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Clinical Development

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

Statistical Analysis Plan (SAP)
Final Clinical Study Report (CSR)

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List of abbreviations

ABL	Abelson leukemia virus
AE	Adverse Event
AESI	Adverse Events of Special Interest
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
ANC	Absolute Neutrophil Count
AP	Accelerated Phase
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
ATP	Adenosine Triphosphate
AUC	Area Under Curve
BC	Blast Crisis
BCR	Break point Cluster Region
BCR-ABL	BCR-ABL oncoprotein product of BCR-ABL fusion gene
BID	*bis in diem*/twice a day
CCyR	Complete Cytogenetic Response
CHR	Complete Hematologic Response
CI	Confidence Interval
Cmin,ss	Lowest steady-state concentration observed
CML	Chronic Myeloid Leukemia
CMO&PS	Chief Medical Office and Patient Safety
CMR	Complete Molecular Response
CP	Chronic Phase
CRF	Case Report/Record Form; the term CRF can be applied to either EDC or Paper
CRO	Contract Research Organization
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CTCAE	NCI Common Terminology Criteria for Adverse Events
CV	Coefficient of Variation
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture
EOS	End of Study
EOT	End of Treatment
CCI	[redacted]
FAS	Full Analysis Set
FDA	Food and Drug Administration (USA)
GCP	Good Clinical Practice
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethic Committee
IRB	Institutional Review Board
IRT	Interactive Response Technology
KM	Kaplan-Meier
LFTs	Liver Function Tests
LLN	Lower Limit of Normal
LLOQ	Lower Limit Of Quantification

LPFV	Last Patient First Visit
LPLV	Last Patient Last Visit
mCyR	minor Cytogenetic Response
MCyR	Major Cytogenetic Response
CCI	[redacted]
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MMR	Major Molecular Response
MR	Molecular Response
MR3.0	Molecular Response 3.0 log reduction from baseline
MR4.0	Molecular Response 4.0 log reduction from baseline
MR4.5	Molecular Response 4.5 log reduction from baseline
MR5.0	Molecular Response 5.0 log reduction from baseline
MRD	Minimal Residual Disease
N	Sample size
NTCS	Nilotinib Treatment Consolidation phase
NTCT	Nilotinib Treatment Continuation phase
NTCT-P	Nilotinib Treatment Continuation Prolonged phase
NTRI	Nilotinib Treatment Re-Initiation phase
OS	Overall Survival
PCR	Polymerase Chain Reaction
PCyR	Partial Cytogenetic Response
PD	Pharmakodynamics
PFS	Progression Free Survival
Ph	Philadelphia chromosome
Ph+ CML	Philadelphia chromosome positive Chronic Myeloid Leukemia
PK	Pharmacokinetic
PPS	Per-Protocol Set
PRO	Patient Reported Outcome
PSUR	Periodic Safety Update Report
QTc	Q-T Corrected
QTcF	Q-T interval in the ECG (corrected according to the formula of Fridericia)
RAP	The Report and Analysis Plan
SAE	Serious Adverse Event
SD	Standard Deviation
SS	Safety Set
TFR	Treatment-Free Remission
TFS	Treatment Free Survival
TKI	Tyrosine Kinase Inhibitor
ULN	Upper Limit of Normal
WBC	White Blood Cell

1 Introduction

This SAP describes the statistical methods for all analyses planned to be included in the 10-year (528-week) final CSR. The analysis of primary efficacy endpoint was performed when all patients completed 48 weeks of the treatment-free remission (TFR) phase or entered the nilotinib treatment re-initiation (NTRI) phase or discontinued from the study.

The main purpose of the report is to include analyses addressing the USA Food and Drug Administration (FDA) post-marketing reporting (PMR) requests:

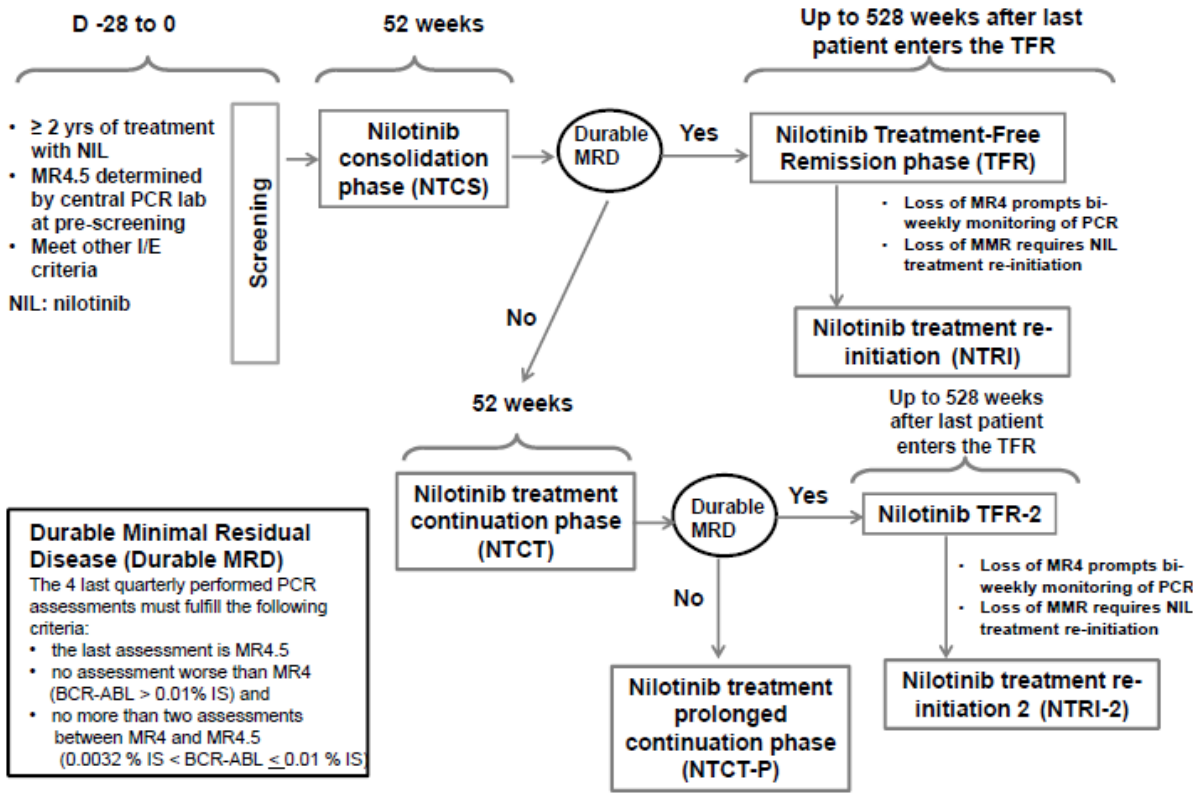
1. PMR 2: Characterize the potential risk of resistance to treatment after discontinuation of Tasigna by collecting and reporting information on late relapses, loss of response, and occurrence of mutations (risk of developing resistance), on a yearly basis from trials CAMN107A2408 and CAMN10712201. Submit 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.

