

Clinical Development

AMN107 (Nilotinib, Tasigna®)

Protocol CAMN107A2408 / NCT01698905

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

Statistical Analysis Plan (SAP)

528-week Update

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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
AP	Accelerated phase
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
ATP	Adenosine triphosphate
AUC	Area under curve
BC	Blast crisis
BCR	Break point cluster region
BCR-ABL	BCR-ABL oncoprotein product of BCR-ABL fusion gene
BID	bis in diem/twice a day
CCyR	Complete cytogenetic response
CHR	Complete hematologic response
CI	Confidence interval
CML	Chronic myeloid leukemia
CMR	Complete molecular response
CP	Chronic phase
CRF	Case Report/Record Form; the term CRF can be applied to either EDC or Paper
CRO	Contract Research Organization
CSP	Clinical study protocol
CSR	Clinical study report
CTCAE	NCI Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
DS&E	Drug Safety and Epidemiology
EC	European Commission
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture
ELN	European Leukemia Net
EOS	End of study
EOT	End of Treatment
CCI	
ER	Emergency room
FAS	Full Analysis Set
FDA	Food and Drug Administration (USA)
FISH	Fluorescent In-situ Hybridization
GCP	Good Clinical Practice
IB	Investigator Brochure
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IFN	Interferon
IN	Investigator Notification
IRB	Institutional Review Board
IS	International scale

KM	Kaplan-Meier
LFTs	Liver Function Tests
LLN	Lower limit of normal
LLOQ	Lower limit of quantification
CCI	
MedDRA	Medical dictionary for regulatory activities
MMR	Major molecular response
MR	Molecular response
MR 4.5	Molecular response 4.5 log reduction from baseline
MR4.0	Molecular response 4.0 log reduction from baseline
MRD	Minimal residual disease
NCCN	National Comprehensive Cancer Network
OS	Overall survival
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
RAP	The Report and Analysis Plan
REB	Research Ethics Board
RQ-PCR	Reverse transcription Quantitative Polymerase Chain Reaction
CCI	
SAE	Serious Adverse Event
SD	Standard deviation
SMC	Study Management Committee
Sp	Specialist
SS	Safety Set
STAT5	Signal transducer and activator of transcription 5
SUSAR	Suspected Unexpected Serious Adverse Reaction
TFR	Treatment-free remission
TFS	Treatment-free survival
TKI	Tyrosine kinase inhibitor
UC	Urgent care
ULN	Upper limit of normal
VAP	Validation and Planning
VAS	Visual analogue scale
WBC	White blood cell

Document History – Changes compared to previous version of SAP.

Version	Date	Changes
CCI		

Version	Date	Changes
		

Version	Date	Changes
		

Version	Date	Changes
		

CCI

Version	Date	Changes
		

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1 Introduction

1.1 Document content

This SAP describes the statistical methods for all safety and efficacy analyses planned to be included in the 528-week CSR. Some additional analyses, such as biomarkers, mutational analysis and pharmaco-economic analyses which might be described separately will be described in separate documents. It is structured as

- a draft of Section 9.7 (Statistical methods planned in the protocol and determination of sample size) of the CSR
- a draft of Appendix 16.1.9 (Documentation of statistical methods) of the CSR

1.2 References

Please refer to the following documents:

- CSR template (Annual report for 9th year and Full Clinical Study Report)
- The Master Analysis Plan for the project (AMN107A2303)
- Guidelines for content of Statistical Appendices of the Clinical Study Report

1.3 Update for the 6-, 7-, 8- 9- and 10 -year report

1. According to team discussion and endorsement, a brief short report instead of a full CSR was implemented for the 6, 7, 8 and 9 year update and full CSR will be prepared for the final 10-year update. Timepoints by 6/7/8/9 years correspond to 312/360/408/468 weeks, respectively, and 10-year correspond to 528-week. The main purpose is to include only analyses addressing the FDA PMR request: PMR 2: Characterize the potential risk of resistance to treatment after discontinuation of Tasigna by collecting and reporting information on late relapses, loss of response, and occurrence of mutations (risk of developing resistance), on a yearly basis from trials CAMN107A2408 and CAMN10712201. Submit annual summaries with the annual post-marketing reporting and submit cumulative 3, 5 and 10 year reports.
2. PMR 3: Characterize safety for patients who are still in remission or experienced loss of major molecular response and restarted Tasigna in trials CAMN107A2408 and CAMN10712201. Assess mortality, late adverse events, incidence of pancreatitis, diabetes, arterial vascular disease, and other comorbid conditions. Submit annual summaries with the annual post-marketing reporting and submit cumulative 3, 5 and 10 year reports.

Only the selected critical efficacy and safety analyses was included in the 6-, 7-, 8-and 9-year short interim report. Below were the main analyses:

- Summary of dose adjustment/interruption,
- Disposition summary,
- Exposure summary.

- Efficacy to be included to address PMR 2:
 - MMR/MR4.5 rates at 96, 144, 192, 264 weeks, and at the end of 6, 7, 8, 9 and 10 years after starting the TFR phase (patients who required re-initiation of treatment will be considered as non-responders),
 - Treatment-free survival (TFS) after the start of the TFR phase,
 - Duration of re-initiated treatment required to regain MMR/MR4.5,
 - Rate of stable MMR/MR4.5 after achievement of response in the nilotinib re-initiation phase for 48 weeks, 96 weeks, 144 weeks, 192 weeks, 240 weeks, 288 weeks, 336 weeks, 384 weeks and 432 weeks, based on availability of appropriate data,
 - BCR-ABL1 mutations in patients who lost MMR during the TFR phase.
- Safety to be included to address PMR 3:
 - key AE summaries (cumulative and by year in TFR summaries): all AEs, AEs related to study drug, SAEs, AEs leading to discontinuation, AEs leading to dose adjustments/interruptions, AESIs.
 - Deaths (cumulative and by year in TFR summaries),
 - Laboratory (cumulative and by year in TFR summaries),
 - Cumulative summaries of ECG,
 - Other safety issues requested by FDA.

For the objective and endpoints please refer to protocol Section 3.

2 CSR Section 9.7 – Statistical methods planned in the protocol and determination of sample size

2.1 CSR Section 9.7.1 – Statistical and analytical plans

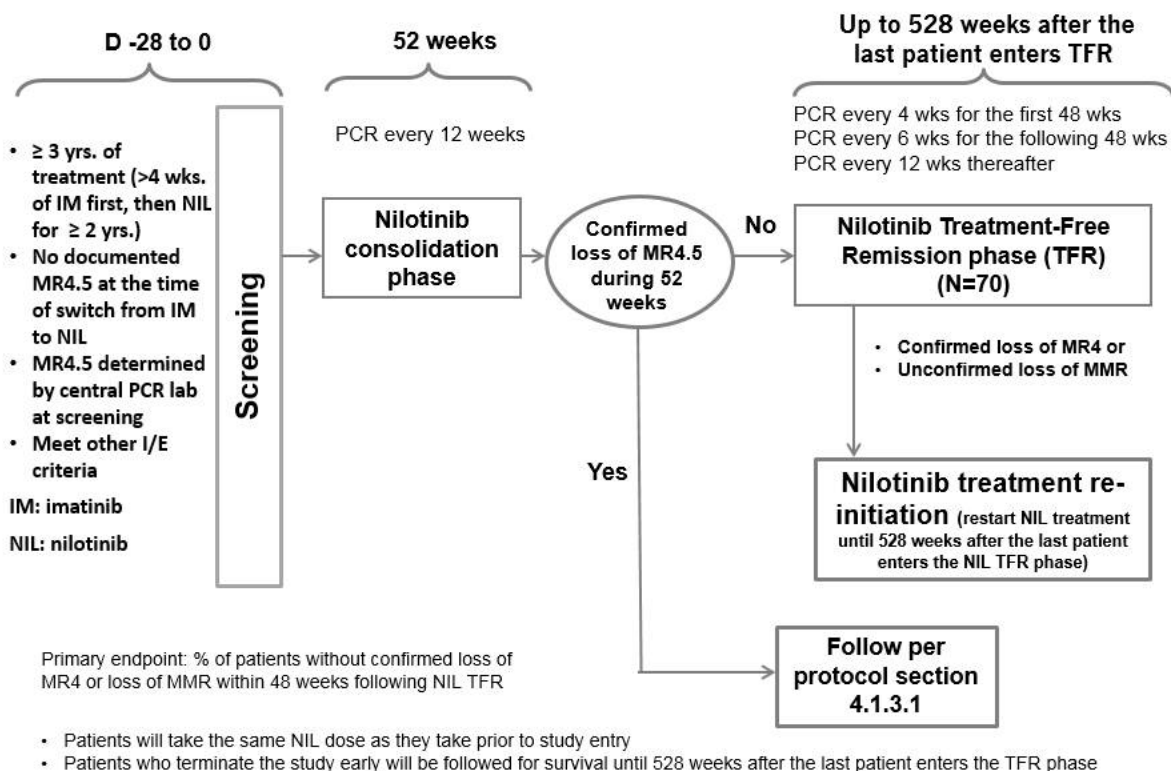
Data will be analyzed by Novartis according to the data analysis Section 10 of the study protocol which is available in Appendix 16.1.1 of the CSR. Important information is given in the following sections and details are provided, as applicable, in Appendix 16.1.9 of the CSR.

This study follows an open-label, prospective, multi-center, non-comparative phase II design. The analysis of the primary efficacy endpoint, proportion of patients without confirmed loss of MR4 or loss of MMR or re-initiation of treatment within 48 weeks following cessation of nilotinib therapy, will be performed 48 weeks after the last patient enter into the TFR phase. This primary analysis at 48 weeks of TFR was only performed based on 48-week data, and is not applicable for 96/144/192/264-week and for 6, 7, 8, 9 and 10 years CSR analyses.

