NOVARTIS

Oncology Clinical Development & Medical Affairs

AMN107 (Nilotinib, Tasigna®)

Protocol CAMN107AIC05 / NCT01743989

A prospective, randomized, open-label, two-arm Phase III study to evaluate treatment-free remission (TFR) rate in patients with Philadelphia chromosome-positive CML after two different durations of consolidation treatment with nilotinib 300 mg BID

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List of abbreviations

ABL	Abelson leukemia virus
AE	Adverse event
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
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
CBA	Chromosome banding analysis
CCyR	Complete cytogenetic response
CgR	Cytogenetic response
C_{max}	Maximum plasma concentration
CML	Chronic myeloid leukemia
CP	Chronic phase
CRO	Contract research organization
CSR	Clinical study report
CTCAE	NCI Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
CVA	Cerebrovascular accident
CYP	Cytochrome P450
DDI	Drug-drug interaction
DMC	Data Monitoring Committee
DS&E	Drug Safety and Epidemiology
EC	European Commission
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Case Report/Record Form; the term CRF can be applied to either EDC or Paper
EDC	Electronic data capture
EOP	End of phase
EOS	End of study
EUTOS	European Treatment Outcome Study
FACS	Fluorescence activated cell sorting
FAS	Full Analysis Set
FDA	Food and Drug Administration (USA)
FISH	Fluorescent in-situ hybridization
GCP	Good Clinical Practice
GI	Gastrointestinal
GP	General practitioner
HBc Ab	Hepatitis B Core Antibody
HBs Ag	Hepatitis B Surface Antigen
IB	Investigator Brochure

[redacted]

ICF	Informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IFN	Interferon
IHD	Ischemic heart disease
IN	Investigator Notification
INR	International normalized ratio
IRB	Institutional Review Board
IS	International scale
IVRS	Interactive voice response system
KM	Kaplan-Meier
LC-MS/MS	Liquid chromatography-tandem mass spectrometry
LLN	Lower limit of normal
LLOQ	Lower limit of quantification
LSC	Leukemic stem cell(s)
LVEF	Left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MMR	Major molecular response
MR	Molecular response
$MR^{4.0}$	4.0 log reduction on international scale (IS)
$MR^{4.5}$	4.5 log reduction on international scale (IS)
OS	Overall survival
PAOD	Peripheral artery occlusive disease
PCR	Polymerase chain reaction
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
QD	Once a day
RDC	Remote data capture
REB	Research Ethics Board
RQ-PCR	Real-time quantitative polymerase chain reaction
RT-PCR	Reverse transcriptase polymerase chain reaction
RU	Resource utilization
SAE	Serious adverse event
SD	Standard deviation
SS	Safety Set
SSMC	Scientific Study Management Committee
STAT5	Signal transducer and activator of transcription 5
$t_{1/2}$	Half-life
TFR	Treatment-free remission
TFS	Treatment-free survival
TKI	Tyrosine kinase inhibitor

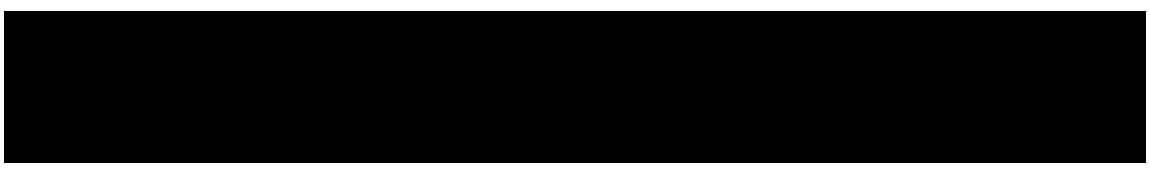
[redacted]

ULN	Upper limit of normal
VAP	Validation and Planning
WBC	White blood cell
WOCBP	Women of childbearing potential

[redacted]

Glossary of terms

CHR	Complete hematologic response = normalization of hematopoiesis
CCyR	Complete cytogenetic response = 0% Ph+ metaphases in a review of a minimum of 20 metaphases in the bone marrow
MMR	Major Molecular Response, MMR is defined as a ≥ 3.0 log reduction in BCR-ABL transcripts compared to the standardized baseline or ≤ 0.1% BCR-ABL according to the international scale as measured by RQ-PCR
$MR^{4.0}$	Defined as either (i) detectable disease ≤ 0.01% BCR-ABL IS; or (ii) undetectable disease in cDNA with ≥ 10,000 ABL transcripts (numbers of ABL transcripts in the same volume of cDNA used to test for BCR-ABL)
$MR^{4.5}$	Defined as either (i) detectable disease ≤ 0.0032% BCR-ABL IS; or (ii) undetectable disease within cDNA with ≥ 32,000 ABL transcripts (numbers of ABL transcripts in the same volume of cDNA used to test for BCR-ABL)
MR^{5}	Defined as either (i) BCR-ABL (IS) ≤0.001%; or (ii) undetectable disease with Total ABL ≥100.000
Assessment	A procedure used to generate data required by the study
Control drug	A study treatment used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Enrollment	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Investigational 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 testing 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
Medication number	A unique identifier on the label of each study treatment package which is linked to one of the treatment groups of a study
Other study treatment	Any drug administered to the patient as part of the required study procedures that was not included in the investigational treatment
Subject Number (Subject No.)	A unique identifying number assigned to each patient/healthy volunteer who enrolls in the study
Period	A subdivision of the study timeline; divides stages into smaller functional segments, such as screening, baseline, titration, washout, etc.
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
Randomization number	A unique treatment identification code assigned to each randomized patient, corresponding to a specific treatment arm assignment
Stage related to study timeline	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
Stop study participation	Point/time at which the patient came in for a final evaluation visit
Study treatment	Includes any drug or combination of drugs in any study arm administered to the patient (subject) as part of the required study procedures, including placebo and active drug run-ins. In specific examples, it is important to judge investigational treatment component relationship relative to a study treatment combination; study treatment in this case refers to the investigational and non-investigational treatments in combination.



Amendment 4 (01-Jun-2016)

Amendment rationale

The recruitment of this study has been completed (LPFV 30-Apr-2015) and 621 patients have been enrolled.

The primary purpose for the amendment is:

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

Changes to protocol

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

- List of abbreviations updated.
- Protocol Summary was updated to add serology in the panel of Safety assessments.
- Section 6.3.4 Hepatitis B reactivation was added to provide information on next steps for patients tested positive for hepatitis B virus.
- Section 7-1 Hepatitis B testing was added to the visit schedule to be performed once and only once at the next possible visit when patient is on treatment or before treatment is re-initiated.
- Section 7.2.2.4.5 Hepatitis B testing was added to provide information on hepatitis B testing.
- Section 8.6 Data Monitoring Committee (DMC) regular and specific reports have been updated
- Section 10.6 Interim analysis minor update
- All other sections, to correct minor inconsistencies and typos

IRBs/IECs

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

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

[redacted]

Summary of previous amendments

Amendment 3

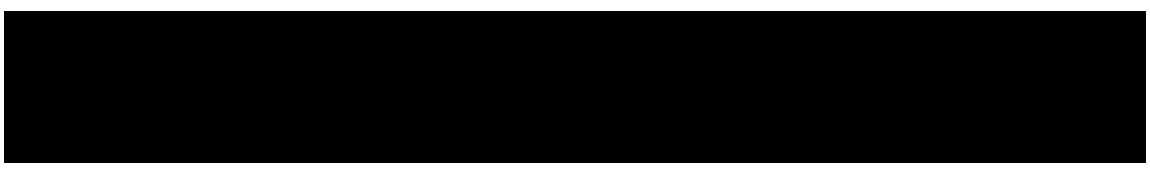
Amendment Rationale

The primary purpose for this substantial amendment is:

- To update the protocol with the latest changes in the Investigator Brochure Edition 11.
- To update the protocol including the 'CML patient's voice' Italian substudy to evaluate the emotional aspects in patients participating to a nilotinib Treatment-free remission (TFR) trial. This substudy aims to examine patients' psycho-emotional characteristics, quality of life and experiences of being involved in CAMN107AIC05 trial and its discontinuation using a qualitative-quantitative mixed method. The 'CML patient's voice' Italian substudy will be conducted in Italy only. It will be coordinated by the Chair of Clinical Psychology, San Paolo Hospital, University of Milan. Further details can be found in the Post Text Supplement 1.

Changes to the protocol

- Section 1.2.1.1: Updated with the mouse carcinogenicity study
- Section 2.7: Updated with the rationale of the 'CML patient's voice' Italian substudy
- Section 4.1.2: Updated with the Italian 'CML patient's voice' Italian substudy
- Section 5.4 and Section 5.5: Updated with the inclusion and exclusion criteria for the 'CML patient's voice' Italian substudy
- Sections 6.4.2 and 6.4.3 are updated with the information on permitted concomitant therapy (CYP3A4 and Antacid drugs)
- Section 11.3: ICF procedure updated with safety data from pre-clinical study
- All other sections: minor typos corrections
- Addition of references to support rationale for 'CML patient's voice' Italian substudy
- IRB/IECA copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.
- Appendix 14.1.1 (List of medications metabolized by CYP3A4, strong, moderate and weak inhibitors of CYP3A4 to be used with caution) is updated.



Amendment 2

Amendment rationale

The primary purpose for this substantial amendment is:

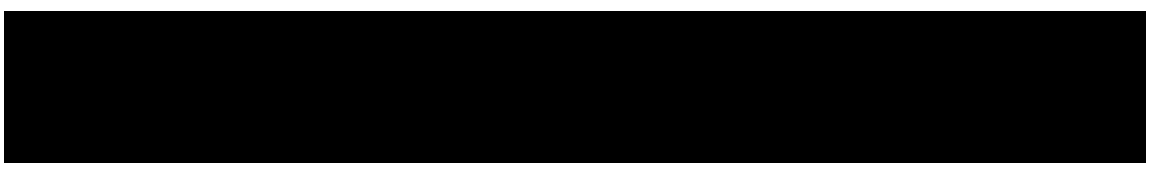
- To modify the study sample size based on new data from the ENESTcmr and STIM studies and a number of recently published clinical trials (Hughes TP, et al. Blood. 2014;124: 729-36; Mahon FX, et al. Blood. 124(21);151; Rea D, et al. Blood. 2014;124(21) [abstract 811])
- To amend the secondary objectives of the study and related endpoints
- To incorporate the safety recommendations provided by the DMC on patients with severe cardiovascular ischemic events experienced before entering the study or while on study i.e.:
  - Patients with prior PAOD, or severe ischemic cardiovascular disease for whom in the opinion of the investigator other treatments might have a more favorable benefit/risk profile will be excluded from the study
  - Patients who experience severe Ischemic vascular or cardiovascular events have to be discontinued from the study whenever in the opinion of the investigator the AE is related to the study drug and other treatments could have a more favorable benefit/risk profile
- To update the efficacy and safety data of nilotinib according to the Investigator's Brochure Edition 10 (April 2014)
- To implement requests of Health Authorities and Ethics Committees/Institutional Review Boards (ECs/IRBs) raised during review of the protocol version number 01
- To update the visit numbering according to the new eCRF design
- To correct minor inconsistencies and typos in the protocol

Changes to the protocol

- Table 3-1: Update of secondary objectives and related endpoints
- Section 4.1: Update of sample size
- Figure 4-1: update of visit numbering
- Section 4.1.1: Addition of time point for determination of PH+ stem cells in bone marrow for patients enrolled in the optional Stem cells ENESTath substudy
- Section 4.2: Addition of information about publication of results
- Section 5.2: Corrections of inclusion criteria numbering and other minor corrections
- Section 5.3: Update of exclusion criteria relating to history PAOD or severe ischemic cardiovascular disease; deletion of refusal to give consent for the optional Stem cells ENESTath substudy from exclusion criteria for main study
- Table 6-2: Update QTc criteria for study discontinuation; update of action to be taken for grade 3 or 4 ischemic vascular or cardiovascular events; update of action to be taken for grade 4 cardiac "other" events

[redacted]

- Table 7-1, Table 7-2, Table 7-3, and Table 7-4: Update of assessments schedule and numbering
- Section 7.1.4: Clarification and update of assessments to be done during the induction /consolidation phase
- Section 7.1.5: Clarification on procedures to be done at the randomization and at eligibility visits
- Section 7.1.6: Update of action patient to take with remaining study drug
- Section 7.1.7: Clarification of procedures to be done during the re-treatment phase
- Section 7.1.8: Update of EOP visits definition
- Section 7.1.8.1: Update of criteria for premature patient withdrawal
- Section 7.2.1.1: Update of methodology to be used to assess molecular response according to the latest EUTOS working guidelines
- Section 7.2.1.3: Clarification of when CgR assessment should be performed
- Section 7.2.2.4.4: Update of when urine analysis is to be performed
- Section 7.2.2.7: Clarification of when the questionnaire is to be administered and action to be taken if questionnaire results are positive
- Section 8.1.1: Update of when adverse event monitoring is to be done
- Section 8.6: Added information about timing of DMC meetings
- Section 10.4.2: Amendment of statistical hypotheses based on new assumptions
- Section 10.4.3: Update of method to handle missing values
- Section 10.5.1: Amendment of the secondary endpoints and corresponding statistical methods
- Section 10.5.2: Amendment of the statistical methods to be applied for the Stem cells ENESTPath substudy.
- Section 10.7: Amendment of assumptions used for sample size calculation for main study and Stem cells substudy
- All other sections: minor typos corrections



Amendment 1

Amendment rationale

The primary purpose for this substantial amendment is:

- Inclusion of the optional Stem cells ENESTpath substudy "Leukemic stem cells quantification in patients with chronic myeloid leukemia included in the ENESTpath trial"; the purpose of this substudy is to evaluate the importance of leukemic stem cells (LSC) in the long-term maintenance of the disease and their role in the relapse of patients during the TFR phase. Participation in this "stem cells" substudy is optional and requires separate specific consent. Patients not wishing to participate in the stem cells substudy may still participate in the main (ENESTpath) study
- To update the efficacy and safety data of nilotinib according to the Investigator's Brochure Edition 9 (June 2013), focusing on the 48-month update of the CAMN107A2303 study in newly diagnosed CML-CP patients
- To include cholesterol testing in the assessment schedule. Elevations in total serum cholesterol and low density lipoprotein cholesterol have been observed very commonly in patients treated with nilotinib or imatinib. Most of the cholesterol elevations were grade 1 (> ULN - 300 mg/dL; > ULN - 7.75 mmol/L) or 2 (> 300 - 400 mg/dL; > 7.75 - 10.34 mmol/L), and some elevations were present prior to initiation of CML therapy. Lipid profiles, including total cholesterol, LDL-C and HDL-C will be assessed at baseline and during the conduct of this study. If test results warrant intervention, investigators should follow their local standards of practice or treatment guidelines, which may recommend treatment even for grade 1 cholesterol elevation. Before prescribing a lipid-lowering medication, the possibility of drug-drug interactions should be considered as some HMG-CoA reductase inhibitors are also metabolized via the CYP3A4 pathway
- To include glucose testing in the assessment schedule. Elevations of blood glucose levels have been observed in CML patients treated with nilotinib. Blood glucose will be assessed at baseline and during the conduct of this study. If test results warrant intervention, investigators should follow their local standards of practice and treatment guidelines
- To provide a harmonization on dose reductions guidelines across Novartis-sponsored Tasigna study protocols
- 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 define ischemic vascular and ischemic cardiovascular events as adverse events of special interest, and their reporting

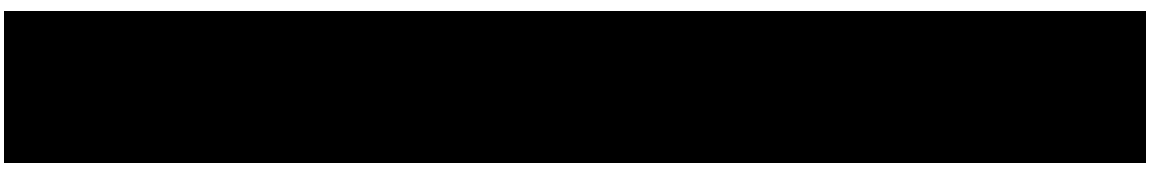
[redacted]

- To implement modifications as requested from different Health Authorities and Ethics Committees/Institutional Review Boards (ECs/IRBs) during review of the original protocol
- To address feedback from investigators received during the study startup
- To correct minor inconsistencies and typos in the protocol

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol, and include the following:

- Section 1.2.1.2.1: Addition of a session on "Ischemic Vascular and Ischemic Cardiovascular Events Reported for CAMN107A2303 (ENESTnd Study)"
- Section 2.6: New section providing rationale for optional Stem cells ENESTpath substudy included in Protocol Amendment 1
- Section 3: Addition of objectives, endpoints, and analyses for optional Stem cells ENESTpath substudy included in Protocol Amendment 1
- Section 4.1: Addition of visit/month information to Figure 4-1 to improve clarity
- Section 4.1.1: Addition of new subsection with study description for the optional Stem cells ENESTpath substudy included in Protocol Amendment 1
- Section 4.4: Changes to early study termination criteria
- Section 5.1: Update of screening criteria for patient population, and addition of details of patient population for the optional Stem cells ENESTpath substudy
- Section 5.2: Update of definition of chronic phase CML, update of inclusion criterion for patients in treatment with imatinib for a minimum of 24 calendar months (even not continuously) and in imatinib treatment at time of enrolment, and addition of requirement for separate specific informed consent for the optional Stem cells ENESTpath substudy
- Section 5.3: Addition/amendment of the following exclusion criteria:
  - Definition of atypical BCR-ABL transcripts
  - Previous anticancer agents for CML except for imatinib, and/or for cytoreduction after CML diagnosis, and/or interferon treatment whose duration was shorter than 1 year
  - Known impaired cardiac function, including any of the following:
    - Inability to determine the QT interval on electrocardiogram [ECG]
    - Complete left bundle branch block
    - Right bundle branch block plus left anterior or posterior hemiblock
    - Use of a ventricular-paced pacemaker
    - Congenital long QT syndrome or a known family history of long QT syndrome;
    - History of or presence of clinically significant ventricular or atrial tachyarrhythmias
    - Clinically significant resting bradycardia (< 50 beats per minute)



    - QTc > 450 msec on the average of three serial baseline ECGs (using the QTcF formula). If QTcF > 450 msec and electrolytes are not within normal ranges, electrolytes should be corrected and the patient re tested for the QTc
    - History of clinically documented myocardial infarction within 1 year prior to study entry
    - History of unstable angina during the last 12 months
    - Other clinically significant heart disease (e.g. congestive heart failure or uncontrolled hypertension)
  - 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. atherothrombotic events [such as ischemic heart disease, peripheral arterial occlusive disease, symptomatic carotid stenosis/cerebrovascular accident (CVA)], uncontrolled diabetes, active or uncontrolled infection, uncontrolled severe hypertension, or uncontrolled severe dyslipidemia). If appropriate measures (e.g. diet, exercise, appropriate therapy) are taken to control blood glucose, or cholesterol LDL levels, or hypertension, the patient can be re-screened for the study
  - Unwillingness to use specified highly efficient forms of contraception in women of childbearing potential (WOCBP)
  - Refusal to provide separate specific consent for the optional Stem cells ENESTpath substudy included in Protocol Amendment 1 (eligibility for the main ENESTpath study remains unaffected)
- Section 6.3: Amendment of dose modification guidelines, and in Section 6.3.2: Amendment of dose reduction guidelines to include ischemic vascular or cardiovascular events, and arrhythmical cardiac toxicity
- Section 6.3.4: Update of suggested management of selected adverse events
- Section 6.4.2: Update to permitted concomitant therapy to include management of hyperglycemia and/or hypertriglyceridemia in some patients
- Section 6.4.3: Update to prohibited concomitant therapy
- Section 7: Addition of assessments in flowcharts and assessments subsections (Edinburgh Claudication Questionnaire, smoking history, and family history of cardiovascular events, urine pregnancy tests, HbA1C, HDL and LDL, microalbuminuria, determination of Ph+ stem cells in bone marrow); addition of two extra optional visits (Day 15 and Month 1 in first trimester of induction/consolidation phase) for hematology/clinical chemistry assessments, plus renumbering of all subsequent visits
- Section 7.1.1: Amendment of screening assessments to include the decision tree for protocol entry based on the molecular response
- Section 7.1.7.1: Expansion of withdrawal criteria relating to pregnancy (occurring during nilotinib treatment or during TFR phase or within 30 days of last dose of nilotinib)
- Section 7.2.2.1: Update of the “Physical Examination” section with the addition of the extramedullary involvement
- Section 7.2.2.4.2: Update of clinical chemistry
- Section 7.2.2.4.3: Update of pregnancy assessments according to the IB Edition 9

[redacted]

- Section 7.2.2.7: Addition of a section regarding the Edinburgh Claudication Questionnaire
- Section 7.2.5: Addition of bone marrow assessments for patients who participate in the Stem cells ENESTpath substudy
- Section 8.1.3: Addition of a section regarding adverse events of special interest (ischemic vascular and cardiovascular events)
- Section 8.4: Expanded statements about pregnancy
- Section 8.6: Changes to data monitoring committee constitution and possible DMC recommendations
- Section 10.1: Update of the "Analysis sets" section
- Section 10.5.1: Update of key secondary objectives
- Section 10.5.2: Addition of secondary objectives for optional Stem cells ENESTpath substudy
- Section 10.5.3: Update of safety objectives
- Section 10.7: Addition of sample size calculation for optional Stem cells ENESTpath substudy
- Section 11.3: Addition of specific informed consent for optional Stem cells ENESTpath substudy
- Section 11.5: Adaptation of authorship rules to comply with SSMC charter
- Addition of references to support rationale for optional Stem cells ENESTpath substudy
- Addition of Appendix containing the lists of CYP3A4 inducers and inhibitors and the Edinburgh Claudication Questionnaire
- Changes to protocol summary to match main protocol
- Minor changes and corrections for clarity

IRB/IEC

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

[redacted]

Protocol summary

Protocol number	AMN107AIC05
Title	A prospective, randomized, open-label, two-arm Phase III study to evaluate treatment-free remission (TFR) rate in patients with Philadelphia chromosome-positive CML after two different durations of consolidation treatment with nilotinib 300 mg BID
Brief title	A randomized phase III study to assess the effect of a longer duration of consolidation treatment with nilotinib on TFR in patients with CML in the chronic phase (CML-CP)
Sponsor and Clinical Phase	Novartis Phase III
Investigation type	Drug
Study type	Interventional
Purpose and rationale	**Purpose**: This study aims to assess the optimal duration of nilotinib 300 mg twice daily (BID, bis in die) consolidation treatment, in order that patients remain in TFR (≥ molecular response [MR]$^{4.0}$) 12 months after starting the TFR phase of the study. **Rationale**: The natural history of chronic myeloid leukemia (CML) was changed dramatically by the introduction of TKIs (tyrosine kinase inhibitors), which have increased patient survival and consequently have prolonged the duration and increased the prevalence of the disease. It is estimated that the number of CML cases will continue to increase over the next half century, with the number of patients expected to exceed 250,000 in the USA alone. In this context, TFR studies may serve to both provide a new treatment paradigm for patients (in respect to the minimization of drug-drug interactions, elimination of chronic side effects, and benefit of pregnancy without exposure to TKIs), and also potentially have a positive impact on health economics, considering the expected increase in the numbers of patients with the disease. CML-CP patients who have received 24 or more months of first-line imatinib treatment, and who have failed to achieve the molecular response threshold for treatment cessation (equal to or more than MR$^{4.0}$, ≥MR$^{4.0}$) have a 50% greater chance of achieving this level of molecular response by switching to nilotinib; however, the optimal duration of consolidation treatment with nilotinib to ensure the highest rate of patients remaining in ≥MR$^{4.0}$ after suspending treatment is not yet known. This protocol therefore aims to assess the potential impact of two durations of consolidation treatment with nilotinib, i.e. 12 months versus 24 months, on molecular relapse rate in the first 12 months of the TFR phase. Rationale for optional Stem cells ENESTPath substudy - “Leukemic stem cells quantification in patients with chronic myeloid leukemia included in the ENESTPath trial”: The focus of this optional Stem cells ENESTPath substudy is to evaluate the importance of leukemic stem cells (LSC) in the long-term maintenance of the disease and their role in the relapse of patients during the TFR phase. This optional Stem cells ENESTPath substudy evaluates: ● The presence and number of LSC and their progenitors in the bone marrow of all patients participating in this substudy before and after completing induction and the first year of the consolidation phase (at Visit 8). ● Whether prolonging the treatment period of consolidation with nilotinib (patients in Arm 2) induces a reduction in the percentage of patients presenting LSC and progenitor cells in bone marrow at the end of the second year of the consolidation phase. Rationale of ‘CML patient’s voice’ Italian substudy - The inner psycho-emotional experiences of CML patients during consolidation and TFR phases are unknown.The ‘CML patient’s voice’ Italian substudy aims to examine patients’ psycho-emotional characteristics, quality of life and experiences of being involved in the ENESTPath study and its discontinuation using a mixed method design qualitative-quantitative. This substudy will be conducted in Italy only. For further details, please refer to the [Post-text Supplement 1]

[redacted]

Primary objective	To assess the optimal duration of consolidation treatment with nilotinib 300 mg BID in order that patients remain in treatment-free remission (≥$MR^{4\,0}$) without molecular relapse 12 months after entering the TFR phase
Secondary objectives	● To evaluate the proportion of patients who are eligible to suspend nilotinib therapy by achieving and maintaining sustained ≥$MR^{4\,0}$ for at least 12 months during consolidation treatment with 300 mg BID nilotinib ● To assess the achievement of MMR, $MR^{4\,0}$, and $MR^{4\,5}$ during induction/consolidation treatment with nilotinib 300 mg BID at the different time points in patients without that response at study entry ● To assess the molecular response in patients during induction/consolidation treatment with nilotinib 300 mg BID at the different time points ● To assess the proportion of patients in TFR at 3, 6, 12, 18, and 24 months after nilotinib cessation in the two treatment arms ● To assess the molecular response in patients after randomization in the two treatment arms ● To assess the kinetics of BCR-ABL transcript during induction/consolidation treatment with 300 mg BID nilotinib, during the TFR phase and during the nilotinib re-treatment phase. ● To assess the progression-free survival (PFS) rate after randomization in both treatment arms ● To assess the treatment-free survival (TFS) rate after the start of TFR phase in the two treatment arms ● To assess the overall survival (OS) rate after randomization in the two treatment arms ● To assess the safety profile of nilotinib during the induction/consolidation phase, the TFR phase, and the re-treatment phase For those patients consenting to participate in the optional Stem cells ENESTPath substudy, the following objectives will be also evaluated: ● To evaluate the presence and number of LSC and their progenitors in the bone marrow before and after completing induction and the first year of the consolidation phase (at Visit 8); ● To evaluate whether prolonging the treatment period of consolidation with nilotinib (patients in Arm 2 versus patients in Arm 1) induces a reduction in the percentage of patients presenting LSC and progenitor cells in bone marrow at the end of the second year of the consolidation phase (Visit 204 for Arm 2 versus Visit 8 for Arm 1). ● To perform an exploratory analysis in order to evaluate whether relapse in patients during the TFR phase in either arm correlates with the presence of LSC and progenitor cells in bone marrow at the end of consolidation phase and at the time of relapse during TFR For those patients consenting to participate to the ‘CML patient’s voice’ Italian substudy, please refer to the [Post-text Supplement 1].