A brief short report instead of a full clinical study report (CSR) was implemented for the 6, 7, 8 and 9 year update while full CSR will be prepared for the final 10-year update. Timepoints by 6/7/8/9 years were corresponded to 312/360/408/468 weeks, respectively, and 10-year corresponds to 528-week.

1.1 Study design

Patients in this study will receive nilotinib treatment for 52 weeks during the consolidation phase and then enter the TFR phase, if they are eligible, or continue nilotinib treatment (nilotinib treatment continuation phase). The TFR phase will last up to 528 weeks after the last patient enters the TFR phase unless patients need to restart nilotinib treatment. In this last case, they will enter nilotinib treatment re-initiation phase. The overall study design is shown in Figure 1-1.

Figure 1-1 Study design



This study has the following 7 phases:

- **Nilotinib consolidation phase**: Patients who satisfy all inclusion/ exclusion criteria will enroll in the consolidation phase. The consolidation phase is scheduled for 52 weeks. In order to be eligible to start the TFR phase, patients have to fulfill the protocol specific definition of durable minimal residual disease (MRD). The 4 last quarterly performed polymerase chain reaction (PCR) assessments must fulfill the following criteria:
  1. the last assessment (at 48 weeks of consolidation phase) is MR4.5 (BCR-ABL ≤ 0.0032% IS)
  2. no assessment worse than MR4 (BCR-ABL > 0.01% IS) and
  3. no more than two assessments between MR4 and MR4.5 (0.0032 % IS < BCR-ABL ≤ 0.01% IS)
- **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). This phase is up to 10 calendar years (528 weeks) after the last patient enters in the TFR phase. When a patient loses MMR (defined as BCR-ABL > 0.1% IS), nilotinib treatment will be re-initiated in the patient.

- **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. Patients will be eligible to enter the TFR-2 phase after the continuation phase if they fulfill the protocol specific definition of durable MRD. Patients who do not qualify to start TFR-2 may continue to receive nilotinib treatment in the nilotinib prolonged continuation phase for up to 528 weeks after the last patient enters the nilotinib TFR phase.
- **Treatment re-initiation phase**: During the TFR phase if a patient loses MMR, he/she will restart nilotinib treatment and will enter in the treatment re-initiation phase. Duration of this phase is up to 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 treatment continuation phase). Duration of this phase is up to 528 weeks after the last patient enters in the TFR phase. A 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 a 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 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 528 weeks after the last patient enters in the TFR phase.

Among these seven phases, the two main phases of interest are the consolidation phase, the TFR phase and the treatment re-initiation phase.

1.2 Study objectives and endpoints

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

Table 1-1 Objectives and related endpoints

Objective	Endpoint	Analysis
Primary		

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

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

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

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

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

Objective	Endpoint	Analysis
Exploratory		
CCI		

2 Statistical methods

It is planned that the data from all centers that participate in this protocol will be pooled and analyzed.

2.1 Data analysis general information

Novartis team will perform the analysis for 10-year report.

All data reported in the database (scheduled, repeat and unscheduled visits) up to the LPLV date of 24-Jan-2025 (one full calendar year since the date of last data cut-off for 9-year report, 5-Jan-2024) will be included in the analyses. Specifically, these include:

1. All data obtained after informed consent was signed.
2. All data in all study phases including treatment-free phases.
3. All data during 30 day safety follow up and post-treatment follow up.

SAS version 9.4 or higher version will be used for data analysis.

2.1.1 General definitions

Study day and phases

In this study, there is no study day 0 defined. Below are defined the different study days used in the analyses:

- Study day 1 = Date of first intake of study drug in this trial as recorded on the Dose Administration Record.
- Study day (of an event after study day 1) = date of event – date of study day 1 + 1 day
- Study day (of an event before study day 1) = date of event – date of study day 1
- Study day in a study phase follows the above rules by taking the first day of the study phase as Study day 1 in the study phase.
- Last study phase = the last study phase before post-treatment follow-up phase or at the time of the LPLV date
- End of study date = the date of the last day in the last study phase

Time to events

Time to events will be given in days, 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 (in particular for the efficacy analyses of the TFR phase):

Time to efficacy event = event date – start date of the study phase + 1

Time to safety event (except for TFR and TFR-2 phases) = event date – first dose date in the study phase + 1

Time to safety event (for TFR and TFR-2 phases) = event date – start date of the study phase + 1.

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

Efficacy analysis time points

There will be ten analysis time points with ten respective cut-off dates defined as the time when all patients who have entered TFR phase will have completed week 48, 96, 144,192 and 264 visit of TFR or discontinued earlier from these respective time points and when all patients who have entered TFR phase will have completed 6, 7, 8, 9 and 10 years in TFR or discontinued earlier from these respective time points. Timepoints at/by 6/7/8/9/10 years correspond to 312/360/408/468/528 weeks, respectively.

Baselines

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

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 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

Phases of CML

At start of the study (prior to entering the nilotinib consolidation phase), in order to comply with the protocol inclusion criteria, all of the following will be evaluated and have to be fulfilled for each patient:

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

- < 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 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.