Unless otherwise specified, all statistical tests will be conducted against a 2-sided alternative hypothesis, employing a significance level of 0.05.

2.2 Study phases

Figure 2-1 Study design



This study has following 7 phases:

- **Consolidation phase:** Patients who satisfy all inclusion/ exclusion criteria will enroll in the consolidation phase. The consolidation phase is scheduled for 52 weeks. If a patient maintains MR4.5 throughout the consolidation phase, he/she will be eligible to enter in the TFR phase. If a patient has confirmed loss of MR4.5 during the consolidation phase, he/she will not be eligible to enter in the TFR phase and will continue nilotinib treatment.
- **TFR phase:** Patients who are eligible to enter in the TFR phase after completing the 52-week consolidation phase, will stop taking nilotinib on the first day of TFR phase (the first day of TFR phase is the first day without any nilotinib treatment after the consolidation phase). Duration of this phase is up to 10 calendar years (528 weeks) after the last patient enters in the TFR phase. Confirmed loss of MR4 or loss of MMR in TFR phase will trigger restarting nilotinib treatment.
- **Treatment continuation phase:** Patients who are not eligible to enter in the TFR phase after completing the 52-week consolidation phase, will enter in the treatment continuation phase and will continue nilotinib treatment for another 52 weeks. If a patient maintains MR4.5 throughout the treatment continuation phase, he/she will be eligible to enter in the second TFR (TFR-2) phase. If a patient has confirmed loss of MR4.5 during the treatment

continuation phase, he/she will not be eligible to enter in the TFR-2 phase and will continue nilotinib treatment.

- **Treatment re-initiation phase:** During the TFR phase if a patient has confirmed loss of MR4 or loss of MMR, he/she will restart nilotinib treatment and will enter in the treatment re-initiation phase. Duration of this phase is up to 10 calendar years (528 weeks) after the last patient enters in the TFR phase.
- **TFR-2 phase:** Patients who are eligible to enter in the TFR-2 phase after completing the 52-week treatment continuation phase, will stop taking nilotinib on the first day of TFR-2 phase (the first day of TFR-2 phase is the first day without any nilotinib treatment after the nilotinib continuation phase). Duration of this phase is up to 10 calendar years 528 weeks after the last patient enters in the TFR phase. Confirmed loss of MR4 or loss of MMR in TFR-2 phase will trigger restarting nilotinib treatment.
- **Treatment re-initiation-2 phase:** During the TFR-2 phase if a patient has confirmed loss of MR4 or loss of MMR, he/she will restart nilotinib treatment and will enter in the treatment re-initiation-2 phase. Duration of this phase is up to 10 calendar year (528 weeks) after the last patient enters in the TFR phase.
- **Prolonged treatment continuation phase:** Patients who are not eligible to enter in the TFR-2 phase after completing the 52-week consolidation phase and 52-week treatment continuation phase, will enter in the prolonged treatment continuation phase. Duration of this phase is up to 10 calendar year (528 weeks) after the last patient enters in the TFR phase.

Data included in the analysis

It is planned that the data from all centers that participate in this protocol will be pooled and utilized. All data reported in the database (scheduled and unscheduled visits) up to the cut-off date will be included in the analyses. Specifically, these include:

- All data obtained after informed consent was signed.
- All data from all 7 study phases.
- All data during 30 day safety follow up and post-treatment follow up.

For patients who discontinue from the study early for any reason, the survival follow-up will be done every three months up to 10 calendar years (528 weeks) after the last patient enters in the TFR phase. In these visits, survival information, stem cell transplantation, TKI therapy status, disease progression to AP/BC according to protocol definition and CML related death will be collected.

The data cut-off date for the primary analysis was done by the date when all patients who had entered the TFR phase have completed the visit of week 48 in the TFR phase, had re-initiated treatment or discontinued early from the study, whatever happens first.

2.3 Open study and blinded data

This study is an open label, single arm study where investigators, patients and Novartis employees involved in the analyses have full knowledge of the treatment allocation.

2.4 Analysis populations

The following populations will be considered for data analysis:

Full Analysis Set (FAS) includes all patients who enter into the TFR phase.

FAS will be used for all efficacy analyses, patient disposition, demographics and baseline characteristics.

Safety Set (SS) includes all patients who received at least one dose of study medication in the consolidation phase. Safety analyses will be presented, both overall (i.e. pooling all study phases) using the overall safety set and also for different study phases using the following safety subsets defined for these study phases:

- **Consolidation Safety Set:** patients who received at least one dose of study medication in the consolidation phase.
- **TFR Safety Set:** patients who enter the TFR phase (equivalent to FAS).
- **Treatment continuation Safety Set:** patients who received at least one dose of study medication during nilotinib treatment continuation phase.
- **Treatment re-initiation Safety Set:** patients who received at least one dose of study medication during treatment re-initiation phase after TFR phase.
- **TFR-2 Safety Set:** patients who entered TFR-2 phase.
- **Treatment re-initiation-2 Safety Set:** patients who received at least one dose of study medication during treatment re-initiation phase 2.
- **Prolonged continuation Safety set:** patients who received at least one dose of study medication during treatment prolonged continuation phase.

Safety data collected during these phases will only be included in safety analyses when a particular safety set is used.

Safety set will be used for all safety analyses.

Per-Protocol Set (PPS) consists of a subset of the patients in the FAS who are compliant with requirements of the clinical study protocol (CSP), without major protocol deviations.

Major protocol deviations leading to exclusion from the PPS are detailed in the protocol deviation tab of study specification document (SSD) and will be documented before DBL.

The per-protocol was also used for supportive analysis of the primary endpoint.

Pharmacokinetic analysis set (PAS) includes all patients who receive at least one dose of study medication and provided evaluable nilotinib trough PK sample at the end of consolidation phase (i.e. pre-dose on D336).

A pre-dose PK trough sample will be considered un-evaluable if:

- the patient did not take nilotinib for at least 3 consecutive days without interruption or dose modification prior to the PK sampling day according to the originally assigned dosage
- or if it cannot be confirmed that the PK sampling day is the next day of the last previous dosing day, and the PK sampling time is earlier than the next dosing time.

- or the trough sample was considered un-evaluable as per scientific judgment by clinical pharmacology expert.

PAS will be used only for pharmacokinetics analysis. Any blood samples missing blood collection date and time or missing associated dosing date and time will be excluded. When a trough sample is considered un-evaluable by clinical pharmacology expert, the reason will be documented.

Other Analysis Sets described in Section 10.1.6 of the protocol are embedded in the 7 Safety subsets described above and are thus not described here again.

2.5 Phases of CML

2.5.1 Definition of CML-CP and Ph+ at baseline

CML-CP (CML in Chronic Phase) requires the following:

- < 15% blasts in peripheral blood or bone marrow aspirate
- < 30% blasts plus promyelocytes in peripheral blood or bone marrow aspirate
- < 20% basophils in the peripheral blood
- $\geq 100 \times 10^9/L$ ($\geq 100,000/mm^3$) platelets
- No evidence of extramedullary leukemic involvement, with the exception of hepato-/splenomegaly.

For evaluation and confirmation that the patient is in CML-CP at start of study, all of the above values are to be checked and fulfilled.

2.5.2 Definition of CML-AP and CML-BC

For the evaluation of progression of CML phase during study treatment, the following criteria will be used. These criteria indicative of CML in AP or BC are not required to be confirmed by another assessment.

CML-AP (CML in accelerated phase) is defined by any of the following:

- $\geq 15\%$ blast cells in the peripheral blood or bone marrow aspirate, but <30% blast cells in both the peripheral blood and bone marrow aspirate
- $\geq 30\%$ blasts plus promyelocytes in peripheral blood or bone marrow aspirate but blast not $\geq 30\%$ in peripheral blood or bone marrow
- $\geq 20\%$ basophils in the peripheral blood
- $< 100 \times 10^9/L$ ($< 100,000/mm^3$) platelets unrelated to therapy*

* As thrombocytopenia is a known adverse reaction to CML therapy, platelets $< 100 \times 10^9/L$ are only considered as CML-AP if the patient had these values within 30 days of discontinuation due to disease progression. In this case, comments are to be provided on the termination page that thrombocytopenia is indicative of progression to AP and an adverse event entered with relationship to study treatment='Not suspected'.

CML-BC (CML in blast crisis) is defined by any of the following:

- $\geq 30\%$ blasts in peripheral blood or bone marrow aspirate
- Appearance of extramedullary involvement other than hepato-splenomegaly proven by biopsy (e.g. chloroma) to be confirmed by medical review at Novartis.

2.6 Patients and treatments

2.6.1 Patient disposition

The number and percentage of patients who entered in the different phases of the study, continuing in that phase at the time of cut-off, completed and discontinued that phase of the study will be summarized by study phase. Among the patients who discontinued a particular study phase or completed, reasons for discontinuation or completion will also be summarized.

Patient disposition will be presented for the SS and FAS.

Number of patients in each analysis population will also be summarized by treatment phase.

In addition, the number of patients with major and minor protocol deviations will be presented by type of deviation for both SS and FAS. In addition, the number (%) of patients in the Safety set and FAS with any COVID-19 related protocol deviation will be tabulated by deviation category.

2.6.2 Background and demographic characteristics

All demographic data (such as age, gender, race, ethnicity, weight, height), active and inactive medical conditions at trial start, disease history (such as time since diagnosis, Sokal risk score, intake of previous CML treatments, subject achieved MR4.5 on nilotinib treatment or not, subject attempt to permanently discontinue imatinib treatment, subject attempt to permanently discontinue nilotinib treatment), and extramedullary involvement at baseline will be summarized and listed for the FAS and SS; qualitative variables (i.e. gender, and race) will be summarized by means of contingency tables (counts and percentages) and quantitative variables (i.e. age and weight) will be summarized by descriptive statistics (n, mean, standard deviation, median, 25th percentile, 75th percentile, minimum, and maximum). Please note that the 48-week CSR (Primary CSR) will be referred to for demographic, prior antineoplastic medications and medical history outputs.