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Study design	This is a prospective, randomized, open-label, multicenter, two-arm Phase III study that includes a 12-month induction phase, followed by a 12 or 24-months consolidation phase (dependent on randomization) and a 36 or 24-months TFR phase, respectively, totaling a 5-year study duration for the individual patient. Eligible patients are adults with a confirmed diagnosis of CP Philadelphia chromosome-positive (Ph+) and/or BCR-ABL+ CML who have been treated with first-line imatinib for 24 months or more, and are in complete cytogenetic response (CCyR). Patients must not have achieved ≥$MR^{4.0}$ at study entry, as assessed by a EUTOS laboratory. Approximately 565 patients will be enrolled into the study and will be treated with nilotinib 300 mg BID for 24 months. Following 24 months of treatment, patients in sustained molecular response for at least the last 12 months will be randomized on a 1:1 basis to either: ● Suspend nilotinib treatment immediately and enter the TFR phase (Arm 1; the nilotinib 24-month treatment arm), or ● Continue nilotinib treatment for a further 12 months then suspend treatment and enter the TFR phase (Arm 2; the nilotinib 36-month treatment arm). Patients not achieving a sustained molecular response at 24 months (and subsequently at 36 months if previously randomized to the treatment arm with 1 year additional consolidation) will exit the study and will be treated at the discretion of the investigator according to standard practice. Information on survival, stem cell transplant, and the status of the patient's disease (i.e. disease progression to AP (accelerated phase)/BC (blast crisis) according to protocol definition, TKI treatment) will be collected until death, or until 5 years from study entry, whichever comes first. Patients relapsing during the TFR phase will enter the nilotinib re-treatment phase of the study, and will be re-treated with the same dose of nilotinib as they were on before the TFR phase (i.e. the re-treatment dose will be nilotinib 300 mg BID or a lower dose of nilotinib if the dose was reduced in the consolidation phase before entering the TFR phase). These patients will remain on study until the completion of the 5-year study period **Optional Stem cells ENESTPath substudy:** The Stem cells ENESTPath substudy adds the determination of Ph+ stem cells in bone marrow in those patients consenting to participate in this substudy, at the following time points: a) At the screening visit, before starting nilotinib treatment b) After 2 years of nilotinib treatment at Visit 8 c) After 3 years of nilotinib treatment, only in patients with 2 years' consolidation treatment (Arm 2) at Visit 204 d) If the patient relapses during the TFR phase, before re-starting the treatment with nilotinib A 10 mL bone marrow sample will be collected and sent to [redacted] for immunophenotype analysis, FACS (fluorescence activated cell sorting) cell purification, *in situ* hybridization, and RT-PCR. Measurement and quantification will be performed by flow cytometry in a bone marrow purified population of stem cells in order to detect the presence of leukemic Ph+ cells or BCR-ABL transcript levels (evaluated by fluorescent *in situ* hybridization [FISH] or RT-PCR). 'CML patients' voice' Italian substudy: Please refer to the [Post-text Supplement 1]

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Key inclusion criteria	● Male or female patients, aged ≥ 18 years ● Eastern Cooperative Oncology Group (ECOG) performance status of 0-2 ● Confirmed diagnosis of Ph+ and/or BCR-ABL+ CML-CP ● Previous first-line treatment with imatinib for a minimum of 24 months (even not continuously) in total and in imatinib treatment at time of enrollment ● Patient in CCyR For those patients consenting to participate in the optional Stem cells ENESTPath substudy, the same inclusion criteria as for the main ENESTPath study will be applicable, plus the following: ● A separate specific written informed consent for the Stem cells ENESTPath substudy must be obtained prior to extraction of additional bone marrow samples. For those patients consenting to participate in the 'CML patient's voice' Italian substudy , the same inclusion inclusion criteria as for the main ENESTPath study will be applicable. This substudy will be conducted in Italy only.

Key exclusion criteria	● Achievement of ≥MR$^{4\ 0}$ at study entry as assessed by a EUTOS standardized laboratory
	● Previous treatment with BCR-ABL inhibitors other than imatinib
	● Patients with detectable atypical BCR-ABL transcripts, defined as absence of typical BCR-ABL transcripts for CML of the types b2(e13)-a2 or b3(e14)-a2 or both of them simultaneously documented at CML diagnosis or at any time before the screening procedure
	● Previous anticancer agents for CML except:
	  ● imatinib, and/or
	  ● cytoreduction after CML diagnosis, and/or
	  ● interferon for less than 1 year
	● Known second chronic phase of CML after previous progression to AP/BC;
	● Known impaired cardiac function, including any of the following:
	  ● Inability to determine the QT interval on ECG
	  ● Complete left bundle branch block
	  ● Right bundle branch block plus left anterior or posterior hemiblock
	  ● Use of a ventricular-paced pacemaker
	  ● Congenital long QT syndrome or a known family history of long QT syndrome
	  ● History of or presence of clinically significant ventricular or atrial tachyarrhythmias
	  ● Clinically significant resting bradycardia (< 50 beats per minute)
	  ● QTc > 450 msec on the average of three serial baseline ECG (using the QTcF formula). If QTcF > 450 msec and electrolytes are not within normal ranges, electrolytes should be corrected and the patient re-tested for the QTc
	  ● History of clinically documented severe PAOD or severe ischemic cardiovascular disease (e.g. myocardial infarction, ischemic cerebral vascular disease) whenever in the opinion of the investigator other treatments could have a more favorable benefit/risk profile.
	  ● Other clinically significant heart disease (e.g. congestive heart failure or uncontrolled hypertension)
	● 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, active or uncontrolled infection, uncontrolled severe hypertension, uncontrolled severe dyslipidemia). If appropriate measures (e.g. diet, exercise, appropriate therapy) are taken to control blood glucose or cholesterol LDL levels, or hypertension, the patient can be re-screened for the study.
	● History of acute pancreatitis within 12 months of study entry, or a medical history of chronic pancreatitis

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	● Known presence of significant congenital or acquired bleeding disorder unrelated to cancer ● History of other active malignancies within 5 years prior to study entry, with the exception of previous or concomitant basal cell skin cancer, or previous cervical carcinoma in situ treated curatively ● Patients who have not recovered from prior surgery ● Treatment with other investigational agents within 30 days of Day 1 ● Patients actively receiving therapy with strong CYP3A4 inhibitors and/or inducers or medications that have the potential to prolong the QT interval that cannot be either discontinued or switched to a different medication prior to starting study drug ● Impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of study drug ● Patients who are: (a) pregnant, (b) breast feeding, (c) of childbearing potential without a negative pregnancy test prior to baseline, or (d) of childbearing potential unwilling to use highly effective contraceptive precautions (as detailed below) throughout the trial (post-menopausal women must be amenorrheic for at least 12 months to be considered of non-childbearing potential) ● Women of child-bearing potential (WOCBP), defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 14 days after the final dose of nilotinib or imatinib. Patients using an oral hormonal contraception method should complete their monthly treatment course. Highly effective contraception methods include: I. Total abstinence (when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception II. Female sterilization (surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least 6 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 III. Male sterilization (at least 6 months prior to screening). For female subjects on the study, the vasectomized male partner should be the subject's sole partner IV. Combination of any two of the following (a+b or a+c or b+c) listed below: a) Use of oral, injected, or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate < 1%), e.g. hormone vaginal ring or transdermal hormone contraception b) Placement of an intrauterine device (IUD) or intrauterine system (IUS) c) Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository In case of use of oral contraception, women should have been stable on the same pill for a minimum of 3 months before taking study treatment ● Patients not able to understand and comply with study instructions and requirements For those patients consenting to participate in the optional Stem cells ENESTPath substudy, the same exclusion criteria as for the main ENESTPath study will apply For those patients consenting to participate in the 'CML patient's voice' Italian substudy, the same exclusion criteria as for the main ENESTPath study will apply. This substudy will be conducted in Italy only.
Investigational therapy	Nilotinib 300 mg BID
Efficacy assessments	● Molecular Response (RQ-PCR, optional mutational analysis) ● Bone marrow assessments and cytogenetics, including evaluation of LSC and progenitor cells in the optional Stem cells ENESTPath substudy

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Safety assessments	● Physical examination ● Vital signs ● ECOG performance status ● Laboratory evaluations (clinical chemistry, hematology, urine analysis); ● Serology (Hep B) ● ECG ● Echocardiography ● Edinburgh Claudication Questionnaire ● Adverse events ● Concomitant medication ● Serum and urine pregnancy test (for WOCBP)
Other assessments	**Optional Stem cells ENESTPath substudy:** ● Presence of Ph+ LSC in bone marrow (CD34+/CD38+ progenitor cells, CD34+/CD38− stem cells, and CD34+/CD56+ aberrant stem cells [the last ones only if detectable]) ● Percentage of total CD34+ cells ● Percentage of Ph+ cells evaluated by FISH ● BCR-ABL transcript levels on sorted cells by RT-PCR ● Percentage of subpopulations (CD34+/CD38+, CD34+/CD38−, and CD34+/CD56+ [if detectable])
Data analysis	Based on new data from the ENESTcmr study, it is expected that 40% of the patients switched from imatinib to nilotinib will achieve $MR^{4.0}$ or better at the end of the 12-month induction phase, and will maintain this level of molecular response by the end of the 12-month consolidation phase prior to randomization. Furthermore, if the patients treated with nilotinib for 24 months before entering the TFR phase (Arm 1) have a similar relapse rate as the patients in the STIM trial (Mahon et al 2011), it is expected that 40% of patients randomized to Arm 1 will not have relapsed after the 12 months TFR phase. Based on new information from a number of recently published studies (Hughes TP et al 2014 Blood;124:729-36; Mahon FX et al 2014 Blood;124(21):151; Rea D et al 2014 Blood.;124(21) [abstract 811]), it is reasonable to assume that a 12-month longer consolidation period with nilotinib (Arm 2) may reduce the molecular relapse rate in the first 12 months TFR phase by approximately 20% (from 60% to 40%, absolute difference of 20%). Therefore it is assumed that the percentage of patients without relapse will be 40% in Arm 1, and 60% in the Arm 2. Considering this, a sample size of 107 patients per group (a total of 214) is needed to detect such a difference. These calculations are based on a two-sided chi-square test at 0.05 alpha level with a power of 80%. Assuming that 5% of patients will be unevaluable after randomization, a total of 226 patients will need to be randomized in order to adequately power the study. Finally, as explained above, assuming that 40% of the patients switched from imatinib to nilotinib will achieve ≥$MR^{4.0}$ at the end of the 12-month induction phase, and will maintain this level of molecular response by the end of the 12-month consolidation phase prior to randomization, a total of 565 patients are required for this study. Primary analysis: The proportion of patients who are in TFR (≥MR4.0) without molecular relapse at the end of 12 months in the TFR phase will be calculated by dividing the number of patients who remain in ≥MR4.0 at the end of 12 months in the TFR phase (without re-starting nilotinib therapy) by the number of patients who entered the TFR phase. A chi-square test will be applied to compare the two treatment arms. A two sided test with alpha = 0.05 will be used. The rate of successful TFR will be presented together with an exact 95% Clopper Pearson confidence interval. No formal interim analyses are planned.
Key words	Phase III, two-arm, open-label, nilotinib, treatment-free remission, sustained $MR^{4.0}$, stem cells, confirmed loss of M $R^{4.0}$, loss of MMR, Ph+ CML-CP.

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1 Background

1.1 Overview of disease pathogenesis, epidemiology and current treatments

Chronic myelogenous leukemia (CML) is a clonal myeloproliferative disorder of transformed, primitive hematopoietic progenitor cells. The hallmark of CML is the Philadelphia (Ph) chromosome, which is found in up to 95% of patients. It results from a reciprocal translocation t(9;22)(q34;q11), which adds a 3' segment of the ABL gene on chromosome 9 to the 5' part of the breakpoint cluster region (BCR) gene on chromosome 22. The resulting fusion gene encodes for a constitutively active tyrosine kinase, the BCR-Abelson (ABL) tyrosine kinase (Faderl et al 1999), which has activity that imparts growth advantage to leukemic cells, increases proliferation and cytokine-independent growth, inhibits apoptosis, and inhibits alternate adhesion pathways (Sawyers 1999; Deininger 2000; van Etten 2004).

Clinically, CML progresses through three distinct phases of increasing refractoriness to therapy: chronic phase (CP; median duration 3 to 4 years; median survival up to 10 years with allogeneic bone marrow transplant, and 5 to 6 years with interferon), accelerated phase (AP; median duration 3 to 9 months; median survival 8 to 18 months), and blast crisis (BC; median survival 3 to 6 months) (Enright and McGlave 2000). Most patients, however, present in the CP, characterized by splenomegaly and leukocytosis with generally few symptoms.

The objectives of CML-CP treatment are the normalization of hematopoiesis (complete hematologic response), the elimination of the Ph+ cells from the bone marrow (complete cytogenetic response [CCyR]), and the reduction of the BCR-ABL transcript levels from samples of peripheral or bone marrow blood by a factor of 3.0 logs compared to the standardized baseline (major molecular response [MMR] international scale [IS]: 0.1%).

Several studies have shown that a further reduction of residual leukemic cells of 4.0 logs or more (i.e. achieving a complete molecular response [$MR^{4.0}$ or better, i.e. $\geq MR^{4.0}$] compared to an MMR) is associated with the most favorable outcome for patients in CML-CP. In a study of 90 patients with a CCyR, only one out of 28 patients with a $\geq MR^{4.0}$ subsequently lost their CCyR, whereas 11 out of 48 with an MMR subsequently lost their CCyR (Press 2007). In a study by Kantarjian (2008) of 276 patients treated with imatinib, 100 patients achieved a $\geq MR^{4.0}$, with no treatment failures (classified as sustained $\geq MR^{4.0}$ for 6 months or more). A third study published by Branford (2008) demonstrated in a series of 144 patients treated with imatinib who achieved an MMR, that the lowest frequency of recurrence occurred in the 55 patients with a $\geq MR^{4.0}$ (1.8%) compared with 89 patients with an MMR but not a $\geq MR^{4.0}$ (7.9%). These studies support the goal of therapy for newly diagnosed CML-CP as being attainment of $\geq MR^{4.0}$, as this is associated with the most favorable outcome.

The gold standard for the treatment of CML was the tyrosine kinase inhibitor (TKI) Glivec® (imatinib). Nilotinib (Tasigna®, AMN107) is a second-generation TKI with improved target specificity over imatinib. Its efficacy and safety in the treatment of patients who are resistant/intolerant to imatinib (Kantarjian 2006; Kantarjian 2007; le Coutre 2008) led to its registration for the second-line treatment of CML-CP and CML-AP. More recently, nilotinib has been approved for the first-line treatment of newly diagnosed CML-CP patients. The

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5-year follow-up from the pivotal nilotinib study [CAMN107A2303] in this indication (Larson 2014) confirmed the superiority of nilotinib 300 mg twice daily (BID) or 400 mg BID over imatinib 400 mg once daily (QD) in terms of the MMR rates (77%, 77%, and 60%, respectively) and in achieving $MR^{4.5}$ (54%, 52%, and 31%) by 5 years. In particular, the estimated rate of progression to AP/BC was also significantly lower in both nilotinib treatment arms (0.7%, 1.1%) than in the imatinib treatment arm (4.2%).

The National Comprehensive Cancer Network guidelines on CML (version 2, 2012) and the European Leukemia Net guidelines (Baccarani et al 2013) recommend continuing TKI treatment (i.e. imatinib or nilotinib) indefinitely in all responding patients. There are currently no recommendations or provisions for temporary or permanent treatment-free remission (TFR) phases with any TKI.

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

1.2.1 Overview of nilotinib

Nilotinib (Tasigna®, AMN107) is a rationally designed second-generation TKI with improved target specificity over imatinib. Tasigna® is approved for the treatment of adult patients with Ph+ CML-CP or -AP resistant to or intolerant to at least one prior therapy, including imatinib, and also for the treatment of adult patients with newly diagnosed Ph+ CML-CP. Efficacy data in patients with CML-BC are not available.

Nilotinib is an adenosine triphosphate-competitive inhibitor of the tyrosine kinase activity of the native ABL as well as the chimeric fusion protein BCR-ABL and thereby prevents the activation of BCR-ABL-dependent mitogenic and anti-apoptotic pathways (e.g. phosphatidylinositol-3kinase [PI-3K] and signal transducer and activator of transcription [STAT5]), leading to the death of the BCR-ABL phenotype in CML (Manley 2010). As well as being a highly potent and selective inhibitor of BCR-ABL, nilotinib also maintains activity against many imatinib-resistant mutant forms of BCR-ABL (Weisberg 2005). In murine models of CML, sole treatment with oral nilotinib reduces tumor burden and prolongs survival. In primary Ph+ leukemia cell lines from CML patients, nilotinib selectively inhibits proliferation and induces apoptosis. Nilotinib has little or no effect against the majority of other protein kinases examined, including Src, except for the platelet-derived growth factor, Kit, and ephrin receptor kinases, which it inhibits at concentrations within the range achieved following oral administration at therapeutic doses recommended for the treatment of CML.

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 2006). 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.

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In a mouse study, skin growth or skin cancer were detected at doses representing approximately 30 to 40 times the human exposure at the maximum approved dose. At doses that were approximately 10 to 20 times the human exposure at the maximum approved dose, no observed overgrowth of the skin was detected. In this study the major non-cancer lesions were in the skin, the growing teeth (degeneration/atrophy of the enamel and inflammation of the gingiva) and the thymus (low lymphocytes). There are currently no clinical data suggesting an increased risk of skin cancer in patients treated with Tasigna.

For more details on non-clinical experience, please refer to the latest [AMN107 Investigator Brochure].

1.2.1.2 Clinical experience

1.2.1.2.1 Clinical safety and tolerability

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

While adverse events (AEs) are common in patients with CML treated with nilotinib, they are generally mild to moderate, reversible, and manageable with dose interruption and/or dose reduction. The most common grade 3 or 4 toxicities are hematologic, which are not unexpected in the CML population and are generally manageable. Hematotoxicity is more frequent in patients with imatinib-resistant or -intolerant CML and in particular in patients with CML-AP and CML-BC. The most commonly reported non-hematologic adverse reactions in patients with newly diagnosed Ph+ CML-CP, resistant or intolerant Ph+ CML-CP, or resistant or intolerant Ph+ CML-AP are rash, pruritus, headache, nausea, fatigue, myalgia, nasopharyngitis, constipation, diarrhea, abdominal pain, vomiting, arthralgia, pyrexia, upper urinary tract infection, back pain, cough, and asthenia. Hematologic adverse drug reactions include myelosuppression: thrombocytopenia, neutropenia, and anemia. In comparison to first-line patients, grade 3/4 AEs were more frequently observed in CML patients resistant to or intolerant of prior therapy, including imatinib. Other significant drug effects reported with nilotinib include modest QTc prolongation, elevations of blood glucose, bilirubin, lipase, and transaminases, which are manageable with dose interruptions and reductions.

No major differences in safety or efficacy have been observed in patients ≥ 65 years of age. Clinical studies have not been performed in patients with impaired renal function.

For detailed information regarding nilotinib clinical safety and tolerability, please refer to the latest [AMN107 Investigator Brochure].

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

Newly diagnosed or worsened ischemic vascular and ischemic cardiovascular events, such as ischemic heart disease (IHD), ischemic cerebrovascular events (ICVE) or peripheral artery occlusive disease (PAOD) have occurred in a relatively small number of CML-CP patients while on study medication. However, such events have been reported with higher frequency in the nilotinib treatment arms compared with the imatinib treatment arm. Up to the data cut-

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off for the 60-month analysis (30-Sep-2013), the number of patients reported with events is as follows:

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

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

1.2.1.2.2 Pharmacokinetics/pharmacodynamics of nilotinib

Approximately 30% of a nilotinib dose is absorbed after oral administration, with peak concentrations reached at 3 hours after dosing. Plasma protein binding is high (approximately 98%) and independent of dose.

Nilotinib is metabolized in the liver via oxidation and hydroxylation pathways, mediated primarily by CYP3A4. Nilotinib was identified as the main circulating component in the serum, while none of the metabolites was found to contribute significantly to the pharmacological activity of nilotinib. In humans, excretion of nilotinib occurred exclusively through the fecal route, with no renal elimination of the drug or its metabolites observed. The average elimination half-life ($t_{1/2}$) of nilotinib is 17 hours.

With multiple oral doses of nilotinib, steady-state conditions were achieved by Day 8 after starting treatment. There were 2-fold and 3.8-fold accumulations with QD and BID dosing, respectively. Inter-patient variability (coefficient of variation [CV%]) in nilotinib pharmacokinetics (PK) was moderate to high, with CV% being 32% to 64% in area under the serum concentration-time curve (AUC) and 34% to 72% in maximum plasma concentration (C_{max}), respectively.

The bioavailability of nilotinib is increased by food: healthy volunteer studies showed increases in C_{max} and AUC of up to 112% and 82%, respectively (30 hours after high-fat meal, versus fasting conditions). Concurrent intake of grapefruit juice increased the nilotinib C_{max} and $AUC_{0-\infty}$, but the median time to reach peak concentration and the mean $t_{1/2}$ were not altered.

With QD dosing of nilotinib from 50 to 1200 mg at steady state, C_{max} and AUC increased with increasing dose from 50 to 400 mg in a generally dose-proportional manner, but appeared to plateau at dose levels above 400 mg. Dividing the daily dose into a BID schedule partially overcame the dose-limiting absorption; exposure to nilotinib with 400 mg BID was approximately 35% greater than with 800 mg QD.

Systemic exposure (AUC) of nilotinib at steady state at a dose level of 400 mg BID was approximately 13.4% higher than at a dose level of 300 mg BID. The average nilotinib C_{max} and minimum plasma concentration (C_{min}) over 12 months were approximately 15.7% and 14.8% higher, respectively, following 400 mg BID dosing compared to 300 mg BID, suggesting a less than proportional dose-exposure relationship between nilotinib 300 mg BID

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and 400 mg BID. Bioavailability and systemic exposure may be lower in male patients; studies have shown 10% to 20% lower systemic exposure in males versus females.

Hepatic impairment has a modest effect on nilotinib PK, increasing $AUC_{0-\infty}$ by 35%, 35%, and 19% in patients with mild, moderate, and severe hepatic impairment, respectively, versus patients with normal hepatic function. Impaired renal function is not expected to influence nilotinib PK. Nilotinib absorption (relative bioavailability) may be reduced by approximately 48% and 22% in patients with total gastrectomy and partial gastrectomy, respectively.

The administration of nilotinib with agents that are strong cytochrome P450 (CYP)3A4 inhibitors (including, but not limited to ketoconazole, itraconazole, voriconazole, clarithromycin, telithromycin, and ritonavir) should be avoided. Concomitant use of nilotinib with medicinal products that are potent inducers of CYP3A4 (e.g. phenytoin, rifampicin, carbamazepine, phenobarbital, and St. John's wort) is likely to reduce exposure to nilotinib to a clinically relevant extent. For further information, see the [AMN107 Investigator Brochure].

1.2.1.2.3 Efficacy of nilotinib

Overall, approximately 11,764 patients have been exposed to nilotinib in clinical trials as of 31 January 2015.

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

The results of study ENESTnd (Evaluating Nilotinib Efficacy and Safety in Clinical Trials–Newly Diagnosed Patients) demonstrated superiority of nilotinib versus imatinib in the CML-CP first-line 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 MMR at 12 months was 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 $MR^{4.5}$ log reduction from standardized baseline was 11%, 25%, and 32% by 12, 24, and 36 months 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 $MR^{4.5}$ in the nilotinib and imatinib arms increased over time.

