

Clinical Development

AMN107 (Nilotinib, Tasigna®)

Protocol CAMN107A2408 / NCT01698905

A phase II, single arm, open label study of treatment-free remission in Chronic Myeloid Leukemia (CML) chronic phase (CP) patients after achieving sustained MR4.5 on nilotinib

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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
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
CYP3A4	Cytochrome 3A4
DDI	Drug-drug interaction
DRID	Dose Reference ID
DS&E	Drug Safety and Epidemiology
EC	European Commission
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture
ELN	European Leukemia Net
EMA	European Medicines Agency
EOS	End of study
EOT	End of Treatment
CCI	
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
GI	Gastrointestinal
GM-CSF	Granulocyte-macrophage colony-stimulating factors
GP	General practitioner
H2	Histamine H2-receptor antagonists
HDL-C	High Density Lipoprotein-Cholesterol (i.e. HDL)
HBc Ab	Hepatitis B Core Antibody
HBs Ag	Hepatitis B Surface Antigen
HMG-CoA	Hydroxy-Methyl-Glutaryl-Coenzyme A
IB	Investigator Brochure
ICF	Informed consent form
ICH	International Conference on Harmonization
ICVE	Ischemic Cerebrovascular Events
IEC	Independent Ethics Committee
IFN	Interferon
IHD	Ischemic Heart Disease
IM	Imatinib
IN	Investigator Notification
IRB	Institutional Review Board
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
LPLV	Last patient last visit
CCI	
MedDRA	Medical dictionary for regulatory activities
mg	Milligram
MMR	Major molecular response
MR	Molecular response
MR 4.5	Molecular response 4.5 log reduction from baseline
MR4.0	Molecular response 4.0 log reduction from baseline
MRD	Minimal residual disease
MCyR	Major cytogenetic response
N	Sample size
NCCN	National Comprehensive Cancer Network
mCyR	Minor cytogenetic response
NIL	Nilotinib
NTCT	Nilotinib treatment continuation
NTRI	Nilotinib treatment re-initiation
OS	Overall survival

PAOD	Peripheral Artery Occlusive Disease
PCR	Polymerase chain reaction
PCyR	Partial cytogenetic response
PD	Pharmacodynamics
PFS	Progression Free Survival
Ph	Philadelphia chromosome
Ph+ CML	Philadelphia chromosome positive chronic myeloid leukemia
PHI	Protected health information
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
RR	Relative Risk
CCI	
SAE	Serious Adverse Event
SD	Standard deviation
SGOT	Serum glutamic oxaloacetic transaminase/AST
SGPT	Serum glutamic pyruvic transaminase/ALT
SMC	Study Management Committee
SmPC	Summary of Product Characteristics
Sp	Specialist
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
WBC	White blood cell

Glossary of terms

Assessment	A procedure used to generate data required by the study
Accelerated phase (AP)	• $\geq 15\%$ 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 ($< 100 \times 10^9/L$) that is unrelated to therapy
Blast crisis (BC)	• $\geq 30\%$ 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 2 years
Confirmed loss of MR 4.0	Two consecutive BCR-ABL $> 0.01\%$ IS
Confirmed loss of MR4.5	Two consecutive BCR-ABL $> 0.0032\%$ IS
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 • AP • BC
Dose level	The dose of drug given to the patient (total daily or weekly etc.)
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	All patients who complete the consolidation phase successfully (i.e. who maintain MR4.5 for the first 52 weeks on study) and enter into 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
Loss of CHR	Loss of CHR is defined as the appearance of any of the following, confirmed by a second determination ≥ 4 weeks later (unless associated with progression to AP/BC or CML-related death): • WBC count that rises to $> 20.0 \times 10^9/L$ • Platelet count that rises to $\geq 600 \times 10^9/L$ • Progressing hepatosplenomegaly to a size ≥ 5 cm below the left intercostal margin • Appearance of $\geq 5\%$ myelocytes + metamyelocytes in the peripheral blood • Appearance of blasts or promyelocytes in the peripheral blood
Loss of MMR	BCR-ABL $> 0.1\%$ IS

Molecular response	MMR – BCR-ABL $\leq$ 0.1% (IS); MR4 – BCR-ABL $\leq$ 0.01% (IS); MR4.5 – BCR-ABL $\leq$ 0.0032% (IS)
Overall survival	The time from the date of discontinuation of nilotinib therapy 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.
Period	A subdivision of the study timeline; divides stages into smaller functional segments such as screening, baseline, titration, washout, etc.
Personal Data	Subject information collected by the Investigator that is transferred to Novartis for the purpose of the clinical trial. This data includes subject identifier information, study information and biological samples.
Premature patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study treatment administration and/or assessments; at this time all study treatment administration is discontinued and no further assessments are planned, unless the patient will be followed for progression and/or survival
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.
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	A unique identifying number assigned to each subject who enrolls in the study
Treatment-free remission (TFR) phase	Patients cease nilotinib therapy after 52 weeks of treatment on study
Treatment-free remission – 2 (TFR-2) phase	Patients who are not eligible to enter the TFR phase and stay on nilotinib treatment for another year and maintain MR4.5 will enter TFR-2 phase and stop taking nilotinib treatment
Treatment-free survival (TFS)	TFS is defined as the lack of any of the following events: loss of MMR, confirmed loss of MR4, re-start of Nilotinib treatment, progression to AP/BC or death from any cause
Variable	Identifier used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified time points
Withdrawal of consent	Withdrawal of consent from the study occurs only when a subject does not want to participate in the study any longer, and does not allow any further collection of personal data

Amendment 5 (05-Jul-2018)

Amendment rationale

The recruitment of this study has been completed (LPFV 13-Dec-2013) and 163 patients have been enrolled. As of 18October2017, 119 patients are ongoing in the study.

The primary purposes for 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 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, MR4, 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.
- 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

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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 (15-Nov-2016)

Amendment rationale

The recruitment of this study has been completed (LPFV 13-Dec-2013) and 163 patients have been enrolled. As of 26Oct2016, 133 patients are ongoing in the study.

The primary purpose for the amendment is:

- 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 update and clarify additional analysis time points.

Changes to the protocol

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Amendment 3 (01-Apr-2016)

Amendment rationale

The recruitment of this study has been completed (LPFV 13-Dec-2013) and 163 patients have been enrolled. Currently, 138 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 the protocol

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IRBs/IECs

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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.

Summary of previous amendments

Amendment 2

Amendment rationale

The study has completed recruitment; 163 patients have been enrolled as of December 2013.

The main purposes for 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 ($> \text{ULN} - 300 \text{ mg/dL}$; $> \text{ULN} - 7.75 \text{ mmol/L}$) or 2 ($> 300 - 400 \text{ mg/dL}$; $> 7.75 - 10.34 \text{ mmol/L}$), 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 the moderate inhibitory effect of nilotinib on CYP3A4 isoenzyme that is involved in the metabolic pathway of some statins (HMG-CoA reductase inhibitors). Appendix Section 14.1.2 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:
 - Hepato-biliary
 - Cardiac QTc prolongation
 - Ischemic cardiovascular evaluation
 - Cardiac “other”
 - Pancreatitis
- 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. In addition, several changes to the protocol will be implemented to address questions identified during study conduct:
 - To include HbA1c lab assessment as an additional monitoring parameter for glucose
 - To clarify the allowed permanent dose reduction dosage at study entry

- To clarify the patient population of interest for study entry
- To clarify the duration of treatment-free remission (TFR) phase
- To clarify the highly contraceptive language
- To clarify biomarker assessments
- To update the statistical section:
 - Details of the analysis sets to be used for exploratory purposes have been removed as these types of details will be provided in the Report and Analysis Plan (RAP).
 - A correction has been made on the alternative hypothesis. Previously the alternative hypothesis considered was $H1: p \geq 0.25$ against the null hypothesis $H0: p \leq 0.10$. In fact, $p=0.25$ was considered as the true rate in order to compute the sample size. To reject the null hypothesis, statistically it is correct to consider the alternative hypothesis to be $H1: p > 0.10$. This change in the alternative hypothesis doesn't impact any aspect of the study design or sample size calculation. The criteria for rejection of the null hypothesis remains the same which is the lower limit of the 95% confidence interval being greater than 0.10. Handling missing data for the primary endpoint has been updated clarifying the fact that for the primary endpoint of proportion of patients without confirmed loss of MR4 or loss of MMR within 48 months, all PCR assessments 'by' 48 months will be used. Therefore the text on imputing missing month-48 assessment with available month-44 and month-52 assessments is not meaningful and therefore removed. Also, the analysis of evaluable patients 'at' 48 months is not meaningful and has been removed. Details on handling of missing data will be discussed in the RAP as needed.
- To evaluate impact of over recruitment in this study, several scenarios on power calculation on rates of patients not eligible for TFR based on planned and over recruited patients have been added. 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
- To clarify patient drug access after the end of study
- To include retrospective Sokal risk score collection
- To clarify the biochemistry laboratory parameter for calcium
- To modify the Pharmacokinetic endpoint and corresponding PK blood collection log
- To address minor editorial changes

Changes to the protocol

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IRB/IEC/REB Approval

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.

Amendment 1

Amendment Rationale

This study is currently in the startup phase; 21 patients have been enrolled as of 25-Jun-2013.

Primary purpose for the amendment:

- This study protocol amendment allows patient access to both clinical and commercial drug supply. Sources of drug supply may change during the course of the study; resulting in different packaging. However, all drug supply used in the study will continue to be provided by Novartis and remain free to patients.

In addition, several changes to the protocol will be implemented to address questions identified during the study startup:

- Ensure alignment and consistency of pregnancy language across all nilotinib clinical trials and clarify how to proceed if pregnancy occurs during the treatment free remission phases
- Extend the screening window from 14 days to 28 days in order to allow more time for screening procedures
- Clarify duration of imatinib therapy prior to switch to nilotinib
- Clarify screening process for patients who are currently enrolled in studies CAMN107A2405 (ENESTcmr) and CAMN107EIC01 (ENEST1st) for study CAMN107A2408. Patients are allowed to be screened for the CAMN107A2408 study without having to first discontinue from either study CAMN107A2405 or CAMN107EIC01. Patients will discontinue from these studies only if they are confirmed eligible for study CAMN107A2408. This practice is in compliance with the ICH Topic E8 guidelines as it constitutes a “justified exception” for the following reasons:
 - Subjects treated in either study CAMN107A2405 or CAMN107EIC01 will be treated with the same drug, nilotinib (Tasigna®), at the same dose/same formulation in the approved indication as in study CAMN107A2408. Therefore, nilotinib (Tasigna®) cannot be considered an additional investigational agent from study CAMN107A2405 or CAMN107EIC01 to study CAMN107A2408.
 - As a consequence of the above:
 - No new toxicities are expected in context of this CAMN107A2408 study
 - No carry-over effect is expected between the studies
 - Based on the two points above, a wash-out period is neither necessary nor advisable.

- Subjects will only participate transiently in more than one study; in particular only during the screening window (28 days) needed to assess eligibility for the CAMN107A2408 study.
- Allow earlier re-screening by reducing re-screening window from 12 weeks to approximately 4 weeks $\pm$ 7 days
- Clarify that adverse events will continue to be monitored for 30 days after the last dose of study treatment or last day of the treatment-free remission (TFR)/treatment-free remission-2 (TFR-2) phase. In addition, serious adverse events (SAEs) will be followed until clinical improvement, resolution, or stabilization.
- Clarify SAE reporting requirements regarding assessments of causality
- Additional biomarker section was added to clarify collection of leftover blood samples prior to study entry and during the course of the study. Exploratory biomarker objective language was also clarified.
- Addition of optional pharmacogenetics study section
- Update the protocol title to include the pathology of the study population of interest
- Move language on exploratory objectives and data analysis from section 10.5.1.1 to the correct section 10.6
- Update inclusion criteria #7 for direct bilirubin allowable range
- Clarify treatment free remission-2 (TFR-2) phase and prolonged nilotinib treatment continuation phase
- Allow both manual and automated differential count of white blood cells and reporting of these assessments to be either in percentage or absolute values.
- Provide dose reduction guidelines for study-drug related non-hematologic toxicity to reflect the latest version of the nilotinib Investigator Brochure
- Convert study duration from years to weeks throughout the protocol to align with definition of 28 days in a month
- Clarify reporting responsibilities to IRBs and/or ECs for early study termination
- Address minor editorial corrections

Changes to the protocol

The image shows a large, bold, red logo consisting of the letters 'C', 'C', and 'I' in a stylized, sans-serif font. The logo is positioned on the left side of a solid black rectangular background that occupies the bottom third of the page.

CCI

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IRB/IEC/REB Approval

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	CAMN107A2408
Title	A phase II, single arm, open label study of treatment-free remission in Chronic Myeloid Leukemia (CML) chronic phase (CP) patients after achieving sustained MR4.5 on nilotinib
Brief title	Nilotinib treatment cessation study
Sponsor and Clinical Phase	Novartis Phase II
Investigation type	Drug
Study type	Interventional
Purpose and rationale	Purpose: The purpose of this study is to determine the rate of successful treatment-free remission (TFR) within the first 48 weeks following therapy cessation in patients who achieved and maintained MR4.5 on nilotinib after a switch from imatinib. TFR phase is often referred to as discontinuation phase in other treatment discontinuation studies. Eligible patients have been previously treated with imatinib but did not have documented MR4.5 at the time of switch to nilotinib, and have been on nilotinib therapy for at least 2 years prior to study entry. MR 4.5 is defined as BCR-ABL transcript level $\leq 0.0032\%$ IS or undetectable BCR-ABL levels with sample sensitivity of at least 4.5 log. Rationale: Stop imatinib study (STIM) (Mahon et al 2010) investigated feasibility of imatinib cessation 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 30 months (Mahon et al 2011), 39% of patients have successfully stopped imatinib therapy. This has provided evidence that achieving and maintaining deep molecular responses is a pre-requisite for successful therapy cessation. Among 61 patients with a molecular recurrence, 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. Twenty one of 22 patients who restarted imatinib regained undetectable BCR-ABL transcript level. 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 cessation 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 cessation from nilotinib is unknown. Based on results of ENESTnd [CAMN107A2303], nilotinib allows 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 be eligible for discontinuation. In ENESTcmr study [CAMN107A2405] twice as many patients randomized to nilotinib vs. imatinib achieved MR4.5 after 12 months of treatment allowing them to be eligible for discontinuation trials. Although the current standard of care is to treat CML-CP patients indefinitely with TKI monotherapy, physicians as well as patients have shown a strong interest to explore cessation strategies for BCR-ABL inhibitors. The potential

