6.5.2 Treatment assignment or randomization

Not applicable.

6.5.3 Treatment blinding

Not applicable.

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.

Table 6-4 Preparation and dispensing

Study treatments	Dispensing	Preparation
AMN107	Capsules (150 mg or 200 mg) are dispensed by study personnel on an outpatient basis and oral instruction on dose administration will be provided by the investigator or responsible site personnel. Patients will be provided with adequate supply of study treatment for self-administration at home until at least their next scheduled study visit.	Not applicable

6.6.1 Study drug packaging and labeling

6.6.1.1 Clinical study supply

The interactive response technology (IRT) will not be used for study drug assignment to the patient. The site personnel will identify the study drug package and provide this information into the IRT system.

The clinical study medication packaging has a 2-part label. A unique medication number is printed on each part of this label which corresponds to one of the dose level. Responsible site personnel will identify the study treatment package(s) to dispense to the patient and enter the batch number (no longer applicable since implementation of protocol amendment 5) and PCN number into the IRT system. Site personnel will add the patient number on the label. Immediately before dispensing the package to the patient, site personnel will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) for that patient's unique patient number.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the drug and the medication number but no information about the patient.

Table 6-5 Packaging and labeling

Study treatments	Packaging	Labeling (and dosing frequency)
AMN107 (nilotinib)	Capsules in bottles	Labeled as 'AMN107'

6.6.1.2 Commercial supply

Medication labels will be in the local language and comply with the legal requirements of each country.

Table 6-6 Packaging and labeling

Study treatments	Packaging	Labeling (and dosing frequency)
AMN107 (nilotinib)	Capsules in blister	Labeled as Tasigna® 'nilotinib'

6.6.2 Drug supply and storage

Study treatments 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/ package leaflet and in the nilotinib latest [Investigator's Brochure].

Table 6-7 Supply and storage of study treatments

Study treatments	Supply	Storage
AMN107 (nilotinib)	Centrally supplied by Novartis	Refer to clinical drug label
Tasigna® (nilotinib)	Locally supplied by Novartis	Refer to product package leaflet

6.6.3 Study drug compliance and accountability

6.6.3.1 Study drug compliance

Total daily dose of nilotinib administered with start and end date will be collected on the Dose Administration Record eCRF page. Name, Start and End Dates of any Concomitant medications and Surgical and Medical procedures will be collected on the Prior and Concomitant medications and Surgical and Medical procedures eCRFs respectively.

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.

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 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 Novartis monitor or to the Novartis address provided in the investigator folder at each site.

6.6.3.3 Handling of other study treatment

Not applicable.

6.6.4 Disposal and destruction

The study drug supply can be destroyed at the local Novartis facility, Drug Supply group, third party, or at the site only if permitted by local regulations and authorized by Novartis in a prior agreement.

7 Visit schedule and assessments

7.1 Study flow and visit schedule

Table 7-1, Table 7-2, Table 7-3, Table 7-4, Table 7-5, Table 7-6 and Table 7-7 list 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 CRF will be used as a source document.

(S) is defined as "Source"

(D) is defined as "Data Based"

Hepatitis B testing will be performed once and only once, at the next possible visit when patient is on treatment or before treatment is re-initiated.

Table 7-1 Visit evaluation schedule 1- Nilotinib Treatment Consolidation phase (NTCS)

	Category	Protocol Section	Screening Phase	Nilotinib Treatment Consolidation phase (NTCS)						End of NTCS (within 7 days of last dose if patient discontinues the study)	Safety Follow-up (30 days following End of NTCS phase)	Post-Treatment Follow-up (patients discontinued from the NTCS phase) Every 12 weeks up to 528 weeks after last patient enters the TFR phase
Visit name			**Screening/ Baseline**	**NTCS-D1**	**NTCS-W12**	**NTCS-W24**	**NTCS-W36**	**NTCS-W48**	**NTCS-W52**	**EOT NTCS**	**SAFETY -FUP**	**POST TREATMENT FUP**
Weeks in the study				**W1**	**W12**	**W24**	**W36**	**W48**	**W52**			
Obtain Pre-screening Informed Consent	D	7.1.1	x									
Obtain Informed Consent	D	7.1.2	x									
Demographics	D	7.1.2.3	x									
Inclusion/exclusion criteria	D	5.2 / 5.3	x									
Eligibility checklist in IRT	D	7.1.2.1	x									
Relevant medical history/current medical conditions	D	7.1.2.3	x									
Disease history	D	7.1.2.3	x									
Prior antineoplastic therapy-medication	D	7.1.2.3	x									
Physical examination	S	7.2.2.1	x	x	x	x	x	x		x		
Height	D	7.2.2.3	x									
Weight	D	7.2.2.3	x	x	x	x	x	x		x		
Vital signs / Blood Pressure / Heart	D	7.2.2.2	x	x	x	x	x	x		x		

	Category	Protocol Section	Screening Phase	Nilotinib Treatment Consolidation phase (NTCS)						End of NTCS (within 7 days of last dose if patient discontinues the study)	Safety Follow-up (30 days following End of NTCS phase)	Post-Treatment Follow-up (patients discontinued from the NTCS phase) Every 12 weeks up to 528 weeks after last patient enters the TFR phase
Visit name			**Screening/ Baseline**	**NTCS-D1**	**NTCS-W12**	**NTCS-W24**	**NTCS-W36**	**NTCS-W48**	**NTCS-W52**	**EOT NTCS**	**SAFETY -FUP**	**POST TREATMENT FUP**
Weeks in the study				**W1**	**W12**	**W24**	**W36**	**W48**	**W52**			
rate												
Performance Status	D	7.2.2.4	x	x	x	x	x	x		x		
Extramedullar involvement	D	7.2.2.1	x	x	x	x	x	x		x		
Laboratory assessments												
Echocardiogram	D	7.2.2.9.2	x									
ECG	D	7.2.2.9.1	x	x				x		x		
Hematology	D	7.2.2.6	x	x	x	x	x	x		x		
Bone marrow assessments/cytogenetics, if applicable	D	7.2.1.2		In case of confirmed loss of MMR not responding on treatment within 12 weeks and whenever clinically indicated at the discretion of the investigator								
Blood Chemistry	D	7.2.2.7	x	x	x	x	x	x		x		
Serum Pregnancy test, if applicable	D	7.2.2.8	x							x		
Urine pregnancy test, if applicable	D	7.2.2.8		x	Every 4 weeks							
Peripheral blood BCR-ABL RQ-PCR	D	7.2.1.1	x		x	x	x	x		x		
Biomarker assessment in blood (optional)	D	7.2.4		x								

	Category	Protocol Section	Screening Phase	Nilotinib Treatment Consolidation phase (NTCS)						End of NTCS (within 7 days of last dose if patient discontinues the study)	Safety Follow-up (30 days following End of NTCS phase)	Post-Treatment Follow-up (patients discontinued from the NTCS phase) Every 12 weeks up to 528 weeks after last patient enters the TFR phase
Visit name			**Screening/ Baseline**	**NTCS-D1**	**NTCS-W12**	**NTCS-W24**	**NTCS-W36**	**NTCS-W48**	**NTCS-W52**	**EOT NTCS**	**SAFETY -FUP**	**POST TREATMENT FUP**
Weeks in the study				**W1**	**W12**	**W24**	**W36**	**W48**	**W52**			
Mutational Analysis	D	7.2.1.1		In case of unconfirmed loss of MMR and as needed								
EDTA blood sample for BCR-ABL RQ-PCR (US only)*	D	7.2.1.1			x	x	x	x		x		
Remaining RNA/blood collected between time of diagnosis (included) and study entry (optional)	D	7.2.4.2	As available									
Optional pharmacogenetics blood sample	D	7.2.4.3						x				
End of Phase Disposition page	D	7.1.5	x							x		x
Communication of next phase	D	7.1.4							x			
Safety												
Adverse events / SAE	D	8.1		Continuous								
Concomitant medications	D	6.4		Continuous								

	Category	Protocol Section	Screening Phase	Nilotinib Treatment Consolidation phase (NTCS)						End of NTCS (within 7 days of last dose if patient discontinues the study)	Safety Follow-up (30 days following End of NTCS phase)	Post-Treatment Follow-up (patients discontinued from the NTCS phase) Every 12 weeks up to 528 weeks after last patient enters the TFR phase
Visit name			**Screening/ Baseline**	**NTCS-D1**	**NTCS-W12**	**NTCS-W24**	**NTCS-W36**	**NTCS-W48**	**NTCS-W52**	**EOT NTCS**	**SAFETY -FUP**	**POST TREATMENT FUP**
Weeks in the study				**W1**	**W12**	**W24**	**W36**	**W48**	**W52**			
Study Drug administration	D	6.1.1		Continuous					x for patients entering the continuation phase			
PK sampling	D	7.2.3						x				
Patient Reported Outcomes												
[redacted]												
Sokal risk category at diagnosis	D	7.2.7	At any timepoint during the study									
Progression to AP/BC	D	7.1.9										x
Stem cell transplant	D	7.1.9										x
Antineoplastic therapies	D	7.1.9										x
Survival Follow-up	D	7.1.9										x

* only until 15-Sep-2017

Table 7-2 Visit evaluation schedule 2- Nilotinib Treatment-Free Remission phase (TFR)

	Category	Protocol Section	Nilotinib Treatment-Free Remission phase (TFR)			End of TFR phase (if patient discontinue the study and is not entering re-initiation phase)	Safety Follow-up (30 days following End of TFR phase)	Post-Treatment Follow-up (patients discontinued from the TFR phase and not re-initiating nilotinib treatment on study) Every 12 weeks up to 528 weeks after last patient enters the TFR phase
Visit Name			**TFR-W4– TFR-W48**	**TFR-W54 TFR-W96**	**TFR-W108 – up to 528 weeks after last patient enters the TFR phase**	**EOTFR**	**SAFETY-FUP**	**POST TREATMENT FUP**
Weeks in the study			**W56 - W100**	**W106 - W148**	**W160 – up to 528 weeks after last patient enters the TFR phase**			
Physical examination	S	7.2.2.1	Every 12 weeks			x		
Weight	D	7.2.2.3	Every 12 weeks			x		
Vital signs / Blood Pressure / Heart Rate	D	7.2.2.2	Every 12 weeks			x		
Performance Status	D	7.2.2.4	Every 12 weeks			x		
Extramedullar involvement	D	7.2.2.1	Every 4 weeks	Every 6 weeks	Every 12 weeks	x		
Laboratory assessments								
Peripheral blood BCR-ABL RQ-PCR	D	7.2.1.1	Every 4 weeks	Every 6 weeks	Every 12 weeks	x		
EDTA blood sample for BCR-ABL RQ-PCR (US only)*	D	7.2.1.1	Every 4 weeks	Every 6 weeks	Every 12 weeks	x		
ECG	D	7.2.2.9.1				x		
Hematology	D	7.2.2.6	Every	Every	Every	x		

	Category	Protocol Section	Nilotinib Treatment-Free Remission phase (TFR)			End of TFR phase (if patient discontinue the study and is not entering re-initiation phase)	Safety Follow-up (30 days following End of TFR phase)	Post-Treatment Follow-up (patients discontinued from the TFR phase and not re-initiating nilotinib treatment on study) Every 12 weeks up to 528 weeks after last patient enters the TFR phase
Visit Name			**TFR-W4– TFR-W48**	**TFR-W54 TFR-W96**	**TFR-W108 – up to 528 weeks after last patient enters the TFR phase**	**EOTFR**	**SAFETY-FUP**	**POST TREATMENT FUP**
Weeks in the study			**W56 - W100**	**W106 - W148**	**W160 – up to 528 weeks after last patient enters the TFR phase**			
			4 weeks	6 weeks	12 weeks			
Serum pregnancy test, if applicable	D	7.2.2.8				x		
Urine pregnancy test, if applicable	D	7.2.2.8	Every 4 weeks					
Bone marrow assessments/cytogenetics, if applicable	D	7.2.1.2	In case of confirmed loss of MMR not responding on treatment within 12 weeks and whenever clinically indicated at the discretion of the investigator					
Blood Chemistry	D	7.2.2.7	Every 12 weeks			x		
Mutation Analysis	D	7.2.1.1	In case of unconfirmed loss of MMR and as needed					
End of Phase Disposition page	D	7.1.5				x		x
Safety								
Adverse events / SAE	D	8.1	Continuous					
Concomitant medications	D	6.4	Continuous					
Patient reported Outcomes								

	Category	Protocol Section	Nilotinib Treatment-Free Remission phase (TFR)			End of TFR phase (if patient discontinue the study and is not entering re-initiation phase)	Safety Follow-up (30 days following End of TFR phase)	Post-Treatment Follow-up (patients discontinued from the TFR phase and not re-initiating nilotinib treatment on study) Every 12 weeks up to 528 weeks after last patient enters the TFR phase
Visit Name			**TFR-W4–TFR-W48**	**TFR-W54 TFR-W96**	**TFR-W108 – up to 528 weeks after last patient enters the TFR phase**	**EOTFR**	**SAFETY-FUP**	**POST TREATMENT FUP**
Weeks in the study			**W56 - W100**	**W106 - W148**	**W160 – up to 528 weeks after last patient enters the TFR phase**			
CCI								
Sokal risk category at diagnosis	D	7.2.7	At any time point during the study					
Progression to AP/BC	D	7.1.9						x
Stem cell transplant	D	7.1.9						x
Antineoplastic therapies	D	7.1.9						x
Survival Follow-up	D	7.1.9						x

* only until 15-Sep-2017

Table 7-3 Visit evaluation schedule 3 - Nilotinib treatment re-initiation phase (patients after unsuccessful Treatment-Free Remission attempt) (NTRI)