For additional details human studies in CML, see the [AMN107 Investigator Brochure].

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2 Rationale

2.1 Study rationale and purpose

The natural history of CML was changed dramatically by the introduction of TKIs, which have increased patient survival and consequently have prolonged the duration and increased the prevalence of the disease. It is estimated that the number of CML cases will continue to increase over the next half century, with the number of patients expected to exceed 250,000 in the USA alone.

The TKI imatinib has been the gold standard in the treatment of Ph+, BCR-ABL+ CML for more than 10 years, with approximate cumulative responses of 70% of patients achieving a CCyR and 50% achieving a 3-log reduction in BCR-ABL IS or an MMR following treatment (Clark et al 2012). Studies have demonstrated that the survival of imatinib-treated patients is similar to that of non-CML patients; however, the proportion of patients who achieve a stable molecular response of below 4-log or more (i.e. $MR^{4.0}$, $MR^{4.5}$, and $MR^{5.0}$) is much smaller, and ranges between 26% for $MR^{4.0}$ and 15% for $MR^{4.5}$ after 3 years of follow-up (Clark et al 2012).

Several results from independent study groups have proven that discontinuation of patients from imatinib treatment is possible, with the risk of relapse being between 40% and 60% and occurring most frequently within the first year of discontinuation (Mahon et al 2010). As a prerequisite for any discontinuation attempt however, patients must have achieved a sustained deep molecular response for an extended duration of time. The depth of molecular remission is not consistent among the trials conducted; however, it is felt that a sustained molecular remission of $\geq MR^{4.0}$ will provide adequate protection from relapse after cessation of treatment for at least a notable proportion of the population. (Cross et al 2012)

Studies have demonstrated that patients who achieve a low level of BCR-ABL can subsequently show fluctuations of their molecular responses due to individual patient biology. Indeed, data from the ENESTnd study ([CAMN107A2303]), a pivotal phase III study of nilotinib versus imatinib in first-line treatment; Novartis, Larson, R, et al. Blood. 2014 [abstract 4541] suggest that approximately 30% of patients will have fluctuations in BCR-ABL above the given threshold of a 4.5-log reduction in BCR-ABL. Therefore a sustained molecular remission of $\geq MR^{4.0}$ serves to reduce the number of patients eligible for treatment cessation further.

From the considerations above, it is recognized that only a small proportion of imatinib-treated patients are eligible for an attempt at treatment cessation; and data have shown that almost 50% of patients undergo a molecular relapse upon treatment interruption. For patients not achieving a deep molecular response on imatinib treatment after 2 years, the chances of doing so at a later date is very small, and therefore the chances of participating in a cessation attempt is further reduced.

Nilotinib is an imatinib derivative that has a greater activity on the kinase activity of BCR-ABL, either wild type or with most mutations associated with imatinib resistance (Weisberg et al 2005), that has been proven to induce a CCyR in about 50% of the patients who were resistant to imatinib treatment (Kantarjian et al 2006). Subsequently, it was

[redacted]

demonstrated that nilotinib induced CCyR and MMR to a greater extent than imatinib in first-line treatment (Saglio et al 2010). Nilotinib is registered for the second-line treatment of CML at a dose of 400 mg BID and for the first-line treatment of CML at a dose of 300 mg BID. The data from the ENESTnd study showed that the molecular response to nilotinib is not only higher and faster, but also deeper, with an $MR^{4.0}$ rate of approximately 30% by 2 years and 50% by 3 years (Clark et al 2012).

In addition, data from the ongoing Evaluating Nilotinib Efficacy and Safety in Clinical Trials-Complete Molecular Response (ENESTcmr) study shows that patients with a lack of deep molecular response on imatinib can benefit from treatment with nilotinib by reaching deeper levels of molecular response compared to continuation of treatment with imatinib (Cervantes et al 2012). In this study the primary endpoint, defined as undetectable BCR-ABL in two consecutive samples was not reached; however, twice as many patients who switched to nilotinib achieved $MR^{4.5}$ versus patients who continued on imatinib. Overall, 9% of patients who were switched to nilotinib discontinued the study prematurely due to AEs, in comparison to 1% of patients who continued on imatinib.

In the context of the increasing prevalence of CML, TFR studies may serve to both provide a new treatment paradigm for patients (with respect to the minimization of drug-drug interactions, elimination of chronic side effects, and benefit of pregnancy without exposure to TKIs), but may also have a positive impact on health economics considering the expected increase in the numbers of patients with the disease.

CML-CP patients who have received 24 or more months of imatinib treatment and have failed to achieve the MR threshold for treatment cessation have a 50% greater chance of achieving this level of MR by switching to nilotinib; however, the optimal duration of consolidation treatment with nilotinib to ensure the highest rate of patients remaining in $\geq MR^{4.0}$ after suspending treatment is not yet known. Several attempts were made to assess the impact of the duration of sustained molecular remission (e.g. Mahon et al 2010, Ross et al 2010) with inconclusive results. Therefore within the current protocol, it is planned to assess this duration as an integral part of the study design, randomizing the patients to either a 12-month or a 24-month consolidation phase before treatment cessation and assessing the potential impact of a longer duration of consolidation treatment with nilotinib on molecular relapse rate in the first 12 months of the TFR phase.

2.2 Rationale for the study design

This is an open-label, multicenter, randomized, two-arm study aiming to identify the duration of nilotinib treatment that enables a highest percentage of patients to remain in TFR ($\geq MR^{4.0}$) 12 months after starting the TFR phase of the study.

In a previous study (ENESTcmr), $MR^{4.5}$ was achieved after 24 months of treatment with nilotinib in 43% of CML-CP patients lacking a deep MR after having been on imatinib for at least 2 years. For this reason, it is expected that 24 and 36 months of treatment with nilotinib 300 mg BID may induce greater percentages of patients to achieve sustained $\geq MR^{4.0}$.

The primary efficacy parameter of the number of patients remaining in TFR ($\geq MR^{4.0}$) will be determined 12 months after starting the TFR phase in both randomized treatment arms. An additional analysis at 24 months will also be performed. Updated results from the STIM study

[redacted]

were reported (Mahon et al 2011), which demonstrated that 39 out of 100 off-treatment patients remained without detectable BCR-ABL transcript levels after a median 34 months of follow-up. Of the 61 patients who had molecular relapses, 58 (95%) relapsed in the first 7 months of the study, and three molecular recurrences occurred at later time points (months 19, 20, and 22). This observation is in line with the molecular recurrence patterns described by both Mahon et al (2010) and Branford et al (2012). It is therefore anticipated that even if patients have a 1- to 2-log lower residual leukemic disease burden at the time of starting the TFR phase (as opposed to patients treated with imatinib in previous studies), those who experience molecular recurrence during this phase will do so within the same time frame as observed in previous discontinuation studies. Assessments of relapse rate at 12 and 24 months in the TFR follow-up period are therefore deemed to be sufficient to detect any clinically significant difference between the two randomized arms.

Patients who are eligible to enter the TFR phase will be monitored every 4 weeks during the first 6 months of the phase, with assessments occurring less frequently in the following 18 months. Studies have shown that in case of molecular recurrence, the increase is on average 1 log per month (Brandford et al 2012; Mahon et al 2010). The monthly monitoring during the first 6 months of the TRF phase (when most recurrences are anticipated) will therefore ensure that impending recurrence is identified early enough to avoid loss of CCyR by timely re-initiation of nilotinib treatment.

It is also hypothesized, primarily from the STIM study, that virtually all patients with molecular recurrence after the TFR phase will regain MMR, as well as $\geq MR^{4.0}$, within approximately 3 months of re-initiating treatment. Therefore, patients with molecular recurrence during the TFR phase will be re-treated immediately with nilotinib 300 mg BID and will remain on study until they complete the 5-year study period.

No formal interim analyses are planned during the study; however, as this study will be overseen by a Data Monitoring Committee (DMC), DMC reports will be provided on a regular basis (see Section 8.6).

2.3 Rationale for dose and regimen selection

In the first 12 months following the switch from imatinib to nilotinib 400 mg BID treatment in the ENESTcmr study, 9% of patients discontinued due to AEs. It is therefore suggested that administration of the currently marketed nilotinib 300 mg BID dose will result in similar efficacy and fewer discontinuations in the current trial due to AEs. Additionally, administration of nilotinib 300 mg BID appears justified, as CML-CP patients on imatinib who have achieved CCyR but less than $MR^{4.0}$ are not considered to be treatment failure patients according to current treatment recommendations. The selection of the 300 mg BID dose is therefore considered appropriate in order to minimize the occurrence of AEs when moving from imatinib to nilotinib, and to provide the best long-term efficacy.

2.4 Rationale for choice of combination drugs

Not applicable.

[redacted]

2.5 Rationale for choice of comparators drug

Not applicable.

2.6 Rationale for optional Stem cells ENESTPath substudy

"Leukemic stem cells quantification in patients with chronic myelogenous leukemia included in the ENESTPath trial":

In two randomized studies ([CAMN107A2303] and [CAMN107A2405]), nilotinib has been shown to be significantly more effective than imatinib in inducing deep MR in CML-CP patients. In ENESTnd [CAMN107A2303], nilotinib allowed a higher number of newly diagnosed patients to achieve deeper MR ($MR^{4.0}$ or $MR^{4.5}$) compared to imatinib. In ENESTcmr [CAMN107A2405] in CML-CP patients after prolonged treatment with imatinib, twice as many patients in the nilotinib arm than in the imatinib arm achieved $MR^{4.5}$ after 12 months of treatment. It is then possible that a deeper MR is a marker for a decreased number or eradication of leukemic stem cells (LSC), and that subsequent relapse after treatment discontinuation may be correlated with the presence and/or the number of persisting LSC.

Taking this hypothesis into account, the focus of this substudy is to evaluate the importance of LSC (CD34+/CD38+ progenitor cells, CD34+/CD38− stem cells and CD34+/CD56+ aberrant stem cells [the last ones only if detectable]) in the long-term maintenance of the disease and their role in the relapse of patients in the TFR phase. This substudy is based on the possibility of detection and quantification of LSC and their progenitors by flow cytometry, and also the possible differential effect of nilotinib compared to imatinib in these cell populations (Defina et al 2012, Janssen et al 2012, Corbin et al 2011).

The hypothesis will be tested by:

1. Evaluating the presence and number of LSC and their progenitors in the bone marrow of all patients participating in this substudy before and after completing induction and the first year of the consolidation phase (at Visit 8).
2. Evaluating, by descriptive statistics, whether prolonging the treatment period of consolidation with nilotinib (patients in Arm 2) causes a reduction in the percentage of patients presenting LSC and progenitor cells in bone marrow at the end of the second year of the consolidation phase.
3. Performing an exploratory analysis in order to evaluate whether relapse in patients during the TFR phase in either arm correlates with the presence of LSC and progenitor cells in bone marrow at the end of the consolidation phase and at the time of relapse during TFR.

2.7 Rationale for 'CML patient's voice' Italian Substudy

The 'CML patient's voice' Italian substudy aims to examine patients' psycho-emotional characteristics, quality of life and experiences of being involved in CAMN107AIC05l trial and its discontinuation using the following mixed method design (qualitative-quantitative). This sub-study will be conducted in Italy only. [Post-text Supplement 1].

[redacted]

3 Objectives and endpoints

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

[redacted]

Table 3-1 Objectives and related endpoints

Objective	Endpoint	Analysis
Primary		Refer to Section 10.4.
To assess the optimal duration of consolidation treatment with nilotinib 300 mg BID in order that patients remain in TFR (≥$MR^{4.0}$) without molecular relapse 12 months after entering the TFR phase.	The number of patients who remain in TFR (≥$MR^{4.0}$) without molecular relapse at the end of 12 months in the TFR phase of the study, in the nilotinib 12-month consolidation treatment arm versus the nilotinib 24-month consolidation treatment arm. Molecular relapse during TFR is defined as the loss of MMR, or the confirmed loss of $MR^{4.0}$ (defined by 3 consecutive tests less than $MR^{4.0}$ assessed at 3 consecutive visits according to the visit schedule of the TFR phase) (see Section 4.1).	The proportion of patients who are in TFR (≥$MR^{4.0}$) without molecular relapse at the end of 12 months in the TFR phase will be calculated by dividing the number of patients who remain in ≥$MR^{4.0}$ at the end of 12 months in the TFR phase (without re-starting nilotinib therapy) by the number of patients who entered the TFR phase. A chi-square test will be applied to compare the two treatment arms.
Secondary		Refer to Section 10.5.
To evaluate the proportion of patients who are eligible to suspend nilotinib therapy by achieving and maintaining a sustained ≥$MR^{4.0}$ for at least 12 months during consolidation treatment with nilotinib 300 mg BID.	The proportion of patients who achieve a sustained ≥$MR^{4.0}$ (defined as having 4 out of 5 quarterly assessments of ≥$MR^{4.0}$ by a (EUTOS) standardized laboratory over the last 12 months and the last assessment before randomization is at least $MR^{4.0}$) during the consolidation phase of the study.	The proportion of patients who are in sustained ≥$MR^{4.0}$ at 24 months after completing the induction/consolidation phase will be calculated by dividing the number of patients who have achieved sustained ≥$MR^{4.0}$ over at least the last 12 months of the consolidation phase by the number of patients enrolled.

[redacted]

Objective	Endpoint	Analysis
To assess the achievement of MMR, $MR^{4\,0}$, and $MR^{4\,5}$ during induction/consolidation treatment with nilotinib 300 mg BID at the different time points in patients without that response at study entry.	The proportion of patients who achieve MMR, $MR^{4\,0}$, or $MR^{4.5}$ on the study at selected time points (every 3 months until Month 24 or Month 36 depending on the randomized arm) during the induction/consolidation phase of the study.	The proportion of patients who achieve MMR, $MR^{4\,0}$ or $MR^{4\,5}$ at selected timepoints during the induction/consolidation phase (every 3 months until Month 24 or Month 36 depending on the randomized arm) will be calculated by dividing the number of patients who are in MMR, $MR^{4.0}$ or $MR^{4\,5}$ by the number of patients without that response at baseline.
To assess the molecular response in patients during induction/consolidation treatment with nilotinib 300 mg BID at the different time points.	The proportion of patients who are in MMR, $MR^{4.0}$, or $MR^{4.5}$ on the study at selected timepoints (every 3 months until Month 24 or Month 36 depending of the randomized arm) during the induction/consolidation phase of the study.	The proportion of patients who are in MMR, $MR^{4.0}$, or $MR^{4\,5}$ at selected timepoints during the TFR phase (every 3 months until Month 24 or Month 36 depending on the randomized arm) will be calculated by dividing the number of patients who are in MMR, $MR^{4\,0}$, or $MR^{4\,5}$ by the number of enrolled patients.
To assess the proportion of patients in TFR at 3, 6, 12, 18 and 24 months after nilotinib cessation in the two treatment arms	The proportion of patients in TFR, i.e. with no confirmed loss of $MR^{4.0}$, no loss of MMR and no restarting of nilotinib therapy within the first 3, 6, 12, 18, and 24 months following nilotinib cessation.	The proportion of patients in TFR will be calculated by dividing the number of patients with no confirmed loss of $MR^{4\,0}$, no loss of MMR, and no re-starting of nilotinib therapy in the first 3, 6, 12, 18, and 24 months following nilotinib cessation by the number of patients who entered the TFR phase
To assess the molecular response in patients after randomization in the two treatment arms.	The proportion of patients who are in MMR, $MR^{4.0}$, or $MR^{4.5}$ at selected time points (at Month 3, 6, 12, and every 3 months thereafter until Month 24 or Month 36 depending on the randomized arm) during the TFR phase in each one of the two treatment arms.	The proportion of patients who are in MMR, $MR^{4.0}$, or $MR^{4\,5}$ at selected time points (at Month 3, 6, 12, and every 3 months thereafter until Month 24 or Month 36 depending on the randomized arm) will be calculated by dividing the number of patients who are in MMR, $MR^{4\,0}$ or $MR^{4.5}$ by the number of patients in the TFR phase in each one of the two treatment arms.
To assess the kinetics of BCR-ABL transcript during induction/consolidation treatment with nilotinib 300 mg BID	BCR-ABL transcript levels (IS) during the induction/consolidation phase	Descriptive statistics of BCR-ABL transcript levels (IS) over time during the induction/consolidation phase
To assess the kinetics of BCR-ABL transcript during the TFR phase in the two treatment arms	BCR-ABL transcript levels (IS) during the TFR phase	Descriptive statistics of BCR-ABL transcript levels (IS) over time during the TFR phase

[redacted]

Objective	Endpoint	Analysis
To assess the kinetics of BCR-ABL transcript during the nilotinib re-treatment phase	BCR-ABL transcript levels (IS) during the nilotinib re-treatment phase	Descriptive statistics of BCR-ABL transcript levels (IS) over time during the nilotinib re-treatment phase
To assess the progression-free survival (PFS) rate after randomization in the two treatment arms.	PFS is defined as progression to AP/BC or death from any cause, where the “failure” event is the earliest occurrence of either of these events.	Kaplan-Meier (KM) estimation of PFS. PFS is measured from the date of randomization to the date of the earliest failure event. Patients not known to have progressed or died on or before the cut-off date for the KM analysis will have their PFS 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 assess treatment-free survival (TFS) after start of the TFR phase in the two treatment arms.	TFS is defined as lack of any of the following events: loss of MMR, confirmed loss of $MR^{4.0}$, re-start of nilotinib treatment for any reason, progression to AP/BC, or death from any cause.	KM estimation of TFS, which is measured from the start of the TFR phase to the date of the earliest of the following: loss of MMR, confirmed loss of $MR^{4.0}$, (see Section 4.1) re-start of nilotinib treatment, progression to AP/BC, or death from any cause. Patients not known to have had any of the events on or before the cut-off date for the KM analysis will have their TFS censored at the earlier of the date of their last assessment (PCR, cytogenetic, hematology, or extramedullary) for patients who are still on study and the date of last contact for patients who are in follow-up.
To assess the overall survival (OS) rate after randomization in the two treatment arms.	Overall survival is defined as the time from randomization to the time of death due to any cause.	KM estimation of OS, which is measured from the date of randomization to the date of death due to any cause. For patients not known to have died on or before the cut-off date, survival time will be censored at the date of last contact.

Objective	Endpoint	Analysis
To assess the safety profile of nilotinib during the induction/consolidation phase, the TFR phase, and during the re-treatment phase.	Safety will be monitored through assessment of Adverse Events, laboratory data, ECG, vital signs.	Descriptive statistics on AEs, laboratory abnormalities, and clinically notable ECG and other safety parameters during the nilotinib induction/consolidation phase, during the TFR phase, and during re-initiation of treatment with nilotinib.
For those patients consenting to participate in the optional Stem cells ENESTPath substudy, the following objectives will be also applicable:	The following endpoints are applicable to all the objectives detailed for the optional Stem cells ENESTPath substudy:	
To evaluate the presence and number of LSC and their progenitors in the bone marrow of all patients participating in this substudy before and after completing induction and first year of consolidation phase (at Visit 8).	Proportion of patients with presence of Ph+ LSC in bone marrow (CD34+/CD38+ progenitor cells, CD34+/CD38− stem cells, and CD34+/CD56+ aberrant stem cells [the last ones only if detectable]) at screening and at Visit 8.	The percentage of patients presenting Ph+ LSC in bone marrow will be calculated at each time point and descriptively analyzed.
To evaluate whether prolonging the treatment period of consolidation with nilotinib (patients in Arm 2 versus patients in Arm 1) induces a reduction in the percentage of patients presenting LSC and progenitor cells in bone marrow at the end of the second year of the consolidation phase (Visit 204 for Arm 2 versus Visit 8 for Arm 1);	Proportion of patients with presence of Ph+ LSC in bone marrow (CD34+/CD38+ progenitor cells, CD34+/CD38− stem cells, and CD34+/CD56+ aberrant stem cells [the last ones only if detectable]) at the end of consolidation arm (Visit 8 for Arm 1 and Visit 204 for Arm 2).	Descriptive statistics.
To perform an exploratory analysis in order to evaluate whether relapse in patients during the TFR phase in either arm correlates with the presence of LSC and progenitor cells in bone marrow at the end of the consolidation phase and at the time of relapse during TFR.	Proportion of patients with or without molecular relapse in the first year of TFR in either arm by presence of LSC in bone marrow (CD34+/CD38+ progenitor cells, CD34+/CD38− stem cells, and CD34+/CD56+ aberrant stem cells [the last ones only if detectable]) at Visit 8 and at the time of relapse during TFR.	Descriptive statistics.

For the ‘CML patient’s voice’ Italian substudy please refer to [Post-text Supplement 1]

[redacted]

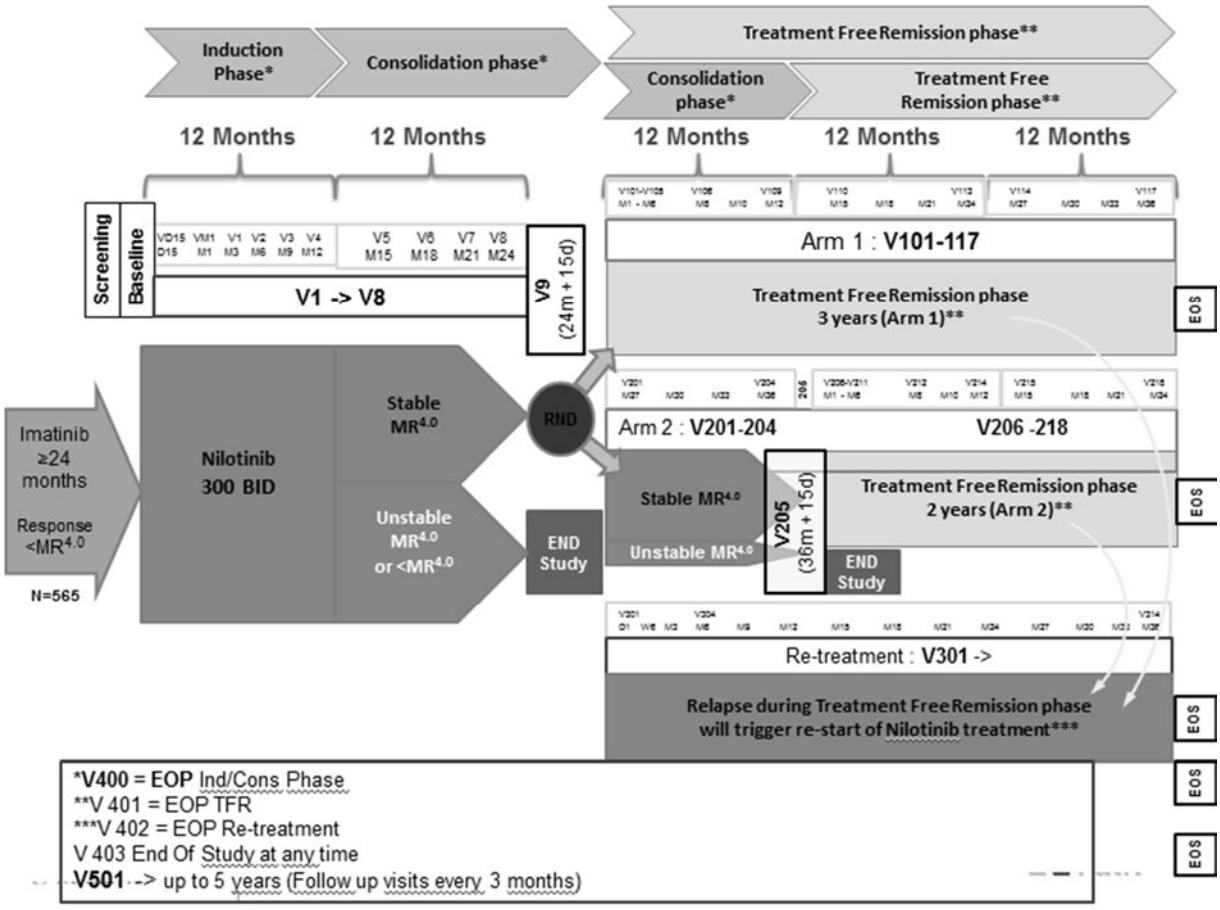
4 Study design

4.1 Description of study design

This is a prospective, randomized, open-label, multicenter, two-arm Phase III study aiming to assess the optimal duration of nilotinib 300 mg BID consolidation treatment, in order that patients remain in TFR ($MR^{4.0}$ or better [$\geq MR^{4.0}$]) 12 months after entering the TFR phase of the study.

The study design includes a 12-month induction phase, followed by a 12- or 24-month consolidation phase, and a 24- or 36-month TFR phase depending on randomization (Figure 4-1).

Figure 4-1 ENESTPath study design



Eligible patients are adults with a confirmed diagnosis of chronic phase Ph+ and/or BCR-ABL+ CML who have been treated with first-line imatinib for 24 months or more, and are at least in CCyR. Patients must not have achieved $\geq MR^{4.0}$ at study entry, as assessed by a EUTOS standardized laboratory.

[redacted]

Approximately 565 patients will be enrolled into the study and will be treated with nilotinib 300 mg BID for 24 months. Following 24 months of treatment, patients in sustained molecular response for at least the last 12 months will be randomized on a 1:1 basis to either:

- Suspend nilotinib treatment immediately and enter the TFR phase (the nilotinib 24-month treatment arm; Arm 1), or
- Continue nilotinib treatment for a further 12 months, then suspend treatment and enter the TFR phase (the nilotinib 36-month treatment arm; Arm 2).