	medical benefits of successful cessation include minimization of drug-drug interactions, elimination of chronic side effects, and pregnancy without exposure to TKIs.
Primary Objective(s) and Key Secondary Objective	Primary objectives: To evaluate the proportion of patients in Treatment-free remission (TFR) within 48 weeks following nilotinib cessation
Secondary Objectives	- To evaluate the proportion of patients in TFR within 96, 144, 192, 264 weeks, and within the end of years 6, 7, 8, 9, and 10 following nilotinib cessation - To estimate progression-free survival (PFS) following nilotinib cessation - To estimate treatment-free survival (TFS) - To estimate overall survival (OS) - To characterize the kinetics of BCR-ABL transcript after re-start of nilotinib therapy
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 (up to 528 weeks after the last patient enters the TFR phase). All patients who have received a minimum of 3 years of tyrosine kinase inhibitor therapy (started therapy with imatinib (> 4 weeks) as initial tyrosine kinase inhibitor then switched to nilotinib for at least 2 years prior to study entry), but did not have documented MR4.5 at the time of switch to nilotinib, and have achieved MR4.5 on nilotinib can be screened (study Day -28 to 0) for study entry. During the first 52 weeks of the study, all patients will be treated with nilotinib with the same dose prior to study entry. Each patient will have PCR assessments every 12 weeks by a Novartis designated central laboratory. If a patient maintains MR4.5 throughout the 52 weeks, he/she will be eligible to start the TFR phase. If a patient has confirmed loss of MR4.5 (two consecutive BCR-ABL > 0.0032% IS), he/she will not be eligible for the TFR phase. Instead, he/she will continue nilotinib treatment. Duration of the TFR phase is up to 528 weeks after the last patient enters the TFR phase. Patients will stop taking nilotinib 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 during the following 48 weeks and every 12 weeks thereafter. All PCR assessments will be performed by a Novartis designated central laboratory. Two consecutive BCR-ABL > 0.01% IS will be considered confirmed loss of MR4, and the patient will restart nilotinib treatment. Loss of MMR will trigger restarting nilotinib immediately and will not require a confirmation. Patients who are not eligible to enter TFR phase and stay on nilotinib treatment and maintain MR4.5 during the next 52 weeks after consolidation phase will be eligible to cease nilotinib on study after a total of 104 weeks of nilotinib treatment. Data from those patients will not be included in the primary analysis. Patients who terminate this study early will be followed for survival until 528 weeks after the last patient enters the TFR phase.
Population	The target population of this study includes adult patients with diagnosis of Ph+ CML-CP and has achieved MR4.5 while on nilotinib treatment prior to study entry. Patients must have received 3 years of TKI therapy (started off with imatinib as initial tyrosine kinase inhibitor (> 4 weeks) treatment then switched to nilotinib for at least 2 year prior to study entry) but did not have documented MR4.5 at the time of switch from imatinib to nilotinib. Patients who have only been treated with nilotinib or imatinib since initial diagnosis are not eligible.
Inclusion criteria	- Male or female patients ≥ 18 years of age - ECOG Performance Status of 0, 1, or 2 - Patient with diagnosis of BCR-ABL positive CML CP

	4. Patient has received a minimum of 3 years of tyrosine kinase inhibitor treatment (first with imatinib (> 4 weeks) and then switched to nilotinib) since initial diagnosis 5. Patient has at least 2 years of nilotinib treatment prior to study entry 6. Patient has achieved MR4.5 during nilotinib treatment, and determined by a Novartis designated central PCR lab assessment at screening 7. Adequate end organ function as defined by: • Direct bilirubin $\leq 1.5 \times \text{ULN}$ except for i) patients with documented Gilbert's syndrome for whom any bilirubin value is allowed and ii) for patients with asymptomatic hyperbilirubinemia (no concomitant liver enzyme elevation) • SGOT(ALT) and SGPT(ALT) $< 3 \times \text{ULN}$ (upper limit of normal) • Serum lipase $\leq 2 \times \text{ULN}$ • Alkaline phosphatase $\leq 2.5 \times \text{ULN}$ • Serum creatinine $< 1.5 \times \text{ULN}$ 8. Patients must have the following electrolyte values $\geq \text{LLN}$ (lower limit of normal) limits or corrected to within normal limits with supplements prior to the first dose of study medication: • Potassium • Magnesium • Total calcium (corrected for serum albumin) 9. Patients must have normal marrow function as defined below: • Absolute Neutrophil Count (ANC) $\geq 1.5 \times 10^9/\text{L}$ • Platelets $\geq 100 \times 10^9/\text{L}$ • Hemoglobin $\geq 9.0 \text{ g/dL}$ 10. Written informed consent obtained prior to any screening procedures
Exclusion criteria	1. Prior AP, BC or allo-transplant 2. Patient has documented MR4.5 at the time when switched from imatinib to nilotinib 3. Patients with known atypical transcript. An atypical transcript is defined by the presence of any transcript in the absence of the major transcripts b3a2 (e14a2) and b2a2 (e13a2) or p210 protein. 4. CML treatment resistant mutation(s) (T315I, E255K/V, Y253H, F359C/V) detected if testing was done in the past (there is no requirement to perform mutation testing at study entry if it was not done in the past) 5. Dose reductions due to neutropenia or thrombocytopenia in the past 6 months 6. Patient ever attempted to permanently discontinue imatinib or nilotinib treatment 7. Known impaired cardiac function including any one of the following: • Inability to determine the QT interval on ECG • Complete left bundle branch block • Long QT syndrome or a known family history of long QT syndrome • History of or presence of clinically significant ventricular or atrial tachyarrhythmias • Clinically significant resting bradycardia • QTc $> 480 \text{ msec}$ • History or clinical signs of myocardial infarction within 1 year prior to study entry • History of unstable angina within 1 year prior to study entry • Other clinically significant heart disease (e.g. uncontrolled congestive heart failure or uncontrolled hypertension) 8. 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 (defined as HbA1c > 9%), uncontrolled infection) 9. History of acute pancreatitis within 1 year prior to study entry or past medical history of chronic pancreatitis 10. Known presence of a significant congenital or acquired bleeding disorder unrelated to cancer 11. History of other active malignancy within 5 years prior to study entry with the exception of previous or concomitant basal cell skin cancer, previous cervical carcinoma in situ treated curatively 12. Patients who have not recovered from prior surgery 13. Treatment with other investigational agents (defined as not used in accordance with the approved indication) within 4 weeks of Day 1 14. Patients actively receiving therapy with strong CYP3A4 inhibitors and/or inducers, and the treatment cannot be either discontinued or switched to a different medication prior to study entry. See Appendix 14.1 for a list of these medications. This list may not be comprehensive. 15. 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 study entry. These herbal medicines may include Echinacea, (including E. purpurea, E. angustifolia and E. pallida), Piperine, Artemisinin, St. John's Wort, and Ginkgo. 16. Patients who are currently receiving treatment with any medications that are known to prolong the QT interval and the treatment cannot be either safely discontinued or switched to a different medication prior to study entry. (Please see www.crediblemeds.org/index.php for a list of agents that prolong the QT interval.) 17. 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) 18. 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. 19. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, must have a negative serum pregnancy test before initiation of study treatment and must also use highly effective methods of contraception while enrolled in the study. The use of highly effective contraception should continue for at least 14 days after the last dose of study treatment or until the last day of TFR/TFR-2, or for the duration of a monthly cycle of oral contraception, whichever is longer. Acceptable forms of highly effective contraception methods include: • 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), 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 screening). 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
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	contraception women should be 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), total 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.
Investigational and reference therapy	NA
Efficacy assessments	• Molecular Response (RT-qPCR, mutation analysis) • Bone marrow assessments (optional)
Safety assessments	• Physical examination • Vital Sign • Height and weight • ECOG performance status • Laboratory chemistry and hematology • Electrocardiogram (ECG) • Serology
Other assessments	• One blood sample for the assessment of nilotinib PK trough level will be collected from all patients on Day 336 of the consolidation phase CCI • Sokal risk score will be collected retrospectively at any time point during the study
Data analysis	Demonstration of successful TFR of nilotinib will be evaluated using the following hypothesis: H0: $p \leq 0.10$, where p is the rate of no documented confirmed loss of MR4, no loss of MMR and no re-starting of nilotinib therapy in the first 48 weeks after starting TFR phase. H1: $p \geq 0.10$, where p is the rate of no documented confirmed loss of MR4, no loss of MMR and no re-starting of nilotinib therapy in the first 48 weeks after starting TFR phase. The rate of successful TFR 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 enter the TFR phase and completed 48 weeks of TFR phase or terminated the study earlier.
Key words	Phase II, single arm, open label, nilotinib, treatment-free remission, MR4.5, confirmed loss of MR4, loss of MMR, Ph+ CML-CP

1 Background

1.1 Overview of disease pathogenesis, epidemiology and current treatment

Chronic myeloid leukemia (CML) is a hematological stem cell disorder associated with a specific chromosomal translocation known as the Philadelphia (Ph) chromosome detected in 95% of patients ([Nowell and Hungerford 1960](#); [Rowley 1973](#)). The molecular consequence of the translocation is the fusion of the ABL proto-oncogene to the BCR gene resulting in the production of an activated form of the ABL protein-tyrosine kinase ([Bartram 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 and 5-6 years with interferon (IFN), 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 LeukemiaNet (ELN) ([Baccarani et al 2009](#)) recommend continuing tyrosine kinase inhibitor (TKI) treatment (i.e. imatinib and nilotinib) indefinitely in all responding patients. There are no recommendations or provisions for temporary or permanent discontinuation of imatinib or nilotinib.

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

1.2.1 Overview of nilotinib (AMN107, Tasigna)

Nilotinib is a novel aminopyrimidine, available as an oral formulation that is an Adenosine triphosphate (ATP)-competitive inhibitor of the protein tyrosine kinase activity of BCR-ABL, 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 [AMN107 Investigator's Brochure, current edition].

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 [AMN107 Investigator's Brochure, current edition].

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

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

- Nilotinib 300 mg 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. 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 [AMN107 Investigator's Brochure, current edition].

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 including imatinib. The recommended adult dosage of nilotinib is 300 mg orally twice daily for newly diagnosed Ph+ CML-CP and 400 mg orally twice daily for resistant or intolerant Ph+ CML-CP and CML-AP.

The results of study ENESTnd [CAMN107A2303] demonstrated superiority of nilotinib vs. imatinib in the CML-CP frontline setting (Saglio et al 2010, Larson et al 2012). More patients treated with nilotinib achieved deeper molecular responses and the differences were significantly superior at each of the analyzed time points to date. The rate of major molecular response (MMR) 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% and 28% by 12, 24 and 36 months in the nilotinib 400 mg BID arm, and was 11%, 25% and 32% in the nilotinib 300 mg BID arm. In the imatinib arm the rates were 1%, 9% and 15% at the same time points. The differences between the rates of MR4.5 in nilotinib and imatinib arms increased over time (6%, 10% and 13% difference by month 12, 24 and 36 for the 400 mg BID arm and 10%, 16% and 17% 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.

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

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

2 Rationale

2.1 Study rationale and purpose

The purpose of this study is to determine the rate of successful treatment-free remission (TFR) within the first 48 weeks following cessation of treatment in patients who achieved and maintained MR4.5 on nilotinib after a switch from imatinib. TFR phase is often referred to as discontinuation phase in other studies. Eligible patients have been previously treated with imatinib as the initial tyrosine kinase inhibitor (> 4 weeks) but did not have documented MR4.5 at the time of switch to nilotinib, and have been on nilotinib therapy for at least 2 years prior to study entry. MR4.5 is defined as BCR-ABL transcript level $\leq 0.0032\%$ IS or undetectable BCR-ABL levels with sample sensitivity of at least 4.5 log.

Stop imatinib study (STIM) ([Mahon et al 2010](#)) investigated feasibility of imatinib cessation 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 30 months ([Mahon et al 2011](#)), 39% of patients have successfully stopped imatinib therapy. This provided the first evidence that achieving and maintaining deep molecular responses is a pre-requisite for successful therapy cessation. In terms of regaining molecular response, 61 patients had a molecular recurrence, 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 RT-qPCR in two consecutive tests). Twenty one of 22 patients who restarted imatinib regained undetectable BCR-ABL transcript level. One patient remains in MMR at the 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 cessation 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 cessation from nilotinib is unknown.

Based on results of ENESTnd [[CAMN107A2303](#)], nilotinib allows 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 be eligible for discontinuation. In the ENESTcmr study [[CAMN107A2405](#)] twice as many patients randomized to nilotinib vs. imatinib achieved MR4.5 after 12 months of treatment allowing them to be eligible for discontinuation trials.

Although the current standard of care is to treat CML-CP patients indefinitely with TKI monotherapy, physicians as well as patients have shown a strong interest to explore cessation strategies for BCR-ABL inhibitors. The potential medical benefits of successful cessation

include minimization of drug-drug interactions, elimination of chronic side effects, and pregnancy without exposure to TKIs.

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 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 the STIM study (Mahon et al 2010) the median time to achieve undetectable BCR-ABL was 19 months (range: 2-56 months.). In contrast, patients who never achieved deep molecular responses after two or more years on imatinib and required a switch to nilotinib to achieve MR4.5 may have disease with distinct biological characteristics. Feasibility of stopping therapy in this large group of patients has not been evaluated in any of the previous clinical trials, and will be explored in the current study.

This single-arm, open label study has the goal of establishing the rate of successful TFR in patients who have been previously treated with imatinib but then switched to nilotinib. These patients did not have documented MR4.5 at the time of switch to nilotinib, and then achieved MR4.5 on nilotinib treatment.

Patients are required to be treated with imatinib and nilotinib for a combined minimum of 3 years. The minimum duration of imatinib treatment is 4 weeks and the minimum duration of nilotinib treatment is two years prior to study entry. The STIM study ([Mahon et al 2010](#); [Mahon et al 2011](#)) enrolled patients with minimum of 3 years of imatinib therapy and demonstrated a 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 cessation attempt is 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 in a central laboratory via polymerase chain reaction (PCR) at screening prior to study entry. MR4.5 ($\text{BCR-ABL} \leq 0.0032\% \text{ IS}$) will also need to be maintained for one year on nilotinib after study entry and before stopping nilotinib. One year of continuing nilotinib treatment on study will allow for a systematic evaluation of BCR-ABL transcript in a Novartis designated central laboratory and ensure that only patients who maintained MR4.5 will be eligible to stop nilotinib.

The duration of the TFR phase is up to 528 weeks after the last patient enters the TFR phase. In the imatinib discontinuation study (STIM), with median follow-up of 30 months, 61 recurrences were observed. Fifty-eight of the recurrences were observed in the first 7 months following the cessation of imatinib. Three additional recurrences were observed on month 19, 20 and 22. The 528 weeks 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 central laboratory. Frequency of PCR during the TFR phase will be every 4 weeks

during the first 48 weeks, every 6 weeks for the following 48 weeks, and every 12 weeks thereafter. 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 will identify all patients who are potential candidates for restarting nilotinib. More frequent monitoring is not necessary. PCR monitoring every 12 weeks after TFR week 96 and until end of study is consistent with the recommended frequency of monitoring in clinical practice ([Baccarani et al 2009](#)). Monitoring every 6 weeks represents an intermediate frequency during the second 48 weeks in TFR. Two consecutive BCR-ABL results $>0.01\%$ international scale (IS) will be considered confirmed loss of MR4 and the patient will restart nilotinib treatment. Loss of MMR (BCR-ABL results $>0.1\%$ IS) will trigger restarting nilotinib 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 restarting treatment ([Rousselot et al 2012](#)). In this study, a second attempt at nilotinib treatment cessation after a patient fails the TFR phase is not allowed.