	Category	Protocol Section	Nilotinib treatment re-initiation phase (NTRI)								End of NTRI phase	Safety Follow-up	Post-Treatment Follow-up (patients discontinued from NTRI phase)
				Every 4 weeks						Every 12 weeks (up to 528 weeks after last patient enters the TFR phase)	within 7 days of last dose	30 days following End of NTRI phase	Every 12 weeks up to 528 weeks after last patient enters the TFR phase
Visit name			NTRI-W1 (Day1)	NTRI-W4	NTRI-W8	NTRI-W12	NTRI-W16	NTRI-W20	NTRI-W24	NTRI-W36 NTRI-W48 NTRI-W60 etc	EOT NTRI	SAFETY FUP	POST TREATMENT FUP
Week of Treatment re-initiation			Day1	W4	W8	W12	W16	W20	W24	W36 - up to 528 weeks after last patient enters the TFR phase			
Physical examination	S	7.2.2.1		x	x	x			x	x	x		
Weight	D	7.2.2.3		x	x	x			x	x	x		
Vital signs /Blood Pressure / Heart Rate	D	7.2.2.2		x	x	x			x	x	x		
Performance Status	D	7.2.2.4		x	x	x			x	x	x		
Extramedullar involvement, if applicable	D	7.2.2.1		x	x	x	x	x	x	x	x		
Laboratory assessments													
Peripheral blood BCR-ABL RQ-PCR	D	7.2.1.1		x	x	x	x	x	x	x	x		
EDTA blood sample for	D	7.2.1.1		x	x	x	x	x	x	x	x		

	Category	Protocol Section	Nilotinib treatment re-initiation phase (NTRI)								End of NTRI phase	Safety Follow-up	Post-Treatment Follow-up (patients discontinued from NTRI phase)
				Every 4 weeks						Every 12 weeks (up to 528 weeks after last patient enters the TFR phase)	within 7 days of last dose	30 days following End of NTRI phase	Every 12 weeks up to 528 weeks after last patient enters the TFR phase
Visit name			**NTRI-W1 (Day1)**	**NTRI-W4**	**NTRI-W8**	**NTRI-W12**	**NTRI-W16**	**NTRI-W20**	**NTRI-W24**	**NTRI-W36 NTRI-W48 NTRI-W60 etc**	**EOT NTRI**	**SAFETY FUP**	**POST TREATMENT FUP**
Week of Treatment re-initiation			**Day1**	**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**W36 - up to 528 weeks after last patient enters the TFR phase**			
BCR-ABL RQ-PCR (US only)*													
ECG	D	7.2.2.9.1	x	x				W48 and every 48 weeks thereafter up to 528 weeks after last patient enters the TFR phase			x		
Hematology	D	7.2.2.6		x	x	x	x	x	x	x	x		
Serum pregnancy test, if applicable	D	7.2.2.8									x		
Urine pregnancy test, if applicable	D	7.2.2.8		Every 4 weeks									
Bone marrow assessments/ cytogenetics, if applicable	D	7.2.1.2		In case of confirmed loss of MMR not responding on treatment within 12 weeks and whenever clinically indicated at the discretion of the investigator									
Blood Chemistry	D	7.2.2.7		x	x	x			x	x	x		
Mutation analysis	D	7.2.1.1		In case of unconfirmed loss of MMR and as needed									

	Category	Protocol Section	Nilotinib treatment re-initiation phase (NTRI)								End of NTRI phase	Safety Follow-up	Post-Treatment Follow-up (patients discontinued from NTRI phase)
				Every 4 weeks						Every 12 weeks (up to 528 weeks after last patient enters the TFR phase)	within 7 days of last dose	30 days following End of NTRI phase	Every 12 weeks up to 528 weeks after last patient enters the TFR phase
Visit name			**NTRI-W1 (Day1)**	**NTRI-W4**	**NTRI-W8**	**NTRI-W12**	**NTRI-W16**	**NTRI-W20**	**NTRI-W24**	**NTRI-W36 NTRI-W48 NTRI-W60 etc**	**EOT NTRI**	**SAFETY FUP**	**POST TREATMENT FUP**
Week of Treatment re-initiation			**Day1**	**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**W36 - up to 528 weeks after last patient enters the TFR phase**			
End of Phase Disposition page	D	7.1.5									x		x
Safety													
Adverse events / SAE	D	8.1	Continuous										
Concomitant medications	D	6.4	Continuous										
Study Drug administration	D	6.1.1	Continuous										
Patient reported Outcomes													

CCI

	Category	Protocol Section	Nilotinib treatment re-initiation phase (NTRI)								End of NTRI phase	Safety Follow-up	Post-Treatment Follow-up (patients discontinued from NTRI phase)
				Every 4 weeks						Every 12 weeks (up to 528 weeks after last patient enters the TFR phase)	within 7 days of last dose	30 days following End of NTRI phase	Every 12 weeks up to 528 weeks after last patient enters the TFR phase
Visit name			**NTRI-W1 (Day1)**	**NTRI-W4**	**NTRI-W8**	**NTRI-W12**	**NTRI-W16**	**NTRI-W20**	**NTRI-W24**	**NTRI-W36 NTRI-W48 NTRI-W60 etc**	**EOT NTRI**	**SAFETY FUP**	**POST TREATMENT FUP**
Week of Treatment re-initiation			**Day1**	**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**W36 - up to 528 weeks after last patient enters the TFR phase**			
CCI													
Sokal risk category at diagnosis	D	7.2.7	At any time point during the study										
Progression to AP/BC	D	7.1.9											x
Stem cell transplant	D	7.1.9											x
Antineoplastic therapies	D	7.1.9											x
Survival Follow-up	D	7.1.9											x

* only until 15-Sep-2017

Table 7-4 Visit evaluation schedule 4- Nilotinib Treatment Continuation phase (patients not eligible for starting TFR) (NTCT)

	Category	Protocol Section	Nilotinib Treatment Continuation phase (NTCT)					End of Treatment NTCT (within 7 days of last dose if patient discontinue the study)	Safety Follow-up (30 days following End of NTCT phase)	Post-Treatment Follow-up (patients discontinued from the NTCT phase) Every 12 weeks up to 528 weeks after last patient enters the TFR phase
Visit name			**NTCT-W12**	**NTCT-W24**	**NTCT-W36**	**NTCT-W48**	**NTCT-W52**	**EOT NTCT**	**SAFETY FUP**	**POST TREATMENT FUP**
Weeks in the study			**W 64**	**W 76**	**W 88**	**W 100**	**W 104**			
Physical examination	S	7.2.2.1	x	x	x	x		x		
Weight	D	7.2.2.3	x	x	x	x		x		
Vital signs / Blood Pressure / Heart rate	D	7.2.2.2	x	x	x	x		x		
Performance Status	D	7.2.2.4	x	x	x	x		x		
Extramedullar involvement	D	7.2.2.1	x	x	x	x		x		
Laboratory assessments										
Peripheral blood BCR-ABL RQ-PCR	D	7.2.1.1	x	x	x	x		x		
EDTA blood sample for BCR-ABL RQ-PCR (US only)*	D	7.2.1.1	x	x	x	x		x		
ECG	D	7.2.2.9.1				x		x		
Hematology	D	7.2.2.6	x	x	x	x		x		
Serum pregnancy test, if applicable	D	7.2.2.8						x		
Urine pregnancy test, if applicable	D	7.2.2.8	Every 4 weeks							
Bone marrow assessments/cytogenetics, if	D	7.2.1.2	In case of confirmed loss of MMR not responding on treatment within 12 weeks and whenever							

	Category	Protocol Section	Nilotinib Treatment Continuation phase (NTCT)					End of Treatment NTCT (within 7 days of last dose if patient discontinue the study)	Safety Follow-up (30 days following End of NTCT phase)	Post-Treatment Follow-up (patients discontinued from the NTCT phase) Every 12 weeks up to 528 weeks after last patient enters the TFR phase
Visit name			**NTCT-W12**	**NTCT-W24**	**NTCT-W36**	**NTCT-W48**	**NTCT-W52**	**EOT NTCT**	**SAFETY FUP**	**POST TREATMENT FUP**
Weeks in the study			**W 64**	**W 76**	**W 88**	**W 100**	**W 104**			
applicable			clinically indicated at the discretion of the investigator							
Blood Chemistry	D	7.2.2.7	x	x	x	x		x		
Mutational Analysis	D	7.2.1.1	In case of unconfirmed loss of MMR and as needed							
End of Phase Disposition page	D	7.1.5						x		x
Communication of next phase	D						x			
Safety										
Adverse events / SAE	D	8.1	Continuous							
Concomitant medications	D	6.4	Continuous							
Study Drug administration	D	6.1.1	Continuous				x for patient entering the NTCT-P phase			

	Category	Protocol Section	Nilotinib Treatment Continuation phase (NTCT)					End of Treatment NTCT (within 7 days of last dose if patient discontinue the study)	Safety Follow-up (30 days following End of NTCT phase)	Post-Treatment Follow-up (patients discontinued from the NTCT phase) Every 12 weeks up to 528 weeks after last patient enters the TFR phase
Visit name			**NTCT-W12**	**NTCT-W24**	**NTCT-W36**	**NTCT-W48**	**NTCT-W52**	**EOT NTCT**	**SAFETY FUP**	**POST TREATMENT FUP**
Weeks in the study			**W 64**	**W 76**	**W 88**	**W 100**	**W 104**			
Patient Reported Outcomes										
CCI [redacted]										
Sokal risk category at diagnosis	D	7.2.7	At any time point during the study							
Progression to AP/BC	D	7.1.9								x
Stem cell transplant	D	7.1.9								x
Antineoplastic therapies	D	7.1.9								x
Survival Follow-up	D	7.1.9								x

* only until 15-Sep-2017

Table 7-5 Visit evaluation schedule 5- Nilotinib Treatment-Free Remission phase-2 (TFR-2)

	Category	Protocol Section	Nilotinib Treatment-Free Remission phase-2 (TFR-2)			End of TFR-2 phase (if patient discontinue the study and is not entering re-initiation-2 phase)	Safety Follow-up (30 days following End of TFR-2 phase)	Post-Treatment Follow-up (patients discontinued from the TFR-2 phase and not re-initiating nilotinib treatment on study) Every 12 weeks up to 528 weeks after last patient enters the TFR phase
Visit Name			**TFR-2-W4 - TFR-2-W48**	**TFR-2-W54 - TFR-2-W96**	**TFR-2-W108 - up to 528 weeks after last patient enters the TFR phase**	**EOTFR-2**	**SAFETY FUP**	**POST TREATMENT FUP**
Weeks in the study			**W108 - W152**	**W158 - W200**	**W212 - up to 528 weeks after last patient enters the TFR phase**			
Physical examination	S	7.2.2.1	Every 12 weeks					
Weight	D	7.2.2.3	Every 12 weeks			x		
Vital signs / Blood Pressure / Heart Rate	D	7.2.2.2	Every 12 weeks			x		
Performance Status	D	7.2.2.4	Every 12 weeks			x		
Extramedullar involvement	D	7.2.2.1	Every 4 weeks	Every 6 weeks	Every 12 weeks	x		
Laboratory assessments								
Peripheral blood BCR-ABL RQ-PCR	D	7.2.1.1	Every 4 weeks	Every 6 weeks	Every 12 weeks	x		
EDTA blood sample for BCR-ABL RQ-PCR (US only)*	D	7.2.1.1	Every 4 weeks	Every 6 weeks	Every 12 weeks	x		
ECG	D	7.2.2.9.1				x		
Hematology	D	7.2.2.6	Every	Every	Every	x		

	Category	Protocol Section	Nilotinib Treatment-Free Remission phase-2 (TFR-2)			End of TFR-2 phase (if patient discontinue the study and is not entering re-initiation-2 phase)	Safety Follow-up (30 days following End of TFR-2 phase)	Post-Treatment Follow-up (patients discontinued from the TFR-2 phase and not re-initiating nilotinib treatment on study) Every 12 weeks up to 528 weeks after last patient enters the TFR phase
Visit Name			**TFR-2-W4 - TFR-2-W48**	**TFR-2-W54 - TFR-2-W96**	**TFR-2-W108 - up to 528 weeks after last patient enters the TFR phase**	**EOTFR-2**	**SAFETY FUP**	**POST TREATMENT FUP**
Weeks in the study			**W108 - W152**	**W158 - W200**	**W212 - up to 528 weeks after last patient enters the TFR phase**			
			4 weeks	6 weeks	12 weeks			
Bone marrow assessments/cytogenetics, if applicable	D	7.2.1.2	In case of confirmed loss of MMR not responding on treatment within 12 weeks and whenever clinically indicated at the discretion of the investigator					
Blood Chemistry	D	7.2.2.7	Every 12 weeks			x		
Serum Pregnancy test, if applicable	D	7.2.2.8				x		
Urine pregnancy test, if applicable	D	7.2.2.8	Every 4 weeks					
Mutation Analysis	D	7.2.1.1	In case of unconfirmed loss of MMR and as needed					
End of Phase Disposition page	D	7.1.5				x		x
Safety								
Adverse events / SAE	D	8.1	Continuous					
Concomitant medications	D	6.4	Continuous					

	Category	Protocol Section	Nilotinib Treatment-Free Remission phase-2 (TFR-2)			End of TFR-2 phase (if patient discontinue the study and is not entering re-initiation-2 phase)	Safety Follow-up (30 days following End of TFR-2 phase)	Post-Treatment Follow-up (patients discontinued from the TFR-2 phase and not re-initiating nilotinib treatment on study) Every 12 weeks up to 528 weeks after last patient enters the TFR phase
Visit Name			**TFR-2-W4 - TFR-2-W48**	**TFR-2-W54 - TFR-2-W96**	**TFR-2-W108 - up to 528 weeks after last patient enters the TFR phase**	**EOTFR-2**	**SAFETY FUP**	**POST TREATMENT FUP**
Weeks in the study			**W108 - W152**	**W158 - W200**	**W212 - up to 528 weeks after last patient enters the TFR phase**			
Patient reported Outcomes								
CCI								
Progression to AP/BC	D	7.1.9						x
Sokal risk category at diagnosis	D	7.2.7	At any time point during the study					
Stem cell transplant	D	7.1.9						x
Antineoplastic therapies	D	7.1.9						x
Survival Follow-up	D	7.1.9						x