For the evaluation of progression of CML phase during study, 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:

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

* As thrombocytopenia is a known adverse reaction to CML therapy, platelets <100 x 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:

- ≥ 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

Molecular response

Molecular response will be assessed by quantitative PCR (RQ-PCR) testing of peripheral blood. The samples will be sent to a central PCR laboratory with validated PCR technology that has a sensitivity of at least 4.5 logs to evaluate BCR-ABL transcript levels by RQ-PCR.

Molecular response will be presented with non-overlapping BCR-ABL ratio (BCR-ABL/ABL) (%) categories. These ratios are expressed on the International Scale (IS).

Major molecular response (MMR) is defined as a value of ≤ 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. The confirmation of the loss of MMR is not required in this study. Loss of MMR may be temporary.

BCR-ABL ratio of ≤ 0.0032% (MR4.5): BCR-ABL ratio of ≤ 0.0032% (corresponds to a ≥ 4.5 log reduction, of BCR-ABL transcripts from a standardized baseline), is defined as a value of ≤ 0.0032% BCR-ABL ratio by international scale. This endpoint will be considered as binary variables with patients achieving BCR-ABL ratio of ≤ 0.0032% grouped as 'responders' and

patients not achieving BCR-ABL ratio of ≤ 0.0032%, patients with missing PCR grouped as 'non-responders'.

Loss of BCR-ABL ratio of ≤ 0.0032% (MR4.5) is defined as increase of the BCR-ABL ratio to > 0.0032% in a single blood sample, by international scale.

2.2 Analysis sets

The following populations will be considered in data analysis:

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

Safety Set includes all patients who received at least one dose of study medication. Safety Set will be split into subsets by study phases. Safety analyses will be presented, both globally (i.e. pooling all study phases) and specifically for the different study phases, with specific focus on certain phases (e.g. TFR phase). The following 7 safety subsets are defined:

- **Nilotinib consolidation phase (NTCS) Safety Set**: patients who received at least one dose of study medication in the consolidation phase.
- **Nilotinib Treatment-Free Remission phase (TFR) Safety Set:** patients who enter the TFR phase (equivalent to FAS).
- **Nilotinib treatment continuation phase (NTCT) Safety Set**: patients who received at least one dose of study medication during nilotinib treatment continuation phase.
- **Nilotinib treatment re-initiation phase (NTRI) Safety Set:** patients who received at least one dose of study medication during treatment re-initiation phase.
- **Nilotinib Treatment-Free Remission 2 phase (TFR-2) Safety Set:** patients who entered TFR-2 phase.
- **Nilotinib treatment re-initiation 2 phase (NTRI-2) Safety Set:** patients who received at least one dose of study medication during treatment re-initiation phase 2.
- **Nilotinib treatment prolonged continuation phase (NTCT-P) Safety set:** patients who received at least one dose of study medication during treatment prolonged continuation phase.

Per-Protocol Set (PPS) consists of a subset of the patients in the FAS who are compliant with requirements of the clinical study protocol (CSP). Protocol deviations leading to exclusion from the PPS include:

1. Administration of other TKI agent
2. Subject not on first line nilotinib treatment
3. Subject did not achieve MR4.5 with nilotinib treatment prior to study entry
4. Subject has no typical BCR-ABL transcript
5. Subject took less than 2 years of nilotinib
6. Previous treatment with alpha-interferon of any duration
7. Subject had prior AP, BC

8. Subject has a history of other active malignancy within 5 years prior to study entry except of previous or concomitant basal cell skin cancer, previous cervical carcinoma in situ treated curatively
9. Subject was treated with other investigational agents
10. Subject had confirmed loss durable Minimal Residual Disease but still entered TFR, TFR-2
11. Subject had loss of MMR in TFR, but did not reinitiate treatment
12. Subject did not receive any study drug
13. Subject took study drug during TFR, TFR-2

The PPS will be used for a supportive analysis of the primary endpoint of the proportion of patients who are in MMR at 48 weeks after starting the TFR phase.

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 (pre-dose on week 48). A pre-dose PK trough sample will be considered unevaluable 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 is considered unevaluable as per scientific judgment by clinical pharmacology expert.

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

Other Analysis Sets described in [Section 10.1.6 of the protocol amendment 6] are embedded in the 7 Safety subsets described above and are thus not described here again.

2.2.1 Subgroup of interest

No subgroup analysis is planned.

2.3 Patient disposition, demographics and other baseline characteristics

2.3.1 Patient disposition

Patient disposition will be presented in the Safety set. The numbers of patients who ended a study phase, will be summarized by study phase. Among the patients who end a study phase, the reasons for end of study phases will be summarized.

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

In addition, the number of patients with protocol deviations will be presented by category of deviation for both Safety set 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.

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 CRF page. Otherwise, the patient will be considered as ongoing on study.

2.3.2 Demographics and other baseline characteristics

All demographic data (such as age, gender, race, ethnicity, weight, height), active and inactive medical conditions at study start, disease history (such as time since diagnosis, time since achievement of MR4.5, and Sokal risk score at diagnosis) and extramedullary involvement reported at baseline will be summarized and listed for the FAS and Safety set. Qualitative variables (i.e. gender) 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 (mean, standard deviation, median, minimum, and maximum).

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

2.4.1 Study treatment / compliance

Dose intensity and exposure

All study drug data will be summarized using the safety subsets 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) phases (i.e., except TFR and TFR-2 phases).

For the purpose of these analyses, the following rules will be applied individually to each phase:

Date of the first dose is defined as the date of first intake of the study drug in the study phase. This will be considered as treatment day 1 for the study phase.

