NOVARTIS

Clinical Development

AMN107 (Nilotinib, Tasigna®)

Protocol CAMN107AUS37 / NCT01744665

A phase II randomized, multicenter study of treatment-free remission in chronic myeloid leukemia in chronic phase (CML-CP) patients who achieve and sustain MR4.5 after switching to nilotinib

Statistical Analysis Plan (SAP)

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Document type: SAP Documentation

Document status: Final Version 1.0

Release date: 21-June-2018

Number of pages: 34

Template Document History – Changes compared to previous version

Date	Version number	Summary of changes
18-May-2017	0.1	First draft version
05-April-2018	0.2	v0.1 comments updated by [redacted]
18-Jun-2018	0.3	Some text formatting updated in section 1.1
21-Jun-2018	1.0	Final version

Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)

Approvals

Role	Signatures	Date (dd-Mmm-yyyy)
Lead Biostatistician	Print Name: [redacted] Ph.D. Sign Name: [redacted] DocuSigned by: Signer Name: [redacted] Signing Reason: I am the author of this document Signing Time: 18-Jun-2018 | 15:59:45 EDT	18-Jun-2018 | 15:59:47 EDT
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List of Abbreviations

ABL	Abelson proto-oncogene
AE	Adverse event
ATC	Anatomical Therapeutic Classification
AUC	Area Under the Curve
BCR	Breakpoint Cluster Region gene/BCR gene product
BCR-ABL	Fusion gene from BCR and ABL
bid	bis in diem/twice a day
[redacted]	[redacted]
CML	Chronic myeloid leukemia
CSR	Clinical Study report
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
[redacted]	[redacted]
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ECOG	Eastern Cooperative Oncology Group
EOC	End of cycle
FAS	Full Analysis Set
[redacted]	[redacted]
HBV	Hepatitis B Virus
HBcAb	Hepatitis B Core Antibody
HBSAb	Antibodies to Hepatitis B Surface Antigen
HBSAg	Hepatitis B Surface Antigen
IVR	Interactive Voice Response
IWR	Interactive Web Response
MDASI-CML	M.D. Anderson Symptom Inventory – Chronic Myeloid Leukemia
MedDRA	Medical Dictionary for Regulatory Activities
MMR	Major molecular response
NCI	National Cancer Institute
NTRI	Nilotinib Treatment Reinitiation
o.d.	Once Daily
OS	Overall Survival
PFS	Progression-Free Survival
PK	Pharmacokinetics
PPS	Per-Protocol Set
PRO	Patient-reported Outcomes
qd	Qua'que di'e / once a day
QoL	Quality of Life
QTcF	Frederica corrected QT interval
RAP	Report and Analysis Process
RECIST	Response Evaluation Criteria in Solid Tumors

RR	Relative Risk (Sokal score)
RR	Respiratory Rate
SAP	Statistical Analysis Plan
SOC	System Organ Class
TFLs	Tables, Figures, Listings
WHO	World Health Organization

1 Introduction

The purpose of this statistical analysis plan (SAP) is to describe the statistical methods for all safety and efficacy analyses planned to be included for the clinical study report (CSR) of study CAMN107AUS37 (A phase II randomized, multicenter study of treatment-free remission in chronic myeloid leukemia in chronic phase (CML-CP) patients who achieve and sustain MR4.5 after switching to nilotinib).

The content of this SAP is based on protocol CAMN107AUS37 Amendment Version 04. All decisions regarding final analysis, as defined in the SAP document, have been made prior to database lock of the study data.

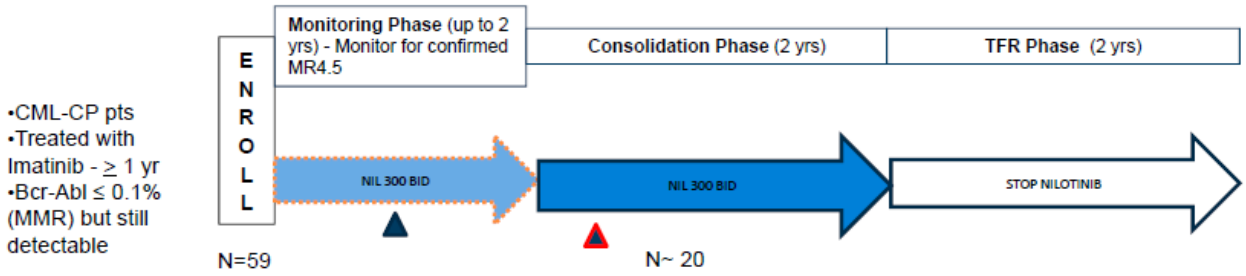
The planned analysis identified in this SAP may be included in clinical study reports (CSRs), regulatory submissions, conference submissions or future manuscripts. [redacted]

In addition to the study protocol, the following documents were reviewed in preparation of this SAP:

- Electronic case report form (eCRF) for Protocol CAMN107AUS37
- ICH Guidance on Statistical Principles for Clinical Trials (E9)

1.1 Study Design

This is an open-label study of imatinib treated patients who are switched to nilotinib and their ability to discontinue TKI treatment once a confirmed MR4.5 is achieved and sustained MR4.0 or better for 2 years.



Monitoring Phase (Years 1 and 2)

Fifty-nine patients have been enrolled and were switched from imatinib to nilotinib 300 mg b.i.d. upon study entry. Patients will be monitored every 3 months for molecular response for up to 2 years.

If during the Monitoring Phase, a patient has a PCR result demonstrating a loss of MR3.0, a subsequent unscheduled visit peripheral blood sample for PCR must be collected within 4 weeks of the most recent sample. If loss of MR3.0 is confirmed, the patient will not be eligible for subsequent phases and will early terminate from the study. Patients who achieve a

MR4.5 will have the result confirmed by another sample drawn 4-6 weeks later. Once MR4.5 is confirmed, patients will then enter the Consolidation Phase.

Consolidation Phase

Patients can enter the Consolidation Phase anytime during and up to the first 2 years on study, as soon as MR4.5 is confirmed. After confirmation of MR4.5, the date of the initial MR4.5 results will be counted as the start of the Consolidation Phase. Patients will continue to be treated with nilotinib for 2 years during the Consolidation Phase.

If during the Consolidation Phase, a patient has one PCR result above MR4.0 or a sample is missing, a subsequent unscheduled visit peripheral blood sample for PCR must be collected within 4 weeks of the most recent sample. If loss of MR4.0 is confirmed by the subsequent sample, the patient will not be eligible for nilotinib discontinuation and will early terminate from the study.

Treatment-Free Remission (TFR) Phase

The Treatment-Free Remission Phase will begin after the last scheduled PCR sample collected in the Consolidation Phase confirms the patient remains in MR4.0 or better.

During the TFR phase patients will be monitored for two years. Once nilotinib treatment is stopped in the TFR Phase, patients will be followed by PCR every month for the first 6 months, then every 2 months for the next 18 months. Confirmed loss of MMR (BCR-ABL>0.1%IS) will trigger restarting nilotinib.

