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Clinical Development

AMN107/Nilotinib/Tasigna®

Oncology Clinical Protocol CAMN107ADE20 / NCT02546674

A Phase IV single arm, multicenter, open-label study assessing deep molecular response in adult patients with newly diagnosed Philadelphia chromosome positive CML in chronic phase after two years of treatment with nilotinib 300mg BID

Statistical Analysis Plan (SAP)

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List of abbreviations

ABL	Abelson leukemia virus
ACE	Angiotensin-converting enzyme
AE	Adverse event
ALL	Acute lymphoid leukemia
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
ANC	Absolute Neutrophil count
Anti HBc	Antibody to hepatitis B core antigen
AP	Accelerated phase
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
AT	Angiotensin
ATC	Anatomical Therapeutic Classification
AUC	Area Under the Curve
BC	Blast crisis
BCR	Break point cluster region
BCR-ABL	BCR-ABL oncoprotein, BCR-ABL fusion gene, BCR-ABL fusion transcript
bid	bis in diem/twice a day
BP	Blood pressure
CCyR	complete cytogenetic response
CKD	Chronic kidney disease
CML	Chronic myeloid leukemia
CP	Chronic phase
CRF	Case Report/Record Form
CSR	Clinical Study report
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CVD	Cardiovascular disease
CYP3A4	Cytochrome P450 3A4
DMC	Data Monitoring Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EFS	Event-free survival
ELN	European Leukemia Net
EMA	European Medicine Agency
EMR	Early molecular response
EORTC	European Organization for Research and Treatment of Cancer
ESC	European Society of Cardiology
EUTOS	European Treatment and Outcome Study for CML
FAS	Full Analysis Set
G-CSF	Granulocyte colony-stimulating factor
GFR	Glomerular filtration rate
GM-CSF	Granulocyte-macrophage colony-stimulating factor

HbA1c	Glycated hemoglobin
HBs Ag	Hepatitis B surface antigen
HCT	Hydrochlorothiazide
HDL	High-density lipoprotein
HMG-CoA	3-hydroxy-3-ethylglutaryl-coenzyme A
HRQOL	Health-related quality of life
IB	Investigator brochure
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
ICVE	Ischemic cerebrovascular event
i.v.	Intravenous(ly)
IHD	Ischemic heart disease
IRB	Institutional Review Board
IS	International scale
IUD	Intrauterine device
IVR	Interactive Voice Response
IVRS	Interactive Voice Response System
IWR	Interactive Web Response
LDL	Low-density lipoprotein
LVEF	Left ventricular ejection fraction
MedDRA	Medical Dictionary for Drug Regulatory Affairs
MR	Molecular response
MR4	Molecular response 4 log reduction from standardized baseline
MR4.5	Molecular response 4.5 log reduction from standardized baseline
MMR	Major molecular response
o.d.	Once Daily
OS	Overall Survival
PFS	Progression-Free Survival
Ph	Philadelphia chromosome
Ph+	Philadelphia chromosome positive
p.o.	per os / by mouth / orally
PPS	Per-Protocol Set
PRO	Patient-reported Outcomes
qd	Qua'que di'e / once a day
QoL	Quality of Life
QT	QT interval
QTcF	Fridericia-corrected QT interval
RAP	Report and Analysis Process
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
TFLs	Tables, Figures, Listings
TKI	Tyrosine kinase inhibitor

1 Introduction

This statistical analysis plan (SAP) module describes the planned statistical methods for all safety and efficacy analyses to be used in Phase IV clinical study CAMN107ADE20. Any changes made to the statistical plan and methodology after the clinical database lock will be documented as an addendum.

The main purpose of this document is to provide summary of the statistical methodology that will be used for this clinical study; this includes a detailed description of data summaries. Analyses plan in this document refers to the related statistical analysis sections in clinical study report.

The analysis described here will be conducted by Novartis using statistical software SAS® Version 9.4 according to the Statistical methods and data analysis Section 10 of the study protocol which will be available in Appendix 16.1.1 of the CSR. Important information will be given in the following sections and further details are provided, as applicable, in the Appendix 16.1.9 of the CSR.

Data will be analyzed by Novartis according to the data analysis Section 10 of the clinical study protocol. That statistical methodology is described below and any deviations from the protocol are documented. Additional detailed information regarding the analysis methodology is contained in the Appendix section.