117 eligible patients will be enrolled in the study, and 70 eligible patients will undergo nilotinib cessation. For detailed patient sample size calculation, please refer to [Section 10.8](#).

Per protocol amendment 5, the study duration will be extended by a further period of 5 years to a minimum of 528 weeks (10 calendar years) after the last patient entered the TFR phase in order 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).

2.3 Rationale for dose and regimen selection

This study will allow patients to take the same nilotinib dose they are taking prior to study entry. Therefore dose of nilotinib used on study will be 300 mg twice a day (BID) or 400 mg BID or at the dose the patient was taking prior to study entry.

The nilotinib 400 mg BID dose is consistent with the nilotinib starting dose in the ongoing ENESTcmr study [[CAMN107A2405](#)]; through which many patients may have been treated prior to entering this study. Patients who achieve and maintain MR4.5 on nilotinib in the ENESTcmr study will be eligible for enrollment. In clinical practice, for patients who switch from imatinib to nilotinib, 400 mg BID is most commonly prescribed.

Patients who required a permanent dose reduction from their original starting dose prior to the study entry, but meet all inclusion criteria, including molecular criteria, will be allowed to continue taking that dose during the study. The dose reduction must be considered permanent and maintained for a minimum of 6 months prior to study entry.

The results of the study ENESTnd [[CAMN107A2303](#)] demonstrated numerically higher response rates in nilotinib 300 mg BID vs. 400 mg BID at every time point and every depth of MR. The cumulative incidence of MR4.5 by 12 months is 11% in nilotinib 300 mg BID and 7% in nilotinib 400 mg BID. By 36 months the cumulative incidence of MR4.5 was 32% in nilotinib 300 mg BID and 28% in 400 mg BID, respectively. Patients treated with nilotinib 300 mg BID experienced fewer adverse events and fewer patients discontinued the study due to adverse events (in 3 year follow-up: 10% vs. 14% in nilotinib 300 mg BID vs. 400 mg BID, respectively).

It is anticipated that with better tolerability of nilotinib 300 mg BID dose, more patients will adhere to therapy which may result in further BCR-ABL transcript reduction. Based on the results of ENESTnd, patients treated with nilotinib 300 mg BID will be eligible and will be allowed to continue this dose on study as long as they meet all other inclusion and exclusion criteria.

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		
To evaluate the proportion of patients in TFR within 48 weeks following nilotinib cessation	No documented confirmed loss of MR4, no documented loss of MMR and no re-starting of nilotinib therapy in the first 48 weeks following nilotinib cessation. Confirmed loss of MR4 is two consecutive BCR-ABL > 0.01% IS. Loss of MMR does not require confirmation	Proportion of patients without confirmed loss of MR4 or loss of MMR within 48 weeks following nilotinib TFR is calculated by dividing the number of patients with no documented confirmed loss of MR4, no documented loss of MMR and no re-starting of nilotinib therapy in the first 48 weeks after starting nilotinib TFR phase by the number of patients who entered nilotinib TFR phase.
Secondary		
To evaluate the proportion of patients in TFR within 96, 144, 192, 264 weeks, and within the end of years 6, 7, 8, 9 and 10 following nilotinib cessation	No documented confirmed loss of MR4, no documented loss of MMR and no re-starting of nilotinib therapy in the first 96, 144, 192, 264 weeks, and within the end of years 6, 7, 8, 9 and 10 following nilotinib cessation. Confirmed loss of MR4 is two consecutive BCR-ABL > 0.01% IS. Loss of MMR does not require any confirmation	Proportion of patients without confirmed loss of MR4 or loss of MMR within 96, 144, 192, 264 weeks, and within the end of years 6, 7, 8, 9 and 10 following nilotinib cessation is calculated by dividing the number of patients with no documented confirmed loss of MR4, no documented loss of MMR and no re-starting of nilotinib therapy in the first 96, 144, 192, 264 weeks and within the end of years 6, 7, 8, 9 and 10 after starting nilotinib TFR phase by the number of patients who entered the nilotinib TFR phase.
To estimate progression-free survival (PFS) following nilotinib cessation	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.	Kaplan-Meier (KM) estimation of PFS. PFS is measured from the date of start of nilotinib TFR phase to the date of the earliest of the event: progression to AP/BC, or death from any cause. Patients not known to have recurred or died on or before the cut-off date for the KM analysis will have their PFS interval right-censored at the earlier of the date of their last assessment (cytogenetic, hematology 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 treatment-free survival (TFS)	TFS is defined as the lack of any of the following events: loss of MMR, confirmed loss of MR4, re-start of nilotinib treatment, progression to AP/BC or death from any cause	Kaplan-Meier (KM) estimation of TFS. TFS is measured from the date of the start of the nilotinib TFR phase to the date of the earliest of the following: loss of MMR, confirmed loss of MR4, re-start of nilotinib treatment, progression to AP/BC or death from any cause. Patients not known to have had any of the events or died on or before the cut-off date for the KM analysis will have their TFS interval right-censored at the earlier of the date of their last assessment (PCR, cytogenetic, hematology or extramedullary) for patients who are still on study and at the date of last contact for patients are in follow-up.

Objective	Endpoint	Analysis
		A TFS sensitivity analysis will be conducted by considering discontinuation from TFR phase due to any reason as an event, in addition to the events as defined above
To estimate overall survival (OS)	OS is defined as the time from the date of cessation of nilotinib therapy to the date of death from any cause.	Kaplan-Meier (KM) estimation of OS. OS is measured from the date of start of nilotinib TFR phase to the date of death from any cause. If a patient is not known to have died, survival will be censored at the date of last contact.
To characterize the kinetics of BCR-ABL transcript after re-start of nilotinib therapy	BCR-ABL transcript changes within 48 weeks after re-start of nilotinib therapy	Descriptive statistics of BCR-ABL over time after re-start of nilotinib therapy.
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 $\leq 0.1\%$ IS (MMR) at 48 weeks, 96 weeks or subsequent time points since first achievement of MR4.5 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 is calculated by dividing the number of patients who restart treatment due to loss of MMR in TFR phase and 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 restart treatment due to loss of MMR in TFR phase and achieved MMR at any time during the nilotinib re-initiation phase
To determine the percentage of patients who are in stable MR4 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 $\leq 0.01\%$ IS (MR4) at 48 weeks, 96 weeks or subsequent time points since first achievement of MR4.5 during the nilotinib re-initiation phase	Proportion of patients who are in stable MR4 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 is calculated by dividing the number of patients achieving MR4 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, irrespective of whether there is loss of MR4 in between, by the number of patients who achieved MR4 at any time during the nilotinib re-initiation phase

Objective	Endpoint	Analysis
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 $\leq$ 0.0032% IS (MR4.5) at 48 weeks, 96 weeks or subsequent time points 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 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

Exploratory

Refer to [Section 10.7](#)



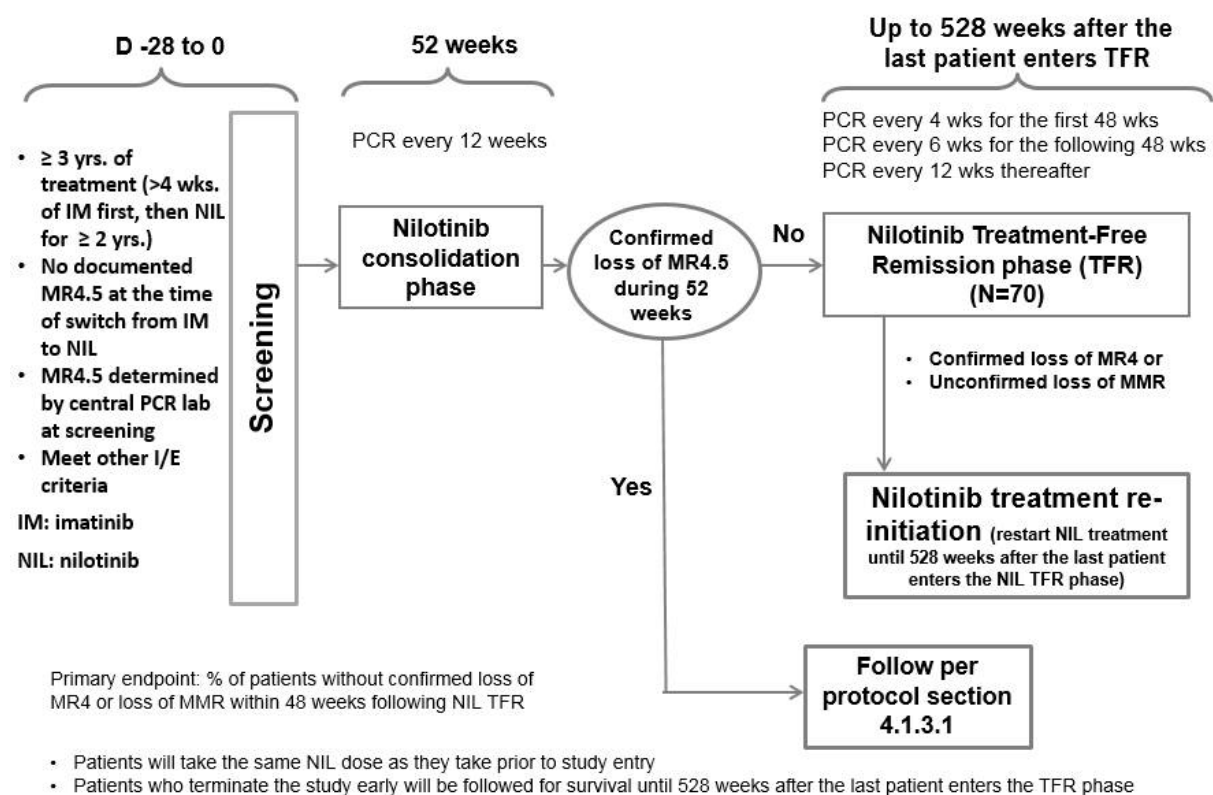
Objective	Endpoint	Analysis
CCI		

4 Study design

4.1 Description of study design

This is a single-arm, open label study designed to determine the rate of successful TFR in patients who achieved and maintained MR4.5 on nilotinib. Eligible patients must have received a minimum of 3 years of TKI therapy (started off with imatinib as initial tyrosine kinase inhibitor treatment (> 4 weeks) then switched to nilotinib for at least 2 years prior to study entry) but did not have documented MR4.5 at the time of switch from imatinib to nilotinib. This study has 2 main phases: nilotinib consolidation, and the TFR phases. Please see [Figure 4-1](#) for study design.

Figure 4-1 Study design



4.1.1 Screening

All patients who have received a minimum of 3 years of tyrosine kinase inhibitor therapy (started therapy with imatinib as the initial tyrosine kinase inhibitor (> 4 weeks) then switched to nilotinib for at least 2 years prior to study entry), but did not have documented MR4.5 at the time of switch to nilotinib, and have achieved MR4.5 on nilotinib can be screened (study Day -

28 to 0) for study entry. During this time the inclusion and exclusion criteria will be assessed and all screening laboratory assessments and procedures will be carried out. Patient's BCR-ABL level will be analyzed with one PCR sample using a Novartis designated central laboratory. In case the MR4.5 status cannot be determined on this sample (e.g. due to technical or logistical issue) another blood sample for RT-qPCR is to be collected immediately and submitted to the central PCR laboratory for determination of the MR4.5 status. Only patients who are in MR4.5 will be eligible. Results of all screening evaluations must be reviewed by the Principal Investigator or his/her designee prior to enrollment of a patient into the study to assure that all inclusion and exclusion criteria have been satisfied.

Patients who are currently enrolled in Novartis study CAMN107A2405 (ENESTcmr) or CAMN107EIC01 (ENEST1st) are allowed to be consented and screened for study CAMN107A2408 without discontinuing from their current enrollment. This is to ensure that patients receive continuous nilotinib treatment. If a patient is eligible for study CAMN107A2408 after screening procedures and assessments, he/she must discontinue from either study CAMN107A2405 (ENESTcmr) or CAMN107EIC01 (ENEST1st), and complete all end of study assessments before enrolling into study CAMN107A2408.

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 any screening evaluations. If a patient is unable to read, an impartial witness should be present during the entire informed consent discussion.

Re-screening of a patient will be allowed for this study approximately 4 weeks $\pm$ 7 days after screen failure. 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.

4.1.2 Nilotinib consolidation phase

During the first 52 weeks of the study, all patients will be treated with nilotinib with the same dose prior to study entry. The consolidation phase is scheduled for 52 weeks or until a 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. Each patient will have PCR assessments every 12 weeks by a Novartis designated central laboratory. If a patient maintains MR4.5 throughout the 52 weeks, he/she will be eligible to start the TFR phase. If during the consolidation phase, a patient has one PCR result above MR4.5 (BCR-ABL $> 0.0032\%$ IS) or if the MR4.5 status cannot be determined on this sample (e.g. due to technical or logistical issue), a subsequent unscheduled visit sample must be collected within 4 weeks. If a patient has confirmed loss of MR4.5 (two consecutive BCR-ABL $> 0.0032\%$ IS), he/she will not be eligible for the TFR phase. Instead, he/she will continue nilotinib treatment as specified in [Section 4.1.3.1](#).

4.1.3 Nilotinib TFR phase

The duration of the TFR phase is up to 528 weeks after the last patient enters the TFR phase. Patients will stop taking nilotinib 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 thereafter. All PCR assessments will be performed by a Novartis designated central laboratory. Two consecutive BCR-ABL $> 0.01\%$ IS will be

considered confirmed loss of MR4 and the patient will then restart nilotinib treatment. Loss of MMR will trigger restarting nilotinib immediately and will not require a confirmation.

Once a patient restarts nilotinib treatment, BCR-ABL level will be monitored by PCR every 4 weeks for the first 24 weeks, then once every 12 weeks. Electrocardiogram (ECG) will be collected prior to the first dose, and then every 48 weeks thereafter. Physical examination and other laboratory assessments will be performed every 4 weeks for the first 12 weeks, then once every 12 weeks. Patients will be on nilotinib treatment for up to 528 weeks after the last patient enters the TFR phase, or until a 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.

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 ($< 100 \times 10^9/L$) that is unrelated to therapy
3. Blast crisis (BC) as defined by any of the following:
 - $\geq 30\%$ blasts in peripheral blood or bone marrow aspirate
 - Appearance of extramedullary involvement other than hepatosplenomegaly proven by biopsy (i.e., chloroma)

In this study, a second attempt at nilotinib treatment cessation after a patient fails the TFR phase is not allowed.