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

- For non-last study phases the date of last dose is defined as the last date in the study phase.
- For the last study phase the date of last dose is defined as the latest date of the last available dates reported on the following records: dose administration record, PCR, bone marrow assessments, extramedullary involvement and laboratory
- For the last study phase and for patients who entered post-treatment follow up phase, 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 quantities will be derived for each study phase:

Duration of exposure (in days) = date of last dose – date of first dose + 1 day

Time on treatment (in days) = (date of last dose – date of first dose) + 1 day - (days of zero total daily dose)

Duration of exposure (in weeks) = Duration of exposure (in days)/7

Time on treatment (in weeks) = Time on treatment (in days)/7

Actual dose intensity (mg/day) = total dose / duration of exposure (periods of zero dose are included)

Average daily dose (mg/day) = total dose / time on treatment (periods of zero dose are excluded)

Relative dose intensity (%) = (actual dose intensity / assigned total daily dose)*100

Duration of treatment free remission

Duration of treatment free remission, TFR/TFR-2, will be summarized for TFR/TFR-2 safety set using the following definition:

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

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.

2.4.2 Prior, concomitant and post therapies

Prior and concomitant medications 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 Dictionary (WHO DD) 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 but no later than 30 days after the last phase, 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 by ATC class and preferred term according to the WHO DD dictionary.

Any prior concomitant medications or significant non-drug therapies starting and ending prior to the start of study treatment will be listed. All concomitant therapies will be listed including therapies starting more than 30 days after the last phase.

2.4.3 Antineoplastic therapy

Prior antineoplastic medications other than nilotinib will be listed. Duration of prior nilotinib use will be summarized descriptively for FAS and Safety Set. Antineoplastic medications after discontinuation of study will be listed by preferred terms using the Safety Set.

2.5 Analysis supporting primary objective

This primary analysis at 48 weeks of TFR is only performed based on 48-week data, and is not applicable for 96/144/192/264-week and 6, 7, 8, 9, and 10 years CSR analyses.

The primary efficacy variable is the proportion of patients who are in MMR at 48 weeks after starting the TFR phase defined as the number of patients with MMR at 48 weeks after starting the TFR phase with no loss of MMR and no re-initiation of nilotinib therapy in the first 48 weeks after starting the TFR phase divided by the number of patients who entered the TFR phase. Loss of MMR is defined as a single assessment of BCR-ABL > 0.1% IS. The primary efficacy variable was fully evaluated based on the 48-week data and reported in the 48-week CSR. Please refer to the primary CSR SAP for the definitions and statistical methods related to the primary efficacy variable.

2.6 Analysis supporting secondary objectives

2.6.1 Secondary endpoint(s)

Secondary efficacy endpoints include:

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

- Proportion of patients who are in MR4.5 at 48, 96, 144, 192, 264 weeks and at 6, 7, 8, 9, and 10 years after starting the TFR phase irrespective of whether or not patients required re-initiation of treatment defined as the number of patients with MR4.5 at 48, 96, 144, 192, 264 weeks and at 6, 7, 8, 9, and 10 years after starting the TFR divided by the number of patients who entered the TFR phase. Patients who have re-initiation of nilotinib treatment but have less than 12 weeks of re-initiated treatment will be excluded from the analysis

2. Proportion of patients who achieve MMR within 12 weeks of re-initiation of treatment with nilotinib defined as the number of patients who are in MMR at least at one assessment within 12 weeks after re-start of nilotinib treatment divided by the number of patients who are re-initiated for at least 12 weeks
3. Kinetics of BCR-ABL transcript levels (IS) over time after re-initiation of nilotinib therapy
4. Occurrences of mutations in patients who lost MMR will be summarized by the following mutation categories:
   - Resistant mutation: T315I
   - Less sensitive mutations: Y253H, F359V/C/I, and E255K/V
   - Unknown sensitivity mutations: E450G and E459G
   - Sensitive mutations: all the other mutations which are not classified as T315I, less sensitive or unknown sensitivity
5. Duration of re-initiated treatment required to regain MMR defined as the time from date of start of re-initiation of treatment after loss of MMR to the date of first achievement of MMR [Duration = date of first MMR - date of start of re-initiation of treatment after loss of MMR (start date of NTRI phase) + 1]. Patients who do not regain MMR after re-initiation of treatment on or before the cut-off date, duration will be censored at the date of last PCR assessment. If a patient discontinues study prior to achieving an MMR, 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, consider the response is impossible to reach)
   - In addition to the duration of retreatment required to regain MMR, cumulative incidence rates of regaining MMR over time in the NTRI phase will be provided by considering censored patients as non-responders. The analysis is described in the subsection “Analyses methods for secondary objectives” below in this section.
6. Duration of re-initiated treatment required to regain MR4.5 which is measured from the time from date of start of re-initiation of treatment after loss of MMR to the date of first achievement of MR4.5 [Duration = date of first MR4.5 - date of start of re-initiation of treatment after loss of MMR (start date of NTRI phase) + 1]. Patients who do not regain MR4.5 after re-initiation of treatment on or before the cut-off date, duration will be censored at the date of last PCR assessment. If a patient discontinues study prior to achieving an MR4.5, 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, consider the response is impossible to reach)

- In addition to the duration of retreatment required to regain MR4.5, cumulative incidence rates of regaining MR4.5 over time in the NTRI phase will be provided by considering censored patients as non-responders. The analysis is described in the subsection "Analyses methods for secondary objectives" below in this section.

7. The proportion of patients with stable molecular response (MR4.5/MMR) after achievement of that response in nilotinib re-initiation phase for 48 weeks, 96 weeks, 144 weeks, 192 weeks, 240 weeks, 288 weeks, 336 weeks, 384 weeks and 432 weeks, based on availability of appropriate data.

   Stable molecular response – 48/96/144/192/240/288/336/384/432 weeks in nilotinib re-initiation period is defined as, achievement of a certain level of response (MR4.5/ MMR) in nilotinib re-initiation period, if again the same response is observed after 48/96/144/192/240/288/336/384/432 weeks beyond the first achievement date of the response during the nilotinib re-initiation period irrespective of whether there is loss of response in between first achievement and week 48/96/144/192/240/288/336/384/432 assessment.

   This proportion will be calculated by dividing the number of patients with stable molecular response (MR4.5/ MMR), by the number of patients who achieved that response (MR4.5/ MMR) at least once in nilotinib re-initiation period.

8. Long term outcomes

   - **Treatment-free survival (TFS)**

     Treatment-free survival is defined as the time from the date of start of TFR to the date of the earliest occurrence of any of the following events in the study up to the end of TFR phase:

     - Loss of MMR
     - 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 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.