Nilotinib Treatment Reinitiation (NTRI) Phase

Patients who re-initiate nilotinib during the TFR Phase will be monitored by PCR once a month for the first 3 months, and then every 3 months until they reach 2 years from the start date of their TFR Phase. For patients who need to re-initiate nilotinib with less than a year left of their TFR Phase, they will be followed for one year in the Nilotinib Treatment Re-initiation Phase.

1.2 Open Study and Blinded Data

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

1.3 Interim and Final Analysis

No interim analysis will be performed for this study.

The primary analyses of all efficacy and safety variables will be performed when all patients enrolled have completed 6 months of the TFR Phase, follow-up or discontinued from the study. All analyses will include patients who entered the TFR Phase following a 12 month Consolidation Phase (Arm A) prior to protocol amendment 2 and a 24 month Consolidation Phase (formerly Arm B).

After all patients enrolled have completed 12 and 24 months of follow-up, analyses of all efficacy and safety will be performed including the same patients as in the primary analyses. These analyses performed after the primary analyses will be considered secondary. No formal

testing of any kind will be performed at these analyses.

1.4 Study Objectives and Endpoints

Objective	Endpoint
Primary	
To evaluate molecular relapse free rates 6 months after discontinuation from nilotinib therapy in patients who have achieved a MR4.5	Molecular relapse free rate at 6 months after discontinuation from nilotinib therapy in patients with MR4.5. Molecular relapse is defined as having a confirmed BCR-ABL ratio above MMR (2 consecutive BCR-ABL levels >0.1%IS taken approximately 4 weeks apart)
Key secondary	
Estimated Relapse-Free Survival	Relapse-free survival
Other secondary	
To evaluate molecular relapse free rates at 12 and 24 months after nilotinib treatment discontinuation	Molecular relapse free rates at 12, and 24 months after nilotinib treatment discontinuation
To evaluate proportion of patients who regain MR4.5 after restarting nilotinib after molecular relapse	Proportion of patients who achieve MR4.5 after restarting nilotinib after relapse
Describe impact of discontinuation of nilotinib attempts on progression to AP/BC and CML-related deaths	Proportion of patients who progress to CML-AP/BC and number of CML-related deaths
To estimate overall survival (OS)	Time from date of discontinuation of nilotinib therapy to the date of death from any cause
To assess the impact of nilotinib discontinuation on patient symptom burden	Change in symptom burden from baseline to the time when MR4.5 is confirmed, and also from the end of the Consolidation Phase to 6 and 12 months into the TFR Phase.
To assess the impact of nilotinib discontinuation on patient health utility	Change in health utility from baseline to the time when MR4.5 is confirmed, and also from the end of the Consolidation Phase to 6 and 12 months into the TFR Phase.
To assess the impact of nilotinib discontinuation on patient quality of life	Change in patient quality of life from baseline to the time when MR4.5 is confirmed, and also from the end of the Consolidation Phase to 6 and 12 months into the TFR Phase.

2 Statistical Methods

2.1 Data Analysis General Information

The final analysis will be performed [redacted]. No interim analysis will be performed for this study. SAS version 9.3 or later software will be used to perform all data analyses and to generated tables, figures, and listings.

2.1.1 Data Included in the Analysis

The analysis cut-off date for the primary analysis of all study data will be established after all enrolled patients have completed 6 months of the TFR Phase, follow-up or discontinued from the study. All statistical analyses will be performed using all data collected in the database up to the data cutoff date. All data with an assessment date or event start date (e.g. vital sign assessment date or start date of an adverse event) prior to or on the cut-off date will be included in the analysis. Any data collected beyond the cut-off date will not be included in the analysis and will not be used for any derivations.

All events with start date before or on the cut-off date and end date after the cut-off date will be reported as 'ongoing. The same rule will be applied to events starting before or on the cut-off date and not having documented end date. This approach applies, in particular, to adverse event and concomitant medication reports. For these events, the end date will not be imputed and therefore will not appear in the listings.

The analysis cut-off date for the secondary final analysis will be established after all enrolled patients have completed 12 and 24 months of follow-up, all efficacy and safety analyses will be performed. All analyses will be performed using all data collected in the database up to the data cutoff date for this secondary set of analyses. The same above rules regarding assessment dates will apply for this analysis.

2.1.2 General Analysis Conventions

Qualitative data (e.g., gender, race, etc.) will be summarized by means of contingency tables by overall patients; a missing category will be included as applicable. Percentages will be calculated using the number of patients in the relevant population or subgroup as the denominator. Percentages will be rounded to 1 decimal place

Quantitative data (e.g., age, body weight, etc.) will be summarized by appropriate descriptive statistics (i.e. mean, standard deviation, median, 25th percentile, 75th percentile, minimum, and maximum) by overall patients. The number of decimal places for the minimum and maximum will be based on the maximum number of decimal places of the data. One additional decimal place will be used to summarize the mean, median, 25th percentile, and 75th percentile. Two additional decimal places will be used to summarize the standard deviation. A maximum of 2 decimal places for the mean and 3 decimal places for the standard deviation will be used.

All data collected on the CRF will be listed. In general, there will be one listing per CRF page, but additional listings could be produced if necessary.

2.1.3 General Definitions

2.1.3.1 Investigational Drug and Study Treatment

Investigational drug, and ***study treatment*** will refer to nilotinib (AMN107, Tasigna) only. No control treatment is administered in this study.

2.1.3.2 Date of First Administration of Investigational Drug

The date of first administration of investigational drug is defined as the first date when a non-zero dose of investigational drug is administered and recorded on the Dosage Administration Record (DAR) (e)CRF. The date of first administration of study drug will also be referred as start of investigational drug.

2.1.3.3 Date of Last Administration of Investigational Drug

The date of last administration of investigational drug is defined as is the last date when a nonzero dose of investigational drug is administered and recorded on DAR eCRF. The date of last administration of investigational drug will also be referred as end of investigational drug.

2.1.3.4 Date of First Administration of Study Treatment

The date of first administration of study treatment is the same as the date of first administration of investigational drug.

2.1.3.5 Date of Last Administration of Study Treatment

The date of last administration of study treatment is the same as the date of last administration of investigational drug.

2.1.3.6 Study Day

The study day, describes the day of the event or assessment date, relative to the reference start date.

The study day is defined as:

- The date of the event (visit date, onset date of an event, assessment date etc.) − reference start date + 1 if event is on or after the reference start date;
- The date of the event (visit date, onset date of an event, assessment date etc.) − reference start date if event precedes the reference start date.

The reference date for all assessments (safety, efficacy, pk, QoL/PRO, etc) is the start of study treatment.

2.1.3.7 Time unit

A year length is defined as 365.25 days. A month length is 30.5 days. If duration is reported in months, duration in days will be divided by 30.5. If duration is reported in years, duration in days will be divided by 365.25.

2.1.3.8 Baseline

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

For safety and efficacy evaluations, the last available assessment on or before the date of start of study treatment is defined as "baseline" assessment. In the rare case that time of assessment and time of treatment start is captured, the last available assessment before the treatment start date/time is used for baseline.