Unless otherwise specified, the statistical methodologies including the analysis sets, analysis models, algorithms and conventions are following the Oncology study protocol CAMN107ADE20 final version.

1.1 Study design

This is a Phase IV open-label, multicenter, single-arm trial of nilotinib 300mg twice a day (BID) in newly diagnosed patients with chronic phase CML to primarily evaluate the rate of deep molecular response (MR4.5) at 24 months of study treatment using European Treatment and Outcome Study for CML (EUTOS) standardized laboratories. Patients will undergo up to 2 weeks of screening period and if deemed eligible, will receive nilotinib 300mg BID formulation for 24 weeks.

The experiment is planned to be take place at 50 sites in Germany and 171 patients are planned to be included. All patients will be given nilotinib 300mg BID. Nilotinib will be prescribed by the investigator according to the individual needs of the patients.

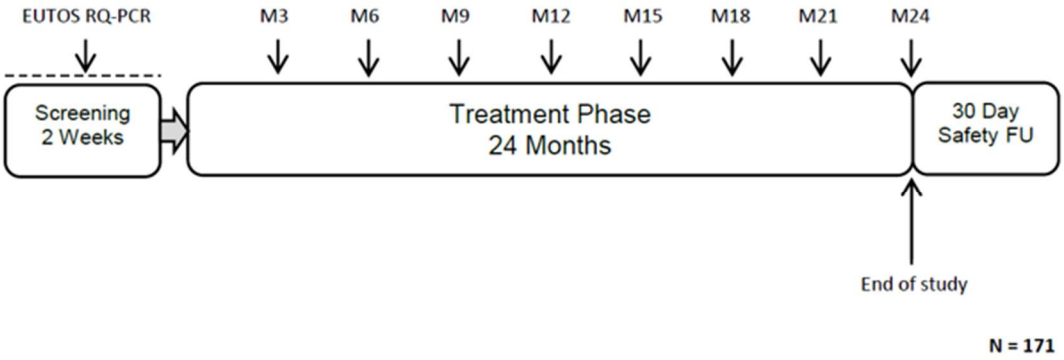
The overall study design is as the following:

- A screening period of 2 weeks will be used to assess eligibility and to taper patients off disallowed medications.
- Patients whose eligibility is confirmed will then enter a 24 months treatment phase. The assessment to address the primary objective will be performed at the end of the treatment phase.

For efficacy analysis, only patients with typical b2a2 or b3a2 BCR-ABL transcripts at baseline will be considered. Other variants will be analyzed separately.

Following figure gives overall study design:

Figure 1.1



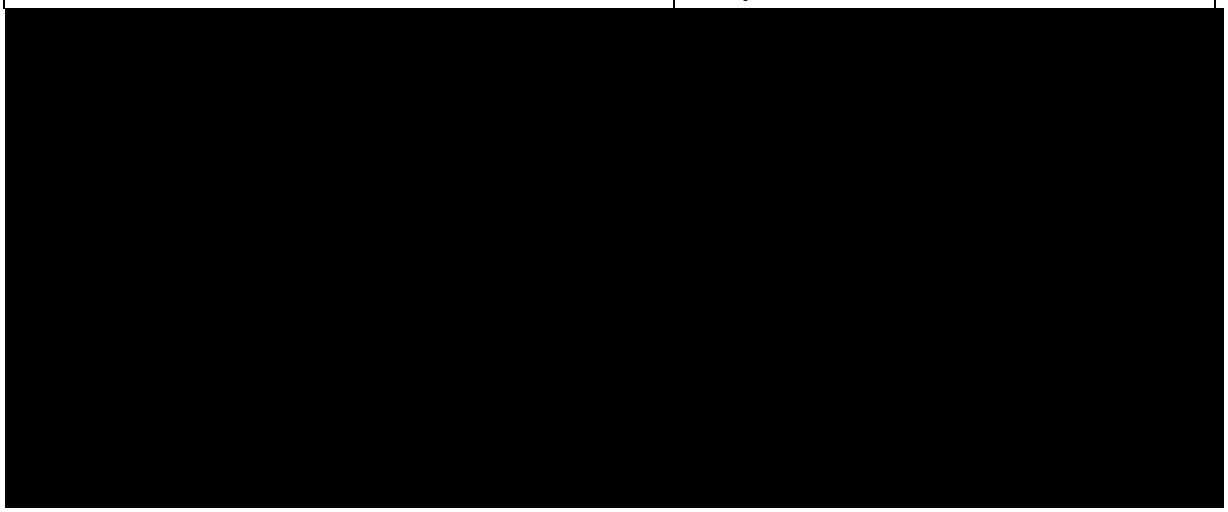
1.2 Study objectives and endpoints

The primary, secondary [redacted] objectives and endpoints are presented in Table 1.1.