Patients will be deemed to be in sustained molecular response if:

- Four out of the preceding five quarterly real-time quantitative polymerase chain reaction (RQ-PCR) assessments were $\geq MR^{4.0}$, and
- The last assessment was $\geq MR^{4.0}$.

Patients not achieving a sustained molecular response at 24 months from treatment start (and subsequently at 36 months from treatment start depending on the randomization arm) will exit the study and will be treated at the discretion of the investigator according to standard practice. Information on survival, stem cell transplantation, status of the patient's disease (i.e. disease progression to AP/BC according to protocol definition, TKI treatment) will be collected until death or until 5 years from study entry, whichever comes first.

Patients relapsing during the TFR phase will enter the nilotinib re-treatment phase of the study and will be re-treated with the same dose of nilotinib as they were on before the TFR phase (i.e. the re-treatment dose will be nilotinib 300 mg BID or a lower dose of nilotinib if the dose was reduced in the consolidation phase before entering the TFR phase). The patient will subsequently remain on study until the completion of the 5-year study period.

Relapse is defined as the loss of MMR, or the confirmed loss of $MR^{4.0}$ (defined by three consecutive tests less than $MR^{4.0}$ assessed at three consecutive visits according to the visit schedule of the TFR phase). If during the three consecutive tests, one of the tests shows loss of MMR, this patient will be declared as relapsing and will start the nilotinib re-treatment phase immediately even if the definition of confirmed loss of $MR^{4.0}$ is not yet fulfilled.

Loss of MMR is considered a more clinically relevant criterion for re-initiating nilotinib treatment than loss of $MR^{4.0}$ due to the anticipated fluctuations in BCR-ABL transcript levels at low levels without systematic rise in patients with minimal residual disease.

4.1.1 Description of optional Stem cells ENESTPath substudy

The Stem cells ENESTPath substudy adds the determination of Ph+ stem cells in bone marrow at the following time points, in patients providing separate specific consent to participate in the substudy (Figure 4-2):

a) During the screening, before starting nilotinib 300 mg BID treatment

b) After 2 years of nilotinib treatment at Visit 8

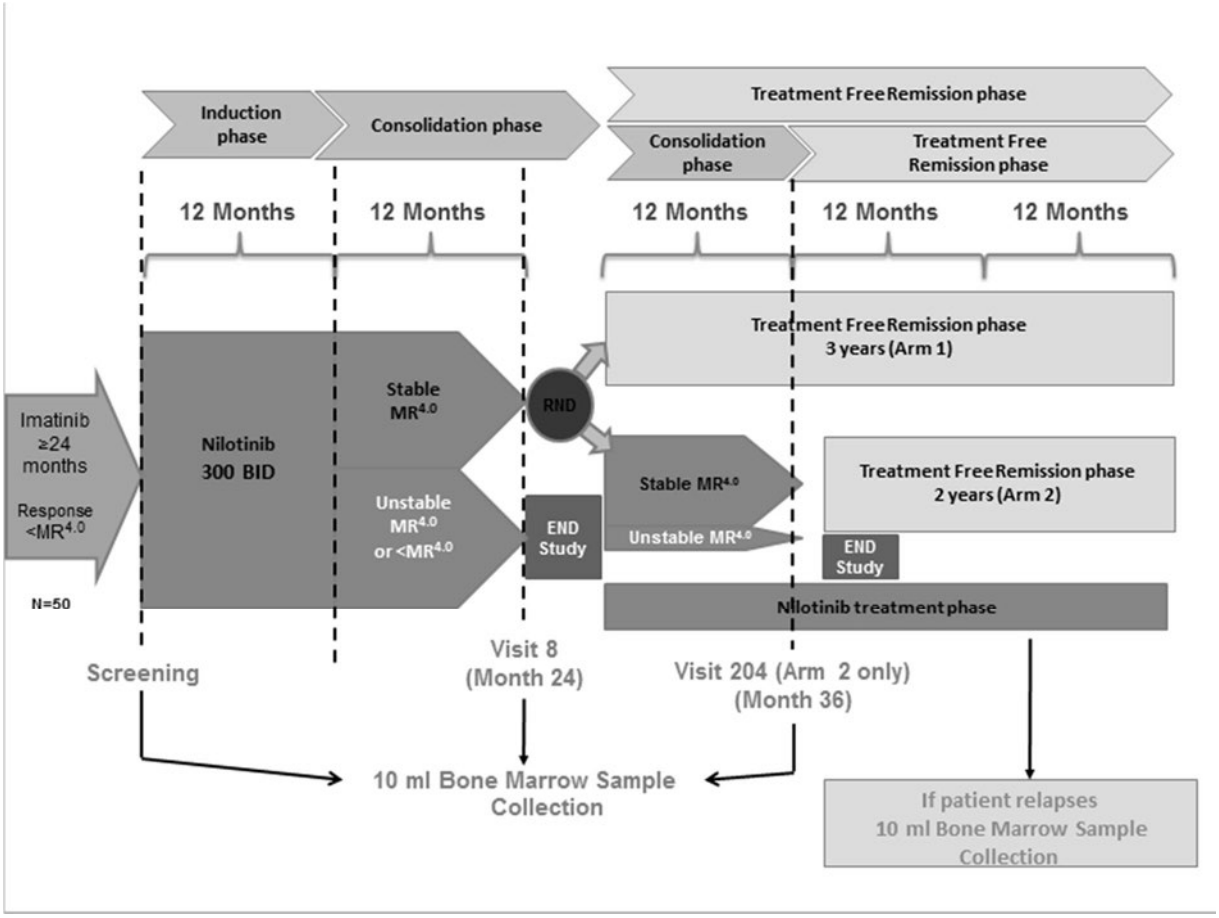
c) After 3 years of nilotinib treatment, only in patients with 2 years of consolidation treatment (Arm 2) at Visit 204

d) If the patient relapses during the TFR phase, before re-starting the treatment with nilotinib

[redacted]

A 10-mL bone marrow sample will be obtained and sent to [redacted] for immunophenotype analysis, FACS cell purification, fluorescent *in situ* hybridization (FISH) and RT-PCR. Measurement will be performed by flow cytometry in a bone marrow purified population of stem cells in order to detect the presence of leukemic Ph+ cells (evaluated by FISH) or BCR-ABL transcripts (evaluated by RT-PCR).

Figure 4-2 Optional Stem cells ENESTPath substudy design



4.1.2 Description of 'CML patient's voice' Italian substudy

Italian CAMN107AIC05 patients in consolidation phase consenting to participate will be included in the 'CML patient's voice' Italian substudy. See [Post-Text Supplement 1]

4.2 Timing of interim analyses and design adaptations

No formal interim analyses are planned. 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.

[redacted]

As this study will be overseen by a Data Monitoring Committee (DMC), DMC reports will be provided on a regular basis.

Should a predetermined number of patients fulfill the criteria of molecular relapse within the TFR phase, the further conduct of the study will be evaluated by the DMC. Any events of progression to AP/BC, loss of CCyR, or failure to regain MMR in case of re-initiation of treatment for molecular recurrence will be closely monitored by the Novartis Clinical Trial Team and the DMC during the entire TFR phase. General stopping rules during the first 12 months of the TFR phase have been predetermined and are presented in Section 4.4.

4.3 Definition of end of the study

The study will continue until the last patient who was eligible for randomization has completed 5 years from study entry, or has been withdrawn from the study. The total maximal study duration is therefore 5 years for every patient.

4.4 Early study termination

Predefined stopping rules during the first 12 months of the TFR phase will trigger an immediate DMC teleconference. It is the DMC's responsibility to take the final decision on the conduct of this trial.

The stopping rules are based on the frequency of specific events occurring in the ENESTnd study [CAMN107A2303]. It is considered crucial that patients treated on this study have outcomes during the TFR phase that are comparable or better than those of patients who were treated with continuous nilotinib therapy (300 mg BID or 400 mg BID) in the ENESTnd study [CAMN107A2303].

Therefore, the following stopping rules for this study will apply to the first 12 months of the TFR phase:

1. More than 2 cases of progression to AP/BC, or
2. More than 2 cases of loss of CCyR without re-achievement of CCyR within 6 months of nilotinib re-treatment, or
3. More than 9 cases of loss of MMR without re-achievement of MMR within 3 months of nilotinib re-treatment

and despite full compliance with BCR-ABL monitoring during the TFR phase for all three groups described above and despite full compliance with nilotinib treatment during the nilotinib re-treatment phase for groups 2 and 3 (patients with loss of CCyR and patients with loss of MMR) according to protocol.

Novartis can terminate the study at any time for appropriate reasons. Should this be necessary, the patient should be seen as soon as possible, and the same assessments should be performed as described in Section 7.1.8 for a prematurely withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing IRBs and/or IECs of the early termination of the trial.

[redacted]

5 Population

5.1 Patient population

The study population will consist of adult patients (male or female, aged ≥18 years) with a confirmed diagnosis of chronic phase Ph+ and/or BCR-ABL+ CML who have been treated first-line with imatinib for 24 months or more, and are at least in CCyR. Patients who have previously discontinued imatinib could be enrolled in the trial provided that they have been treated with imatinib for 24 months (even not continuously) in total and are in imatinib treatment at the time of enrollment. Patients must not have achieved ≥$MR^{4.0}$ at study entry, as confirmed by a EUTOS standardized laboratory with validated PCR technology.

The investigator or designee must ensure that only patients who meet all of the following inclusion and none of the exclusion criteria are offered enrollment into the study. Written informed consent must be obtained prior to any screening procedures. All data for the inclusion/exclusion criteria must be verifiable in the patient's source documents.

Patients enrolled into this study are not permitted to participate in additional parallel investigational drug or device studies.

Optional Stem cells ENESTPath substudy

The study population in the Stem cells ENESTPath substudy will consist of those patients participating in the ENESTPath trial who consent to participate in this substudy and who sign separate specific informed consent for the stem cells substudy.

There is no cap on patient accrual in each single center; accrual is competitive and will continue until the target patient number based on statistical sample size calculation is achieved.

'CML patient's voice' Italian substudy

Italian CAMN107AIC05 patients in consolidation phase consenting to participate will be included in this substudy. [Post-text Supplement 1]

5.2 Inclusion criteria

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

1. Male or female patients, aged ≥ 18 years
2. Eastern Cooperative Oncology Group (ECOG) performance status of 0-2
3. Documented confirmed diagnosis of chronic phase Ph+ and/or BCR-ABL+ CML-CP. Documented chronic phase CML must meet all of the following criteria:
   - < 15% blasts in peripheral blood and bone marrow
   - < 30% blasts plus promyelocytes in peripheral blood and bone marrow
   - < 20% basophils in the peripheral blood
   - ≥ 100 x 10^9/L (≥ 100,000/mm^3) platelets
   - No evidence of extramedullary leukemic involvement, with the exception of hepato- and/or splenomegaly

[redacted]

4. Previous first-line treatment with imatinib for a minimum of 24 months (even not continuously) in total and in imatinib treatment at time of enrollment
5. Patient in CCyR (A patient with MMR is considered to be in CCyR. Therefore, cytogenetic response [CgR] assessment has to be done if a patient has less than MMR in the local laboratory result and/or in the blood sample that was sent to the EUTOS standardized laboratory at the screening visit [patient will be considered screening failure if not in CCyR] see Section 7.1.2 for details);
6. Adequate end-organ function as defined by:
   - Total bilirubin < 1.5 x upper limit of normal (ULN). Does not apply to patients with isolated hyperbilirubinemia (e.g. Gilbert's disease) grade < 3
   - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3 x ULN
   - Serum lipase ≤ 2 x ULN
   - Alkaline phosphatase ≤ 2.5 x ULN
   - Serum creatinine < 1.5 x ULN
7. Patients must have the following electrolyte values within normal limits at screening analysis, or corrected to within normal limits with supplements prior to the first dose of study medication:
   - Potassium
   - Magnesium
   - Total calcium
8. Patients must have normal marrow function as defined below:
   - Absolute Neutrophil Count (ANC) ≥ 1.5 x 10^9/L
     - With the exception of people of North African descent for whom the threshold for ANC will be ≥ 1.0 x 10^9/L due to an increase in the marginal pool of neutrophils
   - Hemoglobin ≥ 9.0 g/dL
   - Platelets ≥ 100 x 10^9/L
9. Willingness and ability to comply with scheduled visits, treatment plans, laboratory tests, and other study procedures;
10. Written informed consent must be obtained prior to any screening procedures.

For those patients consenting to participate in the optional Stem cells ENESTPath substudy or in the 'CML patient's voice' Italian substudy, the same inclusion criteria for the ENESTPath study will be applicable, plus the following:

- Separate specific written informed consent for the Stem cells ENESTPath substudy or for the 'CML patient's voice' Italian substudy must be obtained before starting any sub-study related assessment like but not limited to extraction of additional bone marrow samples for stem cells sub-study.

[redacted]

5.3 Exclusion criteria

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

1. Achievement of $\geq MR^{4.0}$ at study entry as assessed by a EUTOS standardized laboratory
2. Previous treatment with BCR-ABL inhibitors other than imatinib
3. Patients with detectable atypical BCR-ABL transcripts, defined as absence of typical BCR-ABL transcripts for CML of the types b2(e13)-a2 or b3(e14)-a2 or both simultaneously documented at CML diagnosis or at any time before the screening procedure
4. Previous anticancer agents for CML except for:
   - Imatinib, and/or
   - Cytoreduction after CML diagnosis, and/or
   - Interferon for less than 1 year
5. Known second chronic phase of CML after previous progression to AP/BC
6. Known impaired cardiac function, including any of the following:
   - Inability to determine the QT interval on ECG
   - Complete left bundle branch block
   - Right bundle branch block plus left anterior or posterior hemiblock
   - Use of a ventricular-paced pacemaker
   - Congenital long QT syndrome or a known family history of long QT syndrome
   - History of or presence of clinically significant ventricular or atrial tachyarrhythmias
   - Clinically significant resting bradycardia (< 50 beats per minute)
   - QTc > 450 msec confirmed on the average of three serial baseline ECGs (using the QTcF formula). If QTcF > 450 msec and electrolytes are not within normal ranges, electrolytes should be corrected and the patient re-tested for the QTc
   - History of clinically documented severe peripheral occlusive disease or severe ischemic cardiovascular disease (e.g. myocardial infarction, ischemic cerebral vascular disease) whenever in the opinion of the investigator other treatments could have a more favorable benefit/risk profile.
   - Other clinically significant heart disease (e.g. congestive heart failure or uncontrolled hypertension)
7. Severe and/or uncontrolled concurrent medical disease that in the opinion of the investigator could cause unacceptable safety risks or compromise compliance with the protocol (e.g. uncontrolled diabetes, active or uncontrolled infection, uncontrolled severe hypertension, or uncontrolled severe dyslipidemia). If appropriate measures (e.g. diet, exercise, appropriate therapy) are taken to control blood glucose or cholesterol (LDL) levels or hypertension, the patient can be re-screened for the study
8. History of acute pancreatitis within 12 months of study entry, or a past medical history of chronic pancreatitis
9. Known presence of significant congenital or acquired bleeding disorder unrelated to cancer

[redacted]

10. History of other active malignancy within 5 years prior to study entry with the exception of previous or concomitant basal cell skin cancer, or previous cervical carcinoma in situ treated curatively;
11. Patients who have not recovered from prior surgery
12. Treatment with other investigational agents within 30 days of Day 1
13. Patients actively receiving therapy with strong CYP3A4 inhibitors (see link for complete list of these medications: medicine.iupui.edu/flockhart/table.htm or Appendix 14.1) and/or inducers or medications that have the potential to prolong the QT interval (see http://crediblemeds.org/everyone/composite-list-all-qtdrugs/?rf=All) that cannot be either discontinued or switched to a different medication prior to starting study drug
14. Impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of study drug
15. Patients who are: (a) pregnant, (b) breast feeding, (c) of childbearing potential without a negative pregnancy test prior to baseline and (d) female of childbearing potential unwilling to use contraceptive precautions throughout the trial (post-menopausal women must be amenorrheic for at least 12 months to be considered of non-childbearing potential)
16. Women of childbearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 14 days after the final dose of nilotinib or imatinib. Patients using an oral hormonal contraception method should complete their monthly treatment course. Highly effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
    - Female sterilization (surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least 6 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). For female subjects on the study, the vasectomized male partner should be the sole partner for that subject
    - Combination of any two of the following (a+b or a+c, or b+c):
        a. Use of oral, injected, or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate < 1%), e.g. hormone vaginal ring or transdermal hormone contraception;
        b. Placement of an intrauterine device (IUD) or intrauterine system (IUS);
        c. Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository.

      In case of use of oral contraception, women should have been stable on the same pill for a minimum of 3 months before taking study treatment
17. Patients not able to understand and comply with study instructions and requirements

For those patients consenting to participate in the optional Stem cells ENESTPath substudy or in the 'CML patient's voice' Italian substudy, the same exclusion criteria as for the ENESTPath study will apply.

[redacted]

6 Treatment

6.1 Investigational treatment, other study treatment, supportive treatment

Study treatment: nilotinib (AMN107, Tasigna®)

Nilotinib will be supplied as 150 mg hard gelatin capsule. Nilotinib will not be dosed by weight or body surface area.

For detailed safety information, refer to the latest [AMN107 Investigator Brochure] and the approved product labeling.

6.1.1 Dosing regimen

This is an open-label study; therefore, all patients will receive a daily oral nilotinib dose of 300 mg BID, given as two 150 mg capsules BID.

Patients eligible for randomization will either enter the TFR phase immediately or continue nilotinib for an additional 12 months (on a 1:1 basis).

Patients relapsing during the TFR phase will enter the nilotinib re-treatment phase of the study, and will be re-treated with the same dose of nilotinib as they were on before the TFR (i.e., the re-treatment dose will be nilotinib 300 mg BID or a lower dose of nilotinib if the dose was reduced in the consolidation phase before entering the TFR phase). The patient will subsequently remain on study until the patient completes the 5-year study period.

Nilotinib doses should be taken approximately 12 hours apart and must not be taken with food. The capsules should be swallowed whole with water. No food should be consumed for 2 hours before the dose is taken and for at least 1 hour after.

For patients who are unable to swallow capsules, the content of each capsule may be dispersed in one teaspoon of apple sauce (puréed apple) and should be taken immediately. No more than one teaspoon of applesauce and no other food substance must be used.

The dose regimen can be decreased to 450 mg QD in the case of study drug-related non-hematologic and hematologic toxicities. Refer to Section 6.3.2 and Section 6.3.3 for further details.

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

6.1.2 Ancillary treatments

Not applicable.

6.1.3 Rescue medication

Not applicable.

[redacted]

6.1.4 Guidelines for continuation of treatment

In the 12-month induction phase and the subsequent 12- or 24-month consolidation phase of the study, patients may continue treatment until they progress, withdraw consent, experience unacceptable toxicity or start new therapy, or it is believed by the investigator to be in the best interest of the patient to exit the study.

Patients not achieving a sustained molecular response at 24 months from treatment start (and subsequently at 36 months from treatment start dependent of the randomization arm) will exit the study and will be treated at the discretion of the investigator according to standard practice. Survival information, stem cell transplantation, and information on the status of the patient's disease (i.e., disease progression to AP/BP according to protocol definition, TKI treatment) will be collected until death, progression, or until 5 years from study entry, whichever comes first.

Patients relapsing during the TFR phase will enter the nilotinib re-treatment phase of the study, and will be re-treated with the same dose of nilotinib as they were on before the TFR phase (i.e. the re-treatment dose will be nilotinib 300 mg BID or a lower dose of nilotinib if this was reduced in the consolidation phase before entering the TFR phase). The patient will subsequently remain on study until the completion of the 5-year study period.

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

6.1.5 Treatment duration

All patients will initially receive 24 months of nilotinib treatment unless they experience unacceptable toxicity, disease progression or withdrawal of consent, and/or treatment is discontinued at the discretion of the investigator.

Following these 24 months of treatment, patients in sustained $\geq MR^{4.0}$ (as defined in Table 3-1) for at least the last 12 months will be randomized to either suspend treatment immediately or receive a further 12 months of nilotinib therapy.

Patients not achieving a sustained molecular response at 24 months from treatment start (and subsequently at 36 months from treatment start depending on the randomization arm) will exit the study and will be treated at the discretion of the investigator according to standard practice. Survival information, stem cell transplantation, and information on the status of the patient's disease (i.e., disease progression to AP/BC according to protocol definition, TKI treatment) will be collected until death, progression, or 5 years from study entry, whichever comes first.

Patients relapsing during the TFR phase will enter the nilotinib re-treatment phase of the study, and will be re-treated with the same dose of nilotinib as they were on before the TFR phase (i.e., the re-treatment dose will be nilotinib 300 mg BID or a lower dose of nilotinib if the dose was reduced in the consolidation phase before entering the TFR phase). The patient will subsequently remain on study until the patient completes the 5-year study period.

6.2 Dose escalation guidelines

Not applicable.

[redacted]

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 AE that is, with reasonable likelihood according to investigator's judgment, caused by the study drug.

According to International Conference on Harmonization (ICH) E6, the investigator is responsible for all trial-related medical decisions.

During and following a patient's participation in a trial, the investigator should ensure that adequate medical care is provided to a patient for any AEs, including clinically significant laboratory values, related to the study drug. Any dose change must be recorded on the Dosage Administration Record Electronic Case Report Form (eCRF).

Dose escalation above the study dose of 300 mg BID (total 600 mg) nilotinib is not allowed. Dose 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.

If a dose reduction to 450 mg daily is required, the dose should be taken as 300 mg in the evening and 150 mg in the morning. If a dose reduction to 300 mg daily is required, the dose should be taken as 300 mg in the evening.

If multiple toxicities that require dose reduction are present, the greatest dose reduction schedule should be applied.

6.3.2 Dose-reduction guidelines for study drug-related non-hematologic toxicity

A summary of dose-reduction guidelines for study drug-related clinically significant non-hematologic toxicity is presented in Table 6-2.

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

However, for those toxicities detailed in Table 6-2, the following rules (as detailed in the bullet points below) must be strictly followed:

- Any non-hematological toxicity Grade 3 or 4 must be resolved within 28 days to ≤ Grade 2 in order to resume study drug at the reduced dose. If a non-hematological toxicity Grade 3 or 4 does not resolve after 28 days, the patient must be discontinued from the study
- If Grade 4 toxicity of the same type recurs despite dose reduction to 450 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

[redacted]

- 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 from the study unless the reason for QTcF prolongation can be corrected (such as discontinuing or replacing QT-prolonging concomitant drugs)

Patients who experience Grade 2/3/4 ischemic vascular or cardiovascular events should be referred for a cardiac or cardiovascular consult and management decisions (e.g. continue current treatment, dose reduction, or study discontinuation). Patients should be assessed for potential risk factors for the event, including causality secondary to CML therapy.

The Scientific Study Management Committee (SSMC) and DMC will be informed on a regular basis about the Grade 2/3/4 ischemic vascular or cardiovascular events occurring in patients enrolled in the CAMN107AIC05 trial.

[redacted]

Table 6-2 Summary of dose reduction guidelines for study drug-related clinically significant non-hematologic toxicity

Study drug and dose	**Nilotinib 600 mg daily (as 300 mg BID)**
General non-hematologic toxicity	
Grade 2 (persisting > 7 days with optimal supportive care)	The dose of nilotinib may be reduced to 450 mg daily at the discretion of the investigator if clinically appropriate and in the best overall interest of the patient
≥ Grade 3	Hold therapy and resume nilotinib at next lower dose level after recovery to ≤ grade 2 is seen l→ 450 mg daily. If recovery to ≤ grade 2 takes longer than 28 days, the patient must be discontinued from the study. If grade 4 toxicity recurs despite dose reduction to 450 mg daily l→ discontinue from the study.
Serum hypophosphatemia	
Grade 2/3	Continue nilotinib at 300 mg BID and start phosphate supplementation.
Grade 4	Hold therapy and consult Novartis.
Serum creatinine	
Grade 2 > 1.5-3.0 x ULN	The dose of nilotinib may be reduced to 450 mg daily 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 l→ 450 mg daily. If recovery to ≤ grade 2 takes longer than 28 days, the patient must be discontinued from the study. If grade 4 toxicity recurs despite dose reduction to 450 mg daily l→ discontinue from the study.
Hepatobiliary [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, alkaline phosphatase ALP ≤ grade 1, and hemolysis has been ruled out per institutional guidelines (e.g. by determination of haptoglobin), nilotinib may be continued at the same dose, at the discretion of the investigator.	
Grade 2	The dose of nilotinib may be reduced to 450 mg daily at the discretion of the investigator if clinically appropriate and in the best overall interest of the patient.
≥ Grade 3	Hold study drug and resume nilotinib at next lower dose level after recovery to ≤ grade 2 is seen l→ 450 mg daily. If recovery to ≤ grade 2 takes longer than 28 days, the patient must be discontinued from the study If grade 4 toxicity recurs despite dose reduction to 450 mg daily l→ discontinue from the study.