2.6.3 Antineoplastic therapy

Prior antineoplastic medications of any TKI, prior antineoplastic medications other than nilotinib and prior antineoplastic medications- nilotinib will be listed and summarized descriptively by preferred terms for the SS. Duration of prior TKI, imatinib and nilotinib use, reason for discontinuation of Imatinib will be summarized descriptively in the FAS and SS.

Antineoplastic therapies after discontinuation of study drug will be listed by preferred terms using the SS.

2.6.4 Medical History

Medical history and current medical condition will be summarized in the SS. The summaries will be presented by primary system organ class and preferred term. Medical history/current medical conditions will be coded using MedDRA.

2.6.5 Extent of exposure

2.6.5.1 Dose intensity and exposure

All study medication dose administration data will be summarized using the safety subset by phase during which patients are planned to take study drug.

Time on treatment, duration of exposure, actual dose intensity, average daily dose and relative dose intensity will be summarized for consolidation (NTCS), treatment continuation (NTCT), treatment re-initiation (NTRI and NTRI-2) and treatment prolonged continuation (NTCT-P) Phase.

For the purpose of these analyses, the following rule will be applied:

Treatment day: Date of first dose in a particular study phase (consolidation, NTRI etc.) is defined as the date of first intake of the study drug on the Drug Administration Page in that particular study phase. This will be considered as treatment Day 1. There is no treatment day 0.

Date of the last dose is defined as follows within each study phase:

- For non-last study phases and for patients still ongoing on treatment when enter the next phase before the data cut-off date, the date of last dose is defined as the last date in the study phase.
- For the last study phase (in data base at data cutoff date) and for patients ongoing on treatment, the date of last dose is defined as earlier date of the following two dates:
 - Data cut-off date
 - The latest date of the last available dates reported on the following records: dose administration record (DAR), PCR, bone marrow assessments, extramedullary involvement and laboratory.
- For the last study phase (in data base at data cut-off date) and for patients who entered post-treatment follow up phase before the data cut-off date, the date of last dose is defined as the date of the last non-zero dose of study drug reported in the dose administration record CRF page.

The following definitions are used:

Time on treatment in a particular study phase (in week) = [(date of last dose in that study phase – date of first dose in that study phase + 1 day) - (days of zero total daily dose in that study phase)] / 7

Duration of exposure in a particular study phase (in week) = (date of last dose in that study phase – date of first dose in that study phase + 1 day) / 7

Actual dose intensity in a particular study phase (mg/day) = total dose in that study phase / duration of exposure in that study phase * 7 (Periods of zero dose are included)

Average daily dose in a particular study phase (mg/day) = total dose in that study phase / time on treatment in that study phase * 7 (Periods of zero dose are excluded)

Relative dose intensity in a particular study phase (%) = (actual dose intensity in that study phase / assigned total daily dose) * 100

Assign total daily dose is 600mg/day

2.6.5.2 Duration of TFR

Duration of TFR (TFR-2) will be summarized for TFR safety set (TFR-2 safety set) using the following definition:

Duration of TFR (TFR-2) study phase (in week) = (end date of TFR/TFR-2 phase – start date of TFR/TFR-2 phase + 1 day) / 7

For patients ongoing in the TFR/TFR-2 phase at the time of data cut-off, the cut-off date will be used as end date of TFR/TFR-2 phase.

Also, duration of TFR will be presented alongside with duration of treatment exposure in consolidation phase by restricting TFR duration only to the first 48 weeks (336 days) of TFR phase in TFR safety set.

2.6.6 Prior and concomitant therapy

Prior and concomitant medications/significant non-drug therapies will be listed and summarized in the safety set.

Medications will be classified as prior or concomitant based on the following rules and will be coded using the WHO Drug Reference Listing (WHO DRL) dictionary that employs the WHO Anatomical Therapeutic Chemical (WHO ATC) classification system:

- Prior medication are medications that started before the first dose of study drug regardless of whether the medication ended before or after the first dose of study drug
- Concomitant medications are medications that started on or after the first dose of study drug, or started before the first dose of study drug and continued after the first dose of study drug

The number and percentage of patients with prior and concomitant medication will be presented separately by ATC class and preferred term according to the WHO DRL dictionary.

2.7 Efficacy evaluation

2.7.1 Analyses time points

There have been ten analysis time points with ten respective cut-off dates defined as the time when all patients who have entered the TFR phase have completed week 48, 96, 144, 192, and 264 weeks visit of TFR or discontinued earlier from these respective time points. Additionally, all patients who have entered the TFR phase have completed 6, 7, 8, and 9 years in TFR or discontinued earlier from these respective time points. The 10-year analysis is currently ongoing.

The primary analysis was performed at the 48-week time point, with the data cut-off date defined as the date when the last patient completed the week 48 visit after entering the TFR phase. The primary efficacy endpoint was the proportion of patients without confirmed loss of MR4 or loss of MMR within 48 weeks following the cessation of nilotinib therapy. The primary analysis at 48 weeks of TFR was only performed based on the 48-week data cut-off and is not applicable for the 96/144/192/264/312/360/408/468/528-week CSR analyses. All secondary efficacy endpoints will be analyzed accordingly.

2.7.2 Definition of efficacy variables

2.7.2.1 Molecular response

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

Details of RQ-PCR monitoring is described in protocol section 7.2.1.1(Molecular response)

Molecular response and related variables are defined as the following:

- **Major molecular response (MMR)**

Major molecular response is defined as a value of $\leq 0.1\%$ of BCR-ABL ratio on the International Scale (IS). This endpoint corresponds to a ≥ 3 log reduction of BCR-ABL transcripts from a standardized baseline value for untreated CML patients. For statistical comparison purpose, MMR will be considered as a binary variable with patients achieving MMR grouped as 'responders' and patients not achieving MMR, patients with missing PCR evaluations grouped as 'non-responders'.

- **Loss of a major molecular response (MMR)** is defined as a BCR-ABL ratio $> 0.1\%$ (on international scale) in a single blood sample, which corresponds to a less than 3 log reduction of BCR-ABL transcripts from a standardized baseline value for untreated CML patients. The confirmation of the loss of MMR is not required in this study.

- **Molecular response 4 (MR4)**

MR4 is defined as a value of $\leq 0.01\%$ of BCR-ABL ratio on the International Scale (IS). This endpoint corresponds to a ≥ 4 log reduction of BCR-ABL transcripts from a standardized baseline value for untreated CML patients.

- **Loss of MR4** is defined as a BCR-ABL ratio $> 0.01\%$ (on international scale), which corresponds to a less than 4 log reduction of BCR-ABL transcripts from a standardized baseline value for untreated CML patients.
- **Confirm Loss of MR4** is defined as two consecutive BCR-ABL $> 0.01\%$ IS after the achievement of MR4.
- **Molecular response 4.5 (MR4.5) or deep molecular response (DMR)**

MR4.5 is defined as a value of $\leq 0.0032\%$ of BCR-ABL ratio on the International Scale (IS). This endpoint corresponds to a ≥ 4.5 log reduction of BCR-ABL transcripts from a standardized baseline value for untreated CML patients.

- **Loss of MR4.5** is defined as a BCR-ABL ratio $> 0.0032\%$ (on international scale), which corresponds to a less than 4.5 log reduction of BCR-ABL transcripts from a standardized baseline value for untreated CML patients.
- **Confirm Loss of MR4.5** is defined as two consecutive BCR-ABL $> 0.0032\%$ IS after the achievement of MR4.5.

2.7.2.2 Treatment-free survival (TFS)

Treatment-free survival is defined as the time from the date of cessation of nilotinib therapy (date of entering TFR phase) to the date of the earliest of any of the following events up to the end of TFR phase:

- loss of MMR
- confirmed loss of MR4
- progression to AP/BC
- death from any cause
- And re-start of nilotinib treatment due to any cause in the study

Patients not known to have had any of the events, the time will be right censored at the date of their last assessment (PCR, cytogenetic, hematology or extramedullary) up to the end of TFR phase.

A sensitivity analysis will be conducted considering discontinuation from TFR phase due to any reason as an event, in addition to the events as defined above. For example, a discontinuation from TFR phase due to patient decision without any of TFS events as defined above will be considered as an event in the sensitivity analysis, while the patient will be censored in the primary TFS analysis. Patients who completed TFR phase (marked as “Completed” on End of treatment CRF page) will be censored in the TFS sensitivity analysis. TFS in the sensitivity analysis is thus the time from the date of start of TFR to the date of the earliest occurrence of the following events up to the end of TFR phase: discontinuation due to any reason, loss of MMR, confirmed loss of MR4, death due to any cause, progression to AP or BC, and re-initiation of treatment due to any cause in the study. For patients who do not have these events, the time will be censored at the date of their last assessment (PCR, cytogenetic, hematologic or extramedullary) up to the end of TFR phase.

2.7.2.3 Progression-free survival (PFS)

Progression-free survival is defined as the time from the date of cessation of nilotinib therapy (date of entering TFR phase) to the date of the earliest of this event: the first documented disease progression to AP/BC or death from any cause occurring in the study, including the follow-up period after early discontinuation of study.

For patients who do not have events on or before the cut-off date, the time will be censored in following way

- I. patients who are still on study before the follow-up period, the time will be censored at the date of last assessment (PCR, cytogenetic, hematologic or extramedullary)
- II. patients who are in the follow-up period after early discontinuation of study, the time will be censored at the date of last contact.