Table 1-1 Objectives and related endpoints

Objectives	Endpoints
Primary objective	
To evaluate the proportion of patients who are in deep molecular response $MR^{4.5}$ (IS) at 24 months of study treatment, measured in a standardized EUTOS MR4.5 laboratory.	Number and proportion of patients with deep molecular response $MR^{4.5}$ (IS) at 24 months of study treatment
Secondary objectives	
To determine the proportion of patients who are in deep molecular response MR4 (IS) at 24 months of study treatment	Number and proportion of patients with deep molecular response MR4 (IS) at 24 months of study treatment
To determine the proportion of patients who are in MMR at 12 months of study treatment	Number and proportion of patients with MMR at 12 months of study treatment
To determine the proportion of patients who are in CCyR at 6 months of study treatment	Number and proportion of patients who fit the definition of response at 6 month by the total number of Ph+ patients in the analysis set.

Objectives	Endpoints
To evaluate progression-free survival (PFS) and time to progression to AP/BC	Kaplan Meier's product limit estimates and estimated rates by Kaplan Meier's method at various time points in the analysis set
To evaluate quality of life of 300mg nilotinib BID therapy	Absolute change from baseline up to the end of study for the FAS in the analysis set



2 Statistical methods

2.1 Data analysis general information

The data will be analyzed by PLS, Novartis. Analysis datasets and statistical outputs will be produced using the most recent SAS® Version 9.4 (SAS Institute Inc., Cary, NC, USA), and stored in Novartis global programming & statistical environment (GPS).

Once all data including the final visit (containing the primary and secondary endpoints) are complete and clean, the database for that study period will be locked and analyzed. It is planned that the data from all centers that participate in this protocol will be used, so that an adequate number of patients will be available for analysis. Data will be summarized with respect to demographic and baseline characteristics, efficacy observations and safety observations.

Data will be summarized descriptively for both the Safety Set and the Full Analysis Set (FAS). Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation (SD), median, 25th and 75th percentiles, minimum, maximum will be provided. Also, 95% C.I of proportion will be presented, wherever applicable.

2.1.1 General definitions

Study treatment

In this and subsequent analysis plan module (TFL and PDS), the terms “investigational drug”, “study drug” and “study treatment” refers to nilotinib 300mg BID throughout the study.

Study treatment start and end date

Study treatment start date is defined as the first date when a non-zero dose of study drug is administered and recorded on the Drug Administration Record (DAR) CRF page. Similarly, study drug end date is defined as the last study drug administration date.

Study day

Study day will be calculated as (event date – study drug start date + 1 day) for events that occurred on or after study drug start date (e.g. Visit, lab samples, AEs).

For events prior to study drug start date (e.g., time of diagnosis), study day will be negative and calculated as (event date – study drug start date). Note that study drug start date is study day 1.

Due to the study drug dosing schedule, one month will be considered as 28 days. However, for “time since event” data (e.g., medical history), one month will be considered as 365.25/12 days for events that occurred prior to study Day 1.

Baseline

The last available assessment before start of study of study treatment (study day 1) will be taken as baseline. For Patient-reported outcomes, the last available assessment before or on start of study of study treatment (study day 1) will be taken as baseline. Further, if several assessments are taken on the same day, the last assessment will be used for that time point.

Post Baseline assessment

A post-baseline value refers to a measurement taken in the Treatment phase from Day 1 onwards. For patients who discontinued study treatment, all assessments listed in End of Study (EOS) visit will be performed.

Change from baseline:

When change from baseline is of interest, the following formula will be used for each scheduled visit where baseline and post-baseline values are both available:

Change from baseline = post-baseline value – baseline value.

2.1.2 Visit windows

In the protocol assessment schedules, one month is considered as a 4-weekly period. For each parameter (i.e. hematologic, cytogenetic and molecular response), time windows will be used to identify data to be considered for the specific analysis at a specific time point as well as the

cut-off for the analysis of response by a specific time point. The time windows are defined so that there are no gaps between the planned assessments, 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.