4.1.3.1 Patients who are not eligible to enter TFR phase

Data from patients who are not eligible to enter the TFR phase will not be included in the primary analysis.

Patients who are not eligible to enter the TFR phase, will enter the nilotinib treatment continuation phase and continue nilotinib treatment for another 52 weeks. PCR as well as other laboratory assessments will be performed every 12 weeks during this period.

4.1.3.1.1 Nilotinib TFR-2 phase

If a patient maintains MR4.5 throughout the 52 weeks of nilotinib treatment continuation, he/she will be eligible to cease nilotinib treatment on study and enter the treatment-free remission-2 (TFR-2) phase. Duration of the nilotinib TFR-2 phase will last up to 528 weeks after the last patient enters the TFR phase. Patients will stop taking nilotinib therapy on the day they enter this phase. Frequency of assessments for these patients will mimic those of the TFR 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 thereafter. All PCR assessments will be performed by a Novartis designated central laboratory. If a patient has confirmed loss of MR4 or loss of MMR during this phase, he/she will resume nilotinib treatment and enter nilotinib re-treatment-2. Frequency of assessments for nilotinib re-treatment-2 will mimic those of the nilotinib treatment re-initiation phase. For detailed schedule, please refer to [Table 7-5](#) and [Table 7-6](#).

4.1.3.1.2 Prolonged nilotinib treatment continuation

If a patient is not able to maintain MR4.5 during the nilotinib treatment continuation, he/she will have prolonged nilotinib treatment continuation until 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 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. For detailed schedule of nilotinib prolonged treatment continuation, please refer to [Table 7-7](#).

4.1.4 Survival follow up

Survival information, stem cell transplantation, TKI therapy status, 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 from all patients who terminate the study early. The survival follow-up will be done every 12 weeks until 528 weeks after the last patient enters the 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 10.7](#) for details on data monitoring and reporting.

4.3 Definition of end of study

End of study (EOS) occurs 528 weeks after the last patient enters the TFR phase. At this point, all patients will have completed the TFR phase, or completed nilotinib treatment, or discontinued the study early. In addition, the final end of treatment (EOT) visit as well as the end of post-treatment follow up phase will also have been completed.

At the end of the study, all patients still on study treatment will be transitioned to commercial 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.

Patients who are in the treatment free remission phase at the end of the study will be referred to their primary oncologist for continued BCR-ABL monitoring.

4.4 Early study termination

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

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

1. More than 3 cases of progression to AP/BC despite BCR-ABL monitoring and start of TFR according to protocol, or
2. More than 3 cases of confirmed loss of CCyR despite BCR-ABL monitoring and start of TFR according to protocol, or
3. More than 11 cases of failure to achieve MMR (among patients who lost MMR) at 12 months despite BCR-ABL monitoring and start of TFR according to protocol with at least 12 weeks of nilotinib.

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 prematurely withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The Sponsor or 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 target population of this study includes adult patients with diagnosis of Ph+ CML-CP and received imatinib for at least 4 weeks as initial therapy. They then switched treatment from imatinib to nilotinib and have achieved MR4.5 while on nilotinib treatment prior to study entry. Patients must have received a minimum of 3 years of TKI therapy (started off with imatinib treatment as initial tyrosine kinase inhibitor (> 4 weeks) then switched to nilotinib for at least 2 years prior to study entry) but did not have documented MR4.5 at the time of switch from imatinib to nilotinib. Patients who have only been treated with either nilotinib or imatinib since initial diagnosis are not eligible.

Patients who are currently enrolled in Novartis study [CAMN107A2405] (ENESTcmr) or [CAMN107EIC01] (ENEST1st) are allowed to be consented and screened for study CAMN107A2408 without discontinuing from their current enrollment. This is to ensure that patients receive continuous nilotinib treatment. If a patient is eligible for study CAMN107A2408 after screening procedures and assessments, he/she must discontinue from either study CAMN107A2405 (ENESTcmr) or CAMN107EIC01 (ENEST1st), and complete all end of study assessments before enrolling into study CAMN107A2408. Patients must meet

all inclusion criteria and none of the exclusion criteria to enter the study. 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. ECOG Performance Status of 0, 1, or 2
3. Patient with diagnosis of BCR-ABL positive CML CP
4. Patient has received a minimum of 3 years of tyrosine kinase inhibitor treatment (first with imatinib (> 4 weeks) and then switched to nilotinib) since initial diagnosis
5. Patient has at least 2 years of nilotinib treatment prior to study entry.
6. Patient has achieved MR4.5 during nilotinib treatment, and determined by a Novartis designated central PCR lab assessment at screening
7. Adequate end organ function as defined by:
 - Direct bilirubin $\leq 1.5 \times \text{ULN}$ except for i) patient 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) $< 3 \times \text{ULN}$ (upper limit of normal)
 - Serum lipase $\leq 2 \times \text{ULN}$
 - Alkaline phosphatase $\leq 2.5 \times \text{ULN}$
 - Serum creatinine $< 1.5 \times \text{ULN}$
8. Patients must have the following electrolyte values $\geq \text{LLN}$ (lower limit of normal) limits or corrected to within normal limits with supplements prior to the first dose of study medication:
 - Potassium
 - Magnesium
 - Total calcium (corrected for serum albumin)
9. Patients must have normal marrow function as defined below:
 - Absolute Neutrophil Count (ANC) $\geq 1.5 \times 10^9/\text{L}$
 - Platelets $\geq 100 \times 10^9/\text{L}$
 - Hemoglobin $\geq 9.0 \text{ g/dL}$
10. Written informed consent obtained prior to any screening procedures

5.3 Exclusion criteria

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

1. Prior AP, BC or allo-transplant
2. Patient has documented MR4.5 at the time when switched from imatinib to nilotinib

3. Patients with known atypical transcript. An atypical transcript is defined by the presence of any transcript in the absence of the major transcripts b3a2 (e14a2) and b2a2 (e13a2) or p210 protein.
4. CML treatment resistant mutation(s) (T315I, E255K/V, Y253H, F359C/V) detected if a testing was done in the past (there is no requirement to perform mutation testing at study entry if it was not done in the past)
5. Dose reductions due to neutropenia or thrombocytopenia in the past 6 months
6. Patient ever attempted to permanently discontinue imatinib or nilotinib treatment
7. Known impaired cardiac function including any one of the following:
 - Inability to determine the QT interval on ECG
 - Complete left bundle branch block
 - Long QT syndrome or a known family history of long QT syndrome
 - History of or presence of clinically significant ventricular or atrial tachyarrhythmias
 - Clinically significant resting bradycardia
 - QTcF > 480 msec
 - History or clinical signs of myocardial infarction within 1 year prior to study entry
 - History of unstable angina within 1 year prior to study entry
 - Other clinically significant heart disease (e.g. uncontrolled congestive heart failure or uncontrolled hypertension)
8. 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 (defined as HbA1c > 9%), uncontrolled infection)
9. History of acute pancreatitis within 1 year prior to study entry or past medical history of chronic pancreatitis
10. Known presence of a significant congenital or acquired bleeding disorder unrelated to cancer
11. History of other active malignancy within 5 years prior to study entry with the exception of previous or concomitant basal cell skin cancer, previous cervical carcinoma in situ treated curatively
12. Patients who have not recovered from prior surgery
13. Treatment with other investigational agents (defined as not used in accordance with the approved indication) within 4 weeks of Day 1
14. Patients actively receiving therapy with strong CYP3A4 inhibitors and/or inducers, and the treatment cannot be either discontinued or switched to a different medication prior to study entry. See [Appendix 14.1](#) for a list of these medications. This list may not be comprehensive.
15. 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 study entry. These herbal medicines may include Echinacea, (including E. purpurea, E. angustifolia and E. pallida), Piperine, Artemisinin, St. John's Wort, and Ginkgo.

16. Patients who are currently receiving treatment with any medications that are known to prolong the QT interval and the treatment cannot be either safely discontinued or switched to a different medication prior to study entry. (Please see crediblemeds.org/index.php for a list of agents that prolong the QT interval.)
17. 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)
18. 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.
19. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, must have a negative serum pregnancy test before initiation of study treatment and must also use highly effective methods of contraception while enrolled in the study. The use of highly effective contraception should continue for at least 14 days after the last dose of study treatment or until the last day of TFR/TFR-2, or for the duration of a monthly cycle of oral contraception, whichever is longer. Acceptable forms of highly effective contraception methods include:
 - 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), 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 screening). 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 be 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), total 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 is suspected of being pregnant during the study or within 30 days as part of safety evaluations after the final dose of nilotinib, the Study Doctor needs to be informed immediately and any ongoing study treatment with nilotinib has to be stopped immediately.

6 Treatment

6.1 Study treatment

Study treatment: nilotinib (AMN107, Tasigna®)

Study drugs: nilotinib (AMN107, Tasigna®)

Nilotinib study drug will be provided by Novartis. Sourcing of study drug by Novartis can be either through clinical supply or local commercial supply.

Clinical supply will be provided globally though drug supply management and labeled as per local regulations. Local commercial supply will be sourced in the country where appropriate and as per local regulations. If nilotinib is sourced through local commercial supply, drug will be labeled in-country and the locally approved form and packaging of nilotinib will be used.

Nilotinib will not be dosed by weight or body surface area.

All investigational treatment is to be stored in a secure locked area while under the responsibility of the investigator. Receipt and dispensing of investigational treatment must be recorded by an authorized person at the investigator's site.

For detailed safety information refer to the [AMN107 Investigator's Brochure, current edition] and the approved product labeling.

6.1.1 Dosing regimen

Nilotinib 300 mg BID or 400 mg BID will be administered orally 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. Patients are also allowed to enter this study on the same dose they were taking prior to study entry. Patients who required permanent dose reduction from their original starting dose will be allowed to enter this study on the same dose only if the patient maintains this dose for a minimum of 6 months prior to study entry.

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	Daily
Nilotinib	Capsule for oral use	400 mg BID	Daily
Nilotinib	Capsule for oral use	Dose patient was taking prior to study entry	Daily

6.1.2 Guidelines for continuation of treatment

If a patient is not eligible to cease nilotinib therapy (not eligible to enter TFR or TFR-2 phase), or needs to re-start the therapy, he/she will receive nilotinib treatment 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.

If a patient does not tolerate the nilotinib dose, dose modification guidelines specified in [Table 6-2](#) and [Table 6-3](#) should be followed.

6.1.3 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 enter the TFR phase) unless patients discontinue early.

During the nilotinib consolidation phase, all patients will receive 52 weeks of nilotinib treatment or until a 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 52 weeks. Dose of nilotinib will be the same as what a patient is taking prior to study entry. Patients who required subsequent permanent dose reduction from their original starting dose starting dose will be allowed to enter this study on the same dose only if the patient maintains this dose for a minimum of 6 months prior to study entry.

The duration of the TFR phase is up to 528 weeks after the last patient enters the TFR phase. Patients who are not eligible to enter the TFR phase will enter nilotinib treatment continuation phase for 52 weeks.

At the end of the nilotinib treatment continuation, a patient can either be eligible to cease nilotinib therapy and enter TFR-2 phase, or enter nilotinib prolonged treatment continuation until 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 treatment is discontinued at the discretion of the investigator or withdrawal of consent.

At any time during nilotinib treatment cessation, a patient with a confirmed loss of MR4 (two consecutive BCR-ABL > 0.01% IS) or loss of MMR will immediately restart nilotinib treatment until 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 treatment is discontinued at the discretion of the investigator or withdrawal of consent.

A second attempt at nilotinib treatment cessation after a patient fails the TFR phase is not permitted in this study.

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](#) and [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 subject's participation in a trial, the investigator should ensure that adequate medical care is provided to a subject 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) version 4.03 for toxicity and adverse event reporting. CTCAE version 4.03 can be downloaded as a PDF file from the following website:

evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

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 study drug relationship is presented in [Table 6-2](#). This table is only applicable for patients who entered the study on either 300 mg BID or 400 mg BID.

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 below) must be strictly followed:

- Any non-hematological toxicity Grade 3 or 4 must be resolved within 28 days to $\leq$ Grade 2 in order to resume study drug at the reduced dose. If a non-hematological toxicity Grade 3 or 4 does not resolve after 28 days, the patient must be discontinued from the study.
- If Grade 4 toxicity of the same type recurs despite nilotinib dose reduction to 400 mg 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 nilotinib dose reduction guidelines for study drug-related non-hematologic toxicity and for ischemic vascular and cardiovascular events regardless of study drug relationship

Study drug and dose	
Nilotinib 600 mg daily (as 300 mg BID) or Nilotinib 800 mg daily (as 400 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 study drug 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
Serum hypophosphatemia	
Grade 2-3	Continue nilotinib at the full dose and start phosphate supplementation.
Grade 4	Hold study drug and consult Novartis.
Serum creatinine	
Grade 2 > 1.5 -3.0 x ULN	The dose of nilotinib may be reduced to 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 study drug 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
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
≥ Grade 3	Hold study drug 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
Pancreatitis (with abdominal symptoms plus lipase elevation)	

Study drug and dose	Nilotinib 600 mg daily (as 300 mg BID) or Nilotinib 800 mg daily (as 400 mg BID)
Grade 2	Hold study drug and perform abdominal CT with contrast to exclude pancreatic pathology. If CT is positive, continue to hold therapy and repeat CT, at investigator's discretion. If CT is negative, re-start nilotinib at 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 ↳ discontinue from the study
Grade 3	Hold study drug and consult Novartis
Grade 4	Stop study drug. The patient must be discontinued from study
Elevated lipase without symptoms	
≥ Grade 3	Hold study drug Re-start nilotinib at 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, ↳ 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 study drug and resume nilotinib at next lower dose level after recovery to ≤ Grade 2 is seen ↳ 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 study drug and resume nilotinib at next lower dose level after recovery to ≤ Grade 2 is seen ↳ 400 mg QD. If recovery to ≤ Grade 2 is greater than 28 days, the patient must be discontinued from the study.
Skin rash Note: Institute symptomatic therapy as appropriate. If skin rash does not resolve with optimal treatments, take the following actions:	
Grade 2	The dose of nilotinib may be reduced to 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) or Nilotinib 800 mg daily (as 400 mg BID)
≥ Grade 3	Hold study drug and resume nilotinib at next lower dose level after recovery to ≤ Grade 2 is seen ↳ 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 ↳ discontinue from the study
Cardiac QTc prolongation	
QTcF > 480 msec	Hold study drug 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. • 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 from the study. 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 cardiovascular events	

Study drug and dose	Nilotinib 600 mg daily (as 300 mg BID) or Nilotinib 800 mg daily (as 400 mg BID)
Grade 2*	Hold study drug and refer patient for assessment by a vascular or cardiovascular specialist. Resume nilotinib at next lower dose level after recovery to $\leq$ Grade 1 is seen I $\rightarrow$ 400 mg QD. If another recurrence I $\rightarrow$ discontinue from the study If recovery to $\leq$ Grade 1 is greater than 28 days, the patient must be discontinued from the study.
Grade 3* or 4*	Hold study drug and refer patient for assessment by a vascular or cardiovascular specialist. Consideration should be given for discontinuation from the study. The patient must be discontinued from the study if recovery to $\leq$ 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 study drug and resume nilotinib at next lower dose level after recovery to $\leq$ Grade 1 is seen I $\rightarrow$ 400 mg QD. If recovery to $\leq$ 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 $\rightarrow$ discontinue from the study
Grade 4	Stop study drug. The patient must be discontinued from the study

As per [Section 2.3](#), patients on a permanently reduced dose are also allowed to enter this study at the dose they were taking prior to study entry. When a patient on a dosage other than 300 mg BID or 400 mg BID 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 $\geq$ Grade 3 study drug-related hematological toxicity for 300 mg BID or 400 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 $\leq$ Grade 2 within 28 days, the Novartis Clinical Trial Head 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) or Nilotinib 800 mg daily (as 400 mg BID)
≥ Grade 3	Hold therapy and resume nilotinib at the full dose 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: ↳ 400 mg QD If recovery to ≤ Grade 2 is greater than 28 days, consult Novartis. If another recurrence is seen ↳ discontinue.
Note: Dose of study drug need not be reduced or interrupted for hematological toxicity of Grade 2 or lower.	