* only until 15-Sep-2017

Table 7-6 Visit evaluation schedule 6 - Nilotinib treatment re-initiation 2 phase (patients after unsuccessful Treatment-Free Remission-2) (NTRI-2)

	Category	Protocol Section	Nilotinib treatment re-initiation 2 phase (NTRI-2)								End of NTRI-2 phase	Safety Follow-up	Post-Treatment Follow-up (patients discontinued from NTRI-2 phase)
				Every 4 weeks						Every 12 weeks (up to 528 weeks after last patient enters the TFR phase)	Within 7 days of last dose	30 days following End of NTRI-2 phase	Every 12 weeks up to 528 weeks after last patient enters the TFR phase
Visit name			**NTRI-2-W1 (Day1)**	**NTRI-2-W4**	**NTRI-2-W8**	**NTRI-2W12**	**NTRI-2-W16**	**NTRI-2-W20**	**NTRI-2-W24**	**NTRI-2-W36 NTRI-2-W48 NTRI-2-W60 etc**	**EOT NTRI-2**	**SAFETY FUP**	**POST TREATMENT FUP**
Weeks in the Treatment-reinitiation-2			**Day 1**	**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**W36 - up to 528 weeks after last patient enters the TFR phase**			
Physical examination	S	7.2.2.1		x	x	x			x	x	x		
Weight	D	7.2.2.3		x	x	x			x	x	x		
Vital signs /Blood Pressure / Heart Rate	D	7.2.2.2		x	x	x			x	x	x		
Performance Status	D	7.2.2.4		x	x	x			x	x	x		
Extramedullar involvement, if applicable	D	7.2.2.1		x	x	x	x	x	x	x	x		
Laboratory assessments													
Peripheral blood BCR-ABL	D	7.2.1.1		x	x	x	x	x	x	x	x		

	Category	Protocol Section	Nilotinib treatment re-initiation 2 phase (NTRI-2)							End of NTRI-2 phase	Safety Follow-up	Post-Treatment Follow-up (patients discontinued from NTRI-2 phase)
				Every 4 weeks						Every 12 weeks (up to 528 weeks after last patient enters the TFR phase)	Within 7 days of last dose	30 days following End of NTRI-2 phase	Every 12 weeks up to 528 weeks after last patient enters the TFR phase
Visit name			**NTRI-2-W1 (Day1)**	**NTRI-2-W4**	**NTRI-2-W8**	**NTRI-2W12**	**NTRI-2-W16**	**NTRI-2-W20**	**NTRI-2-W24**	**NTRI-2-W36 NTRI-2-W48 NTRI-2-W60 etc**	**EOT NTRI-2**	**SAFETY FUP**	**POST TREATMENT FUP**
Weeks in the Treatment-reinitiation-2			**Day 1**	**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**W36 - up to 528 weeks after last patient enters the TFR phase**			
RQ-PCR													
EDTA blood sample for BCR-ABL RQ-PCR (US only)*	D	7.2.1.1		x	x	x	x	x	x	x	x		
ECG	D	7.2.2.9.1	x	x						W48 and every 48 weeks thereafter up to 528 weeks after last patient enters the TFR phase			
Hematology	D	7.2.2.6		x	x	x	x	x	x	x	x		
Serum pregnancy test, if applicable	D	7.2.2.8									x		
Urine pregnancy test, if applicable	D	7.2.2.8		Every 4 weeks									
Bone marrow	D	7.2.1.2		In case of confirmed loss of MMR not responding on									

	Category	Protocol Section	Nilotinib treatment re-initiation 2 phase (NTRI-2)								End of NTRI-2 phase	Safety Follow-up	Post-Treatment Follow-up (patients discontinued from NTRI-2 phase)
				Every 4 weeks						Every 12 weeks (up to 528 weeks after last patient enters the TFR phase)	Within 7 days of last dose	30 days following End of NTRI-2 phase	Every 12 weeks up to 528 weeks after last patient enters the TFR phase
Visit name			**NTRI-2-W1 (Day1)**	**NTRI-2-W4**	**NTRI-2-W8**	**NTRI-2W12**	**NTRI-2-W16**	**NTRI-2-W20**	**NTRI-2-W24**	**NTRI-2-W36 NTRI-2-W48 NTRI-2-W60 etc**	**EOT NTRI-2**	**SAFETY FUP**	**POST TREATMENT FUP**
Weeks in the Treatment-reinitiation-2			**Day 1**	**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**W36 - up to 528 weeks after last patient enters the TFR phase**			
assessments/cytogenetics, if applicable				treatment within 12 weeks and whenever clinically indicated at the discretion of the investigator									
Blood Chemistry	D	7.2.2.7		x	x	x			x	x	x		
Mutation analysis	D	7.2.1.1		In case of unconfirmed loss of MMR and as needed									
End of Disposition page	D	7.1.5									x		x
Safety	S												
Adverse events / SAE	D	8.1	Continuous										
Concomitant medications	D	6.4	Continuous										
Study Drug administration	D	6.1.1	Continuous										

	Category	Protocol Section	Nilotinib treatment re-initiation 2 phase (NTRI-2)								End of NTRI-2 phase	Safety Follow-up	Post-Treatment Follow-up (patients discontinued from NTRI-2 phase)
				Every 4 weeks						Every 12 weeks (up to 528 weeks after last patient enters the TFR phase)	Within 7 days of last dose	30 days following End of NTRI-2 phase	Every 12 weeks up to 528 weeks after last patient enters the TFR phase
Visit name			**NTRI-2-W1 (Day1)**	**NTRI-2-W4**	**NTRI-2-W8**	**NTRI-2W12**	**NTRI-2-W16**	**NTRI-2-W20**	**NTRI-2-W24**	**NTRI-2-W36 NTRI-2-W48 NTRI-2-W60 etc**	**EOT NTRI-2**	**SAFETY FUP**	**POST TREATMENT FUP**
Weeks in the Treatment-reinitiation-2			**Day 1**	**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**W36 - up to 528 weeks after last patient enters the TFR phase**			
Patient reported Outcomes													
CCI [redacted]													
Sokal risk category at diagnosis	D	7.2.7	At any time point during the study										
Progression to AP/BC	D	7.1.9											x
Stem cell transplant	D	7.1.9											x
Antineoplastic therapies	D	7.1.9											x
Survival Follow-up	D	7.1.9											x

	Category	Protocol Section	Nilotinib treatment re-initiation 2 phase (NTRI-2)								End of NTRI-2 phase	Safety Follow-up	Post-Treatment Follow-up (patients discontinued from NTRI-2 phase)
				Every 4 weeks						Every 12 weeks (up to 528 weeks after last patient enters the TFR phase)	Within 7 days of last dose	30 days following End of NTRI-2 phase	Every 12 weeks up to 528 weeks after last patient enters the TFR phase
Visit name			NTRI-2-W1 (Day1)	NTRI-2-W4	NTRI-2-W8	NTRI-2W12	NTRI-2-W16	NTRI-2-W20	NTRI-2-W24	NTRI-2-W36 NTRI-2-W48 NTRI-2-W60 etc	EOT NTRI-2	SAFETY FUP	POST TREATMENT FUP
Weeks in the Treatment-reinitiation-2			Day 1	W4	W8	W12	W16	W20	W24	W36 - up to 528 weeks after last patient enters the TFR phase			

* only until 15-Sep-2017

Table 7-7 Visit evaluation schedule 7-Nilotinib treatment prolonged continuation phase (patients not eligible for starting TFR-2) (NTCT-P)

	Category	Protocol Section	Nilotinib Prolonged Continuation (NTCT-P)	End of NTCT-P within 7 days of last dose	Safety Follow up (30 days following End of NTCT-P phase)	Post-treatment Follow-up (patients discontinued from the NTCT-P phase) Every 12 weeks up to 528 weeks after last patient enters the TFR phase
Visit Name			**NTCT-P W12 up to 528 weeks after last patient enters the TFR phase**	**EOT NTCT-P**	**SAFETY FUP**	**POST TREATMENT FUP**
Weeks in the study			**W116, W128, up to 528 weeks after last patient enters the TFR phase**			
Physical examination	S	7.2.2.1	Every 12 weeks			
Weight	D	7.2.2.3	Every 12 weeks	x		
Vital signs / Blood Pressure / Heart Rate	D	7.2.2.2	Every 12 weeks	x		
Performance Status	D	7.2.2.4	Every 12 weeks	x		
Extramedullar involvement	D	7.2.2.1	Every 12 weeks	x		
Laboratory assessments						
Peripheral blood BCR-ABL RQ-PCR	D	7.2.1.1	Every 12 weeks	x		
EDTA blood sample for BCR-ABL RQ-PCR (US only)*	D	7.2.1.1	Every 12 weeks	x		
ECG	D	7.2.2.9.1	W48 and every 48 weeks thereafter up to 528 weeks after last patient enters the TFR phase	x		
Hematology	D	7.2.2.6	Every 12 weeks	x		
Serum Pregnancy test, if applicable	D	7.2.2.8		x		

	Category	Protocol Section	Nilotinib Prolonged Continuation (NTCT-P)	End of NTCT-P within 7 days of last dose	Safety Follow up (30 days following End of NTCT-P phase)	Post-treatment Follow-up (patients discontinued from the NTCT-P phase) Every 12 weeks up to 528 weeks after last patient enters the TFR phase
Visit Name			**NTCT-P W12 up to 528 weeks after last patient enters the TFR phase**	**EOT NTCT-P**	**SAFETY FUP**	**POST TREATMENT FUP**
Weeks in the study			**W116, W128, up to 528 weeks after last patient enters the TFR phase**			
Urine pregnancy test, if applicable	D	7.2.2.8	Every 4 weeks			
Bone marrow assessments/cytogenetics, if applicable	D	7.2.1.2	In case of confirmed loss of MMR not responding on treatment within 12 weeks and whenever clinically indicated at the discretion of the investigator			
Blood Chemistry	D	7.2.2.7	Every 12 weeks	x		
Mutation Analysis	D	7.2.1.1	In case of unconfirmed loss of MMR and as needed			
End of Disposition page	D	7.1.5		x		x
Safety						
Adverse events / SAE	D	8.1	Continuous			
Concomitant medications	D	6.4	Continuous			
Study Drug administration	D	6.1.1	Continuous			
Patient reported Outcomes						

CCI

	Category	Protocol Section	Nilotinib Prolonged Continuation (NTCT-P)	End of NTCT-P within 7 days of last dose	Safety Follow up (30 days following End of NTCT-P phase)	Post-treatment Follow-up (patients discontinued from the NTCT-P phase) Every 12 weeks up to 528 weeks after last patient enters the TFR phase
Visit Name			**NTCT-P W12 up to 528 weeks after last patient enters the TFR phase**	**EOT NTCT-P**	**SAFETY FUP**	**POST TREATMENT FUP**
Weeks in the study			**W116, W128, up to 528 weeks after last patient enters the TFR phase**			
CCI						
Sokal risk category at diagnosis	D	7.2.7	At any time point during the study			
Progression to AP/BC	D	7.1.9				x
Stem cell transplant	D	7.1.9				x
Antineoplastic therapies	D	7.1.9				x
Survival Follow-up	D	7.1.9				x

* only until 15-Sep-2017

7.1.1 Pre-screening

Written informed consent must be obtained before pre-screening is performed.

The pre-screening PCR blood samples will be analyzed by a Novartis designated laboratory with validated PCR technology that has a sensitivity of at least MR4.5. When MR4.5 cannot be assessed due to logistical or quality issues (e.g. sample lost, sample not arrived frozen, insufficient ABL copy numbers) repeated pre-screenings for the BCR-ABL transcript level are allowed as soon as possible.

When a patient has not achieved MR4.5 at pre-screening, repeated pre-screening for the BCR-ABL transcript level is allowed after a minimum additional period of 12 weeks of nilotinib. This pre-screening can be repeated until the end of the recruitment. It is under the discretion of the investigator how many times a patient will be re-screened.

If the result confirms a patient is in MR4.5 (BCR-ABL $\leq$0.0032% (IS)), he/she will be screened for eligibility prior to Day 1.

Hematology, chemistry baseline assessments and serum pregnancy test can be performed at pre-screening. Patients with potassium, and/or magnesium, and/or total calcium levels that are < LLN at pre-screening, must have their potassium, and/or magnesium, and/or calcium replenished through supplementation and the levels must be within normal limits prior to the first dose of study drug.

7.1.2 Screening

Written informed consent must be obtained before any study specific medical procedures are performed. Screening visit occurs before Day 1.

During the screening visit, inclusion and exclusion criteria will be assessed. For details of assessments required during screening please refer to Table 7-1.

Laboratory baseline assessments (including hematology, chemistry and serum pregnancy test (if not done at pre-screening)), physical examination including performance status, height, weight and vital signs must be performed prior to Visit NTCS-D1/study Day 1. Patients with potassium, and/or magnesium, and/or total calcium levels that are < LLN at screening, must have their potassium, and/or magnesium, and/or calcium replenished through supplementation and the levels must be within normal limits prior to the first dose of study drug.

In exceptional cases (after discussion with and agreement by Novartis) the pre-screening and screening visits can be combined.

If not all screening assessments can be performed in the 28 day screening period, re-screening starting with the pre-screening assessment is possible after discussion with and agreement by Novartis.

7.1.2.1 Eligibility screening

Following registering in the IRT for screening, patient eligibility will be checked once all screening procedures are completed. The eligibility check will be embedded in the IRT system. Please refer and comply with detailed guidelines in the IRT manual.

7.1.2.2 Information to be collected on screening failures

Patients who sign the study 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 the Screening Phase Disposition Page. The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for Screening Failure patients. 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).

7.1.2.3 Patient demographics and other baseline characteristics

Patient demographics and baseline characteristics collected will include the following: date of birth, gender (and child bearing potential for female), race and ethnicity, height, weight, all relevant medical history including CML disease history, prior antineoplastic medication-nilotinib and other medication.