2.7.2.4 Overall survival (OS)

Overall survival is defined as the time from the date of cessation of nilotinib therapy (date of entering TFR phase) to the date of death from any cause at any time during the study, including the follow-up period after discontinuation of study up to cut-off date.

For patients who do not have events on or before the cut-off date, the time will be censored at the date of last assessment (from the list of sources specified below) for patients who are still in study before the follow-up period and at the date of last contact for patients who are in the follow-up period after early discontinuation of study (from the Disease Progression and Transplant CRF page).

Specific last assessment date sources for this study are:

- PCR (RQ-PCR) testing of peripheral blood sample dates
- Start/End dates from further antineoplastic therapy
- Start/End dates from drug administration record with non-missing total daily dose
- Laboratory/PK collection dates
- Vital signs date with at least one non-missing measurement
- ECOG performance status date
- Start/End dates of AE with non-missing AE name
- Disease Progression and Transplant dates

Further derivation rules for the last contact date will be specified in the Programming Datasets Specification (PDS), including conditions that need to be satisfied for a date to be taken into account in the derivation of the last contact date.

2.7.2.5 Duration of retreatment required to regain MMR/MR4/MR4.5

Duration of retreatment required to regain MMR/MR4/MR4.5 is defined as: date of first specified response - date of starting treatment after either loss of MMR or confirm loss of MR4 (start date of NTRI phase) + 1. Patients will be censored if one of the following situations occurs:

- If a patient does not achieve the specified response, censoring time will be the last PCR assessment date during treatment.
- If a patient discontinues study prior to achieving a specified response, then the patient will be censored at the last PCR assessment date during treatment (except the discontinuation due to progression or death, in such case the censoring time will be set to the longest follow-up time in NTRI phase, that is, considering the response is impossible to reach).

2.7.3 Primary efficacy endpoint

The primary efficacy endpoint is the proportion of patients without confirmed loss of MR4 or loss of MMR within 48 weeks following cessation of nilotinib therapy. The definition of the time window for the 48 weeks visit is provided in Appendix 16.1.9.

Variable

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

Statistical hypothesis, model, and method of analysis

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

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

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

The null hypothesis will be rejected and successful TFR will be demonstrated if the lower limit of the 95% confidence interval is greater than 0.10 which can be achieved if there are at least 13 patients without confirmed loss of MR4 or loss of MMR within 48 weeks following nilotinib TFR phase, assuming 70 patients enrolled in TFR phase.

Primary efficacy analysis will be performed on the FAS.

Handling of missing values/censoring/discontinuations

For the primary analysis of the rate of successful TFR, patients dropping out from the study before week 48 of the TFR phase will be considered as not demonstrating successful TFR and will be included in the FAS.

Below scenarios will be used as follows:

- If a patient lost MR4 for the first time (which is not confirmed) at 48 week in TFR phase and does not lose MMR, this patient will be considered as 'Responder' for primary analysis.

Supportive analyses

The primary analysis was repeated on the per protocol set (PPS).

2.7.4 Secondary endpoint

- Proportion of patients without confirmed loss of MR4 or loss of MMR within 96, 144, 192 and 264 weeks and within the end of years 6, 7, 8, 9, and 10 following cessation of nilotinib therapy: Proportion of patients without confirmed loss of MR4 or loss of

MMR within 96, 144, 192, 264 weeks and within the end of years 6, 7, 8, 9, and 10 following cessation of nilotinib therapy is calculated by dividing the number of patients with no documented confirmed loss of MR4, no documented loss of MMR and no re-starting of nilotinib therapy in the first 96, 144, 192, 264 weeks and within the end of years 6, 7, 8, 9, and 10 respectively following cessation of nilotinib therapy by the number of patients who attempted to cease nilotinib therapy.

- Progression free survival (PFS).
- Treatment-free survival (TFS)
- Overall survival (OS)

The definition of PFS, TFS and OS are given in section 2.7.2.2 to 2.7.2.4.

- The proportion of patients who regain MR4.5 within 48 weeks of nilotinib treatment re-initiation following confirmed loss of MR4 or loss of MMR in the first 48 weeks subsequent to nilotinib cessation will also be calculated by dividing the number of patients who re-achieve MR4.5 within 48 weeks of nilotinib treatment re-initiation, following confirmed loss of MR4 or loss of MMR in the first 48 weeks subsequent to nilotinib cessation, by the number of patients who ceased nilotinib therapy and subsequently had confirmed loss of MR4 or lost MMR in the first 48 weeks following nilotinib cessation and re-initiated nilotinib treatment. In the calculation of this proportion, patients who drop out early without regaining MR4.5 during the re-treatment period (within first 48 weeks of the re-treatment period) will be considered to be unsuccessful re inductions of MR4.5 and will be counted in the denominator in the calculation of the rate.
- The proportion of patients who regain MR4.5 / MR4 within 48 weeks of nilotinib treatment re-initiation, **irrespective of the time of start of re-treatment** after confirmed loss of MR4.

This proportion will be calculated by dividing the number of patients who re-achieve MR4.5/MR4 within first 48 weeks of nilotinib treatment re-initiation, by the number of patients who ceased nilotinib therapy and subsequently had confirmed loss of MR4 and re-initiated nilotinib treatment.

If patients who drop out early without regaining MR4.5 / MR4 during the re-treatment period (within first 48 weeks of the re-treatment period) will be considered to be unsuccessful re inductions of MR4.5/ MR4 and will be counted in the denominator in the calculation of the rate.

- The proportion of patients who regain MR4.5/MR4/MMR within 48 weeks of nilotinib treatment re-initiation following loss of MMR.

This proportion will be calculated by dividing the number of patients who re-achieve MR4.5/ MR4/ MMR within first 48 weeks of nilotinib treatment re-initiation, by the number of patients who ceased nilotinib therapy and subsequently had loss MMR and re-initiated nilotinib treatment.

If patients who drop out early without regaining MR4.5 / MR4/ MMR during the re-treatment period (within first 48 weeks of the re-treatment period) will be considered to be unsuccessful re inductions of MR4.5/ MR4/ MMR and will be counted in the denominator in the calculation of the rate.

- Proportion of patients who are in MR4.5 at 48, 96, 144, 192, 264, 312 and 360 weeks after starting the TFR phase, defined as the number of patients with MR4.5 at 48, 96, 144, 192, 264, 312 and 360 weeks respectively after starting the TFR phase with no loss of MR4.5 and no re-initiation of nilotinib therapy in the first 48, 96, 144, 192, 264, 312, 360, 432, 468 and 528 weeks after starting the TFR phase respectively divided by the number of patients who entered the TFR phase.
- Proportion of patients who are in MR4.5 at 96, 144, 192, 264, 312, 360, 432, 468 and 528 weeks after starting the TFR phase defined as the number of patients with MR4.5 at 96, 144, 192, 264, 312, 360, 432, 468 and 528 weeks after starting the TFR phase with no re-initiation of nilotinib therapy in the first 96, 144, 192, 264, 312, 360, 432, 468 and 528 weeks after starting the TFR phase divided by the number of patients who entered the TFR phase
- Duration of retreatment required to regain MR4.5/ MR4/ MMR defined as the time from date of start of retreatment after loss of MMR to the date of first achievement of MR4.5/ MR4/ MMR. For patients who do not regain MR4.5/ MR4/ MMR after retreatment on or before the cut-off date, duration will be censored as defined in section 2.7.2.5.
 - In addition to duration of retreatment required to regain MR4.5/ MR4/ MMR, cumulative incidence rates of regaining MR4.5/ MR4/ MMR after loss of MMR, over time in the NTRI phase will be provided considering censored patients as non-responders. The analysis is described in the subsection “Analyses methods for secondary objectives” below in this section.
- Duration of retreatment required to regain MR4.5/ MR4 which is measured from the time from date of start of retreatment after confirmed loss of MR4 to the date of first achievement of MR4.5/ MR4. For patients who do not regain MR4.5/ MR4 after retreatment on or before the cut-off date, duration will be censored as defined in section 2.7.2.5.
 - In addition to duration of retreatment required to regain MR4.5/ MR4, cumulative incidence rates of regaining MR4.5/ MR4 after confirmed loss of MR4, over time in the NTRI phase will be provided considering censored patients as non-responders. The analysis is described in the subsection “Analyses methods for secondary objectives” below in this section.
- Duration of retreatment required to regain MR4.5/ MR4 which is measured from the time from date of start of retreatment after either loss of MMR or confirmed loss of MR4 to the date of first achievement of MR4.5/ MR4. For patients who do not regain MR4.5/ MR4 after retreatment on or before the cut-off date, duration will be censored as defined in section 2.7.2.5.
 - In addition to duration of retreatment required to regain MR4.5/ MR4, cumulative incidence rates of regaining MR4.5/ MR4 after either loss of MMR or confirmed loss of MR4, over time in the NTRI phase will be provided considering censored patients as non-responders. The analysis is described in the subsection “Analyses methods for secondary objectives” below in this section.

- Kinetics of BCR-ABL transcript levels (IS) after re-start of nilotinib therapy
- The proportion of patients with stable molecular response (MR4.5/ MR4/ MMR) after achievement of that response in nilotinib re-initiation period for 48 weeks and 96 weeks.
Stable molecular response - 48/96 weeks in nilotinib re-initiation period is defined as, achievement of a certain level of response (MR4.5/ MR4/ MMR) in nilotinib re-initiation period, if again the same response is observed after 48/96 weeks (336/672 days) beyond the first achievement (of response) during the nilotinib re-initiation period irrespective of whether there is loss of response in between achievement and week 48/96 assessment.
This proportion will be calculated by dividing the number of patients with stable molecular response (MR4.5/ MR4/ MMR), by the number of patients who achieved that response (MR4.5/ MR4/ MMR) at least once in nilotinib re-initiation period.