When a patient on a dosage other than 300 mg BID or 400 mg BID 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.

6.3.1.3 Dose re-escalation

Re-escalation of the dose of nilotinib from 400 mg QD back to 300 mg BID or 400 mg BID is permitted. This applies to either dose reductions due to hematological or non-hematological toxicities if the following criteria are met at least one month after dose reduction:

- All ≥ Grade 2 non-hematological toxicities have resolved to ≤ Grade 1
- All ≥ Grade 3 hematological toxicities have resolved to ≤ Grade 1
- Or alternatively, all ≥ Grade 3 hematological and non-hematological toxicities have resolved to ≤ Grade 2 and are manageable with supportive therapy.

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 $\geq$ 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 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 same dose or may be reduced to a minimum of 400 mg/day. If the platelet count remains below $100 \times 10^9/L$, then nilotinib should be ceased or management with anticoagulation therapy re-evaluated at the discretion of the Investigator.

6.3.2.6 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 SMC may be requested via Novartis.

6.3.2.7 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 the 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 [Table 14-2](#) for additional information.

6.3.2.8 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.

6.3.2.9 Management of other cardiac risk factors

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

6.3.2.10 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](#).

6.3.2.11 Hepatitis B reactivation

Hepatitis B virus testing should be performed during the study as indicated in [Section 7.1](#) to identify patients who may be at risk for Hepatitis B reactivation. Experts in liver disease and in the treatment of hepatitis B should be consulted for patients who test positive for hepatitis B virus during nilotinib treatment or for TFR patients who test positive for hepatitis B virus before treatment is re-initiated. Carriers of hepatitis B virus who require treatment with nilotinib should be closely monitored for signs and symptoms of active hepatitis B infection throughout therapy and for several months following termination of therapy.

6.3.3 Follow-up for toxicities

Patients who permanently discontinued the nilotinib consolidation phase or nilotinib treatment continuation 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 the last dose of study drug.

6.3.4 Anticipated risks and safety concerns of the study drug

Not applicable.

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 subjects. These findings suggest that warfarin may be used with nilotinib concurrently if needed ([Yin et al 2011](#)). Low molecular weight heparin and heparin may be substituted for coumarin and other medications for anticoagulation may also be considered at the investigator's discretion.

6.4.2 Permitted concomitant therapy requiring caution and/or action

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

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 [Table 14-2](#).

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. 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 [Table 14-2](#); 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 [Table 14-1](#), however, this list may not be comprehensive.

Every effort should be made to avoid co-administering the study drug and drugs with a “Known risk of Torsades de Pointes,” “Possible risk of Torsades de Pointes,” or “Conditional risk of Torsades de Pointes” (as per <https://crediblemedsorg/>) during the course of the study:

- If concomitant administration of drugs with a “Known risk of Torsades de Pointes” 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 Pointes” is required, based on the investigator assessment and clinical need, study drug may be continued under close ECG monitoring to ensure patient safety.

A list of drugs associated with QT prolongation and/or Torsades de Pointes is available online at <https://crediblemedsorg/>

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.

Cardiac Monitoring

Cardiac monitoring is required upon re-initiation of nilotinib therapy at any point. An ECG must be obtained before the treatment re-initiation, and annually thereafter during nilotinib therapy. **A minimum washout period of 72 hours or longer is required (depending on the half-life of the CYP3A4 inhibitor or QT interval prolonging agent) prior to study drug re-initiation.**

6.5 Patient numbering, treatment assignment or randomization

6.5.1 Patient numbering

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

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 (nilotinib)	Capsules* (150 mg or 200 mg) including instructions for administration are dispensed by study personnel on an outpatient basis. 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

*Different formulations and strengths can be used once they are approved and marketed.

6.6.1 Study drug packaging and labeling

Sourcing of nilotinib study drug by Novartis can be either through clinical supply or local commercial supply.

Clinical supply will be open label supply, packed and labeled under the responsibility of Novartis drug supply management. 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 but no information about the patient. If nilotinib is sourced through local commercial supply, study drug will be labeled in-country and the locally-approved form and packaging of nilotinib will be used.

As per Novartis procedures, investigational treatment will only be shipped directly to the investigational sites. Nilotinib in different formulations and strengths can be used once they are approved and marketed.

Table 6-5 Packaging and labeling

Study treatments	Packaging	Labeling (and dosing frequency)
AMN107 (nilotinib)	Capsules in bottles*	As per local requirements

* For centrally supplied medication. If nilotinib is sourced and labeled in-country/locally, the locally-approved form, packaging, and labeling of nilotinib will be used.

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 and in the [AMN107 Investigator's Brochure, current edition].

Table 6-6 Supply and storage of study treatments

Study treatments	Supply	Storage
AMN107 (nilotinib)	Centrally supplied by Novartis	Refer to study treatment label

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 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

Regardless of the source of study drug (clinical supply or commercial supply), 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 or 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 indicate 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.

	Category	Protocol Section	Screening	Nilotinib consolidation					End of nilotinib consolidation phase	Post-treatment follow-up (patients discontinuing from consolidation phase)	End of post-treatment follow-up completion
Visit Number			1	2	3	4	5	6	777		
Day or Week of study			D -28 to 0	W1	W12	W24	W36	W48	W52/Within 7 days of last dose of study medication if a patient discontinues from study	Every 12 weeks until 528 weeks after the last patient enters the TFR phase	
End of post-treatment follow-up disposition page	(D)	7.1.5									x
Urine pregnancy test, if applicable	(D)	7.2.2.5.3		Every 4 weeks							
Local Laboratory assessments											
Hematology	(D)	7.2.2.5.1	x		x	x	x	x	x		
ECG	(D)	7.2.2.7.1	x						x		
Bone marrow assessments/cytogenetics, if applicable	(D)	7.2.1.2	As needed								
Central laboratory assessments											
Chemistry	(D)	7.2.2.5.2	x		x	x	x	x	x		
Serum Pregnancy test, if applicable	(D)	7.2.2.5.3	x						x		
Peripheral blood BCR-ABL RT-qPCR	(D)	7.2.1.1	x		x	x	x	x	x		
Mutation Analysis	(D)	7.2.1.1	As needed								
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			

Table 7-2 Visit evaluation schedule – Treatment-free remission (TFR)

	Category	Protocol Section	Nilotinib TFR phase			End of TFR phase (patients ending TFR phase for any reason)*	Post-treatment follow-up (patients discontinuing from TFR and not re-initiating nilotinib treatment on study)	End of post-treatment follow-up completion
Visit Number			Visit 101 – Visit 112	Visit 113 – Visit 120	Visit 121...	778	Every 12 weeks until 528 weeks after the last patient enters the TFR phase	
Week of study			W 56 – W 100	W 106 – W 148	W 160 –528 weeks after the last patient enters the TFR phase			
Physical examination	(S)	7.2.2.1						
Performance Status	(D)	7.2.2.4	Every 12 weeks (Visit 103 (W64), Visit 106 (W76)...))			x		
Weight	(D)	7.2.2.3	Every 12 weeks (Visit 103 (W64), Visit 106 (W76)...))			x		
Vital signs / Blood Pressure / Sitting pulse	(D)	7.2.2.2	Every 12 weeks (Visit 103 (W64), Visit 106 (W76)...))			x		
Extramedullary involvement	(D)	7.2.2.1	Every 12 weeks (Visit 103 (W64), Visit 106 (W76)...))			x		
End of phase disposition page	(D)	7.1.5				x		
End of post-treatment follow-up disposition page	(D)	7.1.5						x
Urine pregnancy test, if applicable	(D)	7.2.2.5.3	Every 4 weeks					
Local Laboratory assessments								
Hematology	(D)	7.2.2.5.1	Every 12 weeks (Visit 103 (W64), Visit 106 (W76)...))			x		

	Category	Protocol Section	Nilotinib TFR phase			End of TFR phase (patients ending TFR phase for any reason)*	Post-treatment follow-up (patients discontinuing from TFR and not re-initiating nilotinib treatment on study)	End of post-treatment follow-up completion
Visit Number			Visit 101 – Visit 112	Visit 113 – Visit 120	Visit 121...	778	Every 12 weeks until 528 weeks after the last patient enters the TFR phase	
Week of study			W 56 – W 100	W 106 – W 148	W 160 –528 weeks after the last patient enters the TFR phase			
Bone marrow assessments/cytogenetics, if applicable	(D)	7.2.1.2	As needed					
Central Laboratory assessments								
Chemistry	(D)	7.2.2.5.2	Every 12 weeks (starting from W64)			x		
Serum pregnancy test, if applicable	(D)	7.2.2.5.3				x		
Peripheral blood BCR-ABL RT-qPCR	(D)	7.2.1.1	Every 4 weeks (Visit 101 (W56)...)	Every 6 weeks (Visit 113 (W106)...)	Every 12 weeks (Visit 121 (W160)...)	x		
Mutation Analysis	(D)	7.2.1.1	As needed					
Safety								
Adverse events	(D)	8.1	Continuous					
Concomitant medications	(D)	6.4	Continuous					
Patient reported outcome								

	Category	Protocol Section	Nilotinib TFR phase			End of TFR phase (patients ending TFR phase for any reason)*	Post-treatment follow-up (patients discontinuing from TFR and not re-initiating nilotinib treatment on study)	End of post-treatment follow-up completion
Visit Number			Visit 101 – Visit 112	Visit 113 – Visit 120	Visit 121...	778	Every 12 weeks until 528 weeks after the last patient enters the TFR phase	
Week of study			W 56 – W 100	W 106 – W 148	W 160 – 528 weeks after the last patient enters the TFR phase			
CCI								
Sokal Risk Score collection	(D)	7.2.7	At any one time point during the study					
Assess progression to AP/BC	(D)	7.1.9					x	
Stem cell transplant	(D)	7.1.9					x	
TKI treatment status	(D)	7.1.9					x	
Survival Follow-up	(D)	7.1.9					x	

Table 7-3 Visit evaluation schedule - Nilotinib treatment re-initiation (patients after unsuccessful TFR phase)

	Category	Protocol Section	Nilotinib treatment re-initiation								End of nilotinib treatment re-initiation phase patients ending nilotinib treatment re-initiation phase for any reason)	Post-treatment follow-up (patients discontinuing from nilotinib treatment re-initiation)	End of post-treatment follow-up completion	
			Every 4 weeks							Every 12 weeks				
Visit Number			201	202	203	204	205	206	207	208, 209...	779			
Week of Treatment re-initiation			W1*	W4	W8	W12	W16	W20	W24	W36, W48...– until 528 weeks after the last patient enters the TFR phase	within 7 days of last dose	Every 12 weeks until 528 weeks after the last patients enters the TFR phase		
Physical examination	(S)	7.2.2.1												
Performance Status	(D)	7.2.2.4	x	x	x	x			x	x	x			
Weight	(D)	7.2.2.3	x	x	x	x			x	x	x			
Vital signs /Blood Pressure / Sitting pulse	(D)	7.2.2.2	x	x	x	x			x	x	x			
Extramedullary involvement, if applicable	(D)	7.2.2.1	x	x	x	x			x	x	x			
End of phase disposition page	(D)	7.1.5									x			
End of post-treatment follow-up disposition page	(D)	7.1.5											x	
Urine pregnancy test, if applicable	(D)	7.2.2.5.3		Every 4 weeks										

[illegible]

	Category	Protocol Section	Nilotinib treatment re-initiation								End of nilotinib treatment re-initiation phase patients ending nilotinib treatment re-initiation phase for any reason)	Post-treatment follow-up (patients discontinuing from nilotinib treatment re-initiation)	End of post-treatment follow-up completion
			Every 4 weeks							Every 12 weeks			
Visit Number			201	202	203	204	205	206	207	208, 209...	779		
Week of Treatment re-initiation			W1*	W4	W8	W12	W16	W20	W24	W36, W48...– until 528 weeks after the last patient enters the TFR phase	within 7 days of last dose	Every 12 weeks until 528 weeks after the last patients enters the TFR phase	
Mutation analysis, if applicable	(D)	7.2.1.1	As needed										
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								End of nilotinib treatment re-initiation phase patients ending nilotinib treatment re-initiation phase for any reason)	Post-treatment follow-up (patients discontinuing from nilotinib treatment re-initiation)	End of post-treatment follow-up completion
			Every 4 weeks							Every 12 weeks			
Visit Number			201	202	203	204	205	206	207	208, 209...	779		
Week of Treatment re-initiation			W1*	W4	W8	W12	W16	W20	W24	W36, W48...– until 528 weeks after the last patient enters the TFR phase	within 7 days of last dose	Every 12 weeks until 528 weeks after the last patients enters the TFR phase	
CCI													
Sokal Risk Score collection	(D)	7.2.7	At any one time point during the study										
Assess progression to AP/BC	(D)	7.1.9										x	
Stem cell transplant	(D)	7.1.9										x	
TKI treatment status	(D)	7.1.9										x	
Survival Follow-up	(D)	7.1.9										x	

Table 7-4 Visit evaluation schedule - Nilotinib treatment continuation (patients not eligible for TFR phase)