     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 TFS analysis as defined above. 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, 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.

- **Progression-free survival (PFS)**

  Progression-free survival is defined as the time from the date of start of TFR to the date of event defined as the first occurrence of documented disease progression to AP/BC or the date of death from any cause. For patients who do not have events, the time will be censored at the date of last assessment (PCR, cytogenetic, hematologic or extramedullary) for patients who are still on study before the follow-up period and at the date of last contact for patients who are in the follow-up period.

- **Overall survival (OS)**

  Overall survival (all deaths) is defined as the time from date of start of TFR to death due to any cause at any time during the study, including the follow-up period. For patients who do not have events, 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 (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 PDS, including conditions that need to be satisfied for a date to be taken into account in the derivation of the last contact.

2.6.2 Statistical hypothesis, model, and method of analysis

No hypothesis test is planned for the secondary efficacy endpoints.

The MMR/MR4.5 at certain time points after starting the TFR phase, the rate of patients who succeeded to achieve MMR with re-initiation of nilotinib treatment, and the rate of stable molecular responses in nilotinib re-initiation phase will be presented together with an exact 95% Clopper-Pearson confidence interval.

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

All time to event endpoints including duration of re-initiated treatment required to regain MMR and MR4.5, TFS, PFS and OS will be analyzed using the Kaplan-Meier (KM) method and will be presented by KM plots. 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 the first 24 weeks and then at every 12 weeks thereafter. For duration of re-treatment required to regain MMR and MR4.5, the KM estimated rates will be provided at every 4 weeks from NTRI start date for the first 24 weeks and then at every 12 weeks thereafter.

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

2.6.3 Handling of missing values

For the analysis of patients who are in MMR/MR4.5 at 48, 96, 144, 192 and 264 weeks and at 6, 7, 8, 9, and 10 years after starting the TFR phase, patients dropping out early from the study during the TFR phase will be considered as not in response after starting the TFR phase and will be included in the FAS. In case of missing PCR assessment at 48, 96, 144, 192 and 264 weeks and at 6, 7, 8, 9, and 10 years after starting the TFR phase, if both planned PCR assessment before and after the planned analysis time point of 48, 96, 144 192, 264 weeks and 6, 7, 8, 9, and 10 years are available, and if both assessments are in response, the planned analysis time point assessment will be imputed as “response”, otherwise “non-response”.

2.6.4 Sensitivity analyses

The sensitivity analyses are not planned.

2.7 Safety analyses

For all safety analyses, the Safety Set will be used. Analyses will be done globally and using the 7 Safety subsets by study phase as defined in Section 2.2. 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. These patients are defining the TFR Safety Set.

2.7.1 Adverse events (AEs)

Summary tables for AEs will include only the treatment-emergent AEs (TEAEs), which started or worsened during the 7 study phases including the treatment-free remission phases. The start day used to define the TEAEs in the entire study is the first day of dosing of the Nilotinib Consolidation Phase and the end day of TEAEs is 30 days after the last 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.

However, all safety data (including those collected before study day 1) will be listed and those collected before study day 1 or during post-treatment follow-up period, i.e. more than 30 days after the last day of the last phase are to be 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 in the safety subsets in the treatment phases.

- All AEs
- AEs suspected to be study drug related
- AEs reported as serious AEs (SAEs)
- SAEs suspected to be study drug related
- 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
- AEs that are not SAEs

Adverse Events of Special Interest (AESI) 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. AESI groupings may be obtained from SAS dataset eCRS in the Novartis computing environment. For each specified AESI 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) in TFR phase to allow a fair comparison), side by side. This analysis is planned to be performed only for 48-week CSR, and not to be repeated for CSR at or after 96 weeks.

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

Rate of any AE (or specific AE groupings) will be presented graphically from start of consolidation phase to 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) on a particular day by the number of patients in the TFR safety set who are continuing in the study on that day.

An AE is considered to be present on a particular day x, if study day of AE start date $\leq x \leq$ study day of AE end date

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

This analysis described above is planned to be performed only for 48-week CSR, and not to be repeated for CSR at or after 96 weeks.

The same analysis will be performed between the TFR phase and nilotinib treatment re-initiation phase 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 is planned to be performed only for 48-week CSR, and not to be repeated for CSR at or after 96 weeks.

In addition to the above, analyses will be performed to assess the rate 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 (336 days) of the TFR phase and second 48 weeks (337 – 672 days) of the TFR The same principle to compare rates of AE over time (consolidation phase, and then every 48 weeks of TFR) could be applied to future analyses (if performed) at 144, 192, 264 weeks and at 6, 7, 8, 9, and 10 years.

At the time of the final analysis, for the legal requirements of ClinicalTrials.gov and EudraCT, two required tables on treatment emergent AEs (started or worsened during the 7 study phases including the treatment-free remission phases) which are not serious adverse events with an incidence greater than 5% and treatment emergent SAEs and SAEs suspected to be related to study treatment will be provided by system organ class and preferred term on the safety set population. In addition to the number of patients affected, those tables will also report the number of occurrences of AEs/SAEs.

If for a same patient, several consecutive AEs (irrespective of study treatment causality, seriousness and severity) occurred with the same SOC and PT:

- a single occurrence will be counted if there is ≤ 1 day gap between the end date of the preceding AE and the start date of the consecutive AE
- more than one occurrence will be counted if there is > 1 day gap between the end date of the preceding AE and the start date of the consecutive AE

For occurrence, the presence of at least one SAE / SAE suspected to be related to study treatment / non SAE has to be checked in a block e.g., among AE's in a ≤ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

The number of deaths resulting from SAEs suspected to be related to study treatment and SAEs irrespective of study treatment relationship will also be provided by SOC and PT.

AEs by study phase

For adverse events, 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 >= phase start date).

- Baseline AE grade will be provided for each AE recorded (new or worsening, Figure 2.1) 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 2-1.
- 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.

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 and end dates of the AE record are compared to the start and end dates of this study phase.