In addition to the above baseline for the monitoring phase at the start of the study, three additional baselines will be used for analyses regarding reporting a change from baseline in phase (e.g. shift tables):

- **Monitoring Phase baseline**: is defined above.
- **Consolidation Phase baseline:** last available assessment before the first dose date of the consolidation phase.
- **Treatment-Free Remission phase (TFR) baseline:** last available assessment before the first day of the TFR phase.
- **Nilotinib Treatment Reinitiation phase (NTRI) baseline:** last available assessment before the first dose date of the NTRI phase.

If patients have no value as defined above for the baseline within a given study phase, the baseline result will be missing.

2.1.3.9 On-treatment assessment/event and observation periods

For adverse event (AE) reporting, the overall observation period will be divided into mutually exclusive segments:

- **Pre-treatment period**: any day prior to a patient's first dose of study drug during the monitoring phase
- **Monitoring phase**: from date of first administration of study treatment until the day a patient enters the consolidation phase. Patients enter the consolidation phase after two consecutive BCR-ABL levels $\leq$ 0.0032%. The day of the first measurement is the start of the consolidation phase.
- **Consolidation phase**: from date of first administration of study treatment during the consolidation phase to the date the last scheduled PCR sample collected in the consolidation phase confirms the patient remains in MR4.0 or better.
- **Treatment-Free Remission (TFR) phase:** from the day after the date the last scheduled PCR sample in the consolidation phase confirms a patient remains in MR4.0 or better to one of the following:
    - the day of the last scheduled visit during the TFR phase for patients that maintain MMR throughout the TFR phase
    - the day a scheduled PCR sample shows a confirmed loss of MMR for patients who re-start study treatment

- **Nilotinib Treatment Reinitiation (NTRI) phase:** from the day after a scheduled PCR sample shows a confirmed loss of MMR during the TFR phase until the last scheduled visit during the NTRI phase.
- **Follow-up period:** The follow-up period can have three possible start dates.
    - For patients who maintain MMR throughout the TFR phase, the follow-up period begins the day after the last scheduled visit in the TFR phase.
    - For patients who enter into the NTRI phase, the follow-up period begins the day after the last scheduled visit in the NTRI phase.
    - For patients who discontinue from the study early, the follow-up period begins the day after discontinuation.

The follow-up period lasts until the last follow-up visit in the study. If a subject does not have any follow-up visits, the follow-up period ends 30 days after the start of the follow-up period.

2.1.3.10 Last contact date

The last contact date will be derived for patients not known to have died at the analysis cut-off using the last complete date among the following:

Table 2-1 Last contact date data sources

Source data	Conditions
Last contact date/last date patient was known to be alive from Survival Follow-up page	Patient status is reported to be alive, lost to follow-up or unknown.
Start/End* dates from drug administration record	Non-missing dose. Doses of 0 are allowed.
End of treatment date from end of treatment page	No condition.
Any efficacy assessment date if available	Evaluation is marked as 'done'.
Laboratory/PK collection dates	Sample collection marked as 'done'.
Vital signs date	At least one non-missing parameter value
ECOG Performance Status date	Non-missing performance status
Start/End dates of AE	Non-missing verbatim term

The last contact date is defined as the latest complete date from the above list on or before the data cut-off date . The cut-off date will not be used for last contact date, unless the patient was seen or contacted on that date. No date post cut-off date will be used. Completely imputed dates (e.g. the analysis cut-off date programmatically imputed to replace the missing end date of a dose administration record) will not be used to derive the last contact

date. Partial date imputation is allowed for event (death)/censoring is coming from 'Survival information' eCRF.

The last contact date will be used for censoring of patients in the analysis of overall survival.

2.1.3.11 Withdrawal of Informed Consent

Any data collected in the clinical database after a subject withdraws informed consent from all further participation in the trial will not be included in the analysis. The date on which a patient withdraws full consent or completes the study is recorded in the eCRF.

2.2 Analysis Sets

2.2.1.1 Full Analysis Set (FAS)

The Full Analysis Set for the primary analysis comprises all patients who entered the TFR Phase.

The FAS will be the primary set for all efficacy analyses and safety analyses in the TFR Phase only.

2.2.1.2 Safety Set (SS)

The safety set consists of all patients who receive at least one dose of study drug and had at least one post-baseline safety assessment after enrollment.

The statement that a patient had no adverse events (on the Adverse Event eCRF) constitutes a safety assessment.
Safety analyses will be presented by phase and visit within phase where applicable.

The safety set will be used for all safety and patient reported outcomes in the monitoring and consolidation phase.

2.2.1.3 Per-Protocol Set

No per-protocol set is defined for this study.

2.3 Patient Disposition, Demographics and Other Baseline Characteristics

The FAS and SS will be used for these all disposition, demographics, and baseline characteristics analyses. Separate tables will be produced for the two analysis sets.

All demographic and baseline disease characteristics data will be summarized and listed by overall patients. Categorical data will be summarized by frequency counts and percentages;. Continuous data will be summarized by descriptive statistics (N, mean, standard deviation, median, 25^{th} percentile, 75^{th} percentile, minimum, and maximum).

2.3.1 Patient Disposition

The number of patients enrolled, randomized, and in the safety set will be summarized.

The number and percentage of patients who entered in the different phases of the study, discontinued treatment, discontinued the study, and the study phase in which discontinuation occurred will be summarized.

Patient disposition information will be summarized for the SS and FAS.

2.3.2 Protocol Deviations

The number of patients with major and minor protocol deviations will be summarized using frequencies and percentages by type of deviation for the SS and FAS.

2.3.3 Background and Demographic Characteristics

The following demographic and other baseline data will be summarized for the SS and FAS:

- Age (years)
- Gender
- Race
- Screening ECOG Status
- Prior therapy types

Sokal risk score at time of CML diagnosis will be summarized categorically using low, intermediate, and high categories. If a subject does not have a classification collected on the Sokal risk score relative risk will be derived using the below formula (Sokal, et al 1984).

Relative risk = exp{0.0116*(age(yrs) – 43.4) + 0.0345*(spleen(cm) – 7.51) + 0.188*[(platelets(x10^9L)/700)^2 – 0.563] + 0.0887*(myeloblasts(%) – 2.10)

- Age is the age in years collected on the demography eCRF page at screening
- Spleen is the distance in cm between the spleen and costal margin at screening
- Platelates are collected in the laboratory data at screening
- Myeloblasts are collected in the laboratory data at screening

High, intermediate, and low Sokal risk scores are defined as follows:

- Low risk patients have a relative risk < 0.8
- Intermediate riks patients have relative risk ≥ 0.8 and ≤ 1.2
- High risk patients have relative risk > 1.2

Prior Imatinib Treatment duration will be summarized. Prior Imatinib treatment information will be obtained from the prior antineoplastic therapy data collected. Medications identified as Imatinib or Gleevac will be used for this summary. Partial date imputation rules will be used as specified in section 2.4.2.

[redacted]

2.3.4 Medical History

Relevant medical history and current medical conditions, including condition and symptoms related to CML will be collected until the start of the study drug will be listed.

2.3.5 History of Tobacco

Information related to history of tobacco use will be listed.