Physical examination including extramedullary involvement, performance status, vital signs, ECGs, and laboratory assessments will be performed at screening.

Significant findings that were present prior to the signing of informed consent must be included in the Relevant Medical History/Current Medical Conditions page on the subject's eCRF. Significant new findings that begin or worsen after informed consent must be recorded on the AE page of the patient's eCRF.

7.1.3 Run-in period

Not applicable.

7.1.4 Treatment period

Patients are planned to remain on study for at least 580 weeks (52 weeks of nilotinib consolidation and up to 528 weeks after the last patient enters the nilotinib TFR phase).

Patient visits for all bi-weekly visits (every two weeks) should be completed on the designated day (with an allowed "visit window" of +/- 5 days). Patient visits for all 4-weekly visits should be completed on the designated day (with an allowed "visit window" of +/- 8 days) or as close to it as possible. Patient visits for all 6-weekly or 12-weekly visits should be completed on the designated day (with an allowed "visit window" of +/- 15 days) or as close to it as possible. A delayed visit will have no impact on the following planned visit in order to avoid cumulative additional weeks.

During the consolidation phase, all patients will receive 52 weeks of nilotinib treatment at the planned dose of 300 mg BID (or at a reduced dose level of 400 mg QD if require from the perspective of tolerance), or until patient experiences unacceptable toxicity, disease progression, death, lost to follow-up and/or treatment is discontinued at the discretion of the investigator or withdrawal of consent. During the first 52 weeks, there will be 12-weekly scheduled visits and PCR assessments. Patients not fulfilling the protocol definition of durable Minimal Residual Disease (see Section 2.2) at the end of the nilotinib consolidation phase, will stay on nilotinib treatment for another 52 weeks. Patients will continue to have scheduled

visits every 12 weeks. Assessments for consolidation and treatment continuation phases are specified in Table 7-1 and Table 7-4.

During the nilotinib TFR phase, patients will have PCR assessments every 4 weeks for the first 48 weeks, every 6 weeks for the following 48 weeks, and every 12 weeks during the last period. The PCR assessment schedules as well as other study related assessments are specified in Table 7-2.

During the TFR phase, patients with a loss of MR4.0 will have PCR assessments biweekly (every 2 weeks) to identify loss of MMR early. Biweekly (every 2 weeks) monitoring will begin upon loss of MR4.0 and will end at one of the following time points:

1. When the patient loses MMR (and therefore re-initiates nilotinib treatment),
2. When the BCR-ABL transcript levels return to a range between MR4.0 and MR4.5.
3. When the BCR-ABL transcript levels remain lower than MMR for 4 consecutive measurements (8 weeks from initial loss of MR4.0). At this point, the patient may proceed to monthly BCR-ABL monitoring.

   If after additional 12 consecutive measurements on a monthly monitoring the BCR-ABL transcript levels remain lower than MMR (56 weeks from initial loss of MR4.0) the patient may proceed to 6 weeks BCR-ABL monitoring.

   If after additional 8 consecutive measurements on a 6 weeks monitoring the BCR-ABL transcript levels remain lower than MMR (104 weeks from initial loss of MR4.0) the patient may proceed to 12 weeks BCR-ABL monitoring.

During the TFR phase, patients with a loss of MMR defined as BCR-ABL > 0.1% IS assessed in a single blood sample (confirmation of loss of MMR is not required) will mandate re-initiation of nilotinib treatment at 300 mg BID or at a reduced dose level of 400 mg QD if required from the perspective of tolerance within 5 weeks after the collection date of the blood sample demonstrating loss of MMR and up to 528 weeks after the last patient enters the nilotinib TFR phase, or until patient experiences unacceptable toxicity, disease progression, death, lost to follow-up and/or treatment is discontinued at the discretion of the investigator or withdrawal of consent.

During nilotinib treatment re-initiation, BCR-ABL level will be monitored by PCR every 4 weeks for the first 24 weeks and then every 12 weeks thereafter in patients who regained MMR. The frequency of BCR-ABL monitoring in patients not regaining MMR within the first 24 weeks after re-initiation of treatment will be at least every 12 weeks or more frequently as clinically indicated. Electrocardiograms (ECG) in triplicates will be collected prior to the first dose (on Day 1 of re-initiation phase and before first dose), after 4 weeks of treatment and annually thereafter.

During nilotinib treatment re-initiation, physical examination and other laboratory assessments will be performed every 4 weeks for the first 12 weeks after re-initiation of treatment, every 12 weeks thereafter and whenever clinically indicated. The PCR assessment schedules as well as other study related assessments for nilotinib treatment re-initiation are specified in Table 7-3.

During the TFR-2 phase, patients will have PCR assessments every 4 weeks for the first 48 weeks, every 6 weeks for the following 48 weeks, and every 12 weeks during the last period.

The PCR assessment schedules as well as other study related assessments for TFR-2 are specified in Table 7-5.

During the TFR-2 phase, patients with a loss of MR4.0 will have PCR assessments every 2 weeks to identify loss of MMR early. Biweekly monitoring will begin upon loss of MR4.0 and will end at one of the following time points:

1. When the patient loses MMR (and therefore re-initiates nilotinib treatment),
2. When the BCR-ABL transcript levels return to a range between MR4.0 and MR4.5.
3. When the BCR-ABL transcript levels remain lower than MMR for 4 consecutive measurements (8 weeks from initial loss of MR4.0). At this point, the patient may proceed to monthly BCR-ABL monitoring.

If after additional 12 consecutive measurements on a monthly monitoring the BCR-ABL transcript levels remain lower than MMR (56 weeks from initial loss of MR4.0) the patient may proceed to 6 weeks BCR-ABL monitoring.
If after additional 8 consecutive measurements on a 6 weeks monitoring the BCR-ABL transcript levels remain lower than MMR (104 weeks from initial loss of MR4.0) the patient may proceed to 12 weeks BCR-ABL monitoring.

During the TFR-2 phase, patients with a loss of MMR defined as BCR-ABL > 0.1% IS assessed in a single blood sample (confirmation of loss of MMR is not required) will mandate re-initiation of nilotinib treatment at 300 mg BID or at a reduced dose level of 400 mg QD if required from the perspective of tolerance within 5 weeks after the collection date of the blood sample demonstrating loss of MMR and up to 528 weeks after the last patient enters the nilotinib TFR phase, or until patient experiences unacceptable toxicity, disease progression, death, lost to follow-up and/or treatment is discontinued at the discretion of the investigator or withdrawal of consent.

During nilotinib treatment re-initiation-2, BCR-ABL level will be monitored by PCR every 4 weeks for the first 24 weeks and then every 12 weeks thereafter in patients who regained MMR. The frequency of BCR-ABL monitoring in patients not regaining MMR within the first 24 weeks after re-initiation of treatment will be at least every 12 weeks or more frequently as clinically indicated. Electrocardiograms (ECG) in triplicates will be collected prior to the first dose (on Day 1 of re-initiation phase-2 and before first dose), after 4 weeks of treatment and annually thereafter.

During nilotinib treatment re-initiation-2, physical examination and other laboratory assessments will be performed every 4 weeks for the first 12 weeks after re-initiation of treatment, every 12 weeks thereafter, and whenever clinically indicated. The PCR assessment schedules as well as other study related assessments for nilotinib treatment re-initiation are specified in Table 7-6.

Patients who are not eligible to enter TFR-2 phase will have nilotinib prolonged treatment continuation for up to 528 weeks after the last patient enters the TFR phase, or until the patient experiences unacceptable toxicity, disease progression, death, lost to follow-up and/or the treatment is discontinued at the discretion of the investigator or withdrawal of consent. PCR as well as other laboratory assessments will be performed every 12 weeks during this

period. The PCR assessment schedules as well as other study related assessments for TFR-2 are specified in Table 7-7.

The patients are advised to adhere to the food restrictions during the treatment (fasting status regarding study treatment administration, avoidance of prohibited concomitant medication).

For details of assessments, refer to Table 7-1, Table 7-2, Table 7-3, Table 7-4, Table 7-5, Table 7-6 and Table 7-7.

7.1.5 Discontinuation of Study Treatment or from TFR phases

Patients may voluntarily discontinue from the study for any reason without prejudice to his/her future medical care and at any time without penalty. If a patient decides to discontinue from the study, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for this decision and record this information in the patient's chart and on the appropriate CRF pages; however the patient is not obliged to give a reason for this decision. They may be considered withdrawn if they state an intention to withdraw, fail to return for visits, or become lost to follow-up for any other reason.

The investigator should discontinue study for a given patient if, on balance, he/she believes that continuation would be detrimental to the patient's well-being.

Patients may also be discontinued from the study if any of the following occur: discovery of patient ineligibility; errors in treatment compliance [study treatment, other prescribed or non-prescribed medications]; missed/unscheduled/offschedule/incomplete/incorrect assessments; major protocol deviation.

Patients must be discontinued if pregnancy occurs during the nilotinib treatment consolidation phase, nilotinib treatment re-initiation phases, nilotinib treatment continuation, and the prolonged continuation phase. In case of a pregnancy during TFR phase, the pregnant woman can stay in TFR phases as long as no nilotinib treatment is needed, but she must be discontinued from the study if she loses MMR.

In addition to the general discontinuation criteria, the following study specific criteria will also require study discontinuation:

In the event of disease progression the patient is discontinued from the study. The following events are considered disease progression.

1. 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)
2. Accelerated phase (AP) as defined by any of the following:
   - $\geq$ 15% blasts in the peripheral blood or bone marrow aspirate, but < 30% blasts in both the peripheral blood and bone marrow aspirate
   - $\geq$ 30% blasts plus promyelocytes in peripheral blood or bone marrow aspirate
   - $\geq$ 20% basophils in the peripheral blood
   - Thrombocytopenia (<100 x 10^9/L) that is unrelated to therapy
3. Blast crisis (BC) as defined by any of the following:

- ≥ 30% blasts in peripheral blood or bone marrow aspirate
- Appearance of extramedullary involvement other than hepatosplenomegaly proven by biopsy (i.e., chloroma).

Patients who discontinue study should NOT be considered withdrawn from the study. They should return for the assessments indicated in Section 7.1 choosing the phase specific table of assessments. If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, email, letter) should be made to contact them as specified in Section 7.1.8.

Patients who discontinue study should undergo an end of study visit and then be discontinued from the trial or enter the post-treatment follow-up phase (survival, antineoplastic therapies, stem cell transplant and progression).

The investigator must also contact the IRT to register the patient's discontinuation from study.

7.1.6 Withdrawal of consent

Patients may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a patient:

- Does not want to participate in the study anymore, and
- Does not allow further collection of personal data

In this situation, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the patient's decision to withdraw his/her consent and record this information.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the patient are not allowed unless safety findings require communicating or follow-up.

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the patient's study withdrawal should be made as detailed in the assessment table.

Novartis will continue to keep and use collected study information (including any data resulting from the analysis of a patient's samples until their time of withdrawal) according to applicable law.

For US and Japan: All biological samples not yet analyzed at the time of withdrawal may still be used for further testing/analysis in accordance with the terms of this protocol and of the informed consent form.

For EU and RoW: All biological samples not yet analyzed at the time of withdrawal will no longer be used, unless permitted by applicable law. They will be stored according to applicable legal requirements.

7.1.7 Follow up for Safety Evaluations

All patients must have safety evaluations for 30 days after the last dose of study treatment or the last day in TFR phase.

Data collected should be added to the Adverse Events CRF and the Concomitant Medications CRF.

7.1.8 Lost to follow up

For patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw consent, the investigator should show "due diligence" by contacting the patients, family, or family physician as agreed in the informed consent and by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc. A patient should not be considered lost to follow-up until due diligence has been completed. Patients lost to follow up should be recorded as such on the appropriate Disposition CRF.

7.1.9 Post-treatment Follow-up

Patients who terminate the study early will be followed every 12 weeks up to 528 weeks after the last patient enters the nilotinib TFR phase. Survival information, stem cell transplantation, antineoplastic therapy, as well as information on the status of the patient's disease (i.e. disease progression to AP/BC according to protocol definition, or CML related death) will be collected.

7.2 Assessment types

7.2.1 Efficacy assessments

7.2.1.1 Molecular response

MR will be assessed in all patients. Levels of BCR-ABL transcripts will be determined by real-time quantitative PCR (RQ-PCR) testing of peripheral blood and analyzed at a Novartis designated laboratory with validated PCR technology that has a sensitivity of at least 4.5 logs. The percent ratio of BCR-ABL transcripts versus control gene transcripts converted to IS will be calculated for each sample.

- RQ-PCR will be monitored every 12 weeks during the nilotinib consolidation phase. If during this phase the sample is missing during transit to the PCR laboratory, or the PCR result is difficult to interpret, or if the PCR sample was not collected, a subsequent unscheduled visit sample must be collected within 4 weeks.
- RQ-PCR will continue to be monitored every 12 weeks during nilotinib treatment continuation and nilotinib prolonged treatment continuation.
- RQ-PCR will be monitored during the nilotinib treatment-free remission phase every 4 weeks for the first 48 weeks, every 6 weeks for the following 48 weeks, and every 12 weeks during the last period. If during this phase the sample is missing during transit to the PCR laboratory, or the PCR result is difficult to interpret, or if the PCR sample was not collected, a subsequent unscheduled visit sample must be collected within 4 weeks either at the next scheduled visit (4-weekly PCR assessments during the first 48 weeks of TFR), or as an unscheduled visit.