For all time windows after baseline, only values after first dose of study drug will be used. Time windows are defined based on the first dose of treatment for the analyses.

Table 2-1 Assessment windows

Analysis visit		Target day	Analysis visit window	MR	CCyR / QoL	ECOG	ESC / smoking status	ECG
Baseline		Day 0	-14 – 0	-14 - 1	-14 – 0	-14 – 0	-14 – 0	-14 – 0
Visit 2		Day 1	1 – 8					
Visit 3	Month 1	Day 28	9 - 42					1 - 56
Visit 4	Month 3	Day 84	43 – 126	2 – 126	1 -126			
Visit 5	Month 6	Day 168	127 – 210	127 – 210	127 – 252		1 – 252	
Visit 6	Month 9	Day 252	211 – 294	211 – 294				
Visit 7	Month 12	Day 336	295 – 378	295 – 378	253 – 420		253 – 420	
Visit 8	Month 15	Day 420	379 – 462	379 – 462				
Visit 9	Month 18	Day 504	463 – 546	463 – 546	421 – 588		421 – 588	
Visit 10	Month 21	Day 588	547 – 630	547 – 630				
Visit 11	Month 24	Day 672	631 – 686	631 – 758	589 - 728	1 - 716	589 - 728	
Visit 12	Follow-up	Day 702	687 - 732					

For assessments captured at all visits up to Month 24, follow the visit windows as mentioned in “Analysis visit window” column of Table 2-1. For calculation of dose exposure and dose intensity, the following visit windows will be applied (counting from first dose administration (treatment start)):

Table 2-2 Assessment windows for treatment information

Assessment	Window
< 3 months	Day 1 – Day 83
>=xx - <yy months	Trt day (xx*28) included up to day (yy*28) excluded

2.2 Analysis sets

Full Analysis Set (FAS): The Full Analysis Set (FAS) will consist of all patients who have entered study and received at least one dose of study drug and have at least one post-baseline assessment of the primary efficacy variable.

Safety Set: The Safety Set will consist of all patients who received at least one dose of study drug and had at least one post-baseline safety assessment. Of note, the statement that a patient had no adverse events also constitutes a safety assessment.

Per-Protocol Set: The Per-Protocol Set will consist of all patients who did not show major deviations from the protocol procedures that might have an impact on the study outcome. Criteria that are assumed to have such an impact will be defined in the data validation document (VAP).

The key efficacy analysis will be performed for both, the FAS and the PPS. The FAS is regarded as primary. Any major protocol deviation will lead to exclusion of patients from PPS. The list of PDs is defined in Section 5.5.

2.2.1 Subgroup of interest

To evaluate efficacy of nilotinib in the elderly patients, the population (FAS) will be stratified by age, assessing patients ≥ 65 years versus < 65 years, using the cutoff according to the median age at diagnosis in western populations (Gugliotta et al., 2014), regarding time to assessing cytogenetic and molecular response as well as rates of progression to AP and BC.

2.3 Patient disposition, demographics and other baseline characteristics

Descriptive statistics will be provided for patient disposition, demographics and all baseline characteristics including baseline values of main efficacy endpoints. Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum will be presented.

2.3.1 Number and percentage of missing observations in each category will be summarized. Patient disposition

The Full Analysis Set will be used for the summary and listing of patient disposition. The overall number and percentage of patients who were screened, completed and discontinued the study along with reasons for discontinuation will be summarized.

2.3.2 Patient demographics

Summary statistics will be presented for continuous demographic variables for all patients in both the Safety Set and Full Analysis Set. For categorical variables, number and percentage of patients in each category will be presented.

The following demographic variables will be summarized:

Continuous variable:

- Age (years)

Categorical variables

- Age category (<65 and ≥ 65 years)
- Sex (male, female)
- Is subject of child bearing status (Able to bear children, Premenarche, Post-menopausal, Sterile - of child bearing age)
- Race (Caucasian, Black, Asian, Other, Native American)

Baseline characteristics

Sokal risk score, EUTOS score, extramedullary involvement and vital signs at baseline will be summarized descriptively.

Medical history

Relevant medical history and current medical conditions will be summarized by system organ class and preferred term of the Medical Dictionary for Drug Regulatory Affairs (MedDRA) dictionary. ESC Risk related medical history/conditions will be listed.