2.4 Treatments (study treatment, concomitant therapies, compliance)

2.4.1 Study Treatment

Duration of exposure, actual cumulative dose, dose intensity (DI) and relative dose intensity (RDI) will be summarized. Summaries will be performed for overall study duration and for monitoring, consolidation, and NTRI Phases (If Applicable).

Subject level listing of all doses administered on treatment along with dose change reasons will be produced.

The safety set will be used for all summaries and listings of study treatment.

2.4.1.1 Duration of Exposure to Study Treatment

Duration of exposure to study treatment is considered by taking into account the duration of exposure to the study treatment:

Duration of exposure to study treatment (*months*) = (date of last administration to study treatment) – (date of first administration of study treatment) + 1/ 30.5.

Duration of exposure to study treatment (*days*) = (date of last administration to study treatment) – (date of first administration of study treatment) + 1.

Summary of duration of exposure of study treatment in months will include continuous summaries.

Duration of exposure will also be summarized for Overall study, Monitoring, Consolidation and Nilotinib Reinitaition Phases (if applicable). The duration of exposure to study treatment for each phase will use the same above formula with the exception of using last date of exposure to study treatment within the specified phase and date of first administration of study treatment within the specified phase.

Date of last administration to study treatment is defined as follows within each study phase:

- For non-last study phases and for patients still ongoing on treatment when entering the next phase before the data cut-off date, the date of last administration to study treatment is defined as the last date in the study phase.
- For the last study phase (in database at data cutoff date) and for patients ongoing on treatment, the date of last administration to study treatment is defined as the earlier date of the following two dates:

- Data cut-off date
- The last date of the last available dates reported on the dose administration record.
- For the last study phase (in database at data cut-off date) and for patients who entered post-treatment follow up phase before the data cut-off date, the date of last dose is defined as the date of the last non-zero dose of study drug reported in the dose administration record CRF page.

2.4.1.2 Cumulative Dose

Cumulative dose of a study treatment is defined as the total dose given during the study treatment exposure and will be summarized for overall study, Monitoring, Consolidation and Nilotinib Reinitaition Phases (if applicable).

The **planned cumulative dose** for a study treatment component refers to the total planned dose as per the protocol up to the last date of drug administration.

The **actual cumulative dose** refers to the total actual dose administered, over the duration for which the subject is on the study treatment as documented in the Dose Administration eCRF.

For patients who did not take any drug the cumulative dose is by definition equal to zero.

For continuous dosing, the actual cumulative dose is the sum of the non-zero doses recorded over the dosing period and the planned cumulative dose is the planned starting dose summed over the same dosing period.

2.4.1.3 Average Daily Dose

Average daily dose will be summarized for overall study, Monitoring, Consolidation and Nilotinib Reinitaition Phases (if applicable).

Average daily dose = actual cumulative dose/ Duration of exposure to study treatment (*days*).

2.4.1.4 Dose Intensity and Relative Dose Intensity

Dose intensity (DI) for patients with non-zero duration of exposure is defined as follows:

DI (mg / months) = Actual Cumulative dose (mg) / Duration of exposure to study treatment (months).

For patients who did not take any drug the DI is by definition equal to zero.

Planned dose intensity (PDI) is defined as follows:

PDI (mg / months) = Planned Cumulative dose (mg*)* / Duration of exposure (months*)*

Relative dose intensity (RDI) is defined as follows:

RDI = DI (mg / months)) / PDI (mg / months)

DI and RDI will be summarized for Overall study, Monitoring, Consolidation and Nilotinib Reinitaition Phases (if applicable).

2.4.1.5 Dose Reductions, Interruptions or Permanent Discontinuations

The number of patients who have dose reductions, permanent discontinuations or interruptions, and the reasons, will be summarized.

'Dose interrupted', and 'Dose permanently discontinued' fields from the Dosage Administration CRF pages (DAR) will be used to determine the dose reductions, dose interruptions, and permanent discontinuations, respectively.

The corresponding fields 'Reason for dose changes' will be used to summarize the reasons.

For the purpose of summarizing interruptions and reasons, in case multiple entries for interruption that are entered on consecutive days with different reasons will be counted as separate interruptions. However, if the reason is the same in this mentioned multiple entries on consecutive days, then it will be counted as one interruption.

Reduction: A dose change where the prescribed dose level is lower than the previous prescribed dose level or where the actual dose administered/total daily dose is lower than the planned dose. Only dose change is collected in the CRF, number of reductions will be derived programmatically based on the change and the direction of the change.

Missing data: If dose is recorded but regimen is missing or entered as 'none', it is assumed that the study treatment was taken as per-protocol.

2.4.2 Prior, Concomitant and Post Therapies

2.4.2.1 Data Handling

If partial dates occur, the convention for replacing missing dates for the purposes of calculating derived variables is as follows:

For partial start dates:

- If the year is unknown, then do not impute the date but assign as missing value.
- If the year is known, but month or month and day are unknown, then:
    - If the year matches the year of of first administration of study treatment, then impute the month and day of the of first administration of study treatment.
    - Otherwise, assign 01 January
- If the year and month are known, but day is unknown, then:
    - If the month and year match the month and year of the of first administration of study treatment, then impute the day of the of first administration of study treatment.
    - Otherwise, assign 01

For end dates:

- If the year is unknown, then do not impute the date but assign a missing value.

- If the month is unknown, then assign the last day of the year, 31 December. If this results in a date after the of last administration of study treatment, assign the day and month of the last administration of study treatment.
- If the day is unknown, then assign the last day of the month.

2.4.2.2 Prior Antineoplastic Therapy

The number and percentage of patients who received any prior anti-neoplastic radiotherapy will be summarized. Prior anti-neoplastic therapies will be summarized by therapy type (e.g. chemotherapy, hormonal therapy etc.), and also by lowest ATC class and preferred term. Summaries will also include total number of regimens.

All prior antineoplastic therapy data will be listed.
Anti-neoplastictherapies will be coded using the *WHO Drug Dictionary (WHO-DD);* Details regarding WHO-DD version will be included in the footnote in the tables/listings.

The above analyses will be performed using the safety set.

2.4.2.3 Prior and Concomitant Medications

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

Medications will be classified as prior or concomitant based on the following rules:

- Prior medications are medications that started before the first dose of study drug regardless of whether the medication ended before or after the first dose of study drug
- Concomitant medications are medications that started on or after the first dose of study drug, or started before the first dose of study drug and continued after the first dose of study drug.
    - Medications starting on or after the start of study treatment but no later than 30 days after start of last dose of study treatment and
    - Medications starting prior to start of study treatment and continuing after the start of study treatment

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

Any concomitant medication starting and ending prior to the start of study treatment or starting more than 30 days after the last date of study treatment will be flagged in the listing.

2.5 Efficacy Evaluation

2.5.1 Definition of Efficacy Variables

2.5.1.1 Molecular Response

Molecular response will be assessed in all patients. Levels of BCR-ABL transcripts will be determined by real-time quantitative PCR (RQ-PCR) testing of peripheral blood. The samples

will be sent to a Novartis designated central laboratory with validated PCR technology that has a sensitivity of at least 4.5 logs to evaluate BCR-ABL transcript levels by RQ-PCR. The percent ratio of BCR-ABL transcripts versus control gene transcripts converted to IS will be calculated for each sample.