- If a patient experienced loss of MR4.0 during TFR phase, PCR assessments will be performed every 2 weeks to identify loss of MMR early. Biweekly monitoring will begin upon loss of MR4.0 and will end at one of the following time points:
  - When the patient loses MMR (and therefore re-initiates nilotinib treatment)
  - When the BCR-ABL transcript levels return to a range between MR4.0 and MR4.5
  - When the BCR-ABL transcript levels remain lower than MMR for 4 consecutive measurements (8 weeks from initial loss of MR4.0). At this point, the patient may proceed to monthly BCR-ABL monitoring

    If after additional 12 consecutive measurements on a monthly monitoring the BCR-ABL transcript levels remain lower than MMR (56 weeks from initial loss of MR4.0) the patient may proceed to 6 weeks BCR-ABL monitoring.
    If after additional 8 consecutive measurements on a 6 weeks monitoring the BCR-ABL transcript levels remain lower than MMR (104 weeks from initial loss of MR4.0) the patient may proceed to 12 weeks BCR-ABL monitoring.
- If a patient experienced loss of MMR during the nilotinib TFR phase and re-initiated nilotinib treatment, RQ-PCR will be monitored every 4 weeks for the first 24 weeks, and then once every 12 weeks thereafter in patients who regained MMR.
- RQ-PCR during TFR-2 will be monitored every 4 weeks for the first 48 weeks, every 6 weeks for the following 48 weeks, and every 12 weeks during the last period of 432 weeks. If during this phase the sample is missing during transit to the central PCR laboratory, or the PCR result is difficult to interpret, or if the PCR sample was not collected, a subsequent unscheduled visit sample must be collected within 4 weeks either at the next scheduled visit (every 4 weeks PCR assessments during the first 48 weeks of TFR), or as an unscheduled visit.
- If a patient experienced loss of MR4.0 during the TFR-2 phase, PCR assessments will be performed every 2 weeks to identify loss of MMR early. Biweekly monitoring will begin upon loss of MR4.0 and will end at one of the following time points:
  - When the patient loses MMR (and therefore re-initiates nilotinib treatment)
  - When the BCR-ABL transcript levels return to a range between MR4.0 and MR4.5
  - When the BCR-ABL transcript levels remain lower than MMR for 4 consecutive measurements (8 weeks after initial loss of MR4.0). At this point, the patient may proceed to monthly BCR-ABL monitoring.

    If after additional 12 consecutive measurements on a monthly monitoring the BCR-ABL transcript levels remain lower than MMR (56 weeks from initial loss of MR4.0) the patient may proceed to 6 weeks- BCR-ABL monitoring.
    If after additional 8 consecutive measurements on a 6 weeks monitoring the BCR-ABL transcript levels remain lower than MMR (104 weeks from initial loss of MR4.0) the patient may proceed to 12 weeks BCR-ABL monitoring.
- If a patient experienced loss of MMR during the TFR-2 and re-initiate nilotinib treatment, RQ-PCR will be monitored every 4 weeks for the first 24 weeks, and then once every 12 weeks thereafter in patients who regained MMR.

Details on scheduling and sample collection are described in Table 7-1, Table 7-2, Table 7-3, Table 7-4, Table 7-5, Table 7-6 and Table 7-7. Molecular response and related variables are defined as the following:

- MMR – BCR-ABL ≤ 0.1% (IS)
- MR4.0 – BCR-ABL ≤ 0.01% (IS)
- MR4.5 – BCR-ABL ≤0.0032% (IS).

Mutational analysis will be performed by Sanger sequencing when a patient demonstrates unconfirmed loss of MMR or as needed at a time where BCR-ABL copy numbers are compatible with the assay sensitivity. If result is positive for a mutation, analysis will be performed every 12 weeks until the result is negative (no mutation) or at the discretion of the investigator. Mutational analysis will also be performed at a Novartis designated laboratory. If BCR-ABL mutations are detected in patients who have lost MMR, discussion should be followed between the Novartis clinical study team, the Principal Investigator and the Study Steering Committee (SSC).

During the study, peripheral blood samples will be collected into PAXgene™ Blood RNA tubes for all RQ-PCR assessments. In US only, additional peripheral blood samples will also be collected into EDTA tubes for RQ-PCR assessments. These EDTA samples are planned to be used in the development of a diagnostic test (e.g., for assessing the equivalency between both blood collection methods). Those tubes will be included in the sample collection kits and provided to each site by the central laboratory vendor. Detailed instructions for the collection, handling, and shipment of RQ-PCR and mutation samples are outlined in the [CAMN107I2201 Laboratory Manual]. The collection into EDTA tubes for RQ-PCR assessments (US only) is no longer necessary since 15-Sep-2017 as no more data needs to be collected for the development of a diagnostic test.

7.2.1.2 Bone marrow analysis and cytogenetics

Cytogenetic response will be assessed as the percentage of Ph+ metaphases in the bone marrow and is defined as the following (a review of a minimum of 20 metaphases is required):

- Complete (CCyR) - 0% Ph+ metaphases
- Partial (PCyR) - >0 to 35% Ph+ metaphases
- Major (MCyR) - 0 to 35% Ph+ metaphases
- Minor (mCyR) - >35 to 65% Ph+ metaphases
- Minimal - >65 to 95% Ph+ metaphases
- None - >95 to 100% Ph+ metaphases.

Bone marrow aspirate for cytogenetic analyses will be performed when a patient has loss of MMR during the consolidation phase, continuation phase or prolonged continuation phase or when a patient's BCR-ABL ratio has risen to >1% IS (equivalent to loss of CCyR, or when a patient has a loss of CHR under treatment.

In patients who lost MMR during TFR (or TFR-2) and were re-initiated with nilotinib treatment, a bone marrow aspirate must be performed in case of not responding to treatment or not achieving MMR after 12 weeks of nilotinib re-initiation, or whenever indicated at the discretion of the investigator.

Loss of CHR is defined as the appearance of any of the following, confirmed by a second determination ≥ 4 weeks later:

- WBC count that rises to > 20.0 x 10^9/L
- Platelet count that rises to ≥ 600 x 10^9/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.

A minimum of 20 metaphases must be examined in each bone marrow sample. Quantification of the percentage of Ph+ chromosome metaphases, number of metaphases, number positive for Ph chromosome, additional chromosomal abnormalities as well as data from cytologic evaluation (microscopic analysis) of percentage of blasts and promyelocytes will be recorded on the Bone Marrow eCRF. These exams will be performed and analyzed locally. Fluorescent In-situ hybridization (FISH) analysis will not be accepted.

7.2.2 Safety and tolerability assessments

Safety will be monitored by the assessments described below as well as collecting of the adverse events at every visit. For details on AE collection and reporting, refer to Section 8. Significant findings that were present prior to the signing of informed consent must be included in the Relevant Medical History/Current Medical Conditions page on the patient's eCRF. Significant new findings that begin or worsen after informed consent must be recorded on the AE page of the patient's eCRF.

7.2.2.1 Physical examination

A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological. Information about the physical examination must be present in the source documentation at the study center and will be collected on the following visits:

- Screening
- Day 1
- Every 12 weeks during nilotinib treatment consolidation, nilotinib treatment continuation and nilotinib prolonged treatment continuation
- Every 12 weeks during the nilotinib TFR phase and TFR-2
- On week 4, 8, 12 and every 12 weeks thereafter during nilotinib treatment re-initiation and nilotinib treatment re-initiation-2. Extramedullary involvement is assessed every 4 weeks during the first 24 weeks and every 12 weeks thereafter during nilotinib treatment re-initiation and nilotinib treatment re-initiation-2.
- End of treatment visits of each phase in case of premature discontinuation or at end of participation per protocol.

Significant findings that were present prior to the signing of informed consent must be included in the Medical History page on the patient's eCRF. Significant new findings that begin or worsen after informed consent must be recorded on the Adverse Event page of the

patient's eCRF. Presence of extramedullary leukemic involvement will be checked with each physical examination as outlined above. Findings on physical examination consistent with extra-medullary leukemic involvement will be recorded (e.g. liver and spleen size, any other organ involvement). With regards to lymph nodes, only those palpable lymph nodes should be considered to be CML related if leukemic blast infiltration has been confirmed via biopsy/histology or by technically adequate aspiration cytology. When extra-medullary involvement other than of the spleen or liver is the only evidence of blast crisis, this finding must be confirmed by technically adequate (not contaminated with peripheral blood) aspiration cytology and /or biopsy (especially for isolated lymph nodes) and data entered into the extramedullary involvement eCRF.

7.2.2.2 Vital signs

Vital signs (oral temperature, sitting blood pressure and sitting pulse) must be performed at the following visits:

- Screening
- Day 1
- Every 12 weeks during nilotinib treatment consolidation, nilotinib treatment continuation and nilotinib prolonged treatment continuation
- Every 12 weeks during the nilotinib TFR phase and TFR-2
- On week 4, 8, 12 and every 12 weeks thereafter during nilotinib treatment re-initiation and nilotinib treatment re-initiation-2
- End of treatment visits of each phase or end of TFR in case of premature discontinuation or at end of participation per protocol.

7.2.2.3 Height and weight

Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes) will be measured. Height will be measured at screening only, weight will be measured at:

- Screening
- Day 1
- Every 12 weeks during nilotinib treatment consolidation, nilotinib treatment continuation and nilotinib prolonged treatment continuation
- Every 12 weeks during the nilotinib TFR phase and TFR-2
- On week 4, 8, 12 and every 12 weeks thereafter during nilotinib treatment re-initiation and nilotinib treatment re-initiation-2
- End of treatment visits of each phase or end of TFR in case of premature discontinuation or at end of participation per protocol.

7.2.2.4 Performance status

Assessment ECOG performance status (Table 7-8) will be performed at:

- Screening
- Day 1

- Every 12 weeks during nilotinib treatment consolidation, nilotinib treatment continuation, nilotinib prolonged treatment continuation, nilotinib TFR phase and TFR-2
- On week 4, 8, 12, 24 and every 12 weeks thereafter during nilotinib treatment re-initiation and nilotinib treatment re-initiation-2
- End of treatment visits of each phase or end of TFR in case of premature discontinuation or at end of participation per protocol.

More frequent examinations may be performed at the investigator's discretion, if medically indicated.

Table 7-8 ECOG performance status scale

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

7.2.2.5 Laboratory evaluations

Local laboratories will be used for analysis of hematology and central laboratories will be used for analysis of biochemistry specimens collected (safety monitoring). Details on the collections, shipment of biochemistry samples and reporting of results by the central laboratory are provided to investigators in the [CAMN107I2201 Laboratory Manual]. The time windows granted for laboratory evaluations are identical with the corresponding visit time windows for each visit.

Table 7-9 Central or local Clinical laboratory parameters collection plan

Test Category	Test Name
Hematology (Local)	WBC, full differential in percentage or absolute values, platelet counts, hemoglobin
Chemistry (Central)	Lipase, AST (SGOT), ALT (SGPT), total bilirubin, indirect bilirubin, direct bilirubin, LDH, alkaline phosphatase, fasting glucose, HbA1c, serum creatinine, potassium, magnesium, corrected calcium, serum phosphate, total cholesterol, HDL-C, LDL-C (calculated or direct) and triglycerides
Serology (Central)	Hepatitis B surface antigen (HBs Ag), antibodies to hepatitis B core antigen (HBc Ab / anti HBc)

7.2.2.6 Hematology

Hematology labs are to be done locally at the site. Hematology includes assessment of hemoglobin, platelets count, total white blood cell count (WBC) and a full manual differential count in percentage or absolute values including neutrophils, lymphocytes, eosinophils, basophils, monocytes, promyelocytes, myelocytes, metamyelocytes, and blast cells. In laboratories where manual differentials are not routinely performed, automated differential

counts will be accepted. Consistent assessment method should be maintained throughout the study.

7.2.2.7 Clinical chemistry

Blood chemistry labs are to be analyzed by a central laboratory. Biochemistry includes lipase, AST (SGOT), ALT (SGPT), total bilirubin, indirect bilirubin, direct bilirubin, LDH, alkaline phosphatase, fasting glucose, HbA1c, serum creatinine, potassium, magnesium, corrected calcium, serum phosphate, total cholesterol, HDL-C, LDL-C (calculated or direct), and triglycerides. In case a local biochemistry analysis is required and upon the discretion of the investigator, local biochemistry analysis will be accepted on an exceptional basis.

7.2.2.8 Contraception and Pregnancy/assessments of fertility

Contraception

During all phases of the study, women of childbearing potential should employ the use of highly effective contraception. Highly effective contraception methods include:

- Total abstinence (when this is in line with the preferred and usual lifestyle of the subject). 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), total 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 by follow up hormone level assessment.
- Male sterilization (at least 6 months prior to enrolling). The vasectomized male partner should be the sole partner for that subject.
- Use of oral, injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS), or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception.

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.

Pregnancy/assessments of fertility

All women of childbearing potential have to complete a serum pregnancy test at the screening visit, end of treatment visits of each phase in case of premature discontinuation or at end of participation per protocol. Monthly urine pregnancy test must be performed by all women of child-bearing potential during all phases of the study. Pregnancy testing is not required for patients who are determined to be post-menopausal. The time windows granted for pregnancy testing are identical with the corresponding visit time windows for each visit. Refer to Table 7-1, Table 7-2, Table 7-3, Table 7-4, Table 7-5, Table 7-6 and Table 7-7 of the Visit evaluation schedule. Serum pregnancy test will be performed by a central laboratory. Urine pregnancy tests may be performed at the investigational site or at home during all phases of this study. Test results performed at home should be recorded onto a patient diary and brought

to each scheduled visit for the site to review. If a test result indicates a pregnancy, the patient must contact the investigator immediately. All pregnancies should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the Oncology Novartis Chief Medical Office and Patient Safety (CMO&PS).

7.2.2.8.1 Hepatitis B testing

Patients will be tested once for the following hepatitis B serologic markers: hepatitis B surface antigen (HBs Ag) and antibodies to hepatitis B core antigen (HBc Ab / anti HBc). Patients currently on nilotinib in the NTCT-P or NTRI/NTRI-2 phases of the study should have testing performed at the next possible visit in order to identify chronic carriers.

Patients in the TFR/TFR-2 phases of the study should be tested for hepatitis B virus before re-initiating treatment with nilotinib.