[redacted]

Study drug and dose	**Nilotinib 600 mg daily (as 300 mg BID)**
Pancreatitis (with abdominal symptoms plus lipase elevation)	
Grade 2	Hold study drug and perform abdominal CT with contrast to exclude pancreatic pathology. If CT is positive, continue to hold therapy and repeat CT at investigator's discretion. If CT is negative, re-start nilotinib at 450 mg daily after recovery to ≤ grade 1 is seen. If recovery to ≤ grade 1 take longer than 28 days, the patient must be discontinued from the study. If toxicity recurs l→ discontinue from the study.
Grade 3	Hold therapy 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 450 mg daily after recovery to ≤ grade 2 is seen. If recovery to ≤ grade 2 takes longer 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, l→ continue dosing at 450 mg daily based on investigator's discretion.
Diarrhea **Note**: Antidiarrheal medication is recommended at the first sign of loose stools or overt diarrhea. If diarrhea cannot be controlled with optimal antidiarrheal treatments, take the following actions:	
≥ Grade 3	Hold study drug and resume nilotinib at next lower dose level after recovery to ≤ grade 2 is seen l→ 450 mg daily. If recovery to ≤ grade 2 takes longer 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 interval, such as domperidone, must be avoided. If nausea and vomiting cannot be controlled with optimal antiemetic treatment, take the following actions:	
≥ Grade 3	Hold study drug and resume nilotinib at next lower dose level after recovery to ≤ grade 2 is seen l→ 450 mg daily. If recovery to ≤ grade 2 takes longer than 28 days, the patient must be discontinued from the study.

[redacted]

Study drug and dose	**Nilotinib 600 mg daily (as 300 mg BID)**
Skin rash **Note**: Institute symptomatic therapy as appropriate. If skin rash does not resolve with optimal treatments, take the following actions:	
Grade 2	The dose of nilotinib may be reduced to 450 mg daily at the discretion of the investigator if clinically appropriate and in the best overall interest of the patient.
≥ Grade 3	Hold study drug and resume nilotinib at next lower dose level after recovery to ≤ grade 2 is seen l→ 450 mg daily. If recovery to ≤ grade 2 takes longer than 28 days, the patient must be discontinued from the study. If grade 4 toxicity recurs despite dose reduction to 450mg daily l→ discontinue.
Cardiac QTc prolongation	
QTcF > 480 msec	Hold study drug when an ECG shows 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 1 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 re-started, 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. ECGs must be repeated 7 days after dose re-start for all patients who had therapy held due to QTcF > 480 msec. 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 450 mg daily If QTcF of > 480 msec recurs or QTcF > 500 msec or prolongation of 60 msec to baseline value occurs, the patient is to be discontinued. The investigator should contact Novartis regarding any questions that arise if a patient with QTcF prolongation should be maintained on study. **Note**: QTcB can be used in centers that do not have the ability to automatically measure QTcF for QTc prolongation. In patients with a heart rate lower than 60 beats per minute, decisions are always based on QTcF because QTcB underestimates QT interval prolongation at heart rates below 60 beats per minute.

[redacted]

Study drug and dose	**Nilotinib 600 mg daily (as 300 mg BID)**
Ischemic vascular or cardiovascular events	
Grade 2*	Hold study drug and refer patient for assessment by a vascular or cardiovascular specialist. Resume nilotinib next lower dose level after recovery to ≤ grade 1 is seen l→ 450 mg daily. If another recurrence l→ discontinue. If recovery to ≤ grade 1 takes longer 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. Patients have to be discontinued whenever in the opinion of the investigator the AE is related to the study drug and other treatments could have a more favorable benefit/risk profile
* Patient should be assessed for potential risk factors for the event, including causality secondary to CML therapy	
Cardiac "other"	
Grade 2 or grade 3	Hold study drug and resume nilotinib at next lower dose level after recovery to ≤ grade 1 is seen l→ 450 mg daily. If recovery to ≤ grade 1 takes longer than 28 days, the patient must be discontinued from the study. If grade 3 toxicity recurs despite dose reduction to 450mg daily l→ discontinue.
Grade 4	Stop therapy. The patient must be discontinued from study.

6.3.3 Dose-reduction guidelines for study drug-related hematologic toxicity

A summary of dose-reduction guidelines for ≥ grade 3 study drug-related hematologic toxicity as determined by the investigator is presented in Table 6-3.

No dose adjustments should be made for grade 1 or 2 hematologic toxicities. Any hematologic toxicity must be resolved to < grade 3 within 28 days in order to resume study drug. These guidelines provide some general principles as well as recommendations that are intended to support the investigator's judgment and decision about the appropriate management of toxicity in the individual patient. However, if a hematologic toxicity does not resolve to ≤ grade 2 within 28 days, the investigator should consult with the SSMC. Grade 1 or 2 hematologic AEs should not automatically be reported as serious AEs (SAEs) unless the event meets the criteria of a SAE as per the protocol.

In the case of any SAEs with a suspected causal relationship to study treatment, it should be reported as a SAE, nilotinib treatment may be discontinued, and the SSMC should be contacted for advice on patient management.

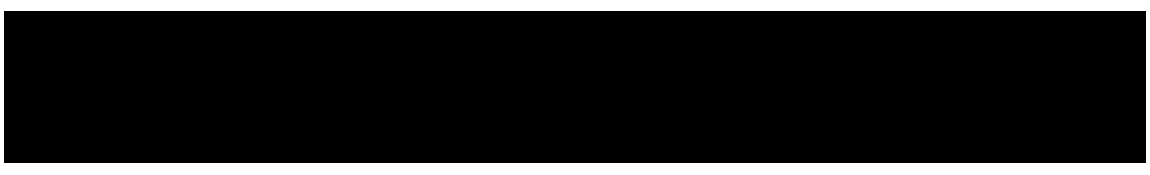


Table 6-3 Summary of dose reduction guidelines for study drug-related hematologic toxicity

Toxicity	Grade 1	Grade 2	Grade 3 Grade 4
ANC or platelets	• No dose reduction	• No dose reduction	• Grade 3/4 first and second time: Stop nilotinib, check at least weekly, resume 600 mg daily dose when < grade 3 (ANC > 1.0 x 10^9/L; platelets > 50 x 10^9/L) • Grade 3/4 third time: Stop nilotinib, check at least weekly, resume nilotinib at 450 mg daily dose when < grade 3 and at 600 mg daily dose after 1 week • Grade 3/4 fourth time: Stop nilotinib, check at least weekly, resume nilotinib at 300 mg daily dose when < grade 3 and at 600 mg daily dose after 1 month • Grade 3/4 fifth or subsequent time: Stop nilotinib until < grade 3, then contact Novartis. It will be discussed with the SSMC whether nilotinib can be resumed or should be discontinued permanently

6.3.4 Suggested management of selected adverse events

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

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 systemic corticosteroids may be initiated for the management of more severe cases, and may be continued until rash has resolved.

Management of edema

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

Management of liver toxicity

Routine liver function tests 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 6-2).

[redacted]

Dose modification for patients on anticoagulants

For patients on treatment with anticoagulants, the following guidelines will apply for thrombocytopenia:

- If platelets ≤ 50 x 10^9/L, withhold treatment with study drug until recovery to at least > 75 x 10^9/L and resume treatment at same dose
- If recurrence of platelets ≤ 50 x 10^9/L, then withhold treatment until recovery to at least > 75 x 10^9/L and resume treatment to a minimum of 300 mg/day
- If the platelet count remains below 75 x 10^9/L, then nilotinib should be discontinued or management with anticoagulation therapy re-evaluated at the discretion of the investigator.

Every time TKI treatment has to be changed, international normalized ratio (INR) should be checked at least twice weekly until stable INR values are established.

Management of cholesterol increases

Blood lipid panel tests should be performed at baseline and throughout the study as indicated in the visit schedule. If test results warrant intervention, investigators should follow their local standards of practice or treatment guidelines, which may recommend treatment even for grade 1 cholesterol elevation. Before prescribing a lipid-lowering medication, the possibility of drug-drug interactions should be considered as some HMG-CoA reductase inhibitors are also metabolized via the CYP3A4 pathway.

Management of glucose increases

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

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.

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 AE, 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.

[redacted]

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.

Follow-up for toxicities

Patients whose treatment is permanently discontinued due to a study drug-related AE or abnormal laboratory value must be followed at least once a week for 4 weeks until resolution or stabilization of the event, whichever comes first.

All patients will be followed for serious adverse events (SAEs) for 30 days following premature discontinuation from any phases of the study or following end of participation as per protocol.

6.3.5 Guidelines for dose-re-escalation

Re-escalation of the dose of nilotinib to the 300 mg BID is permitted at the discretion of the investigator. This applies to either dose reductions due to hematological or non-hematological toxicities if the following criterion is met at least 28 days on treatment on the reduced dose.

- All ≥ Grade 3 toxicities have resolved to ≤ Grade 2

6.4 Concomitant medications

6.4.1 Permitted concomitant therapy

In general, concomitant medications and therapies deemed necessary for the supportive care and safety of the patient are allowed, provided their use is documented in the patient records and on the appropriate case report form, including the medication's duration (start and end dates or if continuing at final visit). These include blood and platelet transfusions for patients with anemia and with thrombocytopenia. 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 and blood transfusions) administered during the study must be listed on the Prior and Concomitant Medications/Significant Non-Drug Therapies eCRF section.

The routine use of systemic corticosteroid therapy, except dexamethasone (as it is a strong CYP3A4 inducer), is permitted.

The use of prophylactic medication for vomiting is not recommended; however, antiemetic medication can be used as clinically indicated or when in the patient's best interest.

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

[redacted]

The use of hormonal contraception is permitted.

6.4.2 Permitted concomitant therapy requiring caution and/or action

The use of therapeutic coumarin derivatives (i.e. warfarin, acenocoumarol, phenprocoumon) is permitted; however, these should be given with caution. Low molecular weight heparin and heparin may be substituted for coumarin, and other medications for anticoagulation should be considered.

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

Cytochrome P450 3A4 substrates

Nilotinib is a moderate CYP3A4 inhibitor *in vivo*. Because of the thepotential risk for drug-drug interactions, the systemic exposure of other drugs known to be sensitive substrates of CYP3A4 and also to have a narrow therapeutic index should be used with caution. A list of these drugs is listed in Appendix 14.1.1.

Antacid drugs:

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

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

6.4.3 Prohibited concomitant therapy

The concomitant administration of investigational drugs other than nilotinib is not allowed. The administration of any other anticancer agents, including chemotherapy and biologic agents, is not permitted except for anticancer treatments of newly diagnosed solid cancers (e.g. prostate cancer) that would not impact the level of minimal residual disease of patients. These patients may remain in study after consultation with Novartis.

The administration of other TKIs 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 the medication 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 14.1.1; however, this list may not be comprehensive.

[redacted]

Every effort should be made NOT to administer a QT interval-prolonging agent during the study. If when a patient is on nilotinib treatment, concomitant administration of an agent known to prolong the QT interval is required and cannot be switched to an alternative therapy, nilotinib must be STOPPED. Please see http://crediblemeds.org/everyone/composite-list-all-qtdrugs/?rf=All for a list of agents that prolong the QT interval (this list may not be comprehensive).

Cardiac monitoring is required upon re-initiation of nilotinib therapy at any point. Triplicate ECGs must be obtained before treatment re-initiation and 4 weeks after re-initiation of nilotinib therapy.

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

6.5 Patient numbering, treatment assignment and randomization

6.5.1 Patient numbering

Each patient is identified in the study by a patient number (Patient 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 Patient 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 (ICF), the patient is assigned to the next sequential Patient No. available to the investigator through the Oracle Clinical RDC interface. Once assigned, the Patient No. must not be reused for any other subject, and the Patient No. for that individual must not be changed, even if the patient is re-screened.

If the patient fails to be randomized for any reason, the reason will be entered into the End of Consolidation Phase page.

6.5.2 Treatment assignment and randomization

All patients will initially receive 24 months of open-label nilotinib treatment. Following this, eligible patients (i.e., those deemed to have achieved sustained $\geq MR^{4.0}$) will be randomized to one of the two study arms (see Section 4.1 and Section 6.1) in a ratio of 1:1 on a continued open-label basis.

A randomization list will be produced by or under the responsibility of Novartis using a validated system that automates the random assignment of treatment groups to randomization numbers in the specified ratio.

6.5.3 Treatment blinding

This is an open-label trial and blinding is not applicable.

[redacted]

6.6 Study drug supply

6.6.1 Study drug preparation and dispensation

No specific preparation instructions are applicable to nilotinib. The investigational agent will be dispensed by site study personnel on an outpatient basis (see Table 6-4 for details). Patients will be instructed on how to take study medication, and will be provided with an adequate supply of study drug for self-administration at home until at least their next scheduled study visit. Records of drug formulation, batch number, and number of capsules dispensed, received, and returned must be recorded.

The study medication is to be stored at room temperature (< 30°C) in a secure, locked area while under the responsibility of the investigator. Receipt and dispensing of study medication must be recorded by an authorized person at the investigator's site. The storage temperature should be checked weekly, and recorded on a Temperature Log.

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

Table 6-4 Preparation and dispensing

Study treatment	Dispensing	Preparation
Nilotinib	Capsules and instructions for administration are dispensed by study personnel on an outpatient basis. Patients will be provided with an adequate supply of nilotinib for self-administration at home until at least their next scheduled study visit.	Not applicable

6.6.2 Study drug packaging and labeling

Nilotinib will be supplied by Novartis as 150 mg hard gelatin capsules. Medication labels will be in the local language and will comply with the legal requirements of each country.

6.6.3 Drug supply and storage

Study medication must be received by a designated person at the study site and be kept in a secured location to which only the investigator and designated assistants have access.

Table 6-5 Packaging and labeling

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

6.6.4 Study drug compliance and accountability

6.6.4.1 Study drug compliance

All dosages prescribed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record eCRF.

[redacted]

6.6.4.2 Study drug accountability

The Investigator or designee must maintain an accurate record of the prescribing of study treatment in a drug accountability ledger. Patients will be asked to return all unused study drug at each visit in order to allow the investigator and/or study personnel to complete a drug accountability check.

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

6.6.5 Disposal and destruction

The drug supply can be destroyed at the local Novartis facility, Drug Supply group, or third party, as appropriate, and according to local regulations and Novartis procedure.

7 Visit schedule and assessments

7.1 Study flow and visit schedule

Table 7-1, Table 7-2, Table 7-3, and Table 7-4 list all of the assessments applicable to each phase of the study and indicate with an "X", when visits are to be performed.

All data obtained from these assessments must be supported in the patient's source documentation. The table indicates which assessments produce data to be entered into the database (D) or remain in source documents only (S) ("Category" column).

All assessments should be performed within ± 7 days of the time points specified.

For patients consenting to participate to the 'CML patient's voice' Italian substudy please refer to [Post Text Supplement 1].

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 (see Section 7.2.2.4.5 for details).

[redacted]

Table 7-1 Visit evaluation schedule 1: screening and induction/consolidation phase

	Category	Screening	Re-Screening		Nilotinib Induction/Consolidation Phase								End of Phase (EOP) Visit [a,b,c]	Safety Follow-up /Study Evaluation Completion	Follow-up [l,j]
Visit number		**Screening**	**Re-Screening**	**Baseline**	**VD15**	**VM1**	**V1**	**V2**	**V3**	**V4-V8**	**V9-Randomization**	**V201-V204 (Only applicable to Arm 2)**	**a: End of Phase (EOP = V400)**	**EOS**	**V501-V520 (if applicable)**
Day/week/ month of study		**D −28 to 0**		**D1**	**D15 [m,g]**	**M1 [m,g]**	**M3[g]**	**M6[g]**	**M9[g]**	**M12, then every 3 months until M24[b,g]**	**Within 15 working days from M24 visit**	**M27, then every 3 months until M36[b,d,g]**	**If patient withdraws during induction/consolidation phase (at any visits from baseline to V8 for Arm 1 or to V204 for Arm 2).**	**30 days following the EOP visit**	**Every 3 months ± 21 days until 5 years from study entry**
Obtain informed consent	D	x	X												
Inclusion/exclusion criteria	D	x	X												
Demographics	D	x	X												
Relevant medical history/current medical conditions[o]	D	x	X												

[redacted]

	Category	Screening	Re-Screening		Nilotinib Induction/Consolidation Phase								End of Phase (EOP) Visit [a,b,c]	Safety Follow-up /Study Evaluation Completion	Follow-up [l,j]
Visit number		**Screening**	**Re-Screening**	**Baseline**	**VD15**	**VM1**	**V1**	**V2**	**V3**	**V4-V8**	**V9-Randomization**	**V201-V204 (Only applicable to Arm 2)**	**a: End of Phase (EOP = V400)**	**EOS**	**V501-V520 (if applicable)**
Day/week/ month of study		**D –28 to 0**		**D1**	**D15** [m,g]	**M1** [m,g]	**M3**[g]	**M6**[g]	**M9**[g]	**M12, then every 3 months until M24**[b,g]	**Within 15 working days from M24 visit**	**M27, then every 3 months until M36**[b,d,g]	**If patient withdraws during induction/consolidation phase (at any visits from baseline to V8 for Arm 1 or to V204 for Arm 2).**	**30 days following the EOP visit**	**Every 3 months ± 21 days until 5 years from study entry**
Disease history (diagnosis of CML)[p]	D	x													
Prior/current antineoplastic therapy	D	x	X												
Echocardiogram	D	x	X												
ECG	D	x	X		x[m]	x[m]	x						x		
Edinburgh Claudication Questionnaire	D	x	X					x		x[n]		x[n]			

[redacted]

	Category	Screening	Re-Screening		Nilotinib Induction/Consolidation Phase								End of Phase (EOP) Visit [a,b,c]	Safety Follow-up /Study Evaluation Completion	Follow-up [l,j]
Visit number		**Screening**	**Re-Screening**	**Baseline**	**VD15**	**VM1**	**V1**	**V2**	**V3**	**V4-V8**	**V9-Randomization**	**V201-V204 (Only applicable to Arm 2)**	**a: End of Phase (EOP = V400)**	**EOS**	**V501-V520 (if applicable)**
Day/week/ month of study		**D –28 to 0**		**D1**	**D15 [m,g]**	**M1 [m,g]**	**M3[g]**	**M6[g]**	**M9[g]**	**M12, then every 3 months until M24[b,g]**	**Within 15 working days from M24 visit**	**M27, then every 3 months until M36[b,d,g]**	**If patient withdraws during induction/consolidation phase (at any visits from baseline to V8 for Arm 1 or to V204 for Arm 2).**	**30 days following the EOP visit**	**Every 3 months ± 21 days until 5 years from study entry**
Physical examination	D	x	X	x*			x	x	x	x	x	x	x		
Vital signs	D	x	X	x*			x	x	x	x	x	x	x		
ECOG performance status	D	x	X	x*			x	x	x	x		x	x		
Hematology	D	x	X	x*	x[m]	x[m]	x	x	x	x	x	x	X		
Clinical chemistry	D	x	X	x*	x[m]	x[m]	x	x	x	x	x	x	X		
Serum pregnancy test (if applicable)	D	x	X	x*							x		X		

[redacted]

	Category	Screening	Re-Screening		Nilotinib Induction/Consolidation Phase								End of Phase (EOP) Visit [a,b,c]	Safety Follow-up /Study Evaluation Completion	Follow-up [l,j]
Visit number		**Screening**	**Re-Screening**	**Baseline**	**VD15**	**VM1**	**V1**	**V2**	**V3**	**V4-V8**	**V9-Randomization**	**V201-V204 (Only applicable to Arm 2)**	**a: End of Phase (EOP = V400)**	**EOS**	**V501-V520 (if applicable)**
Day/week/ month of study		**D –28 to 0**		**D1**	**D15 [m,g]**	**M1 [m,g]**	**M3[g]**	**M6[g]**	**M9[g]**	**M12, then every 3 months until M24[b,g]**	**Within 15 working days from M24 visit**	**M27, then every 3 months until M36[b,d,g]**	**If patient withdraws during induction/consolidation phase (at any visits from baseline to V8 for Arm 1 or to V204 for Arm 2).**	**30 days following the EOP visit**	**Every 3 months ± 21 days until 5 years from study entry**
Serology (Hepatitis B testing)	D				X ONLY once after patient is consented to amendment 04										
Urine pregnancy test[k] (if applicable)	D					x[k]	x[k]	x[k]	x[k]	x[k]		x[k]			
Urine analysis[q]	D	x	X	x*											
Peripheral blood BCR-ABL RQ-PCR result from local laboratory	D	x[e]													

[redacted]

	Category	Screening	Re-Screening		Nilotinib Induction/Consolidation Phase								End of Phase (EOP) Visit [a,b,c]	Safety Follow-up /Study Evaluation Completion	Follow-up [l,j]
Visit number		**Screening**	**Re-Screening**	**Baseline**	**VD15**	**VM1**	**V1**	**V2**	**V3**	**V4-V8**	**V9-Randomization**	**V201-V204 (Only applicable to Arm 2)**	**a: End of Phase (EOP = V400)**	**EOS**	**V501-V520 (if applicable)**
Day/week/ month of study		**D –28 to 0**		**D1**	**D15 [m,g]**	**M1 [m,g]**	**M3[g]**	**M6[g]**	**M9[g]**	**M12, then every 3 months until M24[b,g]**	**Within 15 working days from M24 visit**	**M27, then every 3 months until M36[b,d,g]**	**If patient withdraws during induction/consolidation phase (at any visits from baseline to V8 for Arm 1 or to V204 for Arm 2).**	**30 days following the EOP visit**	**Every 3 months ± 21 days until 5 years from study entry**
Peripheral blood BCR-ABL RQ-PCR (performed in a EUTOS standardized laboratory)	D	x[h]	X				x[h]	x[h]	x[h]	x[h]		x[h]	x[c,h]		
Bone marrow assessments/ cytogenetics	D	x[f]	x[f]		In case of loss of MMR or in case patient has not achieved MMR and it is deemed clinically indicated by the investigator										
Mutational analysis	D				In case of loss of MMR or in case patient has not achieved MMR and it is deemed clinically indicated by the investigator										

[redacted]

	Category	Screening	Re-Screening		Nilotinib Induction/Consolidation Phase								End of Phase (EOP) Visit [a,b,c]	Safety Follow-up /Study Evaluation Completion	Follow-up [l,j]
Visit number		**Screening**	**Re-Screening**	**Baseline**	**VD15**	**VM1**	**V1**	**V2**	**V3**	**V4-V8**	**V9-Randomization**	**V201-V204 (Only applicable to Arm 2)**	**a: End of Phase (EOP = V400)**	**EOS**	**V501-V520 (if applicable)**
Day/week/ month of study		**D –28 to 0**		**D1**	**D15 [m,g]**	**M1 [m,g]**	**M3[g]**	**M6[g]**	**M9[g]**	**M12, then every 3 months until M24[b,g]**	**Within 15 working days from M24 visit**	**M27, then every 3 months until M36[b,d,g]**	**If patient withdraws during induction/consolidation phase (at any visits from baseline to V8 for Arm 1 or to V204 for Arm 2).**	**30 days following the EOP visit**	**Every 3 months ± 21 days until 5 years from study entry**
Determination of Ph+ stem cells in bone marrow[l]	D	x	X							At V8		At V204			
Adverse events	D	Continuous											x	x (SAE)	

[redacted]

	Category	Screening	Re-Screening		Nilotinib Induction/Consolidation Phase								End of Phase (EOP) Visit [a,b,c]	Safety Follow-up /Study Evaluation Completion	Follow-up [l,j]
Visit number		**Screening**	**Re-Screening**	**Baseline**	**VD15**	**VM1**	**V1**	**V2**	**V3**	**V4-V8**	**V9-Randomization**	**V201-V204 (Only applicable to Arm 2)**	**a: End of Phase (EOP = V400)**	**EOS**	**V501-V520 (if applicable)**
Day/week/ month of study		**D −28 to 0**		**D1**	**D15 [m,g]**	**M1 [m,g]**	**M3[g]**	**M6[g]**	**M9[g]**	**M12, then every 3 months until M24[b,g]**	**Within 15 working days from M24 visit**	**M27, then every 3 months until M36[b,d,g]**	**If patient withdraws during induction/consolidation phase (at any visits from baseline to V8 for Arm 1 or to V204 for Arm 2).**	**30 days following the EOP visit**	**Every 3 months ± 21 days until 5 years from study entry**
Concomitant medications	D	Continuous											x	x (SAE)	
Study Drug administration	D	Continuous													
TKI treatment	D														x
Progression to AP/BC	D														x
Stem cell transplant information	D														x
Survival follow-up	D														x

[redacted]

	Category	Screening	Re-Screening	Nilotinib Induction/Consolidation Phase								End of Phase (EOP) Visit [a,b,c]	Safety Follow-up /Study Evaluation Completion	Follow-up [l,j]
Visit number		**Screening**	**Re-Screening**	**Baseline**	**VD15**	**VM1**	**V1**	**V2**	**V3**	**V4-V8**	**V9-Randomization**	**V201-V204 (Only applicable to Arm 2)**	**a: End of Phase (EOP = V400)**	**EOS**	**V501-V520 (if applicable)**
Day/week/ month of study		**D –28 to 0**		**D1**	**D15 [m,g]**	**M1 [m,g]**	**M3[g]**	**M6[g]**	**M9[g]**	**M12, then every 3 months until M24[b,g]**	**Within 15 working days from M24 visit**	**M27, then every 3 months until M36[b,d,g]**	**If patient withdraws during induction/consolidation phase (at any visits from baseline to V8 for Arm 1 or to V204 for Arm 2).**	**30 days following the EOP visit**	**Every 3 months ± 21 days until 5 years from study entry**

* These assessments should be performed only if the Day 1 visit occurred > 8 days after the screening visit.
[a] For patients withdrawing from the induction/consolidation phase, this visit should be performed within 15 working days of stopping study treatment.
[b] If a patient has already had two results with less than $MR^{4.0}$ by Month 24/36, the patient is not eligible for randomization, and in this case the 24 or the 36 months visit should be performed as the EOP visit, including all the assessments of EOP.
[c] For all other patients, this visit should be performed within 15 working days of the M24 visit to check and confirm their eligibility for randomization, or within 15 working days of the M36 visit for patients randomized to study Arm 2 to check and confirm their eligibility to enter the TFR phase-for these eligibility checks at Visits 9/205, no RQ-PCR evaluation will be done.
[d] Assessment schedule for patients randomized to receive 24 months of nilotinib consolidation treatment.
[e] An RQ-PCR result obtained from local laboratory within 14 weeks of signing the ICF is acceptable.
[f] To be performed only if the patient to deemed to be in less than MMR, as determined by the local laboratory or EUTOS BCR-ABL RQ-PCR assessment: no need to re-perform the bone marrow assessment at screening visit if the cytogenetic assessment result shows CCyR and this bone marrow assessment was obtained within 14 weeks of signing the ICF.
[g] A "visit window" of ± 7 days is allowed.
[h] If patients consent, the remaining blood samples after analysis will be stored for biomarker assessment
[i] For patients withdrawing from the induction/consolidation phase, this follow-up should be done until patient completes 5 years from study entry (starting 3 months after the EOP visit).