Molecular response and related variables are defined as the following:

- **Major molecular response (MMR)**

  Major molecular response is defined as a value of ≤ 0.1% of BCR-ABL ratio on the International Scale (IS). 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%
- **Molecular response 4.0 (MR4.0)**

  MR4 is defined as a value of ≤ 0.01% of BCR-ABL ratio on the International Scale (IS).

- **Loss of MR4.0** is defined as a BCR-ABL ratio > 0.01% (on international scale).
- **Confirmed Loss of MR4.0** is defined as is two consecutive BCR-ABL > 0.01% IS after the achievement of MR4.0.
- **Molecular response 4.5 (MR4.5)**

  MR4.5 is defined as a value of ≤ 0.0032% of BCR-ABL ratio on the International Scale (IS).

- **Loss of MR4.5** is defined as a BCR-ABL ratio > 0.0032% (on international scale)
- **Confirmed Loss of MR4.5** is defined as two consecutive BCR-ABL > 0.0032% IS after the achievement of MR4.5.
- **Molecular Relapse** is defined as having two consecutive BCR-ABL levels >0.1%.

2.5.1.2 Relapse-Free Survival (RFS)

Relapse-free survival is defined as time in months from date of cessation of nilotinib therapy (date of entering TFR phase) to the first documented molecular relapse. The duration will be calculated by (date of first document molecular relapse – date of nilotinib treatment discontinuation + 1)/30.5. Molecular relapse is defined as having a confirmed BCR-ABL ratio above MMR (2 consecutive BCR-ABL levels >0.1%IS taken approximately 4 weeks apart) variable

If a patient does not experience molecular relapse after nilotinib treatment discontinuation the relapse-free survival time will be considered censored at the following duration: (date of last RQ-PCR sample prior to treatment discontinuation – date of nilotinib treatment discontinuation + 1)/30.5.

This analysis will be performed on the FAS.

2.5.1.3 Overall Survival (OS)

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

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

Specific last assessment date sources for this study are:

- PCR (RQ-PCR) testing of peripheral blood sample dates
- 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

This analysis will be performed on the FAS.

2.5.1.4 Progression Free Survival (PFS)

Progression free survival is defined as the time in months from the date of cessation of nilotinib therapy (date of entering TFR phase) to the date of progression at any time after the start of the TFR phase. Progression is defined as the first reported progression to accelerated phase (AP) or blast crisis (BC) as reported on the disease response eCRF after the start of the TFR phase. The duration will be calculated by (date of first documented progression – date of nilotinib treatment discontinuation + 1)/30.5. If a subject does not experience progression after the start of the TFR phase, they will be censored at their last AP or BC assessment.

2.5.1.5 Treatment Free Survival (TFS)

Treatment free survival is defined as the time in months from the cessation of nilotinib therapy (date of entering TFR phase) to the date of treatment reinitiation at the start of the NTRI phase. The duration will be calculated by (NTRI start date – TFR start date + 1)/30.5. Subjects who do not reinitiate nilotinib will be censored at their study completion date.

2.5.2 Primary Efficacy Endpoint

The primary efficacy endpoint is the molecular relapse free rate (RFR) at 6 months after discontinuation from nilotinib therapy in patients with MR4.5.

2.5.2.1 Data Handling

Patients with confirmed MR4.5 and without confirmed loss of MR4.5 prior to the start of the TFR phase will be included in this analysis. Patients without consecutive confirmed BCR-ABL >0.1%IS measurements within 6 months after entering the TFR phase will be considered responders.

Unscheduled visits falling between the start of the TFR phase and the scheduled 6 month TFR visit will be considered when determining if a subject is not a responder. If a subject is missing the 6 month TFR visit, any unscheduled visit during the TFR phase occurring ≤ 185 days after the TFR start date will be considered when determining of a subject is not a responder.

2.5.2.2 Statistical Hypothesis, Model, and Method of Analysis

The proportion of patients without molecular relapse within 6 months of starting the TFR phase will be summarized using frequencies and percentages. The demoninator for this proportion will be the number of patients who enter the TFR phase with confirmed MR4.5 and without confirmed loss of MR4.5 prior to the start of the TFR phase. A 95% confidence interval calculated using the exact Clopper-Pearson method will be provided.

No statistical hypothesis will be tested on the primary efficacy variable.

The analysis will be performed on the FAS.

2.5.2.3 Supportive Analyses

An exploratory analysis of the relapse free rate after starting the TFR phase will be performed using a logistic regression model to evaluate the dependence of relapse (Yes or No) on important prognostic variables. The following parameters will be included in the model as covariates:

- Age
- Gender
- Sokal risk score classification (high/medium/low)
- Duration of nilotinib in months defined as (date of last dose of study drug prior to start of consolidation phase – date of first dose of study drug + 1)/30.5.
- Maintenance of MR4.5 in the TFR phase defined as (date of confirmed loss of MR4.5 – start date of MR4.5 + 1)/30.5. If a subject loses MR4.5 after the start of the TFR phase and regains it, only the longest interval of sustained MR4.5 will be considered. The start date of sustained MR4.5 is the date of confirmed MR4.5 at the beginning of a sustained MR4.5 interval. If confirmed MR4.5 for an interval occurs prior to the start of the TFR phase, the start of the TFR phase will be considered the start of the interval. Only patients who achieved MR4.5 when entering the TFR phase will be included in this anlaysis.
    - If the subject does not have confirmed MR4.5 loss throughout the duration of the study, the end date will be taken as the last BCR-ABL assessment collected. This includes patients that early terminate from the study.
    - If the patient has a confirmed loss of MR4.5 after the start of the TFR phase the first of the consecutive BCR-ABL > 0.0032%IS measurements will be considered the end date of MR4.5 maintenance.

Stepwise selection of the covariates will be used. Signficance level is 0.05 for a covariate to remain in the model. Parameter estimates of the covariates as well as odds ratio estimates and 95% confidence intervals will be provided.

This analysis will be performed on the FAS.

2.5.3 Secondary Endpoints

The key secondary objective of the study is to evaluate relapse-free survival.