2.7.4.1 Statistical analysis methods for the secondary efficacy endpoints

The rate of molecular responses by certain time points after starting the TFR phase, rate of stable molecular responses as well as the rate of patients who re-achieve molecular responses (MR4.5/ MR4/ MMR) with nilotinib retreatment will be presented together with an exact 95% Clopper-Pearson confidence interval.

Kinetics of BCR-ABL transcript levels after re-start of nilotinib therapy will be presented by a box-plot of BCR-ABL ratio over time and also will be summarized over time.

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

KM estimated rates will be provided at every 24 weeks from TFR start date for PFS and OS. For TFS, the KM estimated rates will be provided at every 4 weeks from TFR start date for first 24 weeks and then at every 12 weeks thereafter.

Similarly for duration of re-treatment required to regain MMR, MR4 and MR4.5, the KM estimated rates will be provided at every 4 weeks from NTRI start date for first 24 weeks and then at every 12 weeks thereafter.

Rates of regaining MMR/ MR4/ MR4.5 over time in the NTRI phase will also be analyzed with cumulative incidence curves. In addition, the time to by which 50% of all retreated patients have regained MMR/MR4/MR4.5 will be calculated.

Handling of missing values/censoring

For the analysis of proportion of patients who are in TFR phase without confirmed loss of MR4, loss of MMR and no re-starting of nilotinib therapy by 48, 96, 144, 192 and 264 weeks and by 6,7,8,9 and 10 years after starting the TFR phase, patients dropping out from the study before the specific analysis time point of the TFR phase will be considered to be unsuccessful TFR for that analysis time point and will be included in the FAS. If a patient lost the MR4 for the first time (which is not confirmed) at 48, 96, 144, 192 and 264 week and by 6,7,8,9 and 10 years in TFR phase and does not lose MMR, this patient will be considered as 'Responder' for that analysis time point.

Censoring rules for time to event endpoints (PFS, EFS and OS) are provided in the definition of those endpoints in section 2.7.2.2 to 2.7.2.4.

Sensitivity analyses for the secondary endpoints

The missing values will be handled according to the same rule as described above.

2.8 Safety evaluation

For all safety analyses, the safety set will be used. Safety analyses will be presented, both overall (i.e. pooling all study phases) using the overall safety set and also for different study phases using safety subsets defined in Section 2.4. Since the primary interest of the study is to assess the benefit of stopping treatment, particular analyses will be done on the patients who entered the TFR phase.

2.8.1 Adverse events

Summary tables for AEs will include only AEs that started or worsened during the on-treatment period (all 7 study phases including treatment-free remission phases), the **treatment-emergent AEs** (TEAEs). The start day used to define the TEAEs in the entire study is the first day of dosing of the Nilotinib Consolidation Phase.

TEAEs will be reported pooled over the full course of phases a patient will go through in the Safety Set as well as by study phase in the safety subsets. The definition of TEAEs by study phase is given in Appendix 16.1.9.

However, all safety data including those collected before study day 1 or more than 30 days after end of study will be listed and flagged.

The incidence of TEAEs will be summarized by system organ class and preferred term using the latest MedDRA version available. Grading will be based on CTCAE Version 4.03.

Adverse events will be summarized by presenting the number and percentage of patients having any adverse event, having an adverse event in each primary system organ class, and having an adverse event with a particular preferred term within a system organ class.

The following selection of AEs will be listed and summarized separately. All these AEs will be summarized for all grades and for grade 3 or 4 side-by-side for Safety Set as well as by study phase in the safety subsets.

- AEs
- AEs suspected to be study drug related
- AEs reported as serious AEs (SAEs)
- AEs excluding the serious AEs
- SAEs suspected to be study drug related
- AEs reported as AEs of special interest (AESIs)
- AEs associated with discontinuation of study drug, excluding TFR and TFR-2 phases

- AEs associated with discontinuation of study drug that are suspected to be study drug related, excluding TFR and TFR-2 phases
- AEs requiring dose adjustment or study drug interruption (excluding TFR and TFR-2 phases)
- AEs requiring significant additional therapy
- Total deaths which occur within any study phase or within 30 days after discontinuation from the study, as well as the causes of deaths by preferred terms, will be summarized using n (%). All deaths due to any cause at any time in the study, including the follow-up period, will also be summarized using n (%).

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

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

Specific analyses will focus on the differences of the incidence of adverse events between the Nilotinib Consolidation Phase and the TFR phase in the TFR Safety Set (i.e. patients who entered the TFR phase). In this subset of patients, AEs will be presented for the Nilotinib consolidation phase and TFR phase (only within first 48 weeks (336 days) from start of TFR phase to allow a fair comparison), side by side. This analysis was performed only for 48-week CSR, and not repeated for CSR at or after 96 weeks.

Additional analyses will be performed to assess the effect of stopping treatment on the adverse events.

Rate of any AE (or specific AE groupings) will be presented graphically from start of consolidation phase to first 48 weeks in the TFR phases using TFR safety set.

The rate will be calculated by dividing the number of patients with any AE (or specific AE groupings) at a particular time by the number of patients in the TFR safety set who are continuing in the study at that time.

An AE is considered to be present at a particular time x , if study day of start date of AE is $\leq x$ and study day of end date of AE is $\geq x$.

Study day is calculated with respect to start date of TFR phase.

This analysis was performed only for 48-week CSR, and not repeated for CSR at or after 96 weeks

The similar analysis will be performed between the TFR phase and Nilotinib treatment re-initiation phase using Treatment re-initiation Safety Set in order to assess the effect of re-starting treatment on the adverse events.

Rate of any AE (or specific AE groupings) will be presented graphically from 48 weeks before the start of retreatment to 48 weeks after the start of retreatment.

This analysis was performed only for 48-week CSR, and not repeated for CSR at or after 96 weeks

In addition to the above, analyses will be performed to assess of AE over time in the TFR phase in the subset of patients who remain in the TFR phase for more than 48 weeks. The incidence rate of AE will be compared between the consolidation phase, first 48 weeks (up to 336 days) of the TFR phase and second 48 weeks (337 – 672 days) of the TFR phase (This is not to be repeated for the 144/192/264/312/360-week CSR). The same principle to compare rates of AE over time (consolidation phase, and then every 48 weeks of TFR) will be applied to future analyses at 144, 192, 264, 312, 360, 432, 468 and 528 weeks.

Total deaths which occur within any study phase or within 30 days after discontinuation from the study, as well as the causes of deaths by preferred terms, will be summarized using n (%). All deaths due to any cause at any time in the study, including the follow-up period, will also be summarized using n (%).

Specific exploratory analyses will be performed based on the AE grouping musculoskeletal pain:

The image shows the letters 'CCI' in a large, bold, red sans-serif font. The letters are positioned on the left side of a solid black rectangular background that occupies the lower half of the page.

2.8.2 Laboratory values

Laboratory values will be converted to SI units and analyzed using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. For laboratory tests covered by CTCAE, a Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used.

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

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

- Number and percentage of patients with laboratory abnormalities, by parameter and worst post-baseline CTCAE grade. Each patient will be counted only for the worst grade observed post-baseline, regardless of the baseline status.
- Shift tables using CTCAE grades to compare baseline to the worst on-phase value. Five different baseline definitions for the different study phases, as defined in Appendix 16.1.6 Section 3.2.2, will be used.
- For laboratory tests where CTCAE grades are not defined, shift tables using the low/normal/high/(low and high). Five different baseline definitions for the different study phases, as defined in Appendix 16.1.6 Section 3.2.2, will be used.
- Summary statistics by timepoint and by study phase
- Listing of all laboratory data with values flagged to show the corresponding CTCAE grades and the classifications relative to the laboratory normal ranges.

In order to assess the impact of stopping the treatment on blood parameters, boxplots and summary statistics will be presented for hematology and biochemistry parameters over scheduled time points for the Nilotinib Consolidation phase, the TFR phase and the Nilotinib treatment re-initiation phase. These analyses will focus on the 52 weeks of the consolidation phase, the first 48 weeks from the TFR phase and the first 24 weeks from the Nilotinib treatment re-initiation phase. A first analysis will focus on the evolution between the consolidation and TFR phase in the TFR Safety Set with the start date of the TFR as week 0 and time windows for the scheduled samples as defined in Section 3.2.4 (This analysis was performed only for 48-week CSR, and not repeated for CSR at or after 96 weeks). The same analysis will be repeated between the TFR and re-initiation phase in the Treatment re-initiation Safety Set with the start of the re-initiation of Nilotinib defined as week 0.

Additional analyses will be performed to assess impact of stopping the treatment on blood laboratory parameters in the subset of patients who remain in the TFR phase for more than 48 weeks. Worst post-baseline hematology and biochemistry value based on CTC grade will be presented side by side during consolidation, first 48 weeks (336 days) of TFR phase and second 48 weeks (337 – 672 days) of the TFR phase (This is not to be repeated for the 144/192/264-week CSR). The same principle to compare blood parameters over time (consolidation phase, and then every 48 weeks of TFR) will be applied to future analyses at 144, 192 and 264 weeks, and 6, 7, 8, 9 and 10 years.

An additional analysis will be conducted on glycosylated hemoglobin (HbA1c) to describe the number and percentage of patients developing values higher than the clinically meaningful thresholds (alternative to the CTC grading) by phase in Safety Set. See TFL shells for the thresholds evaluated for this parameter.

Risk Handling for Q2 Roche Magnesium Testing

Q2 solutions identified an issue with serum Magnesium (Mg) results from Roche Diagnostics Cobas analyzer in the UK lab (only) from 05 Jun- 09 Jul 2018 and 22 Nov 2018- 02 Jan 2019.