Figure 2-1 provides examples of various scenarios for AEs in consolidation (NTCS) and TFR phases.

Figure 2-1 Examples of new or worsening AEs and baseline AEs for consolidation and TFR phases



NTCS phase	TFR phase	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 is used to identify new/worsening AEs in the TFR phase, where EOT means end of study phase (end of treatment for the treatment phases, and end of phase for TFR/TFR-2 phase):

(TFR start date) ≤ (AE start/worsening date) ≤ (EOT+30 days).

After identifying new/worsening AEs in the TFR phase, 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.

2.7.2 Deaths

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 (%).

2.7.3 Laboratory data

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

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

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

- Shift tables using CTCAE v.4.03 grades to compare baseline to the worst on-phase value. Five different baseline definitions for the different study phases, as defined in Section 2.1.1 will be used.
- For laboratory tests where CTCAE v.4.03 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 Section 2.1.1, will be used.
- Summary statistics by timepoint and by study phase
- Number and percentage of patients with laboratory abnormalities, by parameter and worst post-baseline CTCAE v.4.03 grade in the TFR Safety Set for the consolidation and TFR phases. Each patient will be counted only for the worst grade observed post-baseline, regardless of the baseline status.
- Listing of all laboratory data with values flagged to show the corresponding CTCAE v.4.03 grades and the classifications relative to the laboratory normal ranges.

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 2.1.1 (This analysis is planned to be performed only for 48-week CSR, and not to be repeated for CSR at or after 96 weeks). The same analysis will be repeated between the TFR and re-initiation phase in the NTRI 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 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 necessarily to be repeated for the 144/192/264-week and 6, 7, 8, 9, and 10 years CSR). The same principle to compare blood parameters over

time (consolidation phase, and then every 48 weeks of TFR) could be applied to analyses (if performed) at 144, 192, 264 weeks and at 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, and for consolidation phase and TFR phase in TFR Safety Set. See TFL shells for the thresholds evaluated for this parameter.

2.7.4 Other safety data

2.7.4.1 ECG and cardiac imaging data

For all time points, the average of available values of the serial ECG measurements will be used as the value at that time point (for each of the parameter). The following analyses will be performed over all treatment phases and by safety subset for variables PR, QRS, QT interval, ventricular rate, QTcB and QTcF:

- 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.

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.

Five different baseline definitions for the different study phases, as defined in Section 2.1.1, will be used.

For unscheduled visits, ECGs that are reported on the same day and within 30 minutes apart from each other will be assumed to be sequential ECGs and thus will be used to compute the mean of the ECG parameters.

A listing of all ECG measurements will be provided by time point, reported by study phase.

Only one echocardiogram at screening is planned to ensure healthy status in terms of cardiac anatomy and function. The results of all echocardiograms will be listed.

2.7.4.2 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: ≥ 140mmHg
- Diastolic BP: ≥ 90 mmHg
- Weight at baseline: >= 110 kg; post-baseline: increase from baseline of ≥ 10%

- Heart rate at 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
- Weight at baseline: <= 60 kg; post-baseline: decrease from baseline of ≥ 10%
- Heart rate at 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 Section 2.1.1, will be used.

Patients with notably abnormal values will be listed. All vital signs will be listed.

2.7.4.3 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 Section 2.1.1, will be used.

2.8 Pharmacokinetic endpoints

PK data analysis was done with the primary CSR, PK data was not collected afterwards, hence PK data analysis is not planned for the final CSR.

2.9 PD and PK/PD analysis

No PD and PK/PD analysis is planned for this study.

2.10 CCI




CCI



2.11 Biomarkers



2.12 



2.13 Other Exploratory analyses



2.14 Interim analysis

No formal interim analysis is planned for this study. The cut-off date for primary endpoint analysis is when all patients completed 48 weeks of TFR phase or entered treatment re-initiation phase or discontinued from the study. Thereafter, following the same principles for cut-off date definition, updates will be done at week 96, 144, 192, 264 and at 6, 7, 8, 9, and 10 years.

3 Sample size calculation

Demonstration of successful nilotinib TFR phase will be based on a study designed with a 90% power to test the null hypothesis that the rate of MMR at 48 weeks after start of TFR phase is <50% with the alternative hypothesis that the rate of MMR at 48 weeks after start of TFR phase is >50%. The sample size is based on Fleming's single stage design to test the null hypothesis H0: $p \leq 0.5$, where p is the rate of MMR at 48 weeks after start of TFR phase (considering any patient who required re-initiation of treatment as non-responder). If the true rate $p \geq 0.65$, then with one-sided alpha level of 2.5% and a power of 90%, a minimum of 122 patients are required to be studied. Based on data from study AMN107A2303, among patients treated with nilotinib 300 mg BID who were in MR 4.5 at 24 months, approximately 40% had unconfirmed loss of MR4 (one PCR assessment between 24 and 36 months that showed a BCR-ABL transcript level of >0.01% IS). There may be better treatment adherence in this study due to dedicated counseling of patients and therefore, it is assumed that approximately 30% of the patients (lower than 40% observed in study AMN107A2303) who have MR 4.5 at study entry will not be eligible for starting TFR phase after 48 weeks. As a result, approximately 175 patients will be enrolled into this study. The null hypothesis will be rejected if there are at least 73 patients with MMR at 48 weeks after starting TFR phase (considering any patient who required re-initiation of treatment as non-responder) assuming 122 patients required to start TFR phase.

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

This study had enrolled 216 patients by 20Dec2013, the date when the patient enrollment was closed. With 216 patients enrolled, if assuming approximately 30% of enrolled patients who have MR4.5 at study entry will not be eligible for starting TFR phase, there will be approximately 151 patients entering TFR. Assuming the true rate of MMR at 48 weeks after start of TFR phase is 65%, with a MMR rate of 50% for the null hypothesis, the study will have a 94% power with 1-sided alpha level of 2.5% to test the null hypothesis. Note that the power increases by 4% based on the 216 enrolled patients compared to the originally planned 90% power based on the 175 enrolled patients, with all the other assumptions for the power calculation being the same.