[redacted]

	Category	Screening	Re-Screening	Nilotinib Induction/Consolidation Phase								End of Phase (EOP) Visit [a,b,c]	Safety Follow-up /Study Evaluation Completion	Follow-up [l,j]
Visit number		**Screening**	**Re-Screening**	**Baseline**	**VD15**	**VM1**	**V1**	**V2**	**V3**	**V4-V8**	**V9-Randomization**	**V201-V204 (Only applicable to Arm 2)**	**a: End of Phase (EOP = V400)**	**EOS**	**V501-V520 (if applicable)**
Day/week/ month of study		**D –28 to 0**		**D1**	**D15** [m,g]	**M1** [m,g]	**M3**[g]	**M6**[g]	**M9**[g]	**M12, then every 3 months until M24**[b,g]	**Within 15 working days from M24 visit**	**M27, then every 3 months until M36**[b,d,g]	**If patient withdraws during induction/consolidation phase (at any visits from baseline to V8 for Arm 1 or to V204 for Arm 2).**	**30 days following the EOP visit**	**Every 3 months ± 21 days until 5 years from study entry**

[j] For patients who are not eligible for randomization (have already had two results with less than $MR^{4.0}$ by Month 24/36), this follow-up period should be done until patient completes 5 years from study entry (starting 3 months after the EOP visit).
[k] Urine pregnancy test will be performed on a monthly basis from Month 1 onwards, and test results will be documented in a diary by the patient.
[l] This assessment is only applicable to those patients consenting to participate in the optional Stem cells ENESTPath substudy. It will be performed at the screening visit, at Visit 8 , and (for patients included in Arm 2) at Visit 204.
[m] Optional visits at Day 15 and Month 1 based on local requirements or as clinically indicated.
[n] Edinburgh Claudication Questionnaire to be performed every 6 months during the induction/consolidation phase (at Screening and Months 6, 12, 18, 24, 30, and 36 as applicable depending on randomization).
[o] Includes smoking history and family history of cardiovascular events.
[p] Including if a previous stopping attempt under imatinib was performed and for how long the patient was in TFR.
[q:] only in patients with known diabetes mellitus (see Section 7.2.2.4.4)

[redacted]

Table 7-2 Visit evaluation schedule 2: Nilotinib TFR phase (Arm 1)

	Category	Nilotinib TFR phase			End of Phase (EOP)[a] visit	Safety Follow-up/ Study Evaluation Completion	Follow-up[e]
Visit Number		**V101-V106**	**V107-V109**	**V110-V117**	**EOP = 401**	**EOS**	**V501-V520 (if applicable)**
Day/week/month of study in TFR phase		**M1, then every month until M6[c]**	**M8, then every 2 months until M12[c]**	**M15, then every 3 months until M36[c,d]**	**If patient withdraw during TFR (at any visits from V101 to V117)**	**30 days following EOP visit**	**Every 3 months ± 21 days until 5 years from study entry**
Physical examination	D	Every 6 months			x		
Vital signs	D	Every 6 months			x		
ECOG performance status	D	Every 6 months			x		
ECG	D	As needed			x		
Edinburgh Claudication Questionnaire	D	Every 6 months					
Hematology	D	X	x	x	x		
Clinical chemistry	D	Every 6 months			x		
Serum pregnancy test (if applicable)	D				x		
Urine pregnancy test[f] (if applicable)	D	x[f]	x[f]	x[f]			
Peripheral blood BCR-ABL RQ-PCR[b]	D	x[b]	x[b]	x[b]	x[b]		
Bone marrow assessments/cytogenetics	D	In case of loss of MMR					
Mutational analysis	D	In case of loss of MMR					
Adverse events	D	Continuous			x	x	
Determination of Ph+ stem cells in bone marrow[g]	D	If patient relapses, before re-starting treatment with nilotinib					

[redacted]

	Category	Nilotinib TFR phase			End of Phase (EOP)[a] visit	Safety Follow-up/ Study Evaluation Completion	Follow-up[e]
Visit Number		**V101-V106**	**V107-V109**	**V110-V117**	**EOP = 401**	**EOS**	**V501-V520 (if applicable)**
Day/week/month of study in TFR phase		**M1, then every month until M6[c]**	**M8, then every 2 months until M12[c]**	**M15, then every 3 months until M36[c,d]**	**If patient withdraw during TFR (at any visits from V101 to V117)**	**30 days following EOP visit**	**Every 3 months ± 21 days until 5 years from study entry**
Concomitant medications	D	Continuous			x	x	
TKI treatment	D						x
Progression to AP/BC	D						x
Stem cell transplant information	D						x
Survival follow-up	D						x

[a] Applicable to all patients withdrawing from the TFR phase and not starting the nilotinib re-treatment phase as per protocol.
[b] Performed in a EUTOS standardized laboratory. [redacted]
[c] A "visit window" of ± 7 days is allowed.
[d] For patients completing the TFR phase per protocol, the last scheduled visit of the TFR phase will be the EOP visit (V117 [M36] of the TFR phase).
[e] For patients withdrawing from the TFR phase and not starting the nilotinib re-treatment phase as per protocol, this follow-up should be done until patient completes 5 years from study entry (starting 3 months after EOP phase visit).
[f] Urine pregnancy test will be performed monthly, and test results will be documented in a diary by the patient.
[g] This assessment is only applicable to those patients consenting to participate in the optional Stem cells ENESTPath substudy.

[redacted]

Table 7-3 Visit evaluation schedule 3: Nilotinib TFR phase (Arm 2)

	Category	Nilotinib TFR phase				End of Phase (EOP)[a] visit	Safety Follow-up/ Study Evaluation Completion	Follow-up[e]
Visit Number		**V205**	**V206-V211**	**V212-V214**	**V215-V218**	**EOP = 401**	**EOS**	**V501-V520 (if applicable)**
Day/week/month of study in TFR phase		**Eligibility**	**M1, then every month until M6[c]**	**M8, then every 2 months until M12[c]**	**M15, then every 3 months until M24[c,d]**	**If patient withdraw during TFR (at any visits from V101 to V117)**	**30 days following EOP visit**	**Every 3 months ± 21 days until 5 years from study entry**
Physical examination	D	x	Every 6 months			x		
Vital signs	D	x	Every 6 months			x		
ECOG performance status	D		Every 6 months			x		
ECG	D		As needed			x		
Edinburgh Claudication Questionnaire	D		Every 6 months					
Hematology	D	x	X	x	x	x		
Clinical chemistry	D	x	Every 6 months			x		
Serum pregnancy test (if applicable)	D	x				x		
Urine pregnancy test[f] (if applicable)	D		x[f]	x[f]	x[f]			
Peripheral blood BCR-ABL RQ-PCR[b]	D		x[b]	x[b]	x[b]	x[b]		

[redacted]

	Category	Nilotinib TFR phase				End of Phase (EOP)[a] visit	Safety Follow-up/ Study Evaluation Completion	Follow-up[e]
Visit Number		**V205**	**V206-V211**	**V212-V214**	**V215-V218**	**EOP = 401**	**EOS**	**V501-V520 (if applicable)**
Day/week/month of study in TFR phase		**Eligibility**	**M1, then every month until M6[c]**	**M8, then every 2 months until M12[c]**	**M15, then every 3 months until M24[c,d]**	**If patient withdraw during TFR (at any visits from V101 to V117)**	**30 days following EOP visit**	**Every 3 months ± 21 days until 5 years from study entry**
Bone marrow assessments/ cytogenetics	D		In case of loss of MMR					
Mutational analysis	D		In case of loss of MMR					
Adverse events	D	Continuous				x	x	
Determination of Ph+ stem cells in bone marrow[g]	D	If patient relapses, before re-starting treatment with nilotinib						
Concomitant medications	D	Continuous				x	x	
TKI treatment	D							x
Progression to AP/BC	D							x
Stem cell transplant information	D							x
Survival follow-up	D							x

[redacted]

	Category	Nilotinib TFR phase				End of Phase (EOP)[a] visit	Safety Follow-up/ Study Evaluation Completion	Follow-up[e]
Visit Number		**V205**	**V206-V211**	**V212-V214**	**V215-V218**	**EOP = 401**	**EOS**	**V501-V520 (if applicable)**
Day/week/month of study in TFR phase		**Eligibility**	**M1, then every month until M6[c]**	**M8, then every 2 months until M12[c]**	**M15, then every 3 months until M24[c,d]**	**If patient withdraw during TFR (at any visits from V101 to V117)**	**30 days following EOP visit**	**Every 3 months ± 21 days until 5 years from study entry**

[a] Applicable to patients withdrawing from the TFR phase and not starting the nilotinib re-treatment phase as per protocol.
[b] Performed in a EUTOS standardized laboratory [redacted].
[c] A "visit window" of ± 7 days is allowed.
[d] For patients completing the TFR phase per protocol the last scheduled visit of the TFR phase will be the EOP visit (V117 [M36] of the TFR phase).
[e] For patients withdrawing from the TFR phase and not starting the nilotinib re-treatment phase as per protocol, this follow-up should be done until patient completes 5 years from study entry (starting 3 months after EOP phase visit).
[f] Urine pregnancy test will be performed monthly, and test results will be documented in a diary by the patient.
[g] This assessment is only applicable to those patients consenting to participate in the optional Stem cells ENESTPath substudy.

[redacted]

Table 7-4 Visit evaluation schedule 4: Nilotinib re-treatment phase (if applicable)

	Category	Nilotinib Re-treatment				End of Phase (EOP) visit[a,e]	Safety Followup/Study Evaluation Completion	Follow-up[f]
Visit number		**V301**	**V302**	**V303**	**V304-314 (as applicable)**	**a: EOP = V402**	**EOS**	**V501-V520 (as applicable)**
Day/week/month of study in re-treatment phase		**Day 1**	**W6[d]**	**M3[d]**	**M6, then every 3 months until 5 years from study entry[d,e]**	**Within 15 working days of last dose**	**30 days following the EOP visit**	**Every 3 months ± 21 days until 5 years from study entry**
Physical examination	S	x [c]		x	x	x		
Vital signs	D	x [c]		x	x	x		
ECOG performance status	D	x [c]		x	x	x		
Peripheral blood BCR-ABL RQ-PCR[b]	D		x[b]	x[b]	x[b]	x[b]		
ECG	D	x [c]		x		x		
Edinburgh Claudication Questionnaire	S	x [c,h]			x[h]			
Hematology	D	x [c]		x	x	x		
Clinical chemistry	D	x [c]		x	x	x		
Mutational analysis	D	In case of loss of MMR	As needed					
Serum pregnancy test (if applicable)	D	x [c]				x		
Serology (Hepatitis B testing)	D	X ONLY once after patient is consented to amendment 04						
Urine pregnancy test[g] (if applicable)	D			x[g]	x[g]			
Adverse events/SAE	D	Continuous				x	x (SAE)	
Concomitant medications	D	Continuous				x	x (SAE)	

[redacted]

	Category	Nilotinib Re-treatment				End of Phase (EOP) visit[a,e]	Safety Followup/Study Evaluation Completion	Follow-up[f]
Visit number		**V301**	**V302**	**V303**	**V304-314 (as applicable)**	**a: EOP = V402**	**EOS**	**V501-V520 (as applicable)**
Day/week/month of study in re-treatment phase		**Day 1**	**W6[d]**	**M3[d]**	**M6, then every 3 months until 5 years from study entry[d,e]**	**Within 15 working days of last dose**	**30 days following the EOP visit**	**Every 3 months ± 21 days until 5 years from study entry**
TKI treatment information	D							x
Progression to AP/BC	D							x
Stem cell transplant information	D							x
Survival follow-up	D							x

[a] Applicable to patients withdrawing from the nilotinib re treatment phase before completing the 5-year study period.
[b] Performed in a EUTOS standardized laboratory. [redacted].
[c] The assessment schedule for Day 1 should be completed for those tests that were not performed on the day of confirmed loss of MR[4.0], or loss of MMR.
[d] A "visit window" of ± 7 days is allowed.
[e] For patients completing the nilotinib re-treatment phase per protocol, the last scheduled visit of the nilotinib re-treatment phase in order to complete the 5 years from study entry will be the EOP visit (V314).
[f] For patients withdrawing from the nilotinib re-treatment phase before completing the 5-year study period, this follow-up should be done until patient completes 5 years from study entry (starting 3 months after EOP phase visit).
[g] Urine pregnancy test will be performed monthly and test results will be documented in a diary by the patient.
[h] Edinburgh Claudication Questionnaire to be performed every 6 months during the nilotinib re-treatment phase (Day 1 until patient completes 5 years from study entry as applicable).

[redacted]

7.1.1 Pre-screening assessment

Not applicable.

7.1.2 Screening

Written informed consent must be obtained before any study specific medical procedures are performed. A screening visit should occur between study days -28 and 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.

A recent RQ-PCR result must be available to demonstrate a BCR-ABL level of $<MR^{4.0}$.

If a RQ-PCR was performed by a local laboratory within 14 weeks of signing the informed consent (ICF), a RQ-PCR peripheral blood sample should be sent to a EUTOS standardized laboratory for confirmation of the baseline BCR-ABL levels.

If a RQ-PCR result from a local laboratory is not available within 14 weeks of signing the informed consent (ICF), RQ-PCR peripheral blood samples (two separate vials) for the local and the EUTOS standardized laboratory assessment should be collected at the same time.

The decision tree for protocol entry based on the molecular response assessment is as follows:

- Patients with $<MR^{4.0}$ as measured in the local laboratory and confirmed in the EUTOS standardized laboratory are eligible
- Patients with $<MR^{4.0}$ as measured in the local laboratory, but with $\geq MR^{4.0}$ as assessed by a EUTOS standardized laboratory, are not eligible, and will be considered as screening failures
- Patients with $\geq MR^{4.0}$ as measured in the local laboratory, but with $<MR^{4.0}$ as assessed by a EUTOS standardized laboratory, are eligible
- Patients with $\geq MR^{4.0}$ as measured in the local laboratory and confirmed by a EUTOS standardized laboratory, are not eligible, and will be considered as screening failures.

If BCR-ABL transcript level at screening is <MMR (less than $MR^{3.0}$) as assessed at a local and/or EUTOS standardized laboratory, a bone marrow biopsy/aspirate needs to be performed to assess the patient's cytogenetic response, unless a bone marrow assessment confirming CCyR was obtained within 14 weeks of signing the ICF.

Only patients who are shown to be in CCyR are eligible for ENESTPath. Patients without CCyR are considered screening failures.

Every effort should be made to collect data on the risk assessment factors at the time of CML diagnosis for each patient enrolled in this study (eosinophils, basophils, spleen size, platelets, age).

Re-screening of a patient will be allowed for this study. 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.

[redacted]

7.1.2.1 Eligibility screening

Patients must meet all inclusion and none of the exclusion criteria in order to be eligible for the study. Patient eligibility will be confirmed by the investigative staff and captured within the source documents maintained at the site. This information will be made available during planned interim monitoring visits and compared against the clinical database for accuracy.

7.1.2.2 Information to be collected on screening failures

A patient who signs an informed consent form (ICF) but fails to commence treatment for any reason will be considered a screening failure. The reason for not being started on treatment will be entered on the Screening Log eCRF page. Demographic information, informed consent date, and inclusion/exclusion pages must also be completed for screening failure patients. No other data will be entered into the clinical database for patients who are screening failures, unless the patient experienced a SAE during the screening phase (see Section 8 for SAE reporting details).

7.1.2.3 Patient demographics and other screening characteristics

After the patient has signed the ICF, the following assessments will be performed at the screening visit:

- Demographics (age, gender, race)
- Relevant medical history, including current medical conditions, smoking history, and family history of cardiovascular events;
- Disease history (diagnosis of CML), and whether a previous stopping attempt under imatinib was performed and for how long the patient was in TFR
- Prior/current antineoplastic therapy
- Prior/concomitant medications
- Physical examination (see Section 7.2.2.1 for details)
- Vital signs (see Section 7.2.2.2 for details)
- ECOG performance status
- BCR-ABL RQ-PCR result from local laboratory, performed within 14 weeks of signing the ICF
- Peripheral blood for RQ-PCR to establish a baseline BCR-ABL value will be collected and sent to a EUTOS standardized laboratory. If the patient consents, any blood remaining after analysis will be stored at a EUTOS standardized laboratory;
- Laboratory evaluations:
  - Hematology (see Section 7.2.2.4.1 for details)
  - Clinical chemistry (see Section 7.2.2.4.2 for details)
  - Urine analysis (see Section 7.2.2.4.4 for details)
  - Serum pregnancy test and discussion of contraception measures to be taken (if applicable) (see Section 7.2.2.4.3 for details)

Potassium, calcium, magnesium, and/or sodium supplements may be given to correct values that are < lower limit of normal (LLN). Post-correction values must not be deemed to be a clinically significant abnormality prior to patients being dosed.

- Cardiac assessments (see Section 7.2.2.6 for details)
- Edinburgh Claudication Questionnaire (see Section 7.2.2.7 for details)

All medications and significant non-drug therapies taken within 14 days prior to first dose must be recorded on the Concomitant Medication eCRF page and updated on a continuous basis if there are any new changes to the medications. Medications include physician prescribed and over-the-counter medications, as well as vitamins, herbal, and alternative therapies. Information to be collected on concomitant medications/significant non-drug therapies will include the following:

- Medication/non-drug therapy trade name
- Reason for medication
- Start date and end date or continuing at time of examination
- Dosage regimen

For those patients consenting to participate in the optional Stem cells ENESTPath substudy, a determination of Ph+ stem cells in bone marrow will be performed during the screening visit, before starting nilotinib 300 mg BID treatment.

7.1.3 Run-in-period

Not applicable.

7.1.4 Induction/consolidation phase

Patients in the induction/consolidation phase will undergo the following assessments on the first day of starting study treatment (Day 1 = study entry) and at every subsequent 3-month visit until the end of the consolidation phase (either 24 or 36 months, depending on eligibility and randomization arm):

- Physical examination (see Section 7.2.2.1 for details)
- Vital signs (see Section 7.2.2.2 for details)
- ECOG performance status (see Section 7.2.2.3 for details)
- Hematology (see Section 7.2.2.4.1 for details)
- Clinical chemistry (see Section 7.2.2.4.2 for details)
- Serum pregnancy test only at Day 1 (see Section 7.2.2.4.3)
- Urine analysis only at Day 1 (see Section 7.2.2.4.4)
- Serology (Hep B) if not done at an earlier visit (see Section 7.2.2.4.5 for details)

The patient may be required to attend optional visits at Day 15 and Month 1 based on local requirements or as clinically indicated.

In the event that Day 1 is performed within 8 days from the screening visit, the following evaluations should not be repeated on Day 1:

- Physical examination (see Section 7.2.2.1 for details);

[redacted]

- Vital signs (see Section 7.2.2.2 for details);
- ECOG performance status (see Section 7.2.2.3 for details)
- Hematology (see Section 7.2.2.4.1 for details)
- Clinical chemistry (see Section 7.2.2.4.2 for details)
- Serum pregnancy test (see Section 7.2.2.4.3 for details)
- Urine analysis (see Section 7.2.2.4.4 for details)

Urine pregnancy tests will be performed monthly from Month 1 (see Section 7.2.2.4.3 for details).

Peripheral blood will be taken for BCR-ABL RQ-PCR assessment (performed in a EUTOS standardized laboratory) from Month 3 and at each subsequent 3-month visit until the end of the consolidation phase in order to assess the effectiveness of the study medication (see Section 7.2.1.1 for details).

An ECG will also be performed at Month 3 and at the End of Phase (EOP) visit (and at the optional visits of Day 15 and Month 1, if required) (see Section 7.2.2.6.1 for details).

Patients will complete an Edinburgh Claudication Questionnaire at 6-monthly intervals for the duration of the study (see Section 7.2.2.7 for details).

Bone marrow assessments/cytogenetics and mutational analysis will be performed if a patient demonstrates a loss of MMR or has not achieved MMR and it is deemed clinically indicated by the investigator. If the result is positive for a mutation, further analysis will be performed as needed at the discretion of the investigator (see Section 7.2.1.3 for details).

The recording of study drug dosing, concomitant medications, and assessment of AEs will be performed on a continuous basis throughout the initiation/consolidation phase.

A “visit window” of ± 7 days is allowed during the induction/consolidation phase.

For those patients consenting to participate in the optional Stem cells ENESTPath substudy, a determination of Ph+ stem cells in bone marrow will be performed after 24 months of nilotinib treatment (at Visit 8).

For those patients consenting to participate to the ‘CML patients voice’ Italian substudy, quiestionnaires and expressive writing assessemnts will be conducted at Visit 6 - Month 18. [Post Text Supplement 1].

7.1.5 Randomization/Eligibility visit

After completion of the Month 24 visit, the patient will continue nilotinib treatment until Visit 9-Randomization, which should occur within 15 working days from the last visit.

If the patient has been in sustained $\geq MR^{4.0}$ for the previous 12 months as evaluated and confirmed on Visit 9, randomization to one of the two treatment arms will be done by using an interactive voice response system (IVRS). Detailed instruction on the use of the IVRS will be given in a manual.

[redacted]

Patients will be deemed to be in sustained molecular response if:

- Four out of the preceding five quarterly RQ-PCR assessments were ≥$MR^{4.0}$ (equal or more than $MR^{4.0}$), and
- The last assessment was ≥$MR^{4.0}$ (equal or more than $MR^{4.0}$).

If the patient is randomized to Arm 1, the study treatment will be immediately interrupted and the patient will be instructed to follow the schedule of the Arm 1 TFR phase.

At Visit 9 - Randomization, patients will be asked to return their remaining supply of study drug to site.

If the patient is randomized to Arm 2, the study treatment will continue for an additional 12 months with the same visit schedule as in the first 2 year of consolidation treatment and study drug will be dispensed.

After completion of the Month 36 visit, the patient will continue nilotinib treatment until Visit 205-Eligibility, which should occur within 15 working days from the last visit. If the patient is still eligible to enter the TFR phase, the patient will be instructed by the investigator to follow the visit schedule of the Arm 2 TFR phase.

At Visit 205 - Eligibility, patients will be asked to return any remaining supply of study drug.

For those patients consenting to participate in the optional Stem cells ENEST substudy, and randomized to Arm 2, a determination of Ph+ stem cells in bone marrow will be performed after 36 months of nilotinib treatment (Visit 204).

For those patients consenting to participate to the 'CML patient's voice' Italian substudy, quiestionnaires and expressive writing assessemnts will be conducted at Visit 9 - Randomization. [Post Text Supplement 1]

Patients not having confirmed sustained molecular response at 24 months (or at 36 months depending on eligibility for randomization) will exit the study and will be treated at the discretion of the investigator according to standard practice. Information on survival, stem cell transplant and the status of the patient's disease (i.e. disease progression to AP/BC according to protocol definition, TKI treatment) will be collected until death, progression, or 5 years from study entry, whichever comes first.

For those patients consenting to participate to the 'CML patient's voice' Italian substudy, quality of life quiestionnaires and in-depth qualitative interviews will be conducted at Visit 9 - Randomization. [Post Text Supplement 1]

The following assessments will be performed at the Randomization-Eligibility visits:

- Physical examination (see Section 7.2.2.1 for details);
- Vital signs (see Section 7.2.2.2 for details);
- Hematology (see Section 7.2.2.4.1 for details);
- Clinical chemistry (see Section 7.2.2.4.2 for details);
- Serology (Hep B) if not done at an earlier visit (see Section 7.2.2.4.5 for details);
- Serum pregnancy test (if patient withdrawn from the study).

At this visit, no peripheral blood BCR-ABL RQ-PCR will be done.

[redacted]

If the Randomization/Eligibility visit is done within 15 days from Visit 8 or Visit 204 (depending on randomization arm), the above assessments should not be repeated, except for the serum pregnancy test.

7.1.6 Treatment-free remission phase

Following the cessation of study therapy (at either 24 or 36 months, depending on randomization), patients will attend visits at the following time frames:

- Every month for the first 6 months of the TFR phase (both Arms)
- Every 2 months between Months 8 and 12 of the TFR phase (both Arms)
- Every 3 months between Months 15 and 24 of the TFR phase (both Arms)
- Every 3 months between Months 27 and 36 of the TFR phase for patients enrolled into Arm 1 of the study

At the TFR Month 1 visit, patients will be asked to return their remaining supply of study drug to site if not done at Visit 9 - Randomization or Visit 205 - Eligibility depending on the randomization arm.