A carryover effect from assays run prior to Magnesium test resulted in an increase of measured Mg and Q2 Solutions cannot guarantee that the results for Mg⁺⁺ testing are accurate for the affected time periods.

The invalid values will be flagged in the database and these values will be excluded from the analysis but listed in the CSR.

2.8.3 ECG analysis

A standard 12 lead ECG will be performed at screening, annually while on nilotinib treatment, day 1 of nilotinib treatment re-initiation, and nilotinib treatment re-initiation-2 (visits 201 and 401) – prior to dosing and whenever clinically indicated.

The following analyses will be performed for variables heart rate, PR interval, QRS duration, QT interval, QTcF and QTcB:

- Number and percentage of patients with any post-baseline QTc value of >450 ms, >480 ms or >500 ms.
- Number and percentage of patients who have an increase from baseline in QTc of >30 ms or >60 ms.

In addition, Patients with at least one post-baseline ECG abnormality QTc >450 ms, >480 ms or >500 ms at any time point, or an increase from baseline in QTc >30 ms or >60 ms will be listed.

Five different baseline definitions for the different study phases, as defined in Appendix 16.1.6 Section 3.2.2, will be used.

Unscheduled ECG measurements will be used in the outlier analysis of patients with QTc >450 ms, >480 ms or >500 ms at any time point, or an increase from baseline in QTc >30 ms or >60 ms.

2.8.4 Analysis of vital signs

Vital signs data (weight, pulse rate, systolic blood pressure, diastolic blood pressure) will be summarized by shift table based on notable values. They will be presented by study phase and overall.

The criteria for clinically notable abnormalities are defined as follows:

Clinically notable elevated values

- Systolic BP: ≥ 140 mmHg
- Diastolic BP: ≥ 90 mmHg.
- Body Temperature [$^{\circ}$ C] $\geq 37.5^{\circ}$ C
- Weight: Baseline: ≥ 110 kg; Post-baseline: Increase from baseline of $\geq 10\%$
- Heart rate: Baseline: ≥ 120 beats per minute (bpm); Post-baseline: ≥ 120 beats per minute (bpm) with increase from baseline of ≥ 15 bpm

Clinically notable below normal values

- Systolic BP: ≤ 90 mmHg
- Diastolic BP: ≤ 40 mmHg
- Body Temperature [$^{\circ}$ C] $\leq 35^{\circ}$ C
- Weight: Baseline: ≤ 60 kg; Post-baseline: decrease from baseline of $\geq 10\%$

- Heart rate: Baseline: ≤ 50 bpm; Post-baseline: ≤ 50 bpm with decrease from baseline of ≥ 15 bpm

Five different baseline definitions for the different study phases, as defined in Appendix 16.1.6 Section 3.2.2, will be used.

Along with all vital sign, patients with notably abnormal values will be listed.

2.9 Other Analysis

2.9.1 ECOG performance status

For ECOG performance status, shift tables will be provided comparing baseline with best and worst values during study for each phase and overall.

Five different baseline definitions for the different study phases, as defined in Appendix 16.1.6 Section 3.2.2, will be used.

2.9.2 Pharmacokinetic evaluations

The plasma exposure of nilotinib will be assessed via trough nilotinib concentrations collected at week 48 of consolidation phase and will be summarized using the PAS by descriptive statistics, including geometric and arithmetic means, standard deviation (SD), and coefficient of variation (CV) %. All nilotinib concentrations are listed using the Safety Set. PK data analysis was done with the primary CSR and is not planned in the final CSR.

The potential relationship between nilotinib trough concentration and patient's entry into TFR phase will be assessed by graphic exploration as well as using a logistic regression model (dependent binary variable: TFR entry status; explanatory variable: log-transformed nilotinib trough concentration). A boxplot showing trough concentrations in patients entering and not entering into the TFR phase will be shown.

The following is a list of analyses conducted to investigate nilotinib concentration-efficacy relationship:

- Scatter plot of BCR-ABL ratio (%) at 48 weeks of the consolidation phase vs. PK trough concentration
- TFR entry status will be summarized using contingency tables by the PK concentration categories (by quartiles)

2.9.3 Biomarkers

CCI

2.9.4

CCI

CCI



2.9.5

CCI





2.9.6 Exploratory efficacy endpoints



CCI



2.10 Interim analysis

No formal interim analysis was planned for this study. The cut-off date for primary endpoint analysis was when all patients completed 48 weeks of TFR phase or entered treatment reinitiation phase or discontinued from the study. Thereafter, following the same principles for cut-off date definition, updates were done at week 96, 144, 192 and 264 weeks after the last patient enters the TFR phase and at the end of years 6, 7, 8, and 9. The final analysis will be done at ten years after the last patient enters the TFR phase.

2.11 CSR Section 9.7.2 – Sample size and power considerations

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

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

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

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

This study had enrolled 163 patients by Dec2013, the date when the patient enrollment was closed. With 163 patients enrolled, if assuming approximately 40% of enrolled patients who have MR4.5 at study entry will not be eligible for starting TFR phase, there will be approximately 98 patients entering TFR. Assuming true rate of no documented confirmed loss of MR4, no loss of MMR and no re-starting of nilotinib therapy in the first 48 weeks after nilotinib cessation is 25%, with a 10% rate for the null hypothesis, the study will have a 97% power with 1-sided alpha level of 2.5% to test the null hypothesis. Note that the power increases by 7% based on the 163 enrolled patients compared to the originally planned 90% power based on the 117 enrolled patients, with all the other assumptions for the power calculation being the same.

3 Appendix 16.1.9 Documentation of statistical methods

3.1 Appendix 16.1.9 – Documentation of statistical methods

The statistical methods used to perform the analyses presented in the clinical study report will be described in Section 9.7. Appendix 16.1.9 will provide further details of the statistical methods not already provided in Section 9.7.

All analyses will be performed using SAS[®] Version 9.2 or upper.

3.2 Dates and time windows

3.2.1 Time to events

Durations will be given in weeks or months with **1 month = 30.4375 days**.

The following definitions will be applied for analysis of whole study (in days):

Time to safety event = event date – first dose date in consolidation phase + 1

The following definitions will be applied for analysis of study phases:

- **Time to efficacy event** = event date – start date of the study phase + 1
- **Time to safety event** (except for TFR and TFR-2 phase) = event date – start date of the first dose in that study phase + 1
- **Time to safety event** (for TFR and TFR-2 phase) = event date – start date of the study phase + 1

For time from events prior of the study start, e.g., time since diagnosis of CML, study days will be calculated as: study first dose date in consolidation phase – event date.

3.2.2 Definition of baseline assessments

This study has multiple baselines for different phases of the study.

The last available assessment before or at first dose date (study day 1) of the Nilotinib consolidation phase will be taken as **baseline** irrespective of when the assessment had been made. Further, if several assessments are taken on the same day, the last assessment will be used for that time point.

In addition to the above baseline for the Nilotinib treatment period at the start of the study, which is the baseline for the **Nilotinib consolidation phase (NTCS)**, **Nilotinib treatment continuation phase (NTCT)** and **Nilotinib treatment prolonged continuation phase (NTCT-P)**, 4 additional baselines will be used for analyses regarding reporting a change from baseline in a phase (e.g. shift tables):

- **Nilotinib Treatment-Free Remission phase (TFR) baseline:** last available assessment before or at the first day of the TFR phase.
- **Nilotinib treatment re-initiation phase (NTRI) baseline:** last available assessment before or at first dose date of the NTRI phase.
- **Nilotinib Treatment-Free Remission 2 phase (TFR-2) baseline:** last available assessment before or at the first day of the TFR-2 phase.
- **Nilotinib treatment re-initiation 2 phase (NTRI-2) baseline:** last available assessment before or at first dose date of the NTRI-2 phase.

For adverse events (AEs), an event is considered as a baseline for a given study phase if the AE starts before the study phase start date (AE start date < phase start date) and is ongoing into the phase (AE end date missing or $\geq$ phase start date).

- Baseline AE grade will be provided for each AE recorded (new or worsening, Section 3.2.3 and [Figure 3-1](#)) in the three main study phases: NTCS, TFR and NTRI phases, because they are the main phases from which patients can switch from treatment phase to no treatment phase, or vice versa .
- For each AE (new or worsening) in a patient in a phase (NTCS, TFR or NTRI), if the patient had an AE with the same PT at baseline of that phase, the grade of that baseline record would be assigned as the baseline grade for that AE in that phase. If there is no such equivalent AE record at baseline, then the baseline grade will be 0 (representing none at baseline) for that AE in that phase. See [Figure 3-1](#).
- If there are multiple baseline AE records with the same PT and different grades for a given phase, the worst grade will be used as the baseline AE grade.

Only values after the entry date of a particular study phase will be used as post-baseline.

3.2.3 Definition of assessment dates and Assessments included in the analysis

For “assessment on study phase”, all available assessments in the study phase will be considered for ongoing patients. For patients who discontinued the study phase and moved to the post-treatment follow-up phase, all assessments up to the date of end of the study phase + 30 days will be considered as being collected on treatment even if the study phase is treatment free. For patients who discontinued the study phase and moved to another study phase other than post-treatment follow-up phase, all assessments up to the date of end of the study phase will be considered as being collected for that study phase. When a cut-off date is used for a particular analysis time point, the selection of data described above is restricted to assessments on or before cut-off date.

Any AE record in the database is considered as a separate AE and is assigned to a study phase. For determining if an AE in an individual patient is a new/worsening event or a baseline event, for a given study phase, the start date and end dates of the AE record are compared to the start and end dates of this study phase.

Figure 3-1 provides examples of various scenarios for AEs in consolidation (NTCS) and TFR phases.