4 Change to protocol specified analyses

No change to protocol specified analyses.

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

No imputation is applied to missing/partial start date.

The following notation will be used for the imputation of the missing/partial dose end date:

	Day	Month	Year
Missing/partial dose end date	Not used	MON	YYYY
EOT completion date	Not used	EOTM	EOTY

The following rules should be used for the imputation of the dose end date for a given study treatment component:

Table 5-1 Imputation of dose end dates

	Dose end date		
	Missing	**Partial Date**	
		Day and month are missing	**Day is missing**
No EOT page and no death date	The LPLV date should be used as the dose end date		
EOT completion date is partial			
a) EOT day and month are missing	Set to the earliest of (the latest visit/assessment date*, 31DEC EOTY)	Set to the earliest of (the latest visit/assessment date*, 31DEC YYYY)	Set to the earliest of (the latest visit/assessment date*, last day of the month MON)
b) EOT day is missing	Set to the earliest of (the latest visit/assessment date*, last day of the month EOTM)	Set to the earliest of (the latest visit/assessment date*, 31DEC YYYY, last day of the month EOTM)	Set to the earliest of (the latest visit/assessment date*, last day of the month MON, last day of the month EOTM)
EOT completion date is complete	Set to EOT date		
a) YYYY<EOTY		Set to 31DEC YYYY	Set to last day of the month MON

b) YYYY=EOTY		Set to EOT date	If month < the month of EOT date (EOTM) then set to last day of the month MON. If month = the month of EOT date (EOTM) then set to EOT date.

* latest among lab/ECG/vital signs/AE assessment dates

All other cases should be considered as a data issue and the statistician should contact the data manager of the study.

After imputation, compare the imputed date with start date of treatment, if the imputed date is < start date of treatment:

Use the treatment start date

If start date is missing then end date should not be imputed.

5.1.2 AE and safety assessment date imputation

Table 5-2 Imputation of AE start dates

Missing Element	Rule
day, month, and year	• If AE start date is missing (without partial month/year) then impute with NTCS phase start date.

day, month	• If available year = year of NTCS start date then
	  o If stop date contains a full date and stop date is earlier than NTCS phase start date then set start date = 01JanYYYY
	  o Else set start date = NTCS phase start date+1.
	• If available year > year of NTCS phase start date then 01JanYYYY
	• If available year < year of NTCS phase start date then 01JulYYYY

Missing Element	Rule
Day	• If available month and year = month and year of NTCS phase start date then o If stop date contains a full date and stop date is earlier than NTCS phase start date then set start date= 01MONYYYY. o Else set start date = NTCS phase start date+1. • If available month and year > month and year of NTCS phase start date then 01MONYYYY • If available month and year < month year of NTCS phase start date then 15MONYYYY

Table 5-3 Imputation of laboratory (LAB) assessments dates

Missing Element	Rule
day, month, and year	• No imputation will be done for completely missing LB dates
day, month	• If available year = year of NTCS start date then impute the date with NTCS phase start date. • Otherwise impute the date as 01JanYYYY
day	For the local data impute the day with "01". For the central data: • If available month and year = month and year of NTCS phase start date then impute with NTCS phase start date • Otherwise impute the date as "01"

Table 5-4 Imputation of AE end dates

Missing Element	Rule
day, month, and year	• Completely missing end dates (incl. ongoing events) will be imputed by the last contact date
day, month	• If partial end date contains year only, set end date = earliest of 31DecYYYY or the last contact date
Day	• If partial end date contains month and year, set end date = earliest of last day of the month or the last contact date

Any AEs with partial/missing dates will be displayed as such in the data listings.

Any AEs which are continuing at the time of LPLV will be shown as 'ongoing' rather than the end date provided.

5.1.3 Concomitant medication date imputation

Table 5-5 Imputation of CM start dates

Missing Element	Rule
day, month, and year	• If CM start date is missing (without partial month/year) then impute with 1st January of NTCS phase start date.
day, month	• If available year = year of NTCS start date then impute with 1st January of NTCS phase start date. • If available year > year of NTCS phase start date then 01JanYYYY • If available year < year of NTCS phase start date then 01JulYYYY
Day	• If available month and year = month and year of NTCS phase start date then impute with 01MONYYYY. • If available month and year > month and year of NTCS phase start date then 01MONYYYY • If available month and year < month year of NTCS phase start date then 15MONYYYY

Table 5-6 Imputation of CM end dates

Missing Element	Rule
day, month, and year	• No imputation will be done for completely missing CM end dates
day, month	• If partial end date contains year only, set end date = earliest of 31DecYYYY or end date of the last phase
Day	• If partial end date contains month and year, set end date = earliest of last day of the month or end date of the last phase

Any ConMeds with partial/missing dates will be displayed as such in the data listings

5.1.3.1 Prior therapies date imputation

No imputation is applied to missing/partial start date or end date of prior therapy

5.1.3.2 Post therapies date imputation

No imputation is applied to missing/partial start date or end date of post therapy.

5.1.4 TFR/TFR-2 phase date imputation

No imputation is applied to missing/partial start date. For the last study phase and for patients who discontinued TFR (reason of TFR discontinuation is not missing) and didn't enter post-treatment follow-up phase but with missing TFR/TFR-2 end date, the TFR/TFR-2 end date is defined as the last contact date as defined in Section 2.6.1.

5.1.5 Other imputations

Incomplete date of initial diagnosis of cancer

Missing day is defaulted to the 15th of the month and missing month and day is defaulted to 01-Jan.

Incomplete date of hospitalization

Missing day is defaulted to the 15th of the month and missing month and day is defaulted to 15-Jun.

5.2 AEs coding/grading

AEs will be coded using the latest MedDRA version available. Grading will be based on CTCAE Version 4.03.

5.3 Laboratory parameters derivations

Grading will be based on CTCAE Version 4.03 for gradable laboratory parameters. If laboratory values are provided as '<X' (i.e. below limit of detection) or '>X', prior to conversion of laboratory values to SI unit, these numeric values are set to X.