7.2.2.9 Cardiac assessments

7.2.2.9.1 Electrocardiogram (ECG)

After the subject has rested approximately 10 minutes in a semi-supine position, 12-lead ECGs must be obtained in triplicate with a recommended interval of 5 to 10 minutes between each ECG at the following time points:

- Screening
- NTCS - Day 1
- Annually while on nilotinib treatment
- Whenever clinically indicated
- NTRI/NTRI-2 Week 1 / Day 1 (with an allowed “visit window” of minus 2 weeks)
- NTRI/NTRI-2 Week 4
- End of treatment visits of each phase or end of TFR in case of premature discontinuation or at end of participation per protocol.

ECGs must be obtained post-dose when the patient is on nilotinib treatment and pre-dose when the patient restarts nilotinib treatment at re-initiation or re-initiation-2 phase.

Interpretation of all ECGs must be done by a qualified physician. Judgment must be based on the mean values of triplicate ECGs. Each ECG tracing should be labeled with the study number, patient initials (where regulations permit), subject 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 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.

Before re-initiation of nilotinib treatment, QTcF must be < 450 msec. For patients with QTcF prolongation above 450 msec perform an analysis of serum potassium and magnesium, and if below normal, correct with supplements to within normal limits. Concomitant medication must be reviewed for their potential to inhibit CYP3A4 and/or to prolong QT-interval.

Perform a repeat ECG within one hour of the first QTcF of > 450 msec. If QTcF remains > 450 msec, repeat ECG as clinically indicated, but at least once a day until the QTcF returns to < 450 msec.

Should the patient have a QTcF > 480 msec please refer to Table 6-2.

In addition to the procedures described in Table 6-2, the Investigator should follow their local standards of practice and treatment guidelines for treating prolonged QT intervals. For example in France, this would include consultation with a cardiologist and close cardiac monitoring.

7.2.2.9.2 Cardiac imaging - echocardiogram

At Screening, an echocardiogram will be performed to ensure healthy status in terms of cardiac anatomy and function.

7.2.3 Pharmacokinetics

One blood sample for the assessment of nilotinib PK trough level will be collected from all patients at week 48. The blood sample will be taken by direct venipuncture inserted in a forearm vein at pre-dose as described in Table 7-10. Blood sample of 3 mL volume will be drawn using a Serum Separator (SST) Vacutainer™ tube or Serum Clot Activator Tube with Gel Separator, or equivalent product. The tube will be allowed to stand vertically (avoiding prolonged contact with the rubber stopper) for about 30 minutes at room temperature and will then be centrifuged at about 5°C for 10 minutes at approximately 1100 g. This should be done within 60 minutes of the sample draw. Immediately after the centrifugation, the upper serum sample will be separated into two aliquots and then transferred into two tapered, 2-mL polypropylene screw cap tube that do not have a skirted base or fixed cap (e.g. Sarstedt product N°72.693; or equivalent product). All serum samples will be stored frozen within 90 minutes of collection at ≤ -15°C until shipped to the analytical site for sample analyses.

The exact date and time of blood sample collection must be documented on the PK blood collection eCRF pages.

Refer to the [CAMN107I2201 Laboratory Manual] for detailed instructions for the collection, handling, and shipment of PK samples.

Table 7-10 Pharmacokinetic blood collection log

Week	Scheduled Time Point	DRID		PK Sample No	Volume (ml)
		Prior to PK sampling	Following PK sampling		
48	Pre-dose/0h	1	111	1	3

7.2.3.1 Analytical method

Serum concentrations of nilotinib will be determined using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay. The lower limit of quantification (LLOQ) is approximately 2.50 ng/mL for nilotinib.

7.2.4 Biomarkers

7.2.4.1 CCI



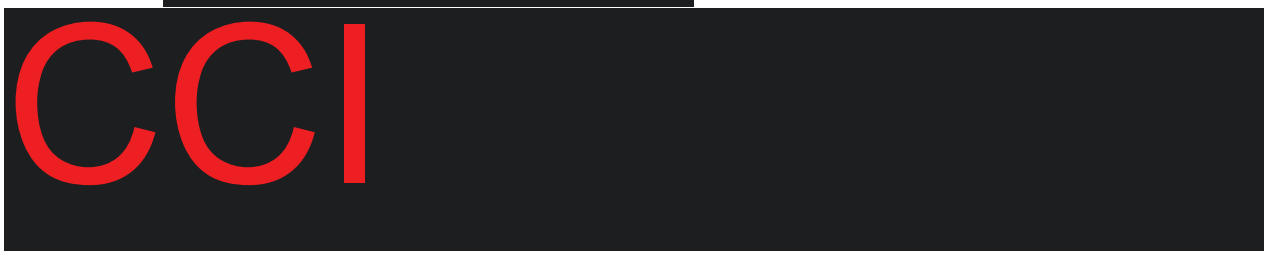
7.2.4.2 CCI



7.2.4.3 CCI



7.2.4.4 CCI



7.2.5 CCI



7.2.6 CCI





Table 7-11 CCI



CCI

7.2.7 Sokal risk category

Sokal risk category at the time of initial diagnosis of CML will be collected retrospectively at any time point during the study. Risk category based on Sokal score is calculated by the investigator using the following formula based on parameters from time of diagnosis:

Table 7-12 Sokal risk category variables and formula

Sokal variables	
Age (years)	0.0116 (age - 43.4)
* Spleen (cm below costal margin)	0.0345 (spleen - 7.51)
Platelets (x 10^9/L)	0.188 [(platelets/700)^2 - 0.563]
^ Blasts (%)	0.0887 (blasts - 2.10)
Relative Risk (RR)	Exponential of the total

* Maximum distance from costal region
^ Percent in peripheral blood
Reference: (Sokal et al 1984)
In the Sokal formulation, all four variables are continuous

Sokal risk categories are defined as:

- 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

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.

For patients who sign the molecular pre-screening ICF, AEs which occur after signature of this consent will only be captured if they meet the definition of serious as outlined in Section 8.2 and are reported to be causally related with study procedures (e.g. an invasive procedure such as biopsy). Once the main study ICF is signed, all AEs per the descriptions below will be captured in the Adverse Event CRF.

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 CRF. Conditions that were already present at the time of informed consent should be recorded in the Medical History page of the patient's CRF. Adverse event monitoring should be continued for at least 30 days following the last dose of study treatment or last day in TFR/TFR-2. 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.

Severity of the 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 not be used in this study but is collected as a seriousness criteria; rather, information about deaths will be collected through a Death form.

The occurrence of adverse events should be sought by non-directive questioning of the patient (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 (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)
3. Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes)
4. Action taken with respect to study or investigational treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)
5. Whether medication or therapy was given (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
6. Outcome (not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown)
7. Whether it is serious, where a serious adverse event (SAE) is defined as in Section 8.2.1 and which seriousness criteria have been met.

If the event worsens the event should be reported a second time in the CRF noting the start date when the event worsens in toxicity. For grade 3 and 4 adverse events only, if improvement to a lower grade is determined a new entry for this event should be reported in the CRF noting the start date when the event improved from having been Grade 3 or Grade 4.

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 CRF.

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.

Study Specific Conventions for Reporting of Adverse Events and Serious Adverse Events:

Natural progression or deterioration of the malignancy under treatment (including loss of response, progression to accelerated phase or blast crisis and death due to disease progression) will be recorded as part of the efficacy evaluation and should NOT be reported as AE/SAE.

Signs and symptoms clearly associated with the disease under study should NOT be reported as AEs unless they are newly emergent (i.e. not previously observed in the patient), judged by the Investigator to be unusually severe or accelerated, or if the Investigator considers deterioration of disease-related signs and symptoms to be caused directly by the study drug. If there is any uncertainty about an AE being due solely to the disease under study, it should be reported as an AE or SAE as appropriate.

Any AE that occurs when a CAMN107EIC01 patient is being screened for CAMN107I2201 study will be recorded in the Adverse Events CRF pages for both studies the patient is consented for.

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 CRF. 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.

8.1.3 Adverse events of special interest

Adverse events of special interest (AESI) are defined as events (serious or non-serious) which are ones of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor may be appropriate. Such events may require further investigation in order to characterize and understand them.

Adverse events of special interest are defined on the basis of an ongoing review of the safety data. AESIs are discussed in detail in the Investigator Brochure but the most important ones for this TFR trial are described below.

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.

The CVE subgroup ‘others’ was added in a comprehensive approach as to include also less well described cardiovascular conditions which could not be categorized into one of IHD, PAOD and ICVE. The AEs reported under ‘others’ category include terms such as or related to arteriosclerosis.

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 (Table 6-2).

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

A musculoskeletal pain grouping is a grouping of any of the following AEs including: musculoskeletal pain, myalgia, pain in extremity, arthralgia, bone pain, and/or spinal pain. Such musculoskeletal pain might occur during nilotinib therapy as well as during the TFR phase.

Reporting of AE of special interest

All AESI 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, 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.

8.2.2 Reporting

For patients who sign the molecular pre-screening ICF, SAE collection will start upon signing the molecular pre-screening ICF. SAEs will only be reported if the event is suspected to be causally related to a study procedure as assessed by the investigator (e.g. an invasive procedure such as biopsy). SAEs will be followed until resolution or until clinically relevant improvement or stabilization. If the main ICF is not signed (molecular screen failure), SAE collection ends 30 days after the last study related procedure.

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided informed consent and until at least 30 days after the patient has stopped study treatment or after last day in TFR/TFR-2 must be reported to Novartis within 24 hours of learning of its occurrence.

Any additional information for the SAE including complications, progression of the initial SAE, and recurrent episodes 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.

Any SAEs experienced after the 30 day safety evaluation follow-up period should only be reported to Novartis if the investigator suspects a causal relationship to the study treatment.

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 the study treatment, complete the SAE Report Form in English, and submit the completed form within 24 hours to Novartis. Detailed instructions regarding the SAE submission process and requirements for signatures are to be found in the investigator folder provided to each site

Follow-up information is submitted in the same way as the original SAE 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 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 Novartis Chief Medical Office and Patient Safety (CMO&PS) 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. Any SAE that occurs when a CAMN107EIC01 patient is being screened for CAMN107I2201 study will be recorded in the Adverse Events CRF pages for both studies the patient is consented for. Novartis will reconcile the cases with annual health authority safety reports (i.e. development safety update report (DSUR), periodic safety update report (PSUR)) to ensure the events are not double reported.

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 either on treatment or in TFR phases 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 Chief Medical Office and Patient Safety (CMO&PS). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to nilotinib any 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 in the latest nilotinib [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 Steering Committee

The Steering Committee (SC) will be established comprising external experts in the field of CML, investigators participating in the trial and Novartis representatives from the Clinical Trial Team.

The SC will ensure transparent management of the study according to the protocol through recommending and approving modifications as circumstances require. The SC will review protocol amendments as appropriate. Together with the clinical trial team, the SC will also develop recommendations for publications of study results including authorship rules. The details of the role of the Steering Committee will be defined in a Steering Committee charter.

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
- 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 (or designated CRO) will review the protocol and CRFs with the investigators and their staff. During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the CRFs, the adherence to the protocol 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 CRFs 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 CRF 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 CRFs are performed according to the study-specific monitoring plan.

9.3 Data collection

For studies using Electronic Data Capture (EDC), the designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, 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.

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.

Data collected by third parties (biochemistry, PCR assessments, biomarkers, PK) will be sent electronically to Novartis.

9.4 Database management and quality control

For studies using eCRFs, Novartis personnel (or 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.

Samples and/or data will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

Data about all study treatments dispensed to the patient and all IRT assigned dosage changes 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 Novartis personnel (or designated CRO).

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

This is a single arm open label phase II study to evaluate the proportion of patients who can be in treatment-free remission (TFR) following a period of 48 weeks in durable MRD with nilotinib treatment.

The analysis of the primary efficacy endpoint is the proportion of patients in MMR at 48 weeks after starting the TFR phase as defined in Table 3-1 and described in Section 10.4.

10.1 Analysis sets

10.1.1 Full Analysis Set

The Full Analysis Set (FAS) comprises all patients who enter the TFR phase.

10.1.2 Safety Set

The Safety Set (SS) includes all patients who received at least one dose of study medication. Safety Set will be split into subsets by study phases and corresponding time windows.

10.1.3 Per-Protocol Set

The Per-Protocol Set (PPS) consists of a subset of the patients in the FAS who are compliant with requirements of the clinical study protocol (CSP).

Protocol deviations leading to exclusion from the PPS will be detailed in the report and analysis plan (RAP) and the validation analysis plan (VAP).

10.1.4 Dose-determining analysis set

Not applicable.

10.1.5 Pharmacokinetic analysis set

The pharmacokinetic analysis set includes all patients who receive at least one dose of study medication and provided evaluable nilotinib trough PK sample at the end of consolidation phase (i.e. pre-dose on week 48).

10.1.6 Other analysis set



10.2 Patient demographics/other baseline characteristics

Demographic and other baseline data will be summarized descriptively for both the Safety Set and the FAS. Categorical data will be presented as frequencies and percentages. For

continuous data, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum will be presented.

10.3 Treatments (study treatment, concomitant therapies, compliance)

All study medication data will be summarized using the safety set and subsets as defined above in Section 10.1.1.

Time on treatment, duration of exposure, percentage of days on treatment, average dose intensity, actual daily dose actual and relative dose intensity will be summarized for these above safety subsets.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be summarized by safety set and subsets.

10.4 Primary objective

The primary objective of the trial is to evaluate the proportion of patients who are in MMR at 48 weeks after starting the TFR phase (patients who required re-initiation of treatment are considered as non-responders).

10.4.1 Variable

The primary efficacy variable is the proportion of patients who are in MMR at 48 weeks after starting the TFR phase defined as the number of patients with MMR at 48 weeks after starting the TFR phase with no loss of MMR **and** no re-initiation of nilotinib therapy in the first 48 weeks after starting the TFR phase divided by the number of patients who entered the TFR phase. Loss of MMR is defined as a single assessment of BCR-ABL > 0.1% IS.