The other secondary objectives of the study are:

- To evaluate molecular relapse free rates at 12 and 24 months after nilotinib treatment discontinuation
- To evaluate the proportion of patients who regain MR4.5 after restarting nilotinib following molecular relapse
- To describe the impact of nilotinib treatment discontinuation on progression to AP/BC and CML-related deaths
- Overall survival

2.5.3.1 Statistical Analysis Methods for the Secondary Efficacy Endpoints

- Relapse-free survival (as described in Section 2.5.1.2) after the start of the TFR phase will be summarized and graphed using the product-limit (Kaplan-Meier) estimates of the 25th, median, 75th percentiles for the relapse-free survival and its 95% confidence intervals will be provided, if applicable. This analysis will be performed on the FAS.
- Overall survival (as described in Section 2.5.1.3) after the start of the TFR phase will be summarized and graphed using the product-limit (Kaplan-Meier) method as described above. Patients who are alive at the date of last contact will be treated as censored observations. This analysis will be performed on the FAS.
- Progression free survival (as described in section 2.5.1.4) after the start of the TFR phase will be summarized and graphed using the product-limit (Kaplan-Meier) method as described above. Progression is defined as the first reported progression to accelerated phase (AP) or blast crisis (BC) as reported on the disease response eCRF after the start of the TFR phase. This analysis will be performed on the FAS.
- Treatment free survival (as described in section 2.5.1.5) after the start of the TFR phase will be summarized and graphed using the product-limit (Kaplan-Meier) method as described above. This analysis will be performed on the FAS.
- The molecular relapse free rates at 12 and 24 months after the start of the TFR phase will be summarized and analyzed using the same multivariate logistic regression model as the primary efficacy endpoint.
- The rate of patients who confirm MR4.5 after restarting nilotinib treatment following a molecular relapse will be presented with an exact 95% Clopper-Pearson method. The time to regain MR4.5 (months) will be summarized and graphed using the product-

limit (Kaplan-Meier) method as described above. The time to regain MR4.5 is defined as (date of confirmed MR4.5 – start date of NTRI phase + 1)/30.5. If a patient does not regain MR4.5 prior to the end of the NTRI phase, the patient will be censored at the last BCR-ABL ratio assessment prior to treatment discontinuation. The time to regain MR4.5 will also be graphed with cumulative curves to depict current MR4.5 rates over time in the NTRI phase by considering censored patients as non-responders. In addition, the time by which 50% of retreated patients have regained MR4.5 will be calculated.

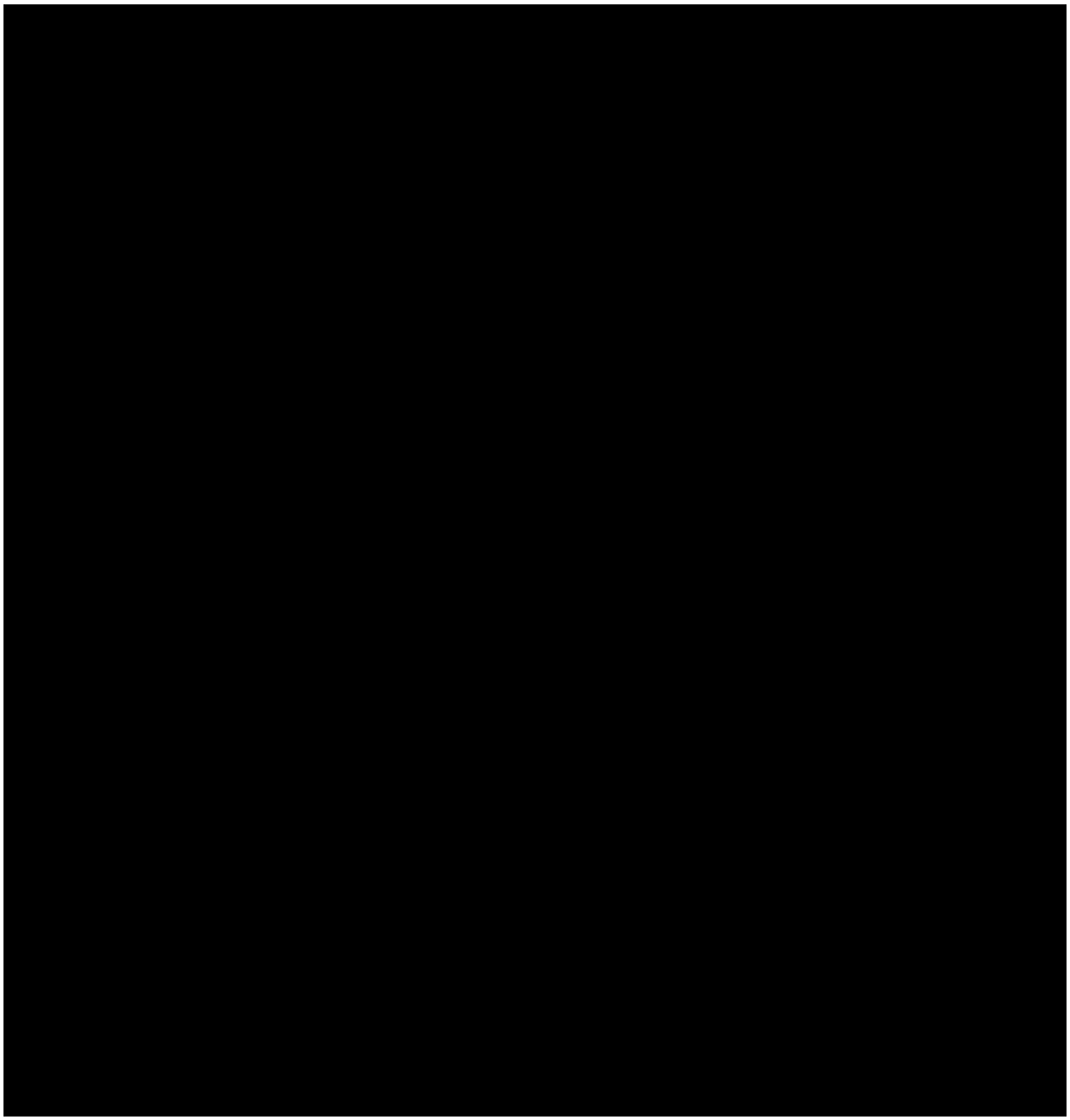
- The rate of patients who confirm MR4.0 and MMR after restarting nilotinib will be summarized using the same method as described above for the rate of patients who confirm MR4.5.
- The number of patients with stable molecular response (MR4.5, MR4.0, or MMR) during the NTRI phase will be summarized using frequencies and percentages. Each response will be summarized separately. Stable molecular response is defined as achievement of confirmed molecular response in the NTRI phase if again the same response is confirmed after 6 months of the original confirmation irrespective of whether there is loss of response in between achievement and 6 months. This analysis will be performed on the FAS only for subjects who have entered the NTRI phase.
- The number of CML related deaths will be summarized using frequencies and percentages.

The FAS for the primary analysis as described above will be used for these analyses.

2.5.3.2 BCR-ABL Ratio (%)

Tables summarizing BCR-ABL Ratio (%) over time by phase and visit within phase for the consolidation and TFR phases will be provided. The frequency and percentage of subjects with BCR-ABL at the following levels will be provided: ≤ 0.1% (MMR), ≤ 0.01% (MR4.0), ≤ 0.001%, ≤ 0.0032% (MR4.5)

The BCR-ABL Ratio over time will be summarized using a box-plot.



2.6 Safety Evaluation

For all safety analyses, the safety set will be used. Safety analyses will be presented overall, by study phase and visit within phase.

2.6.1 Adverse Events

Summary tables for AEs will include only AEs that started or worsened during the on-treatment period (all 4 study phases including treatment-free remission phases), the **treatment-emergent AEs** (TEAEs). The start day used to define the TEAEs in the entire study is the first day of dosing of the Monitoring Phase.

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

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

The following selection of AEs will be listed and summarized separately. All summaries will be by system organ class (SOC), preferred term (PT), and severity grade unless otherwise specified. Summaries will include a total column.