In addition, time since initial diagnosis of CML will be summarized descriptively.

Also, smoking history will be tabulated with descriptive statistics.

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

2.4.1 Study treatment / compliance

All study medication data will be summarized using the Safety set.

Time on treatment, duration of exposure, percentage of days on treatment, average dose intensity, and actual daily dose will be summarized by treatment group. In addition, 95% distribution-free confidence intervals for the median time on treatment and duration of exposure will be provided.

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

Date of the last dose is defined as follows:

- For patient who discontinued study treatment, the date of last dose is defined as the date of the last non-zero dose of any of the study drug reported in the dose administration CRF page.
- For patients still ongoing on treatment, the date of last dose is defined as the last available date reported on any of the following CRF pages: visit, dose administration, PCR, bone marrow,

The following definitions are used:

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

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

Percentage of days exposed = (duration of exposure / time on treatment) * 100

Actual dose intensity (mg/day) = total dose / time on treatment (periods of zero dose are included)

Average daily dose (mg/day) = total dose / duration of exposure (periods of zero dose are excluded)

The following quantities will be derived in relation to the treatment group assigned for safety analysis:

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

Relative daily dose = average daily dose / assigned total daily dose

Dose changes

The number and percentage of patients with dose interruption and/or dose reduction along with reasons for dose interruption/reduction will be summarized in the Safety set.

Dose interruption and dose reduction are defined as follows:

- Interruption is defined as any period of zero daily dose.
- Reduction is defined as any decrease from the immediate prior daily dose. Zero daily doses are not regarded as reduction.

2.4.2 Prior, concomitant and post therapies

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

- Prior medications are defined as treatments taken and stopped prior to first dose of study treatment.
- Concomitant medications are medications that started on or after the first dose of study drug, or started before the first dose of study drug and continued after the first dose of study drug.

The number and percentage of patients receiving prior and concomitant medication or significant non-drug therapy will be presented separately, by Anatomical Therapeutic Classification (ATC) class and preferred term.

Medications will be presented in alphabetical order, by ATC codes and grouped by anatomical main group. Tables will show the overall number and percentage of patients receiving at least one treatment of a particular ATC code and at least one treatment in a particular anatomical main group.

Surgical and medical procedures will be summarized by primary system organ class and MedDRA preferred term.

2.5 Analysis of the primary objective

2.5.1 Primary endpoint

The primary objective of the study is to evaluate the proportion of patients who achieve deep molecular response MR4.5 (IS) at 24 months of study treatment, measured in a standardized EUTOS MR4.5 laboratory. The rate of MR4.5 (IS) at 24 months of study treatment will be computed by dividing the number of patients who fit the definition of response at 24 months by the total number of patients in the analysis set.

MR4.5 is defined as either (i) detectable disease ≤ 0.0032% BCR-ABL (IS) or (ii) undetectable disease in cDNA with 32 000 – 99 999 ABL1 transcripts or 77 000 – 239 999 GUSB transcripts.

Molecular response will be calculated for patients with b2a2 and/or b3a2 BCR-ABL transcripts only. Patients with alternative transcripts will be excluded from the analysis, because their transcripts cannot be used for deep MR or MMR determination.

2.5.2 Statistical hypothesis, model, and method of analysis

The rate of MR4.5 (IS) at 24 months of study treatment will be computed by dividing the number of patients who fit the definition of response at 24 months by the total number of patients in the analysis set. The corresponding 95% confidence interval will be computed by Clopper-Pearson method.

2.5.3 Handling of missing values/censoring/discontinuations

Only patients with a MR4.5 at 24 months of study treatment, or if the assessment at this time point is missing, with a MR4.5 at 21 months are considered responders. Patients dropping out early or not providing sufficient data for any other reason will be considered as early discontinuation or not evaluable, respectively, and will be included in the analysis set as non-responders, even if a MR4.5 was previously achieved. Any patient who achieves MR4.5 before 24 months, but is no longer in MR4.5 at 24 months or progressed (or is no longer in MR4.5 at 21 months if evaluation at 24 months is missing), will be considered as a non-responder.

2.5.4 Supportive analyses

The primary analysis the proportion of patients who are in deep molecular response MR4.5 (IS) at 24 months of study treatment will be repeated on per-protocol population as a sensitivity analysis of robustness of the results. Additionally, primary analysis will be stratified for gender.