10.4.2 Statistical hypothesis, model, and method of analysis

Demonstration of successful treatment-free remission will be evaluated using the following hypothesis: H_0: $p \leq 0.50$, where p is the rate of patients who are in MMR at 48 weeks after starting the TFR phase.

H_1: $p > 0.50$, where p is the rate of patients who are in MMR at 48 weeks after starting the TFR phase.

The rate of patients who are in MMR at 48 weeks after starting the TFR phase will be presented together with an exact 95% Clopper-Pearson confidence interval.

Primary efficacy analysis will be performed on the FAS. For primary efficacy variable, the analysis time point is when all patients who entered the TFR phase completed 48 weeks of the TFR phase or discontinued the study earlier.

10.4.3 Handling of missing values/censoring/discontinuations

For the primary analysis of patients who are in MMR at 48 weeks after starting the TFR phase, patients dropping out early from the study during the TFR phase will be considered as not in MMR at 48 weeks after starting the TFR phase and will be included in the FAS. In case of missing PCR assessment at 48 weeks after starting the TFR phase, if both 44 and 54 weeks

PCR assessments are available and if both assessments show MMR, the 48 weeks assessment will be imputed as "response", otherwise "non-response".

10.4.4 Supportive analyses

The primary analysis will be repeated on the PPS and evaluable patients who have PCR assessment at 48 weeks after starting the TFR phase.

10.5 Secondary objectives

10.5.1 Efficacy objectives

- Molecular response status at certain time points after starting the TFR phase:
  - Proportion of patients who are in MR4.5 at 48 weeks after starting the TFR phase defined as the number of patients with MR4.5 at 48 weeks after starting the TFR phase with no loss of MR4.5 **and** no re-initiation of nilotinib therapy in the first 48 weeks after starting the TFR phase divided by the number of patients who entered the TFR phase
  - Proportion of patients who are in MMR at 96, 144, 192, 264 weeks, and at the end of 6, 7, 8, 9 and 10 years after starting the TFR phase defined as the number of patients with MMR at 96, 144, 192, 264 weeks, and at the end of 6, 7, 8, 9 and 10 years after starting the TFR phase with no loss of MMR **and** no re-initiation of nilotinib therapy during those intervals after starting the TFR phase divided by the number of patients who entered the TFR phase
  - Proportion of patients who are in MR4.5 at 96, 144, 192, 264 weeks, and at the end of 6, 7, 8, 9 and 10 years after starting the TFR phase defined as the number of patients with MR4.5 at 96, 144, 192, 264 weeks, and at the end of 6, 7, 8, 9 and 10 years after starting the TFR phase with no loss of MR4.5 **and** no re-initiation of nilotinib therapy during those intervals after starting the TFR phase divided by the number of patients who entered the TFR phase
  - Proportion of patients who are in MMR at 48, 96, 144, 192, 264 weeks, and at the end of 6, 7, 8, 9 and 10 years after starting the TFR phase irrespective of whether or not patients required re-initiation of treatment defined as the number of patients with MMR at 48, 96, 144, 192, 264 weeks, and at the end of 6, 7, 8, 9 and 10 years after starting the TFR phase divided by the number of patients who entered the TFR phase. Patients who have re-initiation of nilotinib treatment but have less than 12 weeks of re-initiated treatment will be excluded from the analysis
  - Proportion of patients who are in MR4.5 at 48, 96, 144, 192, 264 weeks, and at the end of 6, 7, 8, 9 and 10 years after starting the TFR phase irrespective of whether or not patients required re-initiation of treatment defined as the number of patients with MR4.5 at 48, 96, 144, 192, 264 weeks, and at the end of 6, 7, 8, 9 and 10 years after starting the TFR divided by the number of patients who entered the TFR phase. Patients who have re-initiation of nilotinib treatment but have less than 12 weeks of re-initiated treatment will be excluded from the analysis
- Proportion of patients who achieve MMR within 12 weeks of re-initiation of treatment with nilotinib defined as the number of patients who are in MMR at least at one

assessment within 12 weeks after re-start of nilotinib treatment divided by the number of patients who are re-initiated for at least 12 weeks

- Proportion of patients who are in stable MMR after achievement of that response in the nilotinib re-initiation phase for 48 weeks, 96 weeks, 144 weeks, 192 weeks, 240 weeks, 288 weeks, 336 weeks, 384 weeks and 432 weeks, based on availability of appropriate data, defined as the number of patients achieving MMR any time during the nilotinib re-initiation phase and having the same response 48 weeks, 96 weeks, 144 weeks, 192 weeks, 240 weeks, 288 weeks, 336 weeks, 384 weeks and 432 weeks after the first achievement of MMR, irrespective of whether there is loss of MMR in between, divided by the number of patients who achieved MMR at any time during the nilotinib re-initiation phase
- Proportion of patients who are in stable MR4.5 after achievement of that response in the nilotinib re-initiation phase for 48 weeks, 96 weeks, 144 weeks, 192 weeks, 240 weeks, 288 weeks, 336 weeks, 384 weeks and 432 weeks, based on availability of appropriate data, defined as the number of patients achieving MR4.5 any time during nilotinib re-initiation phase and having the same response 48 weeks, 96 weeks, 144 weeks, 192 weeks, 240 weeks, 288 weeks, 336 weeks, 384 weeks and 432 weeks after the first achievement of MR4.5, irrespective of whether there is loss of MR4.5 in between, divided by the number of patients who achieved MR4.5 at any time during the nilotinib re-initiation phase
- Kinetics of BCR-ABL transcript levels (IS) over time after re-initiation of nilotinib therapy
- Occurrence of nilotinib resistant mutations which include T315I, E255K/V, Y253H, F359V/C/I mutations or occurrence of any other BCR-ABL mutations in patients who lost MMR
- Duration of re-initiated treatment required to regain MMR defined as the time from date of start of re-initiation of treatment after loss of MMR to the date of first achievement of MMR. Patients who do not regain MMR after re-initiation of treatment on or before the cut-off date, duration will be censored at the date of last PCR assessment
- Duration of re-initiated treatment required to regain MR4.5 which is measured from the time from date of start of re-initiation of treatment after loss of MMR to the date of first achievement of MR4.5. Patients who do not regain MR4.5 after re-initiation of treatment on or before the cut-off date, duration will be censored at the date of last PCR assessment
- Long term outcomes
    - Treatment-free survival (TFS) is defined as the time from the date of the start of the TFR phase to the earliest occurrence of the following events: loss of MMR, re-initiation of treatment due to any cause, progression to AP/BC or death due to any cause. For patients without any event on or before the cut-off date, survival time will be censored at the date of their last assessment (PCR, cytogenetic, hematologic or extramedullary)
      A TFS sensitivity analysis will be conducted to consider discontinuation from TFR phase due to any reason as a TFS event, in addition to the TFS events as defined above
    - Progression-free survival (PFS) defined as the time from the date of the start of the TFR phase to the date of the earliest of the following events: progression to AP/BC or

death due to any cause. For patients without any event on or before the cut-off date, survival time will be censored at the date of their last assessment (PCR, cytogenetic, hematologic or extramedullary) for patients who are still on study and at the date of last contact for patients who are in follow-up

- Overall survival (OS) defined as the time from the date of the start of the TFR phase to the date of death due to any cause. For patients without any event on or before the cut-off date, survival time will be censored at the date of their last assessment for patients who are still on study and at the date of last contact for patients who are in follow-up.

10.5.1.1 Analyses methods for secondary objectives

The rate of molecular responses at certain time points after starting the TFR phase as well as the rate of patients who succeeded to achieve MMR with re-initiation of nilotinib treatment will be presented together with an exact 95% Clopper-Pearson confidence interval.

Kinetics of BCR-ABL transcript levels after re-start of nilotinib therapy will be presented by a box-plot of BCR-ABL ratio over time. The presence of new mutations detected among patients who lost MMR during the TFR phase will be summarized by type and frequency of mutations.

All time to event endpoints including duration of re-initiated treatment required to regain MMR and MR4.5, TFS, PFS and OS will be analyzed using the Kaplan-Meier (KM) method and will be presented by KM plots.

10.5.2 Safety objectives

10.5.2.1 Analysis set and grouping for the analyses

For all safety analyses, the safety set will be used. Reporting of safety information for these patients will be split into subsets by study phases.

10.5.2.2 Adverse events (AEs)

Summary tables for adverse events (AEs) have to include only AEs that started or worsened during the on-treatment period, the **treatment-emergent** AEs. However, all safety data (including those from the pre and post-treatment periods) will be listed and those collected during the pre-treatment and post-treatment period are to be flagged.

The incidence of treatment-emergent adverse events (new or worsening from baseline) will be summarized by system organ class and or preferred term, severity (based on CTCAE grades), type of adverse event, relation to study treatment by the three phases or subsets previously described.

Deaths reportable as SAEs and non-fatal serious adverse events will be listed by patient and tabulated by type of adverse event and safety subset.

Specific safety event categories will be considered. Such categories consist of one or more well-defined safety events which are similar in nature and for which there is a specific clinical interest in connection with the study treatment(s).

For each specified safety event category, number and percentage of patients with at least one event part of the safety event category will be reported.

10.5.2.3 Laboratory abnormalities

For laboratory tests covered by the Common Terminology Criteria for Adverse Events (CTCAE v.4.03) the study's biostatistical and reporting team will grade laboratory data accordingly. For laboratory tests covered by CTCAE v.4.03, a Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used.

In some cases (e.g. white blood cell differentials) the lower limits of normal ranges used in CTCAE v.4.03 definition have to be replaced by a clinically meaningful limit expressed in absolute counts.

For laboratory tests where grades are not defined by CTCAE v.4.03, results will be graded by the low/normal/high classifications based on laboratory normal ranges.

The following by-safety subset summaries will be generated separately for hematology, biochemistry and urinary laboratory tests:

- Number and percentage of patients with laboratory abnormalities, by parameter and worst post-baseline CTCAE v.4.03 grade. Each patient will be counted only for the worst grade observed post-baseline, regardless of the baseline status
- Shift tables using CTCAE v.4.03 grades to compare baseline to the worst on-treatment value
- For laboratory tests where CTCAE v.4.03 grades are not defined, shift tables using the low/normal/high/(low and high)
- Listing of all laboratory data with values flagged to show the corresponding CTCAE v.4.03 grades and the classifications relative to the laboratory normal ranges.

10.5.2.4 Other safety data

Other safety data collected (e.g. ECG, vital signs) will be listed and summarized using descriptive statistics as appropriate. Notable values may be flagged. Notable/Abnormal values for safety data will be further specified in the RAP.

10.5.2.5 Supportive analyses for secondary objectives

Not applicable.

10.5.2.6 Tolerability

Not applicable.

10.5.3 Pharmacokinetics

The plasma exposure of nilotinib will be assessed via trough nilotinib concentrations collected at week 48 of consolidation phase prior to the last dose and will be summarized by descriptive statistics, including geometric and arithmetic means, standard deviation (SD), and coefficient of variation (CV) %.

The potential relationship between nilotinib trough concentration and successful TFR phase (eligible or not for TFR) will be assessed by graphic exploration and/or statistical modeling as appropriate. Pharmacokinetics will be analyzed and reported as a separate activity outside the primary study report.

10.5.3.1 Data handling principles

To be described in the RAP.

10.5.4 Biomarkers



10.5.5 CCI



10.5.6 CCI



10.6 Exploratory objectives



10.7 Interim analysis

No formal interim analysis is planned for this study. There will be no publication of results until enrollment has been completed. If Novartis decides to publish interim data after enrollment is completed, details will be specified in the analysis plan. The primary endpoint will be analyzed when all patients completed 48 weeks of TFR phase or entered treatment re-initiation phase or discontinued from the study. Thereafter, updates will be done at week 96, 144, 192, week 264 after the last patient enters the nilotinib TFR phase, at the end of 6, 7, 8, 9 years and final analysis and CSR will be done at 10 years after starting the TFR phase.

10.8 Sample size calculation

Demonstration of successful nilotinib TFR phase will be based on a study designed with a 90% power to test the null hypothesis that the rate of MMR at 48 weeks after start of TFR phase is $\leq$ 50% with the alternative hypothesis that the rate of MMR at 48 weeks after start of TFR phase is > 50%. The sample size is based on Fleming's single stage design to test the null hypothesis H0: $p \leq 0.5$, where p is the rate of MMR at 48 weeks after start of TFR phase (considering any patient who required re-initiation of treatment as non-responder). If the true rate $p \geq 0.65$, then with one-sided alpha level of 2.5% and a power of 90%, a minimum of 122 patients are required to be studied. Based on data from study AMN107A2303, among patients treated with nilotinib 300 mg BID who were in MR4.5 at 24 months, approximately 40% had unconfirmed loss of MR4.0 (one PCR assessment between 24 and 36 months that showed a BCR-ABL transcript level of >0.01% IS). There may be better treatment adherence in this study due to dedicated counseling of patients and therefore, it is assumed that approximately 30% of the patients (lower than 40% observed in study AMN107A2303) who have MR4.5 at study entry will not be eligible for starting TFR phase after 48 weeks. As a result, approximately 175 patients will be enrolled into this study. The null hypothesis will be rejected if there are at least 73 patients with MMR at 48 weeks after starting TFR phase (considering any patient who required re-initiation of treatment as non-responder) assuming 122 patients required to start TFR phase.

Consequently, accrual to the study will close at the earlier of the date on which 122 patients have started the TFR phase or the date on which 175 patients have been enrolled in the consolidation phase.

This study had enrolled 216 patients by 20 Dec 2013, the date when the patient enrollment was closed. With 216 patients enrolled, if assuming approximately 30% of enrolled patients who have MR4.5 at study entry will not be eligible for starting TFR phase, there will be approximately 151 patients entering TFR. Assuming the true rate of MMR at 48 weeks after start of TFR phase is 65%, with a MMR rate of 50% for the null hypothesis, the study will have a 94% power with 1-sided alpha level of 2.5% to test the null hypothesis. Note that the power increases by 4% based on the 216 enrolled patients compared to the originally planned 90% power based on the 175 enrolled patients, with all the other assumptions for the power calculation being the same.