	Category	Protocol Section	Nilotinib treatment continuation				End of nilotinib treatment continuation	Post-treatment follow-up (patients discontinuing from nilotinib treatment continuation)	End of post-treatment follow-up completion
Visit Number			7	8	9	10	780		
Week of study			W64	W76	W88	W100	W104/within 7 days of last dose	Every 12 weeks until 528 weeks after the last patients enters the TFR phase	
Physical examination	(S)	7.2.2.1							
Performance Status	(D)	7.2.2.4	x	x	x	x	x		
Weight	(D)	7.2.2.3	x	x	x	x	x		
Vital signs / Blood Pressure / Sitting pulse	(D)	7.2.2.2	x	x	x	x	x		
Extramedullary involvement	(D)	7.2.2.1	x	x	x	x	x		
End of phase disposition page	(D)	7.1.5					x		
End of post-treatment follow-up disposition page	(D)	7.1.5							x
Urine pregnancy test, if applicable	(D)	7.2.2.5.3	Every 4 weeks						
Local Laboratory assessments									
Hematology	(D)	7.2.2.5.1	x	x	x	x	x		
ECG	(D)	7.2.2.7.1					x		
Bone marrow assessments/cytogenetics, if applicable	(D)	7.2.1.2	As needed						
Central laboratory assessment									
Chemistry	(D)	7.2.2.5.2	x	x	x	x	x		
Serum Pregnancy test, if applicable	(D)	7.2.2.5.3					x		

	Category	Protocol Section	Nilotinib treatment continuation				End of nilotinib treatment continuation	Post-treatment follow-up (patients discontinuing from nilotinib treatment continuation)	End of post-treatment follow-up completion
Visit Number			7	8	9	10	780		
Week of study			W64	W76	W88	W100	W104/within 7 days of last dose	Every 12 weeks until 528 weeks after the last patients enters the TFR phase	
Peripheral blood BCR-ABL RT-qPCR	(D)	7.2.1.1	x	x	x	x	x		
Mutation Analysis	(D)	7.2.1.1	As needed						
Safety									
Adverse events	(D)	8.1	Continuous						
Concomitant medications	(D)	6.4	Continuous						
Study drug administration	(D)	6.1.1	Continuous						
Patient reported Outcomes									
CCI									
Sokal Risk Score collection	(D)	7.2.7	At any one time point during the study						
Assess progression to AP/BC	(D)	7.1.9						x	
Stem cell transplant	(D)	7.1.9						x	
TKI treatment status	(D)	7.1.9						x	
Survival follow-up	(D)	7.1.9						x	

Table 7-5 Visit evaluation schedule – Treatment-free remission phase 2 (TFR-2) (patients who are eligible to start TFR after 52 weeks of treatment continuation)

	Category	Protocol Section	Nilotinib TFR-2 phase			End of TFR-2 phase**	Post-treatment follow-up(patients discontinuing from TFR-2 and not re-initiating nilotinib treatment on study)	End of post-treatment follow-up completion
Visit Number			Visit 301 – Visit 312	Visit 313 – Visit 320	Visit 321...	781	Every 12 weeks until 528 weeks after the last patient enters the TFR phase	
Week of study			W 108 – W 152	W 158 – W 200	W 212 – until 528 weeks after the last patient enters the TFR phase			
Physical examination	(S)	7.2.2.1						
Performance Status	(D)	7.2.2.4	Every 12 weeks (Visit 303 (W116), Visit 306 (W128)...)			x		
Weight	(D)	7.2.2.3	Every 12 weeks (Visit 303 (W116), Visit 306 (W128)...)			x		
Vital signs / Blood Pressure / Sitting pulse	(D)	7.2.2.2	Every 12 weeks (Visit 303 (W116), Visit 306 (W128)...)			x		
Extramedullary involvement	(D)	7.2.2.1	Every 12 weeks (Visit 303 (W116), Visit 306 (W128)...)			x		
End of phase disposition page	(D)	7.1.5				x		
End of post-treatment follow-up disposition page	(D)	7.1.5						x
Urine pregnancy test, if applicable	(D)	7.2.2.5.3	Every 4 weeks					
Local Laboratory assessments								
Hematology	(D)	7.2.2.5.1	Every 12 weeks (Visit 303 (W116), Visit 306 (W128)...)			x		
Bone marrow assessments/cytogenetics, if applicable	(D)	7.2.1.2	As needed					

	Category	Protocol Section	Nilotinib TFR-2 phase			End of TFR-2 phase**	Post-treatment follow-up(patients discontinuing from TFR-2 and not re-initiating nilotinib treatment on study)	End of post-treatment follow-up completion
Visit Number			Visit 301 – Visit 312	Visit 313 – Visit 320	Visit 321...	781	Every 12 weeks until 528 weeks after the last patient enters the TFR phase	
Week of study			W 108 – W 152	W 158 – W 200	W 212 – until 528 weeks after the last patient enters the TFR phase			
Central laboratory assessment								
Chemistry	(D)	7.2.2.5.2	Every 12 weeks (starting from W116)			x		
Serum pregnancy test, if applicable	(D)	7.2.2.5.3				x		
Peripheral blood BCR-ABL RT-qPCR	(D)	7.2.1.1	Every 4 weeks (Visit 301 (W108)...)	Every 6 weeks (Visit 313 (W158)...)	Every 12 weeks (Visit 321 (W212)...)	x		
Mutation Analysis	(D)	7.2.1.1	As needed					
Safety								
Adverse events	(D)	8.1	Continuous					
Concomitant medications	(D)	6.4	Continuous					
Patient reported Outcomes								
CCI								
Sokal Risk Score collection	(D)	7.2.7	At any one time point during the study					
Assess progression to AP/BC	(D)	7.1.9					x	
Stem cell transplant	(D)	7.1.9					x	

	Category	Protocol Section	Nilotinib TFR-2 phase			End of TFR-2 phase**	Post-treatment follow-up(patients discontinuing from TFR-2 and not re-initiating nilotinib treatment on study)	End of post-treatment follow-up completion
Visit Number			Visit 301 – Visit 312	Visit 313 – Visit 320	Visit 321...	781	Every 12 weeks until 528 weeks after the last patient enters the TFR phase	
Week of study			W 108 – W 152	W 158 – W 200	W 212 – until 528 weeks after the last patient enters the TFR phase			
TKI treatment status	(D)	7.1.9					x	
Survival Follow-up	(D)	7.1.9					x	

Table 7-6 Visit evaluation schedule - Nilotinib treatment re-initiation-2 (patients after unsuccessful TFR-2)

	Category	Protocol Section	Nilotinib treatment re-initiation-2								End of nilotinib treatment re-initiation-2	Post-treatment follow-up (patients discontinuing from treatment re-initiation-2)	End of post-treatment follow-up completion
			Every 4 weeks							Every 12 weeks			
Visit Number			401	402	403	404	405	406	407	408, 409...	782		
Week of Treatment re-initiation 2			W1* *	W4	W8	W12	W16	W20	W24	W36, W48...– until 528 weeks after the last patient enters the TFR phase	within 7 days of last dose	Every 12 weeks until 528 weeks after the last patients enters the TFR phase	
Physical examination	(S)	7.2.2.1											
Performance Status	(D)	7.2.2.4	X	x	x	x			x	X	x		
Weight	(D)	7.2.2.3	X	x	x	x			x	X	x		
Vital signs /Blood Pressure / Sitting pulse	(D)	7.2.2.2	X	x	x	x			x	X	x		
Extramedullary involvement, if applicable	(D)	7.2.2.1	X	x	x	x			x	X	x		
End of phase disposition page	(D)	7.1.5									x		
End of post-treatment follow-up disposition page	(D)	7.1.5											x
Urine pregnancy test, if applicable	(D)	7.2.2.5.3	Every 4 weeks										

	Category	Protocol Section	Nilotinib treatment re-initiation-2								End of nilotinib treatment re-initiation-2	Post-treatment follow-up (patients discontinuing from treatment re-initiation-2)	End of post-treatment follow-up completion
			Every 4 weeks							Every 12 weeks			
Visit Number			401	402	403	404	405	406	407	408, 409...	782		
Week of Treatment re-initiation 2			W1* *	W4	W8	W12	W16	W20	W24	W36, W48... – until 528 weeks after the last patient enters the TFR phase	within 7 days of last dose	Every 12 weeks until 528 weeks after the last patients enters the TFR phase	
Local laboratory assessments													
Hematology	(D)	7.2.2.5.1	x	x	x	x			x	X	x		
ECG	(D)	7.2.2.7.1	x	Every 48 weeks							x		
Bone marrow assessments/cytogenetics, if applicable	(D)	7.2.1.2	As needed										
Central laboratory assessments													
Chemistry	(D)	7.2.2.5.2	x	x	x	x			x	X	x		
Serum Pregnancy test, if applicable	(D)	7.2.2.5.3	x								x		
Peripheral blood BCR-ABL RT-qPCR	(D)	7.2.1.1	x	x	x	x	x	x	x	X	x		
Mutation analysis, if applicable	(D)	7.2.1.1	As needed										
Safety													
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								End of nilotinib treatment re-initiation-2	Post-treatment follow-up (patients discontinuing from treatment re-initiation-2)	End of post-treatment follow-up completion
			Every 4 weeks							Every 12 weeks			
Visit Number			401	402	403	404	405	406	407	408, 409...	782		
Week of Treatment re-initiation 2			W1* W4		W8	W12	W16	W20	W24	W36, W48...– until 528 weeks after the last patient enters the TFR phase	within 7 days of last dose	Every 12 weeks until 528 weeks after the last patients enters the TFR phase	
Patient reported Outcomes													

CCI

Sokal Risk Score collection	(D)	7.2.7	At any one time point during the study							
Assess progression to AP/BC	(D)	7.1.9							x	
Stem cell transplant	(D)	7.1.9							x	
TKI treatment status	(D)	7.1.9							x	
Survival Follow-up	(D)	7.1.9							x	

Table 7-7 Visit evaluation schedule – Nilotinib prolonged treatment continuation (patients not eligible for TFR-2)

	Category	Protocol Section	Nilotinib prolonged treatment continuation	End of prolonged treatment continuation	Post-treatment follow-up (patients discontinuing from nilotinib prolonged treatment continuation)	End of post-treatment follow-up completion
Visit Number			11, 12, ...	783		
Week of study			W116, W128, every 12 weeks until 528 weeks after last patient enters the TFR phase	within 7 days of last dose	Every 12 weeks until 528 weeks after the last patients enters the TFR phase	
Physical examination	(S)	7.2.2.1				
Performance Status	(D)	7.2.2.4	Every 12 weeks (Visit 11 (W116)...)	x		
Weight	(D)	7.2.2.3	Every 12 weeks (Visit 11 (W116)...)	x		
Vital signs / Blood Pressure / Sitting pulse	(D)	7.2.2.2	Every 12 weeks (Visit 11 (W116)...)	x		
Extramedullary involvement	(D)	7.2.2.1	Every 12 weeks (Visit 11 (W116)...)	x		
End of phase disposition page	(D)	7.1.5		x		
End of post-treatment follow-up disposition page	(D)	7.1.5				x
Urine pregnancy test, if applicable	(D)	7.2.2.5.3	Every 4 weeks			
Local Laboratory assessments						
Hematology	(D)	7.2.2.5.1	Every 12 weeks (Visit 11 (W116)...)	x		
ECG	(D)	7.2.2.7.1	Every 48 weeks	x		
Bone marrow assessments/cytogenetics, if applicable	(D)	7.2.1.2	As needed			

7.1.1 Molecular pre-screening

Not applicable.

7.1.2 Screening

Written informed consent must be obtained before any study specific medical procedures are performed. The screening visit occurs at study days -28 to 0.

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

The screening PCR blood sample will be analyzed centrally by a Novartis designated PCR laboratory. In case the MR4.5 status cannot be determined on this sample (e.g. due to technical or logistical issue) another blood sample for RT-qPCR is to be collected immediately and submitted to the central PCR laboratory for determination of the MR4.5 status. If the result confirms a patient's BCR-ABL $\leq 0.0032\%$ (IS), he/she will be eligible for the study.

Laboratory baseline assessments (including hematology and chemistry), physical examination including performance status, height, weight and vital signs must be performed within 28 days prior to Visit 2/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. Re-screening of a patient will be allowed for this study approximately 4 weeks ± 7 days after screen failure. 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. It is under the discretion of the investigator how many times a patient can be re-screened. However, repeated re-screening is discouraged.

7.1.2.1 Eligibility screening

Patient eligibility will be checked by the Sponsor once all screening procedures are completed. The eligibility check form will be sent from the site to the Sponsor either via fax or email for evaluation. Upon confirmation of eligibility, the Sponsor will return the signed eligibility check form via fax or email to the site. The investigative site will then be allowed to assign treatment to the patient.

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 subjects who are screen failures, unless the subject 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—imatinib, 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 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.

7.1.3 Run-in period

Not applicable.

7.1.4 Treatment period

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 TFR phase) unless patients discontinue early.

All patient visits occurring every 4 weeks or 6 weeks should be completed on the designated day (with an allowed “visit window” of 7 days) or as close to it as possible. Patient visits for all quarterly visits should be completed on the designated day (with an allowed “visit window” of 14 days) or as close to it as possible. For this study purpose, every month has 28 days.

During the consolidation phase, all patients will receive 52 weeks of nilotinib treatment (at the dose they are taking prior to study entry), or until a 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 52 weeks, there will be quarterly scheduled visits and PCR assessments. Patients with a confirmed loss of MR4.5 (two consecutive BCR-ABL > 0.0032% IS) during the nilotinib consolidation phase, will stay on nilotinib treatment for another 52 weeks (nilotinib treatment continuation). Patients will continue to have scheduled visits every 12 weeks. Assessments for consolidation and treatment continuation are specified in [Table 7-1](#) and [Table 7-4](#).

If a patient maintains MR4.5 during the consolidation, he/she can enter the TFR phase. During the 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 thereafter. The PCR assessment schedules as well as other study related assessments for the TFR phase are specified in [Table 7-2](#).

During the TFR phase, a patient with a confirmed loss of MR4 (two consecutive BCR-ABL > 0.01% IS) or loss of MMR will immediately restart nilotinib treatment either at 300 mg BID or 400 mg BID until 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 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, then once every 12 weeks. Electrocardiogram (ECG) will be collected prior to the first dose, and every 48 weeks thereafter. Physical examination and other laboratory assessments will be performed every 4 weeks for the first 12 weeks, then once every 12 weeks thereafter. Patients who enter the nilotinib treatment re-initiation will not be allowed to re-enter TFR phase. The PCR assessment schedules as well as other study related assessments for nilotinib treatment re-initiation are specified in [Table 7-3](#).

If a patient maintains MR4.5 throughout nilotinib treatment continuation, he/she will be eligible to cease nilotinib treatment on study and enter treatment-free remission-2 (TFR-2) phase until 528 weeks after the last patient enters the TFR phase. 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 thereafter. 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, a patient with a confirmed loss of MR4 (two consecutive BCR-ABL > 0.01% IS) or loss of MMR will immediately restart nilotinib treatment re-initiation-2 either at 300 mg BID or 400 mg BID until 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 treatment is discontinued at the discretion of the investigator or withdrawal of consent. During the treatment re-initiation-2, BCR-ABL level will be monitored by PCR every 4 weeks for the first 24 weeks then once every 12 weeks. Electrocardiogram (ECG) will be collected prior to the first dose, and every 48 weeks thereafter. Physical examination and other laboratory assessments will be performed every 4 weeks for the first 12 weeks, then once every 12 weeks thereafter. The PCR assessment schedules as well as other study related assessments for nilotinib treatment re-initiation-2 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 nilotinib prolonged treatment continuation 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 phase

Patients may voluntarily discontinue from the study for any reason at any time. 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. 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 may discontinue study treatment for a given patient if, he/she believes that continuation would be detrimental to the patient's well-being.