2.6 Analysis of the key secondary objective

Not applicable.

2.7 Analysis of secondary efficacy objective(s)

2.7.1 Secondary efficacy variables

MR_4 (IS)
- MR_4 (IS) is defined in this study as either (i) detectable disease ≤0.01% BCR-ABL$_{IS}$ or (ii) undetectable disease in cDNA with 10 000 – 31 999 ABL1 transcripts or 24.000 – 76 999 GUSB transcripts.

- The rate of MR_4 (IS) at 24 months of study treatment will be computed by dividing the number of patients who fit the definition of response at 24 months by the total number of patients in the analysis set.

MMR
- MMR is defined as a ≥3 log reduction from the standardized baseline or ≤ 0.1% BCR-ABL$_{IS}$

- The rate of MMR at 12 months of study treatment will be computed by dividing the number of patients who fit the definition of response at 12 months by the total number of patients in the analysis set

CCyR
- Complete cytogenetic response is defined as a value of 0% Ph+ metaphases in bone marrow.

- Rate of CCyR at 6 months of study treatment will be calculated by dividing the number of patients who fit the definition of response at 6 month by the total number of Ph+ patients in the analysis set
Cytogenetic response will be assessed as the percentage of Ph+ metaphases in the bone marrow (a review of a minimum of 20 metaphases is required).

Outcome
- Time to progression to AP/BC is defined as the time from the date of start of study treatment to the date of earliest transformation to AP/BC, or CML-related death. Rates of progression at various time points will also be provided.

- Progression-free survival is defined as the time from the date of start of study treatment to the date of event defined as the first documented disease progression to AP/BC or the date of death from any cause, whichever is earlier.

2.7.2 Secondary endpoints

The following secondary outcome measures will be analyzed on FAS:

1. Proportion and percentage of patients with deep molecular response MR^4 (IS).
2. Proportion and percentage of patients with MMR at 12 months.
3. Proportion and percentage of patients with complete cytogenetic response defined as 0% Ph+ metaphases in bone marrow.
4. Kaplan Meier's product limit estimates and estimated rates by Kaplan Meier's method at various time points.

5. Absolute change from baseline in HR-QoL, up to the end of study.

2.7.3 Statistical hypothesis, model, and method of analysis

1. Proportion and percentage of patients with deep molecular response MR4 (IS)

The rate of MR^4 (IS) at 24 months of study treatment will be computed by dividing the number of patients who fit the definition of response at 24 months by the total number of patients in the analysis set. The corresponding 95% confidence interval will be computed by Clopper-Pearson method.

2. Proportion and percentage of patients with MMR at 12 months of study

The rate of MMR at 12 months of study treatment will be computed by dividing the number of patients who fit the definition of response at 12 months by the total number of patients in the analysis set. The corresponding 95% confidence interval will be computed by Clopper-Pearson method.

3. Proportion of patients who are in CCyR at 6 months of study treatment.

Proportion of CCyR at 6 months of study treatment will be calculated by dividing the number of patients who fit the definition of response at 6 month by the total number of patients in the analysis set.

4. To evaluate progression-free survival (PFS) and time to progression to AP/BC

Kaplan Meier's product limit estimates will be used for time to event endpoints - time to progression to AP/BC and progression-free survival (PFS). The estimated rates by Kaplan Meier's method at various time points will be provided. Percentiles (25%, median, 75%) of the event time distribution will be presented along with their two-sided 95% confidence interval.

The Kaplan-Meier curve will also be displayed. The plots will display the number of patients at risk every 3 months. Time to progression and death will be listed per patient presenting the start and end date of treatment, the progression status (Y/N), progression date, last progression-free date, death status (Y/N), date of death along with principal cause of death and date of last adequate AP/BC assessment which is used for censoring.

- Time to progression to AP/BC is defined as the time from the date of start of study treatment to the date of earliest transformation to AP/BC, or CML-related death. Rates of progression at various time points will also be provided.
- Progression-free survival is defined as the time from the date of start of study treatment to the date of event defined as the first documented disease progression to AP/BC or the date of death from any cause, whichever is earlier.

For time to progression to AP/BC and PFS patients will be censored if one of the following situations occurs:

- If a patient does not experience an event before the cut-off date for the analysis, censoring time will be the last assessment date before the cut