At each of the visit times stated above, peripheral blood will be taken for BCR-ABL RQ-PCR assessment (performed in a EUTOS standardized laboratory) and hematologic assessments (see Section 7.2.2.4.1 for details).

In addition, the following assessments will be performed at 6-month intervals:

- Physical examination (see Section 7.2.2.1 for details)
- Vital signs (see Section 7.2.2.2 for details)
- ECOG performance status; clinical chemistry (see Section 7.2.2.4.2 for details)
- ECG if needed (see Section 7.2.2.6.1)
- Edinburgh Claudication Questionnaire (see Section 7.2.2.7 for details)
- Clinical chemistry (see Section 7.2.2.4.2 for details);

A urine pregnancy test will also be performed monthly, and test results will be documented in a diary by the patient (see Section 7.2.2.4.3);

Bone marrow assessments/cytogenetics and mutational analysis will be performed if a patient demonstrates a loss of MMR. If the result is positive for a mutation, further analysis will be performed as needed at the discretion of the investigator.

Patients who need to re-start the treatment with Nilotinib due to a relapse in the TFR phase need to be assessed for Hepatitis B if not done at an earlier visit to identify chronic carriers of the virus (see Section 7.2.2.4.5 for details).

For those patients consenting to participate to the ‘CML patient’s voice’ Italian substudy, quality of life quiestionnaires and in-depth qualitative interviews will be conducted in this phase. [Post Text Supplement 1]

The recording of concomitant medications and assessment of AEs will be performed on a continuous basis throughout the TFR phase.

A “visit window” of ± 7 days is allowed during the TFR phase.

[redacted]

7.1.7 Nilotinib re-treatment phase (if applicable)

If according to the EUTOS standardized laboratory result, the definition of relapse (loss of MMR/confirmed loss of $MR^{4.0}$) is met, the investigator should contact the patient for immediate start of the nilotinib re-treatment phase. Treatment with nilotinib should re-start at the same dose taken before the TFR phase (i.e., the re-treatment dose will be nilotinib 300 mg BID or a lower dose of nilotinib if the dose was reduced in the consolidation phase before entering the TFR phase).

The following assessments should be performed on Day 1 of the re-treatment phase if not already performed on the day of confirmed loss of $MR^{4.0}$, or loss of MMR:

- Physical examination (see Section 7.2.2.1 for details)
- Vital signs (see Section 7.2.2.2 for details)
- ECOG performance status (see Section 7.2.2.4.2 for details)
- ECG (see Section 7.2.2.6.1 for details)
- Hematology (see Section 7.2.2.4.1 for details)
- Clinical chemistry (see Section 7.2.2.4.2 for details)
- Serum pregnancy test (see Section 7.2.2.4.3 for details)
- Serology (Hep B) if not done at an earlier visit (see Section 7.2.2.4.5 for details)
- Edinburgh Claudication Questionnaire (see Section 7.2.2.7 for details)

Peripheral blood for BCR ABL RQ PCR (done in a EUTOS standardized laboratory) and mutational analysis should not be repeated On Day 1 of the re-treatment phase.

Subsequently, patients will attend study visits every 3 months until they complete 5 years from study entry, and will undergo the assessments as per Table 7-4:

Bone marrow assessments/cytogenetics and mutational analysis will be performed if a patient demonstrates a loss of MMR. If the result is positive for a mutation, further analysis will be performed as needed at the discretion of the investigator.

Patients will complete an Edinburgh Claudication Questionnaire at 6-month intervals for the duration of the study (see Section 7.2.2.7 for details).

A "visit window" of ± 7 days is allowed during the re-treatment phase.

The recording of study drug dosing, concomitant medications and assessment of AEs will be performed on a continuous basis throughout the re-treatment phase.

7.1.8 End of Phase visit, including premature withdrawal and study discontinuation visit

Patients will attend the following EOP visits depending on the time points they will interrupt the study:

- Visit 400: end of induction/consolidation phase if the patient withdraws at any time from baseline to Visit 8 for Arm 1 or to Visit 204 for Arm 2 or if the patient does not achieve stable $\geq MR^{4.0}$ during the second year of the induction/consolidation phase

[redacted]

- Visit 401: end of the TFR phase if the patient withdraws during the TFR phase at any time from Visit 101 to Visit 117 for Arm 1 or from Visit 206 to Visit 218 for Arm 2 and patient doesn't start re-treatment phase
- Visit 402: end of re-treatment phase for patients withdrawn from the nilotinib re-treatment phase at any time from Visit 301 to Visit 314

The following assessments will be performed at the above-mentioned EOP visits:

- Physical examination (see Section 7.2.2.1 for details)
- Vital signs (see Section 7.2.2.2 for details)
- ECOG performance status (see Section 7.2.2.4.2 for details)
- ECG (see Section 7.2.2.6.1 for details)
- Hematology (see Section 7.2.2.4.1 for details)
- Clinical chemistry (see Section 7.2.2.4.2 for details)
- Serology (Hep B) if not done at an earlier visit (see Section 7.2.2.4.5 for details)
- Peripheral blood BCR-ABL RQ-PCR
- Serum pregnancy test (if patient is withdrawn from the study)

The recording of concomitant medications and assessment of AEs will also be performed.

An EOP eCRF page should be completed, giving the date and reason for stopping the study period prematurely (if applicable).

If a patient refuses to return for the EOP visit or is unable to do so, every effort should be made to contact them or a knowledgeable informant by telephone to obtain information. The investigator should show "due diligence" by documenting in the source documents the steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc. An EOP eCRF page should be completed.

All patients who discontinue the study (whether due to successful completion of any of the study phases, or premature withdrawal) should be contacted for safety evaluations 30 days from the EOP visit in order to follow any safety issues and record/update concomitant medications. This information may be collected by a telephone call or a clinic visit, if conducted by a telephone call this may trigger a safety follow-up visit if a medical intervention is necessary.

For patients returning to the site for a safety follow-up visit a Hepatitis B testing will be performed once if not performed at an earlier visit to identify chronic carriers of the virus (see Section 7.2.2.4.5 for details). The patient should then be informed about the outcome of the serology test and the potential risk for Hepatitis B reactivation if the test result was positive.

For patients who discontinue earlier in any phase and don't accept to be followed for survival, an EOS eCRF page should be completed.

For patients who accept to be followed for survival see Section 7.1.9.

7.1.8.1 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:

- AEs
- Abnormal laboratory value(s), if deemed necessary by the investigator
- Abnormal test procedure result(s), if deemed necessary by the investigator
- Pregnancy (patients must be withdrawn if pregnancy occurs during the nilotinib induction/consolidation phase or the nilotinib re-treatment phase. In case of a pregnancy during the TFR phase, the pregnant woman can stay in the TFR phase as long as no nilotinib treatment is needed, but she must be withdrawn from the study when/if she meets the definition of relapse [loss of MMR/confirmed loss of $MR^{4.0}$])
- Protocol violation
- Subject withdrew consent
- Lost to follow-up
- Administrative issues
- Death

In addition, patients should be withdrawn from the study in the event of disease progression, defined as:

- Progression to CML-AP, i.e.:
  - ≥ 15% blasts in peripheral blood or bone marrow aspirate, but < 30% blasts in both peripheral blood and bone marrow aspirate
  - ≥ 30% blasts plus promyelocytes in peripheral blood or bone marrow aspirate
  - ≥ 20% basophils in peripheral blood
  - Thrombocytopenia (< 100 x 10^9/L) that is unrelated to therapy
- Progression to BC, as defined by any of the following:
  - ≥ 30% blasts in peripheral blood or bone marrow aspirate
  - Appearance of extramedullary involvement other than hepato- and/or splenomegaly proven by biopsy (i.e. chloroma)

7.1.9 Follow-up period

Patients who terminate the study early in any phase for any reason and accept to be followed (see Section 7.1.8.1 for details) will be contacted every 3 months ± 21 days until 5 years from study entry. Information on survival, stem cell transplant, and the status of the patient's disease (i.e. disease progression to AP/BC according to protocol definition, TKI treatment) will be collected. Patients lost to follow-up during this time should be recorded as such on the eCRF. For patients who are lost to follow-up, the investigator should show "due diligence" by documenting in the source documents the steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc.

[redacted]

The EOS page should be completed when the patient completes/interrupts the follow-up period.

7.2 Assessment types

7.2.1 Efficacy assessments

Efficacy assessments will be performed at the time points indicated Table 7-1, Table 7-2, and Table 7-3.

7.2.1.1 Molecular response

Molecular response will be assessed in all patients. Levels of BCR-ABL transcripts will be determined by RQ-PCR testing of peripheral blood and analyzed at a EUTOS standardized laboratory according to the methodology described in the EUTOS guidelines (version published in Feb 2015).

The percent ratio of BCR-ABL transcripts versus control gene transcripts converted to IS will be calculated for each sample.

If a suitable peripheral blood sample for RQ-PCR testing was not obtained during the normal visit schedule, then a subsequent sample must be collected at an unscheduled visit within 4 weeks. Examples for deeming a sample unsuitable include:

- A sample becoming lost during transit to the PCR laboratory in the consolidation/TFR and re-treatment phases
- Insufficient sample quality (degraded/insufficient RNA)

Molecular response and related variables are defined as the following (see detailed definition in Glossary of terms):

- MMR ($MR^{3.0}$): BCR-ABL $\leq$ 0.1% (IS)
- $MR^{4.0}$: BCR-ABL $\leq$ 0.01% (IS)
- $MR^{4.5}$: BCR-ABL $\leq$0.0032% (IS)
- MR^{5}: BCR-ABL $\leq$0.001% (IS)

7.2.1.2 Mutational analysis

Mutational analysis will be performed at a EUTOS standardized laboratories.

During the study, in a patient with loss of MMR, mutational analyses will be performed on the cDNA available from the RQ-PCR at this time point. Continued mutational analyses may be performed as clinically indicated.

Sites will use standard materials for sample collection and shipment. Collection, storage, and shipment of samples for mutational analysis will follow the standard practice of the designated EUTOS standardized laboratory, as described in the Study Site Laboratory Manual. Samples will be refrigerated (2°C to 8°C) after preparation, and shipped to the designated EUTOS standardized laboratory at room temperature as described in the [Laboratory Manual].

[redacted]

7.2.1.3 Bone marrow analysis and cytogenetics

If a patient is deemed to be in less than MMR, as assessed by a EUTOS standardized laboratory, CgR assessment must be performed as soon as possible. Cytogenetics must be performed by chromosome banding analysis (CBA) of marrow cell metaphases. If marrow cells cannot be obtained, CBA can be substituted with interphase FISH of blood cells, using dual color dual fusion probes that allow the detection of BCRABL+ nuclei. However, based on interphase FISH, one cannot assess the degree of CgR, (minimal, minor, partial) but can establish only if the CgR is complete (< 1% BCR-ABL+ nuclei out of at least 200 nuclei).

Bone marrow assessments/cytogenetics will be performed if a patient demonstrates a loss of MMR during the study.

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

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 the 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 examinations will be performed and analyzed locally.

7.2.2 Safety and tolerability assessments

Safety and tolerability assessments will be performed at the time points indicated in Table 7-1, Table 7-2, and Table 7-3.

Safety will be monitored by performing the assessments described below, in addition to collecting AE data at every visit. For details on AE collection and reporting, please 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 signing of informed consent must be recorded on the AE page of the patient's eCRF.

[redacted]

7.2.2.1 Physical examination

Physical examination will include an assessment of height (measured in cm at screening only), body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes) and an examination of the general appearance of the patient, including skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular, and neurological.

Patients are encouraged to measure their body weight regularly and to report to the study investigator any body-weight change of more than 2 kg as compared to their pre-study body weight to detect early signs of fluid retention. Rapid weight gain of ≥ 2 kg should be carefully investigated and other measures considered as appropriate.

Information about the physical examination must be present in the source documentation at the study site.

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 signing of informed consent must be recorded on the AE page of the patient's eCRF.

Presence of extramedullary leukemic involvement will be checked at each physical examination as outlined above. Findings on physical examination consistent with extramedullary leukemic involvement will be recorded (e.g. lymph nodes, liver, and spleen size). With regards to lymph nodes, palpable lymph nodes should be considered to be CML related only if leukemic blast infiltration has been confirmed via biopsy/histology or by technically adequate (not contaminated with peripheral blood) aspiration cytology.

When extramedullary 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 (blood pressure, heart rate, and body temperature) will be assessed with the patient in the sitting position after 2 minutes of rest. Body temperature may be measured orally or via ear.

7.2.2.3 Performance status

The patient's performance status will be assessed according to the ECOG performance status scale (see Table 7-5).

[redacted]

Table 7-5 ECOG performance criteria

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

Source: Oken MM, Creech RH, Tormey DC, et al (1982). Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol; 5:649-55.

7.2.2.4 Laboratory evaluations

The laboratory evaluations will be performed by a local laboratory. Novartis must be provided with a copy of the certification and tabulation of the normal ranges for all local laboratories used.

Abnormal laboratory values or test results constitute an AE only if they induce clinical signs or symptoms, and are considered clinically significant (i.e. requires dose modification and/or interruption of study drug, leads to clinical symptoms, causes study discontinuation, or itself constitutes a SAE) or require therapy. These events should be recorded on the AE eCRF, as well as the appropriate laboratory eCRF and/or comment eCRF page. If the administration of nilotinib is delayed/modified due to unacceptable toxicities (see Section 6.3), re-evaluation should be performed prior to the next study treatment at a minimum.

All available laboratory evaluations should be performed and results reviewed prior to administration of study drug. More frequent examinations may be performed at the investigator's discretion if medically indicated; results should be recorded on the Unscheduled Visit eCRF.

7.2.2.4.1 Hematology

Hematology includes assessment of hemoglobin, platelet count, total (absolute) white blood cell (WBC) count and an automated and/or manual full differential count, including absolute values and percentages of neutrophils, lymphocytes, eosinophils, basophils, monocytes, promyelocytes, myelocytes, meta myelocytes, and blast cells.

7.2.2.4.2 Clinical chemistry

Clinical chemistry tests will include AST (SGOT), ALT (SGPT), direct bilirubin, indirect bilirubin, total bilirubin, alkaline phosphatase, lipase, amylase (optional), lactate dehydrogenase (LDH), albumin, triglycerides, high-density lipoprotein (HDL), low density lipoprotein (LDL), total cholesterol, fasting glucose, serum creatinine, potassium, magnesium, calcium, inorganic phosphorus, and sodium. Potassium, calcium, magnesium, and/or sodium supplements may be given to correct values that are < LLN. Post-correction values must not be deemed to be a clinically significant abnormality prior to patients being dosed.

[redacted]

HDL, LDL, total cholesterol, and triglycerides should be assessed under fasting conditions. Thus, those parameters in addition to the evaluation of fasting glucose may be conducted in the external laboratory within 7 days prior to scheduled visits. If HDL, LDL, total cholesterol, and triglycerides assessments are not performed under fasting conditions, an unscheduled assessment should be performed within 15 days in order to collect these parameters under fasting conditions. If the assessment of fasting glucose was not performed at either the external laboratory or at site visit, the HbA1C assessment will replace the missing fasting glucose test, but every effort should be made to collect the fasting glucose result.

HbA1C will be included in the clinical chemistry assessment for every patient during the duration of the trial (screening, every 3 months while under nilotinib treatment, and every 6 months during the TFR phase).

7.2.2.4.3 Pregnancy assessment

All women of childbearing potential (WOCBP) should undergo serum and urine pregnancy testing at the time points stated in Table 7-1, Table 7-2, Table 7-3, and Table 7-4.

Urine pregnancy testing will be performed by the patient on a monthly basis during the induction/consolidation phase, the TFR phase, and the re-treatment phase. The results of these tests should be recorded in the patient diary, which should be shown to the investigator at each visit to confirm that any WOCBP is not pregnant. If a test result indicates a pregnancy, the patient must contact the investigator immediately.

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

Pregnancy testing is not required for patients who are determined to be post-menopausal. Women are considered post-menopausal and not of childbearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate) or have had surgical bilateral oophorectomy with or without hysterectomy or tubal ligation at least 6 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 to be not of childbearing potential.

7.2.2.4.4 Urine analysis

At the screening and Baseline visits, a urine test will be performed to assess the presence of microalbuminuria in patients with known diabetes mellitus.

7.2.2.4.5 Serology (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 induction and consolidation phases of the study should have testing performed at the next possible visit in order to identify chronic carriers.

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

[redacted]

7.2.2.5 Radiological examinations

No radiological examinations will be performed for the assessment of safety.

7.2.2.6 Cardiac assessments

7.2.2.6.1 Electrocardiogram

A 12-lead ECG should be obtained at screening and at the time points indicated in Table 7-1, Table 7-2, Table 7-3, and Table 7-4.

Interpretation of the standard 12-lead ECG tracing must be made by a qualified physician and documented on the ECG eCRF page. QTc will be calculated according to Fridericia's formula. Each ECG tracing should be labeled with the study number, patient initials (where regulations permit), patient number and 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. New or worsened clinically significant findings occurring after informed consent must be recorded on the Adverse Events eCRF page.

At Day 1 of nilotinib re-treatment, QTcF must be < 450 msec prior to re-starting nilotinib. For patients with QTcF prolongation above 450 msec, an analysis of serum potassium and magnesium should be performed, and if below normal, corrected with supplements to within normal limits. Concomitant medications must be reviewed for their potential to inhibit CYP3A4 and/or to prolong QT interval. A repeat ECG should be performed within 1 hour of the first QTcF of > 450 msec. If QTcF remains > 450 msec, then repeat ECG as clinically indicated, but at least once a day until the QTcF returns to < 450 msec.

In case of a grade 3 QT interval prolongation, a cardiologist's opinion should be requested, and an appropriate and closer cardiac monitoring of the patient must be put in place until the QTcF decreases to < 500 msec.

Additional ECGs can be performed at any time at the investigator's discretion.

7.2.2.6.2 Echocardiogram

Echocardiography will be performed at screening to assess left ventricular ejection fraction and may be repeated at the investigator's discretion if there are signs or symptoms of cardiotoxicity.

7.2.2.7 Edinburgh Claudication Questionnaire

Patients will complete an Edinburgh Claudication Questionnaire at screening and at 6-month intervals thereafter for the duration of the study (provided in Appendix 14.2).

The questionnaire will be used to see whether it may predict a higher chance of developing PAOD/ICVE in patients treated with nilotinib. The rate of specific AEs of interest will be calculated in the two groups of patients with either positive or negative tests. The test however will not be used as a selection criterion to include or exclude patients.

In case the questionnaire results positive at any visits, please refer to a cardiovascular expert for further assessments.

[redacted]

7.2.2.8 Tolerability

Not applicable.

7.2.3 Pharmacokinetics

Not applicable.

[redacted]

7.2.5 Other assessments

No additional tests will be performed on patients entered into the main ENESTPath study.

For those patients consenting to participate in the optional Stem cells ENESTPath substudy, a 10 mL bone marrow sample will be obtained and sent to [redacted] for immunophenotype analysis, FACS cell purification, *in situ* hybridization, and RT-PCR. Measurement will be performed by flow cytometry in a bone marrow purified population of stem cells in order to detect the presence of leukemic Ph+ cells (evaluated by FISH) or BCR-ABL transcript levels (evaluated by RT-PCR). For more detailed information, see the Study Site Manual for bone marrow samples for inmunophenotypic analysis, FACS cell purification, *in situ* hybridization, and RT-PCR.

For those patients, remaining samples will be stored at the National DNA Bank Carlos III, University of Salamanca, Salamanca, Spain, for a maximum of 15 years.

For those patients conseting to participate to 'CML patient's voice' Italian substudy qualitative-quantitative assessment on psycoemotional characteristics will be conducted. [Post text Supplement 1]

8 Safety monitoring and reporting

8.1 Adverse events

8.1.1 Definitions and reporting

An AE 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 AEs 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).

[redacted]

Adverse events that begin or worsen after informed consent should be recorded in the Adverse Events eCRF. Conditions that were already present at the time informed consent was signed should be recorded in the Medical History eCRF. Adverse event monitoring should be continued during TFR phase, and for at least 30 days following the last dose of study treatment or the last day of the TFR phase. Adverse events (including laboratory 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 AE.

Adverse events will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. If CTCAE grading does not exist for an AE, the severity of mild, moderate, severe, and life-threatening, corresponding to grades 1 to 4, will be used. CTCAE grade 5 (death) will not be used in this study; rather, information about deaths will be collected though a Death form.

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

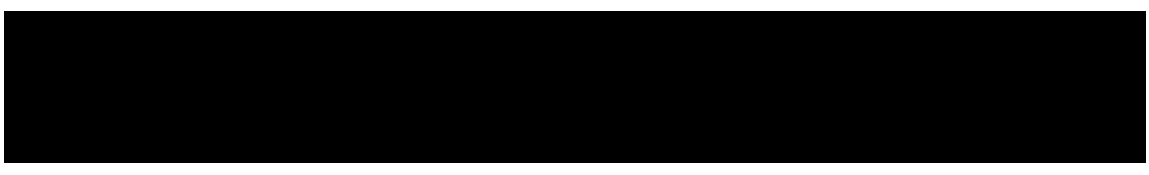
- The severity grade (CTCAE grade 1-4)
- Its duration (start and end dates)
- Its relationship to the study treatment (reasonable possibility that AE is related: No, Yes)
- Action taken with respect to study or investigational treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)
- Whether medication or therapy taken (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
- Outcome (not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequalae, fatal, unknown)
- Whether it is serious, where a SAE is defined as in Section 8.2.1

All AEs 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 AE 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.

Natural progression or deterioration of the malignancy under treatment (including loss of response, progression to AP/BC, and death due to disease progression) will be recorded as part of the efficacy evaluation and should not be reported as an AE/SAE.

AEs separate from the progression of malignancy (e.g. 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.



8.1.2 Laboratory test abnormalities

8.1.2.1 Definitions and reporting

Laboratory abnormalities that constitute an AE in their own right (i.e. 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 an AE 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 AE, it is not necessary to separately record the laboratory/test result as an additional event.

Laboratory abnormalities that do not meet the definition of an AE should not be reported as AEs. 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 laboratory abnormality may be required by the protocol, in which case the laboratory abnormality should still be reported as an AE.

8.1.3 Adverse events of special interest

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

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

If patients experience ischemic vascular or ischemic cardiovascular events (i.e. ischemic, cardiac, cerebrovascular, or peripheral artery-related), carefully consider protocol guidance for dose reduction or study drug discontinuation (Protocol Table 6-2).

The investigator should ensure that the patient is assessed by a vascular or cardiovascular specialist. It is recommended that the standard of care for concurrent ischemic vascular or cardiovascular events should be given to the patients while they are receiving nilotinib therapy. All patients should have their risk factors for such diseases appropriately managed and follow the current recommendations. Careful consideration should be given to the recommendations outlined in the study protocol (Table 6-2, Table 6-3). Additional laboratory assessments of lipid profile and glucose should be performed where clinically indicated.

The SSMC and DMC will be informed on regular basis on the grade 2-4 ischemic vascular or cardiovascular events occurring to the patients enrolled in the AMN107AIC05 trial.

[redacted]

8.2 Serious adverse events

8.2.1 Definitions

A 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, unless hospitalization is for:
    - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (specify what this includes)
    - 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
    - Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
    - Social reasons and respite care in the absence of any deterioration in the patient's general condition

Protocol-exempt SAEs are SAEs specifically defined in the protocol where there has been a clear agreement with regulators not to collect these SAEs in the safety database, provided the information is collected elsewhere. For example, this may include SAEs that are also a primary outcome measure, such as mortality, survival rate, or number of flares of the condition being studied.

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

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form in English, and send the completed, signed form by fax within 24 hours to the oncology Novartis Drug Safety and Epidemiology (DS&E) department.

[redacted]

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

Follow-up information is sent to the same contact(s) to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. Each reoccurrence, 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.

8.3 Emergency unblinding of treatment assignment

Not applicable.

8.4 Pregnancies

To ensure patient safety, each pregnancy in a patient in the induction/consolidation phase, the TFR phase, or the re-treatment phase, or within 30 days of the last dose of nilotinib, must be reported to Novartis within 24 hours of learning about it. 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. If a study patient becomes pregnant or suspects being pregnant during the study or within 30 days of the last dose of nilotinib, the Study Doctor needs to be informed immediately, and study treatment with nilotinib has to be stopped immediately.

Pregnancy should be recorded on a Clinical Study Pregnancy Form and reported by the investigator to the oncology Novartis DS&E department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship of any pregnancy outcome to the Novartis study treatment. 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 ICF and should be discussed with the patient during the study as needed.

8.6 Data Monitoring Committee (DMC)

A Data Monitoring Committee (DMC) will be established prior to the randomization of the first patient. The DMC will be responsible for reviewing the trial. It is expected that the DMC will consist of four hematologists, one cardiologist, and one PAG member. There will be a DMC charter describing their roles and responsibilities and discussing potential data format and process issues.

[redacted]

DMC reports will be provided regularly and specifically:

- When at least 200 patients enrolled in the trial have been treated with nilotinib 300 mg BID for 6 months or discontinued earlier
- When 300 patients have been treated for 1 year (expected in March 2015), with objectives to assess both efficacy and safety.
- When 300 patients have been treated for 2 years (expected in March 2016) with the objectives to assess both efficacy and safety.
- After 100 patients have had a minimum of 6 months' follow-up in the TFR phase

DMC reports will include a first assessment of molecular response and early discontinuation rate after switching treatment to nilotinib. If the response rates or the attrition rate makes the achievement of the target number of patients randomized unlikely, the overall number of patients needing to be enrolled into the trial will be reassessed in coordination with the study statistician.