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 has confirmed loss of MR4 or loss of MMR and needs to restart nilotinib treatment.

Patients may also be discontinued from the study if any of the following occur:

- Use of prohibited treatment refer to Section 6.4.3
- Any protocol deviation that results in a significant risk to the patient's safety

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 ($< 100 \times 10^9/L$) that is unrelated to therapy
3. Blast crisis (BC) as defined by any of the following:
 - $\geq 30\%$ blasts in peripheral blood or bone marrow aspirate
 - Appearance of extramedullary involvement other than hepatosplenomegaly proven by biopsy (i.e., chloroma).

Patients who discontinue the study treatment 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).

Patients who complete the nilotinib consolidation phase and are entering the TFR phase or nilotinib treatment continuation will need to complete the End of treatment phase visit (777, [Table 7-1](#)). For this group of patients, visit 777 should fall on week 52 and on the same day or one day prior to the first day of the TFR phase.

Patients who complete the nilotinib treatment continuation and are entering TFR-2 or nilotinib prolonged treatment continuation will need to complete the End of nilotinib treatment

continuation visit (780, [Table 7-4](#)). For this group of patients, visit 780 should fall on week 104 of the study and on the same day or one day prior to the first day of nilotinib TFR-2 phase.

Patients who complete the post-treatment follow-up phase ([Section 7.1.6](#)) will need to complete the End of post-treatment follow-up disposition page.

For details of assessments and schedule of end of phase 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](#).

7.1.5.1 Criteria for premature patient withdrawal

Patients may voluntarily withdraw from the study or be dropped from it at the discretion of the investigator at any time. Patients may be withdrawn from the study if any of the following occur: discovery of patient ineligibility; errors in treatment compliance (study treatment, other prescribed or non-prescribed medications); missed/unscheduled/off-schedule/incomplete/incorrect assessments; major protocol deviation. Female patients must be withdrawn from the study if they become pregnant during any of the following phases: nilotinib treatment consolidation phase, nilotinib treatment re-initiation phases, nilotinib treatment continuation phase and prolonged continuation phase. In case of pregnancy during TFR/TFR-2 phases, the pregnant female patient can stay in TFR phases as long as no nilotinib treatment is needed but must be withdrawn from the study when there is a confirmed loss of MR4 or unconfirmed loss of MMR.

7.1.5.2 Replacement policy

Not applicable.

7.1.6 Withdrawal of consent

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

- 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 subject'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 subject 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 subject'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 subject'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 patient, 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 until 528 weeks after the last patient enters the TFR phase. Survival information, stem cell transplantation, TKI therapy status, 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. This period is named post-treatment follow-up phase in this study.

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

7.2 Assessment types

7.2.1 Efficacy assessments

7.2.1.1 Molecular response

MR will be assessed in all patients. Levels of BCR-ABL transcripts will be determined by real-time quantitative PCR (RT-qPCR) testing of peripheral blood and analyzed at a Novartis designated central laboratory. The percent ratio of BCR-ABL transcripts versus control gene transcripts converted to IS will be calculated for each sample.

- RT-qPCR will be monitored every 12 weeks during the nilotinib consolidation phase. If during this phase, a patient has one PCR result above MR4.5 (BCR-ABL > 0.0032% IS),

or 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.

- RT-qPCR will continue to be monitored every 12 weeks during nilotinib treatment continuation and nilotinib prolonged treatment continuation.
- In the TFR phase, RT-qPCR will be monitored every 4 weeks for the first 48 weeks, every 6 weeks for the following 48 weeks and every 12 weeks thereafter. If during this phase, a patient has one PCR result above MR4 (BCR-ABL > 0.01% IS), or 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 (PCR assessments every 4 weeks during the first year of TFR), or as an unscheduled visit.
- If a patient experienced confirmed loss of MR4 or loss of MMR during the TFR phase and restart nilotinib treatment, RT-qPCR will be monitored every 4 weeks for the first 24 weeks, and then once every 12 weeks 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 treatment is discontinued at the discretion of the investigator or withdrawal of consent.
- RT-qPCR 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 until 528 weeks after the last patient enters the TFR phase. If during this phase, a patient has one PCR result above MR4 (BCR-ABL > 0.01% IS), or 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 (PCR assessments every 4 weeks during the first year of TFR), or as an unscheduled visit.
- If a patient experienced confirmed loss of MR4 or loss of MMR during the TFR-2 and restart nilotinib treatment (nilotinib treatment re-initiation-2), RT-qPCR will be monitored every 4 weeks for the first 24 weeks, and then once every 12 weeks until 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 treatment is discontinued at the discretion of the investigator or withdrawal of consent.

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 $\leq$ 0.1% (IS)
- MR4 – BCR-ABL $\leq$ 0.01% (IS)
- MR4.5 – BCR-ABL $\leq$ 0.0032% (IS)

Mutational analysis will be performed when a patient demonstrates confirmed loss of MR4 or loss of MMR when BCR-ABL copy numbers are appropriate for this 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 central laboratory.

During the study, peripheral blood samples will be collected into PAXgene™ Blood RNA tubes for all RT-qPCR assessments. 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 RT-qPCR and mutation samples are outlined in the [\[CAMN107A2408 Laboratory Manual\]](#).

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 $> 20.0 \times 10^9/L$
- Platelet count that rises to $\geq 600 \times 10^9/L$
- Progressing hepatosplenomegaly to a size ≥ 5 cm below the left intercostal margin
- Appearance of $\geq 5\%$ myelocytes + metamyelocytes in the peripheral blood
- Appearance of blasts or promyelocytes in the peripheral blood

Bone marrow assessment is also allowed as an optional procedure if clinically indicated.

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
- Every 12 weeks during nilotinib treatment consolidation, nilotinib treatment continuation, and nilotinib prolonged treatment continuation
- Every 12 weeks during the TFR phase and TFR-2
- Day 1 of nilotinib treatment re-initiation, and nilotinib treatment re-initiation-2 (visits 201 and 401), week 4, 8, 12 and every 12 weeks thereafter during those two phases
- End of treatment visits 777, 778, 779, 780, 781, 782 and 783

Significant findings that were present prior to the signing of informed consent must be included in the Medical History page on the patient's CRF. Significant new findings that begin or worsen after informed consent must be recorded on the Adverse Event page of the patient's CRF. Presence of extra-medullary 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. lymph nodes, liver and spleen size). 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 (not contaminated with peripheral blood) 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
- Every 12 weeks during nilotinib treatment consolidation, nilotinib treatment continuation, and nilotinib prolonged treatment continuation
- Every 12 weeks during the TFR phase and TFR-2
- Day 1 of nilotinib treatment re-initiation, and nilotinib treatment re-initiation-2 (visits 201 and 401), week 4, 8, 12 and every 12 weeks thereafter during those 2 phases
- End of treatment visits 777, 778, 779, 780, 781, 782 and 783

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
- Every 12 weeks during nilotinib treatment consolidation, nilotinib treatment continuation, and nilotinib prolonged treatment continuation
- Every 12 weeks during the TFR phase and TFR-2
- Day 1 of nilotinib treatment re-initiation, and nilotinib treatment re-initiation-2 (visits 201, and 401), week 4, 8, 12 and every 12 weeks thereafter during those 2 phases
- End of treatment visits 777, 778, 779, 780, 781, 782 and 783

7.2.2.4 Performance status

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

- Screening
- Every 12 weeks during nilotinib treatment consolidation, nilotinib treatment continuation, and nilotinib prolonged treatment continuation
- Every 12 weeks during the TFR phase and TFR-2
- Day 1 of nilotinib treatment re-initiation, and nilotinib treatment re-initiation-2 (visits 201 and 401), week 4, 8, 12 and every 12 weeks thereafter during those 2 phases
- End of treatment visits 777, 778, 779, 780, 781, 782 and 783

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 specimens collected 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 [\[CAMN107A2408 Laboratory Manual\]](#). The time windows granted for laboratory evaluations are identical with the corresponding visit time windows for each visit.

Table 7-9 (Local/Central) Clinical laboratory parameters collection plan

Test Category	Test Name
Hematology (local)	hemoglobin, platelets, white blood cells, differential in percentage or absolute value (neutrophils, lymphocytes, eosinophils, basophils, monocytes, promyelocytes, myelocytes, meta myelocytes, blast cells, other)
Chemistry (central)	creatinine, sodium, potassium, fasting glucose, HbA1c, total cholesterol, HDL-C, calculated LDL-C, triglycerides, corrected calcium, serum phosphate, magnesium, uric acid, LDH, total protein, albumin, ALT (SGPT), AST (SGOT), alkaline phosphatase, direct bilirubin, indirect bilirubin, total bilirubin, lipase
Serology (Central)	Hepatitis B surface antigen (HBs Ag), antibodies to hepatitis B core antigen (HBc Ab / anti HBc)

7.2.2.5.1 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 or automated differential count in percentage or absolute values including neutrophils, lymphocytes, eosinophils, basophils, monocytes, promyelocytes, myelocytes, meta myelocytes, and blast cells. A consistent assessment method should be maintained throughout the study.

7.2.2.5.2 Clinical chemistry

Blood chemistry labs are to be analyzed by a central laboratory. Biochemistry includes creatinine, sodium, potassium, fasting glucose, HbA1c, total cholesterol, HDL-cholesterol, calculated LDL-cholesterol, triglycerides, corrected calcium, serum phosphate, magnesium, uric acid, LDH, total protein, albumin, ALT (SGPT), AST (SGOT), alkaline phosphatase, direct bilirubin, indirect bilirubin, total bilirubin, and lipase. 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.

7.2.2.5.3 Contraception and Pregnancy/assessments of fertility

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 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), 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 screening). 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 be stable on the same pill for a minimum of 3 months before taking study treatment.

Pregnancy/assessments of fertility

All women of childbearing potential must have a serum pregnancy test at the screening visit, visits 777, 778, 779, 780, 781, 782 and 783. In addition, urine pregnancy test every 4 weeks is also mandatory for all women of child bearing potential throughout the duration of this 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](#), for the schedule of pregnancy assessments. Serum pregnancy test will be performed by a central laboratory. Urine pregnancy tests should be performed at home by the patient throughout the duration of this study. All urine pregnancy test results should be recorded in patient diaries and brought to each scheduled visit for the site to review. Sites are to document the results of the home urine pregnancy test recorded in the diary to an eCRF page. If a positive urine pregnancy test result is discovered at home, the patient should contact the investigator immediately. All pregnancies should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the oncology Novartis Chief Medical Office and Patient Safety (CMO&PS).

7.2.2.5.4 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.

7.2.2.6 Radiological examinations

Not applicable.

7.2.2.7 Cardiac assessments

7.2.2.7.1 Electrocardiogram (ECG)

A standard 12 lead ECG will be performed at:

- Screening
- Annually while on nilotinib treatment
- Whenever clinically indicated
- Day 1 of nilotinib treatment re-initiation, and nilotinib treatment re-initiation-2 (visits 201 and 401) – prior to dosing (see note below)

Interpretation of the tracing must be made by a qualified physician and documented on the ECG eCRF page. Each ECG tracing should be labeled with the study number, patient 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.

At visits 201 and 401 (day 1 of nilotinib treatment re-initiation) QTcF must be < 450 msec prior to restarting nilotinib. 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.

7.2.2.8 Tolerability

Not applicable.

7.2.3 Pharmacokinetics

One blood sample for the assessment of nilotinib PK trough level will be collected from all patients at Visit 6 (study Day 336). 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 [\[CAMN107A2408 Laboratory Manual\]](#) for detailed instructions for the collection, handling, and shipment of PK samples.

Table 7-10 Pharmacokinetic blood collection log

Day	Scheduled Time Point	DRID		PK Sample No	Volume (mL)
		Prior to PK sampling	Post PK sampling		
336	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

CCI

7.2.4.2 CCI

CCI

7.2.4.3 CCI

CCI

7.2.4.4 CCI

CCI

CCI

7.2.5 CCI

CCI

7.2.6 CCI

CCI

CCI

Table 7-11

CCI

CCI



7.2.7 Sokal Risk Score

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

Table 7-12 Sokal formulation

Sokal variables	
Age (years)	0.0116 (age - 43.4)
* Spleen (cm)	0.0345 (spleen - 7.51)
Platelets (x 109/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.

- Low risk patients have a Relative Risk (RR) < 0.8
- Intermediate risk patients have a $RR \geq 0.8$ 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.

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.

Adverse events will be assessed and graded 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 (subject) 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 (subject) 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) or
Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes, investigational treatment, Yes, the study treatment (non-investigational), Yes, both and/or indistinguishable)
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 eCRF.

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

Progression of malignancy (including fatal outcomes), if documented by use of appropriate method (for example, as per RECIST criteria for solid tumors or as per Cheson's guidelines for hematological malignancies), should not be reported as a serious adverse event. 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 an AE/SAE.

Adverse events separate from the progression of malignancy (for example, deep vein thrombosis at the time of progression or hemoptysis concurrent with finding of disease progression) will be reported as per usual guidelines used for such events with proper attribution regarding relatedness to the drug.

Any AE that occurs when a CAMN107A2405 (ENESTcmr) or CAMN107EIC01 (ENEST1st) patient is being screened for CAMN107A2408 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 eCRF. Whenever possible, a diagnosis, rather than a symptom should be provided (e.g. anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for Adverse Events should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported adverse event, it is not necessary to separately record the lab/test result as an additional event.

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

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. Described below are the most important ones for this TFR trial, note this is not a complete list.

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

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 last day in TFR/TFR-2 must be reported to Novartis within 24 hours of learning of its occurrence. SAEs will be followed until resolution or until clinically relevant improvement or stabilization.

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 CAMN107A2405 (ENESTcmr) or CAMN107EIC01 (ENEST1st) patient is being screened for CAMN107A2408 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 nilotinib treatment and/or in the TRF/TFR-2 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) department. 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 [Investigator Brochure]. Additional safety information collected between IB updates will be communicated in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

8.6 Data Monitoring Committee

Not applicable.

8.7 Study Management Committee

A Study Management Committee (SMC) will be established comprising investigators participating in the trial who are clinical experts in CML.

The SMC will ensure transparent management of the study according to the protocol through recommending and approving modifications as circumstances require, to interpret/clarify PCR results as appropriate. The SMC will review protocol amendments as appropriate. Together with the clinical trial team, the SMC will also develop recommendations for publications of study results including authorship rules. The details of the role of the SMC are defined in the SMC 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.