5.4 Statistical models and SAS procedures

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

The 100 × (1 – *alpha 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);
```

Pearson-Clopper CI for response rate

The 100 × (1 – *alpha 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;
```

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% - $LCL_{LEVEL="No"}$ (%)

5.4.1 Analysis supporting primary objective

The PPS will be used for a supportive analysis of the primary endpoint of the proportion of patients who are in MMR at 48 weeks after starting the TFR phase. This analysis was done with the primary CSR and is not planned in the final CSR.

5.4.2 Analysis supporting secondary objectives

No supporting analysis is planned for secondary objectives.

5.5 Rule of exclusion criteria of analysis sets

See PPS definition for listed protocol deviations leading to exclusion from the PPS.

5.6 Windows for data analysis

5.6.1 Time windows for analyses of response

For efficacy parameter (i.e. molecular response), 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. If there is a duplicate analysis of the same sample (for PCR assessments), only the valid analysis result will be considered; if both 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 BCR-ABL ratio will be considered.

There will be three sets of time-windows defined for analysis of primary and secondary endpoints:

- Starting from day 1 of TFR phase
- Starting from day 1 of treatment re-initiation phase
- Starting from day 1 of TFR-2 phase

All samples taken after the start of the study phase will be assigned a time window based on the protocol scheduled sample collection in that phase. In order to allow the conduct of secondary analyses where the molecular response is analyzed regardless of whether the patient re-initiated therapy, samples taken during the treatment re-initiation phase (or re-initiation phase 2) will still be assigned a time window based on the TFR (or TFR-2) scheduled assessments.

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

Table 5-7 Time windows for analyses of molecular assessments

Time windows after start of TFR phase:

Planned assessment	Time window
Week 4 (Day 28)	Day 1 to Day 42
Week 8 (Day 56)	Day 43 to Day 70
Week xx (Day xx * 7)	Day ((xx – 2) * 7 + 1) to Day ((xx + 2) * 7)
Week 44 (Day 308)	Day 295 to Day 322
Week 48 (Day 336)	Day 323 to Day 357
Week 54 (Day 378)	Day 358 to Day 399
Week yy (Day yy * 7)	Day ((yy – 3) * 7 + 1) to Day ((yy + 3) * 7)
Week 96 (Day 672)	Day 652 to Day 714
Week zz (Day zz * 7)	Day ((zz – 6) * 7 + 1) to Day ((zz + 6) * 7)
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 the end of TFR phase

Notes:

[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 PCR samples will still be assigned a time-window based on the start of TFR.

Time windows after start of treatment re-initiation phase:

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

xx = Every 4 weeks until week 24

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

Note:

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

Time windows after start of TFR-2 phase:

Planned assessment	Time window
Week 4 (Day 28)	Day 1 to Day 42
Week 8 (Day 56)	Day 43 to Day 70
Week xx (Day xx * 7)	Day ((xx – 2) * 7 + 1) to Day ((xx + 2) * 7)
Week 44 (Day 308)	Day 295 to Day 322
Week 48 (Day 336)	Day 323 to Day 357
Week 54 (Day 378)	Day 358 to Day 399
Week yy (Day yy * 7)	Day ((yy – 3) * 7 + 1) to Day ((yy + 3) * 7)
Week 96 (Day 672)	Day 652 to Day 714

Planned assessment	Time window
Week zz (Day zz * 7)	Day ((zz – 6) * 7 + 1) to Day ((zz + 6) * 7)
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 the end of TFR-2 phase

Notes:

[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-initiation phase 2, the PCR samples will still be assigned a time-window based on the start of TFR-2.

In addition, since an exploratory objective of the study is to explore the kinetics of BCR-ABL ratio during the consolidation phase for patients not entering the TFR phase, time windows are also defined for that period.

Table 5-8 Time windows for analyses of kinetics of BCR-ABL transcripts during consolidation phase

Planned assessment	Time window
Baseline	Baseline; see definition in section 3.2.2
Week 12 (Day 84)	Day 2 to Day 126
Week 24 (Day 168)	Day 127 to Day 210
Week 36 (Day 252)	Day 211 to Day 294
Week 48 (Day 336)	Day 295 to Day 364

Note:

[1] 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 day prior to the start of TFR phase.

5.6.2 Time windows for analyses of 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. If there is a duplicate analysis of the same sample (both central and local results on the same day), the central laboratory result will be considered in the analysis.

Table 5-9 Time windows for analyses of hematologic parameters

Time windows between consolidation and TFR phase in patients who enter TFR phase

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 -1**
TFR Week 4	**Day 1** to Day 42
TFR Week 8	Day 43 to Day 70
TFR Week xx	Day (xx-2)*7 +1 to Day (xx+2)*7
TFR Week 48	Day 323 to Day 350

Note:

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

[2]. xx = Every 4 weeks after week 4 until week 48

Time windows between TFR and re-initiation phases in patients who enter re-initiation phase after ending TFR.

Timepoint	Time window
TFR week -48	Day -350 to Day -323
TFR week -xx	Day (-(xx+2)*7) to Day – ((xx-2)*7+1)
TFR week -8	Day -70 to Day -43
TFR week -4	Day -42 to **Day -1**
NTRI Week 4	**Day 1** to Day 42
NTRI Week 8	Day 43 to Day 70
NTRI Week yy	Day (yy-2)*7 +1 to Day (yy+2)*7
NTRI Week 24	Day 155 to Day 210

Notes:

[1].Day 1 is the start day of the re-initiation phase; Day -1 is the last day of the TFR phase. Days are reported as negative for the TFR phase.

[2].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]. xx = Every 4 weeks from TFR week -48 until TFR week -4

yy = Every 4 weeks from NTRI week 4 until NTRI week 24

Table 5-10 Time windows for analyses of blood chemistry parameters

Time windows between consolidation and TFR phase in patients who enter TFR phase

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

Time windows between TFR and re-initiation phases in patients who enter re-initiation phase after ending TFR.

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 -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 210

Notes:

[1].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.

[2].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.

5.6.3 CCI

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Table 5-11 CCI



6 Reference

1. ICH E9(R1) Harmonized Guideline: addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials. Final version on 20 November 2019.