Figure 3-1 Examples of new or worsening AEs and baseline AEs for consolidation and TFR phases

NTCS phase start date TFR phase start date				NTCS phase		TFR phase	
				Grade at baseline	New or worsening grade ¹	Grade at baseline	New or worsening grade ¹
Vomiting/grade 1		Vomiting /grade 1		1	-	0	1
Vomiting /grade 2				0	2	0	-
Vomiting /grade 2				2	-	2	-
Vomiting /grade 1				0	1	1	-
Vomiting /grade 1		Vomiting /grade 1		0	1	1	1
Vomiting /grade 1		Vomiting /grade 3		0	1	1	3
Vomiting /grade 2		Vomiting /grade 1		0	2	0	1

¹ This is the grade that will be reported in summary tables of newly occurring or worsening of AEs presented by study phase.

NTCS = nilotinib treatment consolidation phase. The arrows represent the start and end dates of an occurrence of an event. The same specifications also apply to any study phase.

All summary tables of AEs presented in the CSR will be based on the notion of “new/worsening” events described above for individual patient data:

- For analyses of the incidence of AEs within the TFR phase: any patient who entered the TFR phase, and who reported at least one AE record identified as new/worsening in the TFR phase for a given MedDRA PT, is counted in the numerator for the incidence of that MedDRA PT. The denominator for the TFR phase in this analysis is the number of patients who entered the TFR phase.
- For analyses comparing the incidence of AEs in Consolidation (NTCS) vs TFR first 48 weeks presented in the 48-week CSR:
 - TFR: any patient who entered the TFR phase, and who reported at least one AE record identified as new/worsening in the first 48 weeks of the TFR phase for a given MedDRA PT, is counted in the numerator for the incidence of that MedDRA PT in the “TFR” column. The denominator for the TFR phase in this analysis is the number of patients who entered the TFR phase.
 - Consolidation: any patient who entered the TFR phase, and who reported at least one AE record identified as new/worsening in the Consolidation phase for a given

MedDRA PT, counted in the numerator for the incidence of that MedDRA PT in the “Consolidation” column. The denominator for the Consolidation phase in this analysis is the number of patients who entered the TFR phase.

- For analyses comparing the incidence of AEs in Consolidation (NTCS) vs TFR first 48 weeks vs TFR second 48 weeks in patients who remained in the TFR phase >48 weeks, to be performed for the 96-week CSR:
 - Consolidation: any patient who remained in the TFR phase >48 weeks, and who reported at least one AE record identified as new/worsening in the Consolidation phase for a given MedDRA PT, counted in the numerator for the incidence of that MedDRA PT in the “Consolidation” column. The denominator for the Consolidation in this analysis is thus the number of patients who remained in the TFR phase >48 weeks.
 - TFR 1st 48 weeks: any patient who remained in the TFR phase >48 weeks, and who reported at least one AE record identified as new/worsening in the first 48 weeks of the TFR phase for a given MedDRA PT, is counted in the numerator for the incidence of that MedDRA PT in the “TFR first 48 weeks” column. The denominator for the TFR first 48 weeks in this analysis is the number of patients who remained in the TFR phase >48 weeks.
 - TFR 2nd 48 weeks: any patient who remained in the TFR phase >48 weeks, and who reported at least one AE record identified as new/worsening in the second 48 weeks interval of the TFR phase for a given MedDRA PT, is counted in the numerator for the incidence of that MedDRA PT in the “TFR second 48 weeks” column. The denominator for the TFR 2nd 48 weeks in this analysis is the number of patients who remained in the TFR phase >48 weeks.
- For analyses comparing the incidence of AEs in Consolidation (NTCS) vs TFR first 48 weeks vs TFR second 48 weeks vs TFR third 48 weeks, in patients who remained in the TFR phase >96 weeks, to be performed for the 144-week CSR:
 - Consolidation: any patient who remained in the TFR phase >96 weeks, and who reported at least one AE record identified as new/worsening in the Consolidation phase for a given MedDRA PT, counted in the numerator for the incidence of that MedDRA PT in the “Consolidation” column. The denominator for the Consolidation in this analysis is thus the number of patients who remained in the TFR phase >96 weeks.
 - TFR 1st 48 weeks: any patient who remained in the TFR phase >96 weeks, and who reported at least one AE record identified as new/worsening in the first 48 weeks of the TFR phase for a given MedDRA PT, is counted in the numerator for the incidence of that MedDRA PT in the “TFR first 48 weeks” column. The denominator for the TFR first 48 weeks in this analysis is the number of patients who remained in the TFR phase >96 weeks.
 - TFR 2nd 48 weeks: any patient who remained in the TFR phase >96 weeks, and who reported at least one AE record identified as new/worsening in the second 48 weeks interval of the TFR phase for a given MedDRA PT, is counted in the numerator for the incidence of that MedDRA PT in the “TFR second 48 weeks” column. The

denominator for the TFR 2nd 48 weeks in this analysis is the number of patients who remained in the TFR phase >96 weeks.

- TFR third 48 weeks: any patient who remained in the TFR phase >96 weeks, and who reported at least one AE record identified as new/worsening in the third 48 weeks interval of the TFR phase for a given MedDRA PT, is counted in the numerator for the incidence of that MedDRA PT in the “TFR third 48 weeks” column. The denominator for the TFR third 48 weeks in this analysis is the number of patients who remained in the TFR phase >96 weeks.

The similar logic will be used to compare the consolidation phase and 48-weeks intervals in the TFR phase, in patients who entered the specified last 48-week interval in the TFR phase.

If a patient entered and ended TFR phase and then entered survival follow-up without entering NTRI phase, the following rule of EOT+30 days was used to identify new/worsening AEs in the TFR phase:

$(\text{TFR start date}) \leq (\text{AE start/worsening date}) \leq (\text{EOT}+30 \text{ days}).$

After identifying new/worsening AEs in the TFR phase, then the event can be further flagged as whether in the first 48 weeks, second 48 weeks, or one of the subsequent 48-week intervals of the TFR phase.

The rule of EOT+30 days also applies to any other study phase, if a patient ended the study phase and discontinued the entire study without entering the next study phase.

For the analyses of molecular response, the PCR sample date will be taken as assessment date. For the analyses of cytogenetic responses, the bone marrow aspirate date will be taken as assessment date. For the analyses of hematologic response, the latest date of laboratory or extramedullary disease evaluation will be taken as assessment date. In all cases, all assessments on treatment as defined above will be considered.

If there is progression to AP/BC, the earliest assessment date indicating this progression will be taken: if there are 20% blasts in bone marrow, the bone marrow aspirate date will be taken, if there are 20% blasts in peripheral blood, the laboratory sample date will be taken as progression date. All assessments on treatment as defined above will be considered including information from the follow-up CRF page.

3.2.4 Definition of time windows for analyses of response

Time windows for analysis will be based on weeks. For each parameter (i.e. hematologic, cytogenetic and molecular response), time windows will be used to identify data to be considered for the specific analysis at a specific time point as well as the cut-off for the analysis of response by a specific time point. The time windows are defined so that there are no gaps between the time windows, i.e. every assessment – including additional unscheduled assessments - would be assigned to one specific time point. If there is more than one assessment within the time window, the last available assessment in that time window will be used. If there is a duplicate analysis of the same sample, only the valid analysis result will be considered; if

both the analysis results of the same sample are valid, the result from the first analysis will be considered; if both analysis results of the same sample are valid, and it is not possible to sort them chronologically (not based on analyses dates nor based on tubes identification), the highest BCRABL ratio will be considered.

Time windows are defined based on date of study phase entry.

The following table shows the time windows for the analyses of molecular based on the planned assessment schedule.

Table 3-1 Time window for analyses of molecular assessments

Consolidation Phase:

Planned assessment	Time window
Baseline	Baseline; see definition in 3.2.2
Week 12 (Day 84)	Day 2 – Day 126
Week 24 (Day 168)	Day 127 – Day 210
Week 36 (Day 252)	Day 211 – Day 294
Week 48 (Day 336)	Day 295 – Day 350
Week 52 (Day 364)	Day 351 – End of Consolidation Phase

Note: In case that a patient enters TFR phase on day other than day 365 (week 52 + 1 day) per protocol, the last assessment window of consolidation phase will be ended on: the date of the start of TFR phase – 1day.

TFR Phase:

Planned assessment	Time window
Week 4 (Day 28)	Day 1 – Day 42
Week 8 (Day 56)	Day 43 – Day 70
Week xx (Day $xx * 7$)	Day $((xx - 2) * 7 + 1)$ – Day $((xx + 2) * 7)$
Week 44 (Day 308)	Day 295 – Day 322
Week 48 (Day 336)	Day 323 – Day 357
Week 54 (Day 378)	Day 358 – Day 399
Week yy (Day $yy * 7$)	Day $((yy - 3) * 7 + 1)$ – Day $((yy + 3) * 7)$
Week 96 (Day 672)	Day 652 – Day 714
Week zz (Day $zz * 7$)	Day $((zz - 6) * 7 + 1)$ – Day $((zz + 6) * 7)$
Week 192 (Day 1344)	Day 1303 – Day 1386
Week 264 (Day 1848)	Day 1807 to Day 1890
Week 312 (Day 2184)	Day 2143 to Day 2226
Week 360 (Day 2520)	Day 2479 to Day 2562
Week 408 (Day 2856)	Day 2815 to Day 2898
Week 468 (Day 3276)	Day 3235 to Day 3318
Week 528 (Day 3696)	Day 3655 to Day 3738

xx = Every 4 weeks after week 4 until week 48

yy = Every 6 weeks after week 48 until week 96

zz = Every 12 weeks after week 96 until end of TFR phase.

Note:

[1] Time-windows are based on TFR Day 1(the first day without any nilotinib treatment after the consolidation phase).