Prior to entering key sensitive personally identifiable information (Subject Initials and exact Date of Birth), the system will prompt site to verify that this data is allowed to be collected. If the site indicates that country rules or ethics committee standards do not permit collection of these items, the system will not solicit Subject Initials. Year of birth will be solicited (in the place of exact date of birth) to establish that the subject satisfies protocol age requirements and to enable appropriate age-related normal ranges to be used in assessing laboratory test results.

9.2 Site monitoring

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

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information recorded on eCRFs must be traceable to source documents in the patient's file. The investigator must also keep the original signed informed consent form (a signed copy is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm its consistency with the eCRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria and documentation of SAEs. Additional checks of the consistency of the source data with the eCRFs are performed according to the study-specific monitoring plan.

9.3 Data collection

This study will use 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 (i.e. biochemistry, PCR assessments, biomarkers, PK, etc.) will be sent electronically to Novartis.

9.4 Database management and quality control

Novartis personnel 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 staffs 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.

PCR, PK and biochemistry samples and/or data will be processed centrally and the results will be sent electronically to Novartis.

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 following a period of 52 weeks in MR4.5 with nilotinib treatment.

10.1 Analysis sets

10.1.1 Full Analysis Set

The Full Analysis Set (FAS) comprises all patients who complete the consolidation phase successfully (i.e. who maintain MR4.5 for the 52 weeks on study) and enter into the TFR phase.

10.1.2 Safety Set

The Safety Set (SS) includes all patients who received at least one dose of study medication. Reporting of safety information for these patients will be split into subsets by consolidation phase, TFR phase, treatment re-initiation, and treatment continuation.

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 and planning (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 (pre-dose on study day D336).

10.1.6 Other analysis set

Other analyses subsets used for exploratory purposes will be discussed in the Report and Analysis Plan (RAP), in detail.

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 subsets of patients who continue study medication and those who re-start the treatment with Nilotinib after TFR phase as defined above in [Section 10.1.1](#).

Time on treatment, duration of exposure, percentage of days on treatment, average dose intensity and actual daily dose 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 for the safety set but split by the four safety subsets (consolidation, TFR, treatment re-initiation and treatment continuation) of patients.

10.4 Primary objective

The primary objective of the trial is to evaluate the proportion of patients without confirmed loss of MR4 or loss of MMR within 48 weeks following cessation of nilotinib therapy.

10.4.1 Variable

The primary efficacy variable is the binary outcome variable, proportion of patients without confirmed loss of MR4 or loss of MMR within 48 weeks following nilotinib TFR is defined as the number of patients with no documented confirmed loss of MR4, no loss of MMR **and** no re-starting of nilotinib therapy in the first 48 weeks after starting nilotinib TFR phase divided by the number of patients who entered nilotinib TFR phase. Confirmed loss of MR4 is two consecutive BCR-ABL > 0.01% IS. Loss of MMR does not require confirmation

10.4.2 Statistical hypothesis, model, and method of analysis

Demonstration of successful TFR of nilotinib will be evaluated using the following hypothesis:

- H_0 : $p \leq 0.10$, where p is the rate of no documented confirmed loss of MR4, no loss of MMR and no re-starting of nilotinib therapy in the first 48 weeks after starting TFR phase.
- H_1 : $p \geq 0.10$, where p is the rate of no documented confirmed loss of MR4, no loss of MMR and no re-starting of nilotinib therapy in the first 48 weeks after starting TFR phase.

The rate of successful TFR will be presented together with an exact 95% Clopper-Pearson confidence interval. The null hypothesis will be rejected and successful TFR will be demonstrated if the lower limit of the 95% confidence interval is greater than 0.10.

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

10.4.3 Handling of missing values/censoring/discontinuations

For the primary analysis of the rate of successful TFR, patients dropping out early from the study during the TFR phase will be considered to be unsuccessful TFR and will be included in the FAS.

But if ongoing patients who failed to cease Nilotinib treatment drop out early from the study during the TFR phase, they will not be included in their analyses.

10.4.4 Supportive analyses

The primary analysis will be repeated on the PPS.

10.5 Secondary objectives

10.5.1 Secondary Efficacy variables:

- Proportion of patients without confirmed loss of MR4 or loss of MMR within 96, 144, 192, 264 weeks and within the end of years 6, 7, 8, 9, and 10 following cessation of nilotinib therapy: Proportion of patients without confirmed loss of MR4 or loss of MMR within 96, 144, 192, 264 weeks and within the end of years 6, 7, 8, 9, and 10 following cessation of nilotinib therapy is calculated by dividing the number of patients with no documented confirmed loss of MR4, no documented loss of MMR and no re-starting of nilotinib therapy in the first 96, 144, 192, 264 weeks and within the end of years 6, 7, 8, 9, and 10 respectively following cessation of nilotinib therapy by the number of patients who attempted to cease nilotinib therapy.
- Progression free survival (PFS): The estimation of PFS following nilotinib cessation will use the Kaplan-Meier (KM) method. PFS is measured from the date of cessation of nilotinib therapy to the date of the earliest of this event: progression to AP/BC or death from any cause. Patients not known to have progressed or died on or before the cut-off date for the KM analysis will have their PFS interval right-censored at the earlier of the date of their last assessment of molecular response status and the cut-off date.
- Treatment-free survival: TFS is defined as lack of any of the following: loss of MMR, confirmed loss of MR4, re-start of nilotinib treatment, progression to AP/BC or death from any cause. TFS is measured from the date of cessation of nilotinib therapy to the date of the earliest of this event.
- A TFS sensitivity analysis will be conducted considering discontinuation from the TFR phase due to any reason as an event, in addition to the events as defined above.
- Overall survival (OS): OS is defined as the time from the date of cessation of nilotinib therapy to the date of death from any cause. If a patient is not known to have died, survival will be censored at the date of last contact. Similar method of analysis will be used to estimate time to regain MR4.5 from the date of re-start nilotinib treatment.
- The proportion of patients who regain MR4.5 within 48 weeks of nilotinib treatment re-initiation following confirmed loss of MR4 or loss of MMR in the first 48 weeks subsequent to nilotinib cessation will also be calculated by dividing the number of patients who re-achieve MR4.5 within 48 weeks of nilotinib treatment re-initiation, following confirmed loss of MR4 or loss of MMR in the first 48 weeks subsequent to nilotinib cessation, by the number of patients who ceased nilotinib therapy and subsequently had confirmed loss of MR4 or lost MMR in the first 48 weeks following nilotinib cessation and re-initiated nilotinib treatment. In the calculation of this proportion (rate of patients who regained MR4.5 after treatment re-initiation following confirmed loss of MR4 or loss of MMR subsequent to nilotinib cessation), patients who drop out early without regaining MR4.5 during the re-treatment period will be considered to be unsuccessful reinductions of MR4.5 and will be counted in the denominator in the calculation of the rate.
- Duration of retreatment required to regain MMR defined as the time from date of start of retreatment after loss of MMR to the date of first achievement of MMR. Patients who do not regain MMR after retreatment on or before the cut-off date, duration will be censored at the date of last PCR assessment. Duration of retreatment required to regain MR4.5

which is measured from the time from date of start of retreatment after confirmed loss of MR4 or loss of MMR to the date of first achievement of MR4.5 in retreatment period. Patients who do not regain MR4.5 after retreatment on or before the cut-off date, duration will be censored at the date of last PCR assessment.

- 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, is calculated by dividing the number of patients who restarted the treatment due to loss of MMR in TFR phase and 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 (based on availability of appropriate data) after the first achievement of MMR, irrespective of whether there is loss of MMR in between, by the number of patients who restarted the treatment due to loss of MMR in TFR phase and achieved MMR at any time during the nilotinib re-initiation phase
- Proportion of patients who are in stable MR4 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, is calculated by dividing the number of patients achieving MR4 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 (based on availability of appropriate data) after the first achievement of MR4, irrespective of whether there is loss of MR4 in between, by the number of patients who achieved MR4 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, 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 (based on availability of appropriate data) 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
- Kinetics of BCR-ABL transcript levels (IS) after re-start of nilotinib therapy

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 failed to achieve MR4 and MMR with nilotinib retreatment 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.

All time to event endpoints including duration of retreatment 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 consolidation phase, TFR phase, treatment re-initiation, and treatment continuation.

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 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) version 4.03 the study's biostatistical and reporting team will grade laboratory data accordingly. For laboratory tests covered by CTCAE, 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 definition have to be replaced by a clinically meaningful limit expressed in absolute counts.

For laboratory tests where grades are not defined by CTCAE, 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 grade. Each patient will be counted only for the worst grade observed post-baseline, regardless of the baseline status
- shift tables using CTCAE grades to compare baseline to the worst on-treatment value
- for laboratory tests where CTCAE grades are not defined, shift tables using the low/normal/high/(low and high)

- classification to compare baseline to the worst on-treatment value.
- listing of all laboratory data with values flagged to show the corresponding CTCAE 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

Trough nilotinib concentrations 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 discontinuation 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

CCI

10.5.5 CCI

CCI

CCI

10.5.6 CCI

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10.6 Exploratory objectives

CCI



10.7 Interim analysis

The SMC will monitor the incidence of progressions to AP/BC and CML-related deaths, rate of unsuccessful discontinuations and rate of unsuccessful re-achievement of MMR after restarting nilotinib in the study on an ongoing basis.

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, and 264 weeks after the last patient enters the TFR phase and at the end of years 6, 7, 8, and 9. The final analysis and CSR will be done at ten years after the last patient enters the TFR phase.

10.8 Sample size calculation

Demonstration of successful TFR of nilotinib will be based on the study designed with a 90% power to test the null hypothesis that the rate of no documented confirmed loss of MR4, no loss of MMR **and** no re-starting of nilotinib therapy in the first 48 weeks after nilotinib TFR is 10% or less with an alternative hypothesis that this rate is above 10%.

The sample size is based on an exact test for single proportion to test the null hypothesis $H_0: p \leq 0.10$, where p is the rate of no documented confirmed loss of MR4, no loss of MMR **and** no re-starting of nilotinib therapy in the first 48 weeks after nilotinib cessation. If the true rate $p \geq 0.25$, then with one-sided alpha level of 2.5% and a power of 90%, a minimum of approximately 70 patients are required to enter the TFR phase after the consolidation phase.

Based on the results of ENESTcmr study, approximately 30% of patients may experience a loss of MR4.5 once it is achieved during the consolidation phase. Considering an additional 10% attrition rate, it is assumed that approximately 40% of the patients will not be eligible for TFR after 52 weeks of consolidation phase. Thus, a total of approximately 117 patients will be enrolled into this study.

Consequently, accrual to the study will close at the earlier of the date on which 70 patients have entered the TFR phase or the date on which 117 patients have been enrolled in the consolidation phase.

Although the study planned to recruit 117 patients, a total of 163 patients were enrolled by December, 2013 when the patient enrollment was closed. In order to assess the impact of this over recruitment, different scenarios on power calculation have been provided below in [Table 10-1](#). Under the assumption that 40% of the recruited patients will not be eligible for TFR (as in the original protocol), the power increases by 7% (97% vs. 90%). All the assumptions related to study design and the effect size remain the same and also the criteria for rejection of the null hypothesis (which is the lower limit of the 95% confidence interval being greater than 0.10) is not changed.

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 (at least)
117 (planned)	10%	105	97%
	20%	94	97%
	30%	82	94%
	40%	70	90%
163 (actually enrolled)	10%	147	99%
	20%	130	99%
	30%	114	98%
	40%	98	97%
Assumptions on the rate of no documented confirmed loss of MR4, no loss of MMR and no re-starting of nilotinib therapy in the first 48 weeks after nilotinib cessation: Null hypothesis H0: p=10%; and true rate p=25%. 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. A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC/REB must be given to Novartis before study initiation. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/IECs/REBs and regulatory authorities as required.

11.3 Informed consent procedures

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

Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents. The date when a subject's Informed Consent was actually obtained will be captured in their eCRFs.

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

The exploratory global gene alteration/expression profiling on samples collected during this study will be covered under the main consent and is not optional, unless otherwise indicated by local IRB/EC or Health Authority requirements.

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.

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. 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 their writing of a publication, either directly

from Novartis or through the professional 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 eCRFs and all other required reports. Data reported on the eCRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. All data requested on the eCRF must be recorded. Any missing data must be explained. For electronic CRFs an audit trail will be maintained by the system.

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

Table 14-1 CYP3A4 Inducers

Category	Drug Names
Strong inducers of CYP3A4 ¹	avasimibe, carbamazepine, enzalutamide, lumacaftor, phenobarbital, phenytoin, rifabutin, rifampicin, mitotane, St. John's wort (<i>Hypericum perforatum</i>) 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 (<i>Salvia miltiorrhiza</i>) ⁴ , dexamethasone, echinacea (<i>Echinacea purpurea</i>) ¹ , elvitegravir-cobicistat-emtricitabine-tenofovir (Stribild), eslicarbazepine, ginkgo (<i>Ginkgo biloba</i>) 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, sulfapyrazole, 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.

Table 14-2 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 (<i>Ferula asafoetida</i>) ⁴ , atazanavir, cimetidine, casopitant, ciprofloxacin, crizotinib, cyclosporine, darunavir, diltiazem, dronedarone, erythromycin, faldaprevir, fluconazole, grapefruit juice ⁶ , imatinib, isavuconazole, netupitant, nilotinib, <i>Schisandra sphenanthera</i> (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 (<i>Lepidium sativum</i>) ⁵ , ginkgo (<i>Ginkgo biloba</i>) ⁴ , goldenseal (<i>Hydrastis canadensis</i>) ⁴ , grazoprevir, guan mai ning ⁴ , isoniazid, ivacaftor, lacidipine, linagliptin, lomitapide, obeticholic acid, oral contraceptives, palbociclib, pazopanib, peppermint oil ⁵ , piperine ⁵ , pomelo (<i>Citrus grandis</i>) 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-fold but 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.

Table 14-3 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, <i>Cannabis sativa</i> ⁴ , carbamazepine, dexlorglutamide, 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 ($\Delta 9$ THC) and cannabidiol (CBD) are major constituents. $\Delta 9$ THC is primarily metabolized by CYP2C9 to an active metabolite 11-hydroxy- $\Delta 9$ -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 $\Delta 9$ THC, 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 C_{max} and AUC₀₋₂₄ of $\Delta 9$ THC by 1.2- and 1.8-fold, respectively, increased the C_{max} and AUC₀₋₂₄ of 11-OH-THC by 3.0- and 2.6-fold, respectively, and increased the C_{max} and AUC₀₋₂₄ of CBD by 2- and 2-fold, respectively. Rifampicin decreased the C_{max} and AUC₂₄ of $\Delta 9$ THC by 40 and 20%, respectively, decreased the C_{max} and AUC₀₋₂₄ of 11-OH-THC by 85 and 87%, respectively, and decreased the C_{max} 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.