In addition to the planned DMC reports, additional safety analyses may also be performed at the discretion of the DMC.

The above timing for meetings will be discussed with the DMC and modified if requested during the course of the trial.

It is envisioned that the DMC may make four types of recommendations, namely:

1. No safety issues, ethical to continue the study as planned
2. Recommendation to continue the study but proposing an amendment to the protocol (e.g. incorporate additional safety assessments)
3. Serious safety concerns precluding further study conduct, regardless of efficacy
4. Other recommendations per DMC decision

8.7 Scientific Study Management Committee

An SSMC will be established comprising investigators participating in the trial who are clinical experts in CML.

The SSMC will ensure:

- Transparent management of the study according to the protocol through recommending and approving modifications as circumstances require
- Review of protocol amendments as appropriate

At a minimum, the SSMC will meet once a year. The details of the role of the SSMC are defined in the SSMC charter.

9 Data collection and management

9.1 Data confidentiality

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

[redacted]

- 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 patient revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of patient authorization. For patients who have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. whether the patient is alive) 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.

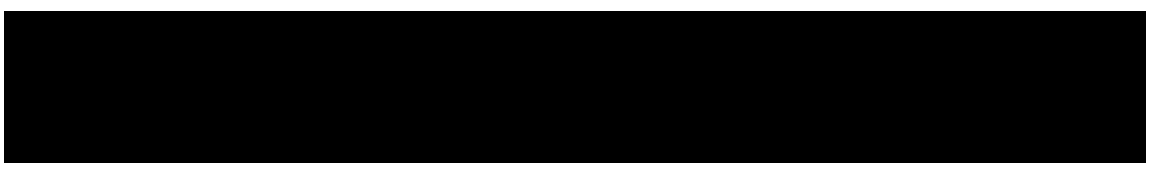
Prior to entering key sensitive personally identifiable information (patient initials and exact date of birth), the system will prompt the site to verify that this data is allowed to be collected. If the site indicates that country rules or ethics committee standards do not permit collection of these items, the system will not solicit patient initials. Year of birth will be solicited (in the place of exact date of birth) to establish that the patient 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 (or designated Contract Research Organization [CRO]) 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 and to Good Clinical Practice (GCP), 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, ECGs, 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 ICF (a signed copy is given to the patient).

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



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 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 and accurate, and that entry and updates are performed in a timely manner.

9.4 Database management and quality control

Novartis personnel (or designated CRO) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the remote data capture (RDC) system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments entered into the database will be coded using the World Health Organization Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

Randomization codes and data about which arm the patient has been assigned to will be tracked using IVRS. The data will be sent electronically to Novartis personnel (or designated CRO).

For RDC 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

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 sustained $MR^{4.0}$ or better ($\geq MR^{4.0}$) for the last 12 months on study) and are randomized.

10.1.2 Patients entering the TFR phase

This population includes all patients who are randomized and enter the TFR phase. For Arm 1, this population matches the FAS. For Arm 2, it includes all patients entering the TFR phase after the additional 12-month treatment period.

[redacted]

10.1.3 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 study phases and corresponding time windows.

10.1.4 Per-Protocol Set

The PPS consists of a subset of the patients in the FAS who are compliant with requirements of the clinical study protocol.

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

10.1.5 Other analysis sets

Secondary [redacted] efficacy analyses will be performed in the following analysis populations:

- **All patients enrolled** who received at least one dose of study medication;
- **Patients entering the optional Stem cells substudy** who received at least one dose of study medication.
- **Patients entering the 'CML patient's voice' Italian substudy**

10.2 Patient demographics/other screening characteristics

Demographic and other data will be summarized descriptively for both the SS and the FAS. Categorical data will be presented as frequencies and percentages. For continuous data, summary statistics, such as mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum, will be presented.

10.3 Treatments (study treatment, concomitant therapies, compliance)

All study medication data will be summarized using the safety set (SS).

Time on treatment, duration of exposure, percentage of days on treatment, average dose intensity, and actual daily dose will be summarized.

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

10.4 Primary objective

The primary objective of this trial is to assess the optimal duration of consolidation treatment with nilotinib 300 mg BID in order that patients remain in TFR ($\geq MR^{4.0}$) without molecular relapse 12 months after entering the TFR phase.

10.4.1 Variable

The primary efficacy variable is the number of patients who remain in TFR ($\geq MR^{4.0}$), without molecular relapse and without re-starting nilotinib therapy, at the end of 12 months in the TFR phase of the study, in the nilotinib 12 months consolidation treatment arm (total trial time 24

[redacted]

months + 36 months) versus the nilotinib 24 months consolidation treatment arm (total trial time 36 months + 24 months).

10.4.2 Statistical hypothesis, model, and method of analysis

The optimal duration of a nilotinib 300 mg BID treatment will be evaluated using the null hypothesis that the rate of no documented confirmed loss of $MR^{4.0}$, no loss of MMR in the first 12 months after nilotinib cessation is the same in both the arms, with an alternative hypothesis that this rate is 40% in Arm 1 versus 60% in Arm 2.

- H0: p1 = p2, where p1 and p2 are the rates of no documented confirmed loss of $MR^{4.0}$, no loss of MMR in the first 12 months after starting TFR phase in the two arms of the study
- H1: p1 $\neq$ p2, where p1= 0.40 and p2 = 0.60

A two-sided test with $\alpha = 0.05$ will be used to test this hypothesis.

The rate of successful TFR will be presented together with an exact 95% Clopper-Pearson confidence interval.

The chi-square test will be carried out to compare the percentage of patients with no documented confirmed loss of $MR^{4.0}$, no loss of MMR in the first 12 months after starting TFR phase in the two arms of the study.

A primary efficacy analysis will be performed on the patients entering the TFR phase.

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 as unsuccessful TFR. In case of missing PCR assessment at 12 months after starting the TFR phase, the PCR assessments at 10 and 15 months will be taken into account, if available. Details will be provided in the RAP.

10.4.4 Supportive analyses

The primary analysis will be repeated on the FAS and PPS. Patients randomized to Arm 2 not entering the TFR phase will be considered as unsuccessful TFR. The same rule described in the previous section will be used to deal with any missing PCR assessment at Month 12.

The proportion of patients treatment free ($\geq MR^{4.0}$) after 2 years and after 3 years from randomization will also be computed based on the FAS and descriptively summarized by arm.

10.5 Secondary objectives

10.5.1 Key secondary objective(s)

The key secondary objectives for this trial are:

- To evaluate the proportion of patients who are eligible to suspend nilotinib therapy by achieving and maintaining a sustained $\geq MR^{4.0}$ for at least 12 months during consolidation treatment with nilotinib 300 mg BID:
  - Determined by the proportion of patients who have achieved a sustained $\geq MR^{4.0}$ (defined as having four out of five quarterly assessments of $\geq MR^{4.0}$ by a EUTOS

[redacted]

standardized laboratory over the last 12 months and the last assessment before randomization is $\geq MR^{4.0}$) during the consolidation phase of the study

- The proportion of patients who are in sustained $\geq MR^{4.0}$ at 24 months after completing the induction/consolidation phase will be calculated by dividing the number of patients who have achieved sustained $\geq MR^{4.0}$ over at least the last 12 months of the consolidation phase by the number of patients who entered the study protocol

- To assess the achievement of MMR, $MR^{4.0}$, and $MR^{4.5}$ during induction/consolidation treatment with nilotinib 300 mg BID at the different time points in patients without that response at study entry:
  - Determined by the proportion of patients who achieve MMR, $MR^{4.0}$, or $MR^{4.5}$ on the study at selected timepoints (every 3 months until Month 24 or 36 depending on the randomized arm) during the induction/consolidation phase
  - The proportion of patients achieving MMR, $MR^{4.0}$, or $MR^{4.5}$ at selected timepoints will be computed based on the number of patients without that response at baseline
- To assess the molecular response in patients during the induction/consolidation phase with nilotinib 300 mg BID at the different time points:
  - Determined by the proportion of patients in MMR, $MR^{4.0}$, or $MR^{4.5}$ at selected time points (every 3 months until Month 24 or 36 depending on the randomized arm) during the induction/consolidation phase of the study
  - The proportion of patients in MMR, $MR^{4.0}$ or $MR^{4.5}$ at selected time points will be descriptively analyzed on all patients enrolled
- To assess the proportion of patients in TFR at 3, 6, 12, 18, and 24 months after nilotinib cessation in the two treatment arms:
  - Determined by the proportion of patients with no confirmed loss of $MR^{4.0}$, no loss of MMR, and no re-starting of nilotinib therapy within the first 3, 6, 12, 18 and 24 months following nilotinib cessation
  - The proportion of patients in TFR will be calculated by dividing the number of patients with no confirmed loss of $MR^{4.0}$, no loss of MMR, and no re-starting of nilotinib therapy in the first 3, 6, 12, 18 and 24 months following nilotinib cessation by the number of patients entering the TFR phase in the two treatment arms
- To assess the molecular response in patients after randomization in the two treatment arms:
  - Determined by the proportion of patients who are in MMR, $MR^{4.0}$ or $MR^{4.5}$ at selected time points (i.e. Month 3, Month 6, Month 12 and every 3 months thereafter until Month 24 or 36 depending on the randomized arm) during the TFR phase in each of the two treatment arms
  - The proportion of patients in MMR, $MR^{4.0}$ or $MR^{4.5}$ at selected time points during the TFR phase will be descriptively analyzed on the number of patients in the TFR phase in each of the two treatment arms
- To assess the kinetics of BCR-ABL transcript level during induction/consolidation treatment with 300 mg BID nilotinib, during the TFR phase and during the nilotinib re-treatment phase:

[redacted]

  - Descriptive statistics of BCR-ABL transcript levels (IS) over time separately for the induction/consolidation phase, TFR phase, and nilotinib re-treatment phase will be provided
- To assess the PFS rate after randomization in the two treatment arms:
  - Failure of PFS is defined as the earliest occurrence of: progression to AP/BC or death from any cause
  - KM estimation of PFS, which is measured from the randomization date to the date of the earliest failure event, will be used for this analysis. Patients not known to have progressed or died on or before the cut-off date for the KM analysis will have their PFS censored at the earlier of the date of their last assessment for patients who are still on study and the date of last contact for patients who are in follow-up.
- To assess the TFS rate after start of the TFR phase in the two treatment arms:
  - Failure of TFS is defined as lack of any of the following events: loss of MMR, confirmed loss of $MR^{4.0}$, re-start of nilotinib treatment, progression to AP/BC, or death from any cause
  - KM estimation of TFS, which is measured from the start of TFR phase to the date of the earliest failure event, will be used for this analysis. Patients not known to have had any of the events on or before the cut-off date for the KM analysis will have their TFS censored at the earlier of the date of their last assessment for patients who are still on study and the date of last contact for patients who are in follow-up.
- To estimate the OS rate after randomization in the two treatment arms:
  - KM estimation of OS, which is measured from the date of randomization to the date of death due to any cause, will be used for this analysis. For patients not known to have died on or before the cut-off date, survival time will be censored at the date of last contact.
- To assess the safety profile of nilotinib during the induction/consolidation phase, the TFR phase, and the re-treatment phase (see Section 10.5.3)

10.5.2 Other secondary efficacy objectives

For those patients consenting to participate in the optional Stem cells ENESTPath substudy, the following secondary objectives will also be evaluated:

- To evaluate the presence and number of LSC and their progenitors in the bone marrow of all patients participating in this substudy before and after completing induction and first year of consolidation phase (at Visit 8):
  - The proportion of patients presenting LSC in the bone marrow will be calculated at each time point and descriptively analyzed.

[redacted]

- To evaluate whether a longer treatment period of consolidation with nilotinib (patients in Arm 2 versus patients in Arm 1) induces a reduction in the percentage of patients presenting LSC and progenitor cells in bone marrow at the end of consolidation phase and to quantify this reduction:
  - The proportion of patients presenting LSC in the bone marrow at the end of the consolidation arm (Visit 8 for Arm 1 and Visit 204 for Arm 2) will be descriptively analyzed by treatment arm
- To perform an exploratory analysis in order to evaluate whether relapse in patients during the TFR phase in either arm correlates with the presence of LSC and progenitor cells in bone marrow at the end of the consolidation phase and at the time of relapse during TFR.

Please refer to the [Post-Text Supplement 1] to see the objectives of the 'CML patient's voice' Italian substudy.

10.5.3 Safety objectives

10.5.3.1 Analysis set and grouping for the analyses

Safety analyses will be based on the SS and presented by study phase. The safety summary tables will include only assessments collected no later than 30 days after study treatment discontinuation. All safety assessments will be listed, and those collected later than 30 days after treatment discontinuation will be flagged.

10.5.3.2 Adverse events

The incidence of treatment-emergent AEs (new or worsening from screening visit) will be summarized by MedDRA System Organ Class and Preferred Term, severity (based on CTCAE grades), type of AE, and relation to study treatment.

Deaths reportable as SAEs and non-fatal SAEs will be listed by patient and tabulated by type of AE and study phase.

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

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

10.5.3.3 Laboratory abnormalities

For laboratory tests covered by the CTCAE version 4.03, the study's biostatistician will grade laboratory data accordingly. Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used.

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

The following summaries, split by treatment and study phase, will be generated separately for hematology and clinical chemistry:

[redacted]

- 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
- Listing of all laboratory data with values flagged to show the corresponding CTCAE grades and the classifications relative to the laboratory normal ranges

[redacted]

10.5.3.4 Other safety data

Other safety data collected (e.g. ECG, vital signs, Edinburgh Claudication Questionnaire) 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.

10.5.3.5 Supportive analyses for secondary objectives

Not applicable.

10.6 Interim analysis

No formal interim analyses are planned. Analyses may be performed periodically (e.g. annually), if needed, to fulfill regulatory requests, safety updates as per recommendation of the DMC (see Section 8.6 , DMC) or for publication purposes.

10.7 Sample size calculation

In total, it is expected that approximately 565 patients from approximately 300 centers will be recruited into this study.

This sample size calculation has been based on an estimation of the difference in the percentage of patients relapsing during the 12-month TFR phase of the study between the two treatment arms.

Based on new data from the ENESTcmr it is expected that 40% of the patients switched from imatinib to nilotinib will achieve $MR^{4.0}$ or better at the end of the 12-month induction phase, and will maintain this level of molecular response by the end of the 12-month consolidation phase prior to randomization. Furthermore, if the patients treated with nilotinib for 24 months before entering the TFR phase (Arm 1) have a similar relapse rate as the patients in the STIM trial (Mahon et al 2011), it is expected that 40% of patients randomized to Arm 1 will not have relapsed after the 12-month TFR phase. Based on new information from a number of recently published studies (Hughes TP et al 2014; Blood 124:729-736; Mahon FX et al 2014; Blood 124(21):151; Rea D et al 2014 811; Blood 124 (21)) it is reasonable to assume that a 12-month longer consolidation period with nilotinib (Arm 2) may reduce the molecular relapse rate in the first 12-month TFR phase by approximately 20% (i.e. from 60% to 40%, absolute difference of 20%).

[redacted]

Therefore, it is assumed that the percentage of patients without relapse will be 40% in Arm 1, and 60% in Arm 2. Considering this, a sample size of 107 patients per group (a total of 214) is needed to detect such difference. These calculations are based on a two-sided chi-square test at the 0.05 alpha level and with a power of 80%.

Assuming that 5% of patients will be unevaluable after randomization, a total of 226 patients will need to be randomized in order to adequately power the study.

Finally, as explained above, assuming that 40% of the patients switched from imatinib to nilotinib will achieve $\geq MR^{4.0}$ at the end of the 12-month induction phase, and will maintain this level of MR by the end of the 12-month consolidation phase prior to randomization, a total of 565 patients are required for this study.

10.8 Power for analysis of key secondary variables

Not applicable.

11 Ethical considerations and administrative procedures

11.1 Regulatory and ethical compliance

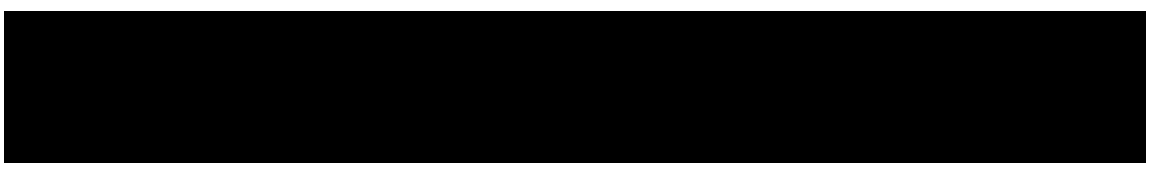
This clinical study was designed, shall be implemented, and will be reported in accordance with the International Conference on Harmonization (ICH) Harmonised Tripartite Guidelines for GCP, with applicable local regulations (including European Directive 2001/20/EC and US Code of Federal Regulations Title 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 ICF must be reviewed and approved by a properly constituted IRB/IEC/Research Ethics Board (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 be included in the study only after providing written (witnessed, where required by law or regulation) and 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's source documents. The date when a patient's informed consent was actually obtained will be captured in their eCRFs.



Novartis will provide investigators in a separate document with a proposed 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 childbearing 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 into the study.

Those patients who decide to participate in the optional Stem cells ENESTPath substudy will sign a specific ICF, separate from the ICF for the core protocol. Refusal to give consent for the stem cells study will not affect eligibility for the main ENESTPath study.

Those patients who decide to participate in the **'CML patient's voice' Italian sub study** will sign a specific ICF, separate from the ICF for the core protocol. This substudy will be conducted in Italy only.

11.4 Discontinuation of the study

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

11.5 Publication of study protocol and results

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

Together with the clinical trial team, the DMC chair and the SSMC Chair will also develop recommendations for publication of study results, including authorship rules.

All authors must have:

- Contributed substantially to the concept, design and/or conduct of the (i.e. patient accrual), or to the acquisition, analysis, and interpretation of data, AND
- Drafted or critically revised the proposed clinical publication for important intellectual content, AND
- Approved the final proposed clinical publication for submission, AND
- Have intimate knowledge of trial implementation/analysis

Authors may be external or internal to Novartis. There is no predetermined ratio of internal to external authors but due consideration will be given to balance.

The details of the publication guidelines are summarized in the ENESTPath publication charter.

[redacted]

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 patients. 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 patient files and records kept at the pharmacy, laboratories, and medico-technical departments involved in the clinical trial.

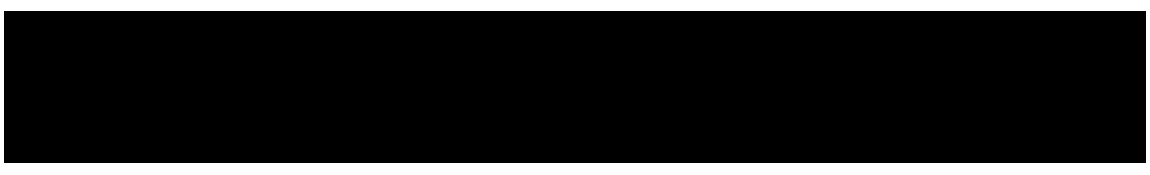
Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site Principal Investigator. The study eCRF is the primary data collection instrument for the study. The investigator should ensure the accuracy, completeness, legibility, and timeliness of the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

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

Essential documents (written and electronic) should be retained for a period of not less than 15 years from the completion of the clinical trial unless the 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 ICFs and the 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 the study personnel who is directly involved in the treatment or evaluation of patients at the site, prior to study start.

12 Protocol adherence

Investigators must 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 Clinical Study Report.

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/REB at the study site should be informed within 10 working days.

[redacted]

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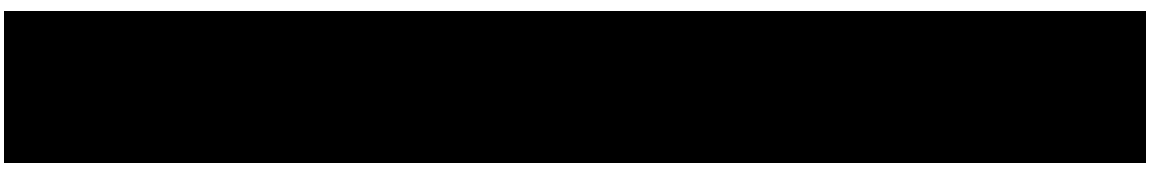
For the 'CML patients' voice' Italian substudy, please refer to the Post text Supplement 1



14 Appendices

14.1 Appendix 1 List of CYP3A4 inducers and inhibitors

14.1.1 List of medications metabolized by CYP3A4, strong, moderate and weak inhibitors of CYP3A4 to be used with caution

CYP3A4 substrates permitted but patients should be carefully monitored for drugs indexed 1 and 2		**Strong inhibitors**	**Moderate inhibitors**	**Weak inhibitors**
alfentanil[1,2]	fentanyl[2]	clarithromycin	aprepitant	alprazolam
fluticasone[1]	diergotamine[2]	conivaptan	atazanavir	AMD070
cyclosporine[2]	adinazolam	indinavir	cimetidine	amlodipine
maraviroc[1]	alprazolam	itraconazole	ciprofloxacin	azithromycin
midazolam[1]	amlodipine	ketoconazole	darunavir	bicalutamide
alpha-dihydroergocryptine[1]	aripiprazole	lopinavir	diltiazem	chlorzoxazone
sildenafil[1]	chlorpheniramine	mibefradil	erythromycin	cilostazol
tipranavir[1]	diazepam	nefazodone	fluconazole	cyclosporine
triazolam[1]	estazolam	nelfinavir	grapefruit juice	fluvoxamine
perospirone[1]	nisoldipine	posaconazole	imatinib	ginkgo
darifenacin[1]	quinine	ritonavir	tofisopam	goldenseal
ebastine[1]	trazodone	saquinavir	verapamil	isoniazid
eletriptan[1]	nitrendipine	telithromycin		lacidipine
eplerenone[1]	mevastatin	troleandomycin		M100240
everolimus[1]	lovastatin[1]	voriconazole		oral contraceptives
felodipine[1]	atorvastatin[1]			peppermint oil
brotizolam[1]	simvastatin[1]			propiverine
budesonide[1]	fluvastatin			ranitidine
buspirone[1]				ranolazine
sirolimus[1,2]				roxithromycin
ergotamine[2]				Seville orange juice
				tabimorelin

[1] Sensitive substrates: drugs whose plasma AUC values have been shown to increase 5-fold or higher when co-administered with a potent inhibitor of the respective enzyme.

[2] Substrates with narrow therapeutic index (NTI): drugs whose exposure-response indicates that increases in their exposure levels by the concomitant use of potent inhibitors may lead to serious safety concerns (e.g., Torsades de Pointes).

Note:

- Inhibitor classification:
  - Strong inhibitors may result in a substrate AUC > 5-fold increase.
  - Moderate inhibitors may result in a substrate AUC ≥ 2-fold increase and < 5-fold increase.

[redacted]

- Weak inhibitors may result in a substrate AUC ≥ 1.25-fold increase and < 2-fold increase.

This list is compiled based on the FDA's "Guidance for Industry, Drug Interaction Studies", the Indiana University School of Medicine's Drug Interactions Database, and 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 30 August 2010) for update or more details.

[redacted]

14.2 Edinburgh Claudication Questionnaire

The Edinburgh Claudication Questionnaire

(1) Do you get a pain or discomfort in your leg(s) when you walk?
Yes ☐
No ☐
I am unable to walk ☐

If you answered "Yes" to question (1)—please answer the following questions. Otherwise you need not continue.

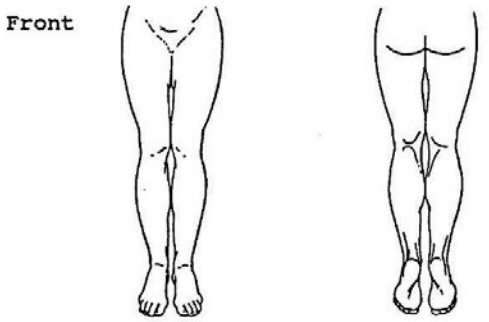
(2) Does this pain ever begin when you are standing still or sitting? Yes ☐ No ☐

(3) Do you get it if you walk uphill or hurry? Yes ☐ No ☐

(4) Do you get it when you walk at an ordinary pace on the level? Yes ☐ No ☐

(5) What happens to it if you stand still?
Usually continues more than 10 minutes ☐
Usually disappears in 10 minutes or less ☐

(6) Where do you get this pain or discomfort?
Mark the place(s) with "×" on the diagram below.



Definition of positive classification requires all of the following responses: "Yes" to (1), "No" to (2), "Yes" to (3), and "usually disappears in 10 minutes or less" to (5); grade 1 = "No" to (4) and grade 2 = "Yes" to (4). If these criteria are fulfilled, a **definite** claudicant is one who indicates pain in the calf, regardless of whether pain is also marked in other sites; a diagnosis of *atypical* claudication is made if pain is indicated in the thigh or buttock, in the absence of any calf pain. Subjects should not be considered to have claudication if pain is indicated in the hamstrings, feet, shins, joints or appears to radiate, in the absence of any pain in the calf.

FIGURE 4. *The Edinburgh Claudication Questionnaire. (Reprinted with permission from Leng GC, Fowkes FGR. The Edinburgh Claudication Questionnaire: An improved version of the WHO/Rose Questionnaire for use in epidemiological surveys.* J Clin Epidemiol. *1992;45:1109.[19])*

[redacted]