[2] In case a patient enters treatment re-initiation phase, the last assessment window of TFR phase will be ended on: the date of the start of treatment re-initiation phase – 1day.

Treatment re-initiation Phase:

Planned assessment	Time window
Week 4 (Day 28)	Day 1 – Day 42
Week xx (Day $xx * 7$)	Day $((xx - 2) * 7 + 1)$ – Day $((xx + 2) * 7)$
Week 24 (Day 168)	Day 155 – Day 210
Week zz (Day $zz * 7$)	Day $((zz - 6) * 7 + 1)$ – Day $((zz + 6) * 7)$

xx = Every 4 weeks until 24 weeks

zz = Every 12 weeks after week 24 until end of treatment re-initiation phase.

Note:

[1] Time-windows are based on treatment re-initiation phase Day 1.

TFR2 Phase:

Planned assessment	Time window
Week 4 (Day 28)	Day 1 – Day 42
Week 8 (Day 56)	Day 43 – Day 70
Week xx (Day $xx * 7$)	Day $((xx - 2) * 7 + 1)$ – Day $((xx + 2) * 7)$
Week 44 (Day 308)	Day 295 – Day 322
Week 48 (Day 336)	Day 323 – Day 357
Week 54 (Day 378)	Day 358 – Day 399
Week yy (Day $yy * 7$)	Day $((yy - 3) * 7 + 1)$ – Day $((yy + 3) * 7)$
Week 96 (Day 672)	Day 652 – Day 714
Week zz (Day $zz * 7$)	Day $((zz - 6) * 7 + 1)$ – Day $((zz + 6) * 7)$
Week 192 (Day 1344)	Day 1303 – Day 1386
Week 264 (Day 1848)	Day 1807 to Day 1890
Week 312 (Day 2184)	Day 2143 to Day 2226
Week 360 (Day 2520)	Day 2479 to Day 2562
Week 408 (Day 2856)	Day 2815 to Day 2898
Week 468 (Day 3276)	Day 3235 to Day 3318
Week 528 (Day 3696)	Day 3655 to Day 3738

xx = Every 4 weeks after week 4 until week 48

yy = Every 6 weeks after week 48 until week 96

zz = Every 12 weeks after week 96 until end of TFR2 phase.

Note:

[1] Time-windows are based on TFR-2 Day 1(the first day without any nilotinib treatment after treatment continuation phase).

[2] In case a patient enters treatment re-initiation2 phase, the last assessment window of TFR2 phase will be ended on: the date of the start of treatment re-initiation2 phase – 1day.

3.2.4.1 Time windows for analyses laboratory parameters

For laboratory parameters (i.e. hematology, biochemistry), time windows will be used to identify data to be considered for the specific analysis at a specific time point. The time windows are defined so that there are no gaps between the time windows, i.e. every assessment – including additional unscheduled assessments - would be assigned to one specific time point. If there is more than one assessment within the time window, the last available assessment in that time window will be used.

Table 3-2 Time windows between consolidation and TFR phases

Timepoint	Time window
NTCS Week -52	first dose date in consolidation phase +1 to Day -323
NTCS Week -40	Day -322 to Day -239
NTCS Week -28	Day -238 to Day -155
NTCS Week -16	Day -154 to Day -71
NTCS Week -4	Day -70 to Day -16
NTCS Week 0	Day -15 to Day -1
TFR Week 12	Day 1 to Day 126
TFR Week 24	Day 127 to Day 210
TFR Week 36	Day 211 to Day 294
TFR Week 48	Day 295 to Day 378

Note: Day 1 is the start of the TFR phase; Day -1 is the last day of the NTCS phase. Days are reported as negative for the consolidation phase.

Table 3-3 Time windows between TFR and re-initiation phases

Timepoint	Time window
TFR week - 48	Day -378 to Day -295
TFR week - 36	Day -294 to Day -211
TFR week - 24	Day -210 to Day -127
TFR week -12	Day -126 to Day - 8
TFR week 0	Day -7 to Day -1
NTRI Week 4	Day 1 to Day 42
NTRI Week 8	Day 43 to Day 70
NTRI Week 12	Day 71 to Day 126
NTRI Week 24	Day 127 to Day 182

Notes:

- Day 1 is the start of the re-initiation phase; Day -1 is the last day of the TFR phase. Days are reported as negative for the TFR phase. TFR time points only consider the last 48 weeks prior to entry in the NTRI phase, even if patients remained longer on the TFR phase.

3.2.4.2

CCI

CCI

CCI

Table 3-4

CCI

CCI

3.3 Patient disposition

A patient will be considered to have discontinued from study if the answer is “No” to the question “Will the subject continue into the next phase of the trial?” in the study phase completion eCRF page. Otherwise, the patient will be considered as ongoing on study.

3.4 Derivation of response rates and categories

3.4.1 Response rate at a specific time point

The molecular response evaluations will be summarized by the following binary variables for response: MMR, MR4 and MR4.5 (as defined in Section 2.8.2.1). For an analysis time point the determination of the response status is based on the assessments within the time window.

- **Response:** Patients with a last available assessment at that time point (within time window) indicating a response.
- **No response:** Patients with a last evaluable assessment at that time point (within time window) indicating 'no response' or with missing assessment.

For analyses where patients that needed to restart therapy before the analysis time point are considered as non-responders (in particular the primary analysis within week 48 of the TFR phase), they will be considered as ‘no response’, regardless of the presence of an available sample within the time window.

In addition, the rules for handling missing assessments at a specific time point as described in Section 2.8.3 will be applied.

3.4.2 Response rate by a specific time point (best response)

In this analysis, patients who had achieved any response at or before the time point will be displayed in their best response category, no matter if they lost the response/discontinued or not. Therefore this response rate represents the best observed response rate up to that specific time point (including the time window).

3.5 Derivation of PCR results and loss of response

If a patient has a detectable p190 BCR-ABL transcript or any other minor BCR-ABL transcript (atypical transcripts for CML patients) different than the major p210 BCR-ABL transcript (typical transcript for CML patients) in the study (regardless of having or not having any PCR results based on p210 transcript in this patient), then all PCR results, and Fragment Analysis results at all time points for this patient will be coded as “Atypical transcript”. This patient is considered as a molecular non-responder throughout all time points, and is excluded from per protocol analysis set.

Scaling towards an international standard will be performed for all molecular results using laboratory specific conversion factors. In this process, the ratio between BCR-ABL and the control gene ABL is calculated and multiplied by the lab-specific conversion factor (Hughes et al, 2006). Therefore, using the international unit, the BCR-ABL ratio will be presented in %. The MRDx assay from MMD laboratory will be used in this study. The lab conversion factor for this assay is 1.

The BCR-ABL ratio is calculated as follows:

- Multiply the BCR-ABL ratio with the lab-specific conversion factor and then by 100:

$$\text{BCR-ABL ratio (in \%)} = (\text{BCR-ABL} / \text{ABL}) * \text{conversion factor} * 100$$

For consistency with elsewhere reported molecular response rates, the result may be expressed also as log-reduction. This is defined as the following:

$$\text{BCR-ABL Log-Reduction} = -\log_{10} (\text{BCR-ABL ratio in \%})$$

For example, $-\log_{10} (0.001) = 3$ log reduction for a ratio of 0.1%.

The following binary variables will be used when molecular response is reported.

Table 3-5 Response categories for molecular response

MR (Molecular Response)		BCR-ABL ratio (%)	Log-reduction category
MMR	Yes	$\leq 0.1\%$	≥ 3 -log reduction
	No	$> 0.1\%$	< 3 -log reduction
MR4	Yes	$\leq 0.01\%$	≥ 4 -log reduction
	No	$> 0.01\%$	< 4 -log reduction
MR4.5	Yes	$\leq 0.0032\%$	≥ 4.5 -log reduction
	No	$> 0.0032\%$	< 4.5 -log reduction

- Loss of MMR is defined as BCR-ABL ratio $> 0.1\%$ IS. **Loss of MMR will not require confirmation.**
- Loss of MR4 is defined as BCR-ABL ratio $> 0.01\%$ IS

- Confirmed loss of MR4 is two consecutive BCR-ABL > 0.01% IS
- Loss of MR4.5 is defined as BCR-ABL ratio > 0.0032% IS

4 SAS procedures used for inferential analysis computation

4.1 Pearson-Clopper CI for response rate

The $100 \times (1 - \alpha \text{ level})$ % Pearson-Clopper CI for the proportion of responders (binary outcome = 1 or “Yes”), is obtained from the following:

```
proc freq data = dataset;
```

```
table binary event / binomial(exact level = "Yes") alpha = alpha level; run;
```

When there are no responders, SAS does not produce a CI by default. To obtain a CI in this situation, PROC FREQ is used as specified above except changing `level="No"`. From the results of this modified procedure, the values in percent of the LCL and UCL of a 0% response rate are calculated as follows:

- $LCL_{LEVEL="Yes"} (\%) = 100\% - UCL_{LEVEL="No"} (\%)$
- $UCL_{LEVEL="Yes"} (\%) = 100\% - LCL_{LEVEL="No"} (\%)$

4.2 Kaplan-Meier CI for estimated median time to event and estimated rate

The $100 \times (1 - \alpha \text{ level})$ % CI for the Kaplan-Meier estimated median time to event and estimated rate of an event at different time points, using the LOGLOG transformation, is obtained from the following:

```
proc lifetest data = dataset alpha = estimated rate alpha level
```

```
alphaqt = estimated median alpha level conftype = loglog;
```

```
time time to event * censor(1);
```

```
run;
```

4.3 Logistic regression

```
proc logistic data = dataset Order =data ;
```

```
class subject / Param = glm ;
```

```
model [binary response variable] = function of independent variables / solution;
```

```
run;
```