Table 10-1 presents the powers given the numbers of patients enrolled (actually enrolled versus planned) and various rates of enrolled patients who are not eligible for entering TFR. With the number of enrolled patients increased from the planned 175 to the actually enrolled 216, the power of the test increases slightly in each scenario.

Table 10-1 Power calculation for various sample size scenarios

Patients enrolled in the study (n)	Rate of patients not eligible for TFR	Patients entering TFR (n)	Power
175 (planned)	10%	157	95%
	20%	140	93%
	30%	122	90%
	40%	105	83%
216 (actually enrolled)	10%	194	98%
	20%	172	97%
	30%	151	94%
	40%	129	91%
Assumptions on the rate of MMR at 48 weeks after start of TFR: Null hypothesis H0: p=50%; and true rate p=65%. One-sided alpha level: 2.5%. Based on exact binomial distribution. NQuery used for power calculations.			

10.9 Power for analysis of key secondary variables

Not applicable.

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. 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 CRFs.

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 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.

Additional biomarker consent form

The optional biomarker assessments will have a separate consent form covering those projects. The optional additional biomarker informed consent form will be submitted for ethical approval together with the study protocol and the main informed consent form of the study. If a subject opts not to participate in the optional biomarker assessments, this in no way affects the subject's ability to participate in the main research study. Additional pre-screening consent form.

This study also has a pre-screening component which is covered by a separate pre-screening informed consent form. The pre-screening informed consent form will be submitted for ethical approval together with the Study Protocol and the main informed consent form of the study. Patients must sign the pre-screening consent form before any pre-screening assessment is performed.

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 is committed to following high ethical standards for reporting study results for its innovative medicine, including the timely communication and publication of clinical trial results, whatever their outcome. Novartis assured that the key design elements of this protocol were posted on the publicly accessible database, e.g.www.clinicaltrials.gov, before study start. In addition, results of interventional clinical trials in adult patients are posted on www.novartisclinicaltrials.com, a publicly accessible database of clinical study results within 1 year of study completion (i.e., LPLV).

Novartis follows the ICMJE authorship guidelines (www.icmje.org) and other specific guidelines of the journal or congress to which the publication will be submitted.

Authors will not receive remuneration for medical writing agency. Author(s) may be requested to present poster or oral presentation at scientific congress; however, there will be no honorarium provided for such presentations.

As part of its commitment to full transparency in publications, Novartis supports the full disclosure of all funding sources for the study and publications, as well as any actual and potential conflicts of interest of financial and non-financial nature by all authors, including medical writing/editorial support, if applicable.

For the Novartis Guidelines for the Publication of Results from Novartis-sponsored Research, please refer to www.novartis.com.

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, 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 (CRF) 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 CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. All data requested on the CRF must be recorded. Any missing data must be explained. Any change or correction to a paper CRF 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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14 Appendices

14.1 Appendix 1 List of CYP3A4 inducers, inhibitors and substrates

14.1.1 CYP3A4 inducers

Category	Drug Names
Strong inducers of CYP3A4[1]	avasimibe, carbamazepine, enzalutamide, lumacaftor, phenobarbital, phenytoin, rifabutin, rifampicin, mitotane, St. John's wort (*Hypericum perforatum*)[4]
Moderate inducers of CYP3A4[2]	bosentan, dabrafenib, efavirenz, etravirine, genistein[5], lersivirine , lopinavir, modafinil, nafcillin, semagacestat[6], talviraline[6], telotristat, thioridazine, tipranavir/ritonavir
Weak inducers of CYP3A4[3]	amprenavir, aprepitant, armodafinil, artesunate/mefloquine, bexarotene, boceprevir, brivacetam, clobazam, danshen (*Salvia miltiorrhiza*)[4], dexamethasone, echinacea (*Echinacea purpurea*)[1], elvitegravir-cobicistat-emtricitabine-tenofovir (Stribild), eslicarbazepine, ginkgo (*Ginkgo biloba*)[4], ginseng[4], glycyrrhizin[5], isavuconazole, lesinurad, methylprednisolone, nevirapine, ombitasvir/paritaprevir/dasabuvir/ritonavir (Viekira Pak), oritavancin, oxcarbazepine, pioglitazone, pleconaril, prednisone, pretomanib, primidone, quercetin[5], raltegravir, ritonavir, rufinamide, sarilumab, sirukumab, sorafenib, sulfinpyrazone, telaprevir, terbinafine, ticagrelor, ticlopidine, topiramate, troglitazone[6], vemurafenib, vicriviroc/ritonavir, vinblastine, yin zhi huang[4]
[1] A strong inducer for a specific CYP is defined as an inducer that decreases the AUC of a sensitive substrate for that CYP by equal or more than 80%. [2] A moderate inducer for a specific CYP is defined as an inducer that decreases the AUC of a substrate for that CYP by 50-80%. [3] A weak inducer for a specific CYP is defined as an inducer that decreases the AUC of a substrate for that CYP by 20-50%. [4] Herbal product [5] Food product [6] Drugs not available on US market	

This list was based on information from the FDA's "Guidance for Industry, Drug Interaction Studies", from the Indiana University School of Medicine's "Clinically Relevant" Table, from the University of Washington's Drug Interaction Database. This list may not be comprehensive and may be updated periodically. Refer to Novartis Oncology Clinical Pharmacology Internal Memorandum, Drug-drug interactions (DDI) Database (last updated January 2018) for update or more details.

14.1.2 CYP3A4 inhibitors

Category	Drug Names
Strong inhibitors of CYP3A4[1]	atazanavir/ritonavir[7], boceprevir, cobicistat, conivaptan, clarithromycin, danoprevir/ritonavir[7], darunavir/ritonavir[7], elvitegravir/ritonavir[7], grapefruit juice[6], idelalisib, indinavir, indinavir/ritonavir[7], itraconazole, ketoconazole, lopinavir/ritonavir[7], mibefradil, nefazodone, nelfinavir, ombitasvir/paritaprevir/dasabuvir/ritonavir (Viekira Pak)[7], posaconazole, ritonavir, saquinavir/ritonavir[7],, saquinavir, telaprevir, telithromycin, tipranavir/ritonavir[7], troleandomycin, , voriconazol
Moderate inhibitors of CYP3A4[2]	aprepitant, amprenavir, asafoetida resin (*Ferula asafoetida*)[4], atazanavir, cimetidine, casopitant, ciprofloxacin, crizotinib, cyclosporine, darunavir, diltiazem, dronedarone, erythromycin, faldaprevir, fluconazole, grapefruit juice[6], imatinib, isavuconazole, netupitant,

	nilotinib, *Schisandra sphenanthera* (nan wu wei zi)[4], tofisopam, verapamil
Weak inhibitors of CYP3A4[3]	almorexant, alprazolam, amiodarone, amlodipine, atorvastatin, azithromycin, berberine[4], bicalutamide, blueberry juice[8], brodalumab, chlorzoxazone, cilostazol, clotrimazole, cranberry juice[8], daclatasvir, delavirdine, evacetrapib, everolimus, flibanserin, fluvoxamine, fosaprepitant (IV), fostamatinib, garden cress seeds (*Lepidium sativum*)[5], ginkgo (*Ginkgo biloba*)[4], goldenseal (*Hydrastis canadensis*)[4], grazoprevir, guan mai ning[4], isoniazid, ivacaftor, lacidipine, linagliptin, lomitapide, obeticholic acid, oral contraceptives, palbociclib, pazopanib, peppermint oil[5], piperine[5], pomelo (*Citrus grandis*)[5], propiverine, ranitidine, ranolazine, resveratrol[4], roxithromycin, Seville orange juice[5], simeprevir, sitaxentan, suvorexant, tabimorelin, tacrolimus, teriflunomide, ticagrelor, tolvaptan, tong xin luo[4]
[1] A strong inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a sensitive substrate for that CYP by equal or more than 5-fold. [2] A moderate inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a sensitive substrate for that CYP by less than 5-fold but equal to or more than 2-fold. [3] A weak inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a sensitive substrate for that CYP by less than 2-foldbut equal to or more than 1.25-fold. [4] Herbal product [5] Food product [6] The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation-dependent. Studies have shown that it can be classified as a “strong CYP3A inhibitor” when a certain preparation was used (e.g., high dose, double strength) or as a “moderate CYP3A inhibitor” when another preparation was used (e.g., low dose, single strength). [7] Combination ritonavir-boosted regimens are listed here in the DDI memo as strong CYP3A inhibitors (to avoid potential confusion), even though some are considered moderate CYP3A inhibitors in the UW DDI Database. [8] The effect of certain fruit juices varies widely among brands and is concentration-, dose-, and preparation-dependent.	

This list is based on information from the FDA’s “Guidance for Industry, Drug Interaction Studies”, from the Indiana University School of Medicine’s “Clinically Relevant” Table and from the University of Washington’s Drug Interaction Database. Please note that this is not an exhaustive list. Please refer to footnotes. Refer to Novartis Oncology Clinical Pharmacology Internal Memorandum, Drug-drug interactions (DDI) Database (last updated January 2018) for update or more details.

14.1.3 CYP3A4 substrates: Narrow therapeutic index, sensitive, and others.

Category	Drug Names
Narrow Therapeutic index substrates of CYP3A4[1]	alfentanil, astemizole, cisapride, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, terfanadine, thioridazine
Sensitive substrates of CYP3A4[2]	alfentanil, alpha-dihydroergocryptine, almorexant , alisoporivir, aplaviroc, aprepitant, atazanavir, atorvastatin, avanafil, bosutinib, brecanavir, brotizolam, budesonide, buspirone, capravirine, casopitant, cobimetinib, conivaptan, danoprevir, darifenacin, darunavir, dasatinib, dronedarone, ebastine, eletriptan, elvitegravir, eplerenone, everolimus, felodipine, fluticasone, grazoprevir, ibrutinib, indinavir, isavuconazole, ivabradine, ivacaftor, levomethadyl (LAAM), lomitapide, lopinavir, lovastatin, lumefantrine, lurasidone, maraviroc, midazolam, midostaurin, naloxegol, neratinib, nisoldipine, paritaprevir, perospirone, quetiapine, ridaforolimus, saquinavir, sildenafil, simeprevir, simvastatin, tacrolimus, terfenadine, ticagrelor, tilidine, tipranavir, tolvaptan, triazolam, ulipristal, vardenafil, venetoclax, vicriviroc, voclosporin
Other Substrates of CYP3A4[3]	alprazolam, ambrisentan, amlodipine, antipyrine, aripiprazole, artemether, avosentan, boceprevir, bosentan, buprenorphine, *Cannabis sativa*[4], carbamazepine, dexloxiglumide, dextromethorphan, diazepam, docetaxel, enzalutamide, gemigliptin, halofantrine, imipramine, lansoprazole, lidocaine, linagliptin, loperamide, loratadine, losartan, lurasidone, macitentan, methadone, mirodenafil, montelukast, morphine, nelfinavir, netupitant, nevirapine, nifedipine,

	nilotinib, nitrendipine, omeprazole, ospemifene, oxycodone, paclitaxel, pazopanib, pioglitazone, quinine, ranolazine, repaglinide, rifabutin, ritonavir, roflumilast, saxagliptin, selegiline, sertraline, sibutramine, sotrastaurin, telaprevir, theophylline, tirilazad, tolterodine, udenafil, vincristine, voriconazole

[1] Narrow therapeutic index substrates are drugs whose exposure-response relationship indicates that increases in their exposure levels by the concomitant use of an inhibitor may lead to serious safety concerns or drugs which have <2-fold difference in the minimum toxic concentrations and minimum effective concentrations in the blood (thus safe and effective use requires careful dosage titration and patient monitoring).
[2] Sensitive substrates are drugs that demonstrate an increase in AUC of ≥5-fold with strong index inhibitors of a given metabolic pathway in clinical DDI studies.
[3]Other substrates are drugs that demonstrate an increase in AUC of ≥2 to <5-fold with strong index inhibitors of a given metabolic pathway in clinical DDI studies.
[4]Tetrahydrocannabinol (∆9THC) and cannabidiol (CBD) are major constituents. ∆9THC is primarily metabolized by CYP2C9 to an active metabolite 11-hydroxy-∆9-THC (11-OH-THC). CBD is extensively metabolized by CYP2C19 and CYP3A4 to eight monohydroxylated metabolites. The effects of multiple daily doses of rifampicin 600 mg for 10 days, ketoconazole 400 mg for 6 days and omeprazole 40 mg for 6 days on the PK of ∆9THC, 11-OH-THC and CBD after a single dose (4 sprays) of an oromucosal spray were determined in a randomized, crossover, parallel study in three groups of 12 male subjects. Ketoconazole increased the Cmax and AUC0-24 of ∆9THC by 1.2- and 1.8-fold, respectively, increased the Cmax and AUC0-24 of 11-OH-THC by 3.0- and 2.6-fold, respectively, and increased the Cmax and AUC0-24 of CBD by 2- and 2-fold, respectively. Rifampicin decreased the Cmax and AUC24 of ∆9THC by 40 and 20%, respectively, decreased the Cmax and AUC0-24 of 11-OH-THC by 85 and 87%, respectively, and decreased the Cmax and AUC24 of CBD by 50 and 60%, respectively. There were no effects of omeprazole on the plasma concentrations of all three cannabis constituents.

This list of CYP substrates was compiled from the Indiana University School of Medicine's "Clinically Relevant" Table; from the FDA's "Guidance for Industry, Drug Interaction Studies" and from the University of Washington's Drug Interaction Database. This list may not be comprehensive and may be updated periodically. Refer to Novartis Oncology Clinical Pharmacology Internal Memorandum, Drug-drug interactions (DDI) Database (last updated January 2018) for update or more details.