- AEs by system organ class (SOC) and preferred term (PT)
- AEs by PT
- AEs by relationship to study drug
- AEs occurring in >= %5 of all patients
- AEs by severity grade group (Grade 1 or 2 and Grade 3 or 4)
- AEs that are dose-limiting
- AEs reported as serious (SAEs)
- AEs excluding the serious AEs
- AEs associated with discontinuation of study drug
- AEs associated with death
- Adverse events of special interest
    - Ischemic Heart Disease (IHD): angina pectoris, coronary artery disease, acute myocardial infarction and coronary artery stenosis
    - Ischemic Cerebrovascular Events (ICVE): ischemic cerebrovascular accident, and transient ischemic attack
    - Peripheral Artery Occlusive Disease (PAOD): intermittent claudication, arterial stenosis of a limb
    - Musculoskeletal Pain

All summaries, except for AEs by relationship to study drug will be repeated using only AEs suspected to be related to study drug.

Summaries will be repeated for the safety set, safety set by phase, full analysis set, and full analysis set by phase. Full anlaysis set by phase tables will only include the TFR and NTRI phases.

Figures for incidences of AEs occurring in the consolidation and TFR phases and for incidences of AEs occurring in the TFR and NTRI phases will be provided for both the SS and FAS. The incidence rate will be calculated by dividing the number of patients with any AE at a particular time by the number of patients in the safety set who are continuing in the study at that time.

If partial dates occur, the convention for replacing missing dates for the purposes of calculating derived using the same method as described in section 2.4.2.

If an AE has a missing severity, it will be imputed as "Grade 4"; any missing relationship to study drug of an AE will be imputed as related. No other missing data will be imputed unless otherwise specified.

2.6.2 Laboratory Values

2.6.2.1 Hematology

Hematology tests will include hemoglobin, total white blood cell count, platelet count, and a differential count (neutrophils, bands, lymphocytes, monocytes, eosinophils, basophils, promyelocytes, myelocytes, metamyelocytes, blasts, and atypical cells.

2.6.2.2 Blood Chemistry

Chemistry tests will include creatinine, uric acid, albumin, total protein, total bilirubin, direct bilirubin and/or indirect bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, sodium chloride, fasting glucose, HbA1c, calcium, lipase, potassium, magnesium, phosphorus, total cholesterol, triglycerides, low density lipoprotein, and high density lipoprotein.

2.6.2.3 Hepatitis B Serology

Patients will be tested once for the following hepatitis B serologic markers: hepatitis B surface antigen (HBsAg), antibodies to hepatitis B surface antigen (HBsAb) and antibodies to hepatitis B core antigen (HBcAb). The results will be listed and summarized by phase.

2.6.2.4 Analysis

Laboratory values will be converted to SI units and analyzed using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. For laboratory tests covered by CTCAE, a Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used. A table of CTCAE grades for the parameters of interest in the study is given below (U.S. HHS Dept., 2010).

Parameter	**Event**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Hemoglobin (g/L)	Anemia	<LLN – 100	<100 – 80	<80	Life-threatening consequences; urgent intervention indicated
Hemoglobin (g/L)	Hemoglobin increased	Increase in >0 – 20 above ULN or above BL if BL is above ULN	Increase in >20 – 40 above ULN or above BL if BL is above ULN	Increase in >40 above ULN or above baseline if baseline is above ULN	N/A
White blood cells (10^9/L)	White blood cell decreased	<LLN – 3x10^9/L	<3 – 2x10^9/L	<2 – 1x10^9/L	<1x10^9/L
Lymphocytes (10^9/L)	Lymphocyte count decreased	<LLN – 0.8x10^9/L	<0.8 – 0.5x10^9/L	<0.5 – 0.2x10^9/L	<0.2x10^9/L
Lymphocytes (10^9/L)	Lymphocyte count increased	N/A	>4 - 20	>20	N/A
Neutrophils (10^9/L)	Neutrophil count decreased	<LLN – 1.5x10^9/L	<1.5 – 1.0x10^9/L	<1.0 – 0.5x10^9/L	<0.5x10^9/L
Platelets (10^9/L)	Platelet count decreased	<LLN – 75.0x10^9/L	<75.0 – 50.0x10^9/L	<50.0 – 25.0x10^9/L	<25.0x10^9/L
Albumin (g/L)	Hypoalbuminemia	<LLN – 30	<30 – 20	<20	Life-threatening consequences; urgent intervention indicated
Alkaline phosphatase (IU/L)	Alkaline phosphatase increased	>ULN – 2.5xULN	>2.5 – 5.0xULN	>5.0 – 20.0xULN	>20.0xULN
Alanine aminotransferase (IU/L)	Alanine aminotransferase increased	>ULN – 3.0xULN	>3.0 – 5.0xULN	>5.0 – 20.0xULN	>20.0xULN
Aspartate aminotransferase (IU/L)	Aspartate aminotransferase increased	>ULN – 3.0xULN	>3.0 – 5.0xULN	>5.0 – 20.0xULN	>20.0xULN
Bilirubin (umol/L)	Blood bilirubin increased	>ULN – 1.5xULN	>1.5 – 3.0xULN	>3.0 – 10.0xULN	>10.0ULN

Parameter	Event	Grade 1	Grade 2	Grade 3	Grade 4
Calcium (mmol/L)	Hypocalcemia	Corrected serum calcium <LLN – 2.0; Iodized calcium <LLN – 1.0	Corrected serum calcium <2.0 - 1.75; Ionized calcium <1.0- 0.9	Corrected serum calcium<1.75 - 1.5; Ionized calcium <0.9-0.8; hospitalization indicated	Corrected serum calcium <1.5; Ionized calcium <0.8; life-threatening consequences
Calcium (mmol/L)	Hypercalcemia	Corrected serum calcium of >ULN -2.9; Ionized calcium >ULN - 1.5	Corrected serum calcium of >2.9 - 3.1; Ionized calcium >1.5- 1.6; symptomatic	Corrected serum calcium of >3.1 - 3.4; Ionized calcium >1.6-1.8; hospitalization indicated	Corrected serum calcium of >3.4; Ionized calcium >1.8; life-threatening consequences
Cholesterol (mmol/L)	Cholesterol high	>ULN – 7.75	>7.75 – 10.34	>10.34 – 12.92	>12.92
Creatinine	Creatinine increased	>1 - 1.5 x baseline; >ULN - 1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 -3.0 x ULN	>3.0 baseline; >3.0 - 6.0 xULN	>6.0 x ULN
Glucose (mmol/L)	Hypoglycemia	<LLN – 3.0	<3.0 – 2.2	<2.2 – 1.7	<1.7; life-threatening consequences; seizures
Glucose (mmol/L)	Hyperglycemia	>ULN – 8.9	>8.9 – 13.9	>13.9 – 27.8; hospitalization indicated	>27.8; life-threatening consequences
Lipase	Lipase increased	>ULN – 1.5xULN	>1.5 – 2.0xULN	>2.0 – 5.0xULN	>5.0xULN
Magnesium (mmol/L)	Hypomagnesemia	<LLN – 0.5	<0.5 – 0.4	<0.4 – 0.3	<0.3; life-threatning consequences
Magnesium (mmol/L)	Hypermagnesemia	>ULN – 1.23	N/A	>1.23 – 3.30	>3.30; life-threatening consequences
Phosphate (mmol/L)	Hypophosphatemia	<LLN – 0.8	<0.8 – 0.6	<0.6 – 0.3	<0.3; life-threatening consequences
Potassium (mmol/L)	Hypokalemia	<LLN – 3.0	<LLN – 3.0; symptomatic;	<3.0 – 2.5; hospitalization indicated	<2.5; life-threatening

Parameter	Event	Grade 1	Grade 2	Grade 3	Grade 4
			intervention indicated		consequences
Potassium (mmol/L)	Hyperkalemia	>ULN – 5.5	>5.5 – 6.0	>6.0 – 7.0; hospitalization indciated	>7.0; life-threatening consequences
Sodium (mmol/L)	Hyponatremia	<LLN - 130	N/A	<130 - 120	<120; life-threatening consequences
Sodium (mmol/L)	Hypernatremia	>ULN - 150	>150 - 155	>155 – 160; hospitalization indicated	>160; life-threatening consequences
Triglycerides (mmol/L)	Hypertriglyceridemia	1.71 – 3.42	>3.42 – 5.7	>5.7 – 11.4	>11.4; life-threatening consequences

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

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

- Shift tables using CTCAE grades to compare baseline to the worst on-phase value. Four different baseline definitions for the different study phases, as defined in section 2.1.3.8, will be used.
- For laboratory tests where CTCAE grades are not defined, shift tables using the low/normal/high/(low and high). Four different baseline definitions for the different study phases, as defined in section 2.1.3.8, will be used.
- Summary statistics of raw values and change from baseline by time point and by study phase
- Listing of all laboratory data with values flagged to show the corresponding CTCAE grades and the classifications relative to the laboratory normal ranges.

2.6.3 Serum and urine pregnancy test results will be listed.ECG Analysis

A standard 12 lead ECG will be performed at screening, Day 1, and Day 8. After a dose interruption or after any dose changes, additional (unscheduled) ECGs are required.

Summary statistics for raw values and change from baseline of heart rate, PR interval, QRS duration, QT interval, QTcF, QTcB, and frequencies and percentages of investigator interpretation will be presented by phase and visit within phase.

A shift table for QTinterval and QTc values by phase will be provided using the following categories:

- <= 450 ms
- >450 to 480
- >480 to 500
- >500

The largest post-baseline result in each phase will be included in the shift table.

Four different baseline definitions for the different study phases, as defined in section 2.1.3.8, will be used.

2.6.4 Vital Signs

Vital signs raw values and change from baseline (weight, pulse rate, systolic blood pressure, diastolic blood pressure) will be summarized by phase and visit within phase

Vital signs data will be summarized by shift table based on notable values by phase.

The criteria for clinically notable abnormalities are defined as follows:

Clinically notable values above normal

- Systolic BP: ≥ 140 mmHg

- Diastolic BP: ≥ 90 mmHg
- Body Temperature (C): ≥ 37.5˚C
- Weight: Baseline ≥ 110kg; Post-baseline: increase from baseline of ≥ 10%
- Heart rate: Baseline: ≥ 120 beats per minute (bpm); Post-baseline: ≥ 120 beats per minute (bpm) with increase from baseline of ≥ 15 bpm

Clinically notable values below normal

- Systolic BP: ≤ 90 mmHg
- Diastolic BP: ≤ 40 mmHg
- Body Temperature (C): ≤ 35˚C
- Weight: Baseline ≤ 60kg; Post-baseline: decrease from baseline of ≥ 10%
- Heart rate: Baseline: ≤ 50 bpm; Post-baseline: ≤ 50 bpm with decrease from baseline of ≥ 15 bpm

Four different baseline definitions for different study phases, as defined in section 2.1.3.8, will be used.

Vital signs data will be listed.

2.6.5 Physical Examination

Significant physical examination findings that are present prior to the start of study drug must be summarized with the medical history data. Significant findings made after the start of study drug, which meets the definition of an adverse event, will be summarized with the adverse event data.

2.6.6 Extramedullary Involvement

Extramedullary involvement data such as presence and location will be listed.

2.6.7 ECOG Performance Status

Eastern Cooperative Oncology Group (ECOG) performance status will be summarized using frequencies and percentages by phase and visit within phase.

2.6.8 Patient-reported outcomes

2.6.8.1 MDASI-CML

The M.D. Anderson Symptom Inventory for CML patients (MDASI-CML) will be used to assess the nature and impact of symptom burden on life. The MDASI-CML consists of 20 validated symptom items and 6 validated core interference items. Each item is assessed on an 11 point scale with responses from 0-10, = being “not present” and 10 being “as bad as you can imagine”.

The interference score will be calculated when a patient scores at least 4 items out of the 6 interference items using the formula: (sum of scores for the items answered) / number of items answered. If a subject responds to less than 4 interference items, the interference score will be considered missing.

The symptom score will be calculated when a patient scores at least 8 items out of the 14 symptom items using the formula: (sum of scores for the items answered) / number of items answered. If a subject responds to less than 8 symptom items, the symptom score will be considered missing (Ceeland, 2009).

The symptom and interference subscale total scores with their change from baseline will be summarized descriptively at all post-baseline time points by phase and visit within phase.

This analysis will be performed on the SS.

2.6.8.2 EQ-5D-3L

The EQ-5D-3L will be used to assess the impact of nilotinib treatment discontinuation in patient utility. The questionnaire comprises 5 items: mobility, self-care, usual activities, pain/discomfort and anxiety/depression and the EQ visual analog scale. Each item has 3 levels (no problems, some problems, and extreme problems) and visual analog has a scale of 0 to 100 (0=works imaginable health state, 100=best imaginable health state).

The percentages of patients at each level of the five items of the EQ-5D-3L will be summarized overall as appropriate at baseline and all post-baseline time points by phase and visit within phase.

The visual analog scale raw values and change from baseline will be summarized using numeric summary statistics by visit and phase.

This analysis will be performed on the SS.

2.6.8.3 SF-8 Questionnaire

The SF-8 Questionnaire consists of 8 items (general health, physical functioning, role-physical, bodily pain, vitality, social functioning, role-emotional, and mental health) will be used to assess the impact of nilotinib treatment discontinuation on the quality of life. Each item has a 5 or 6 point response range. Physical and mental component summary measures (calculated using Optum's norm-based scoring method) will be summarized at baseline and all post-baseline time points using numeric summary statistics. Individual item scores will be listed.

This analysis will be performed on the SS.

3 References

Ceeland CS., (2009) The M.D. Anderson Symptom Inventory User Guide, Version 1. Retrieved from https://www.mdanderson.org.

Sokal JE, Cox EB, Baccarani M, et al (1984) Prognostic discrimination in "Good-Risk" chronic granulocytic leukemia. Blood: 63: 789-99.

U.S. Department of Health and Human Services, (2010) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03. Retrieved from https://evs.nci.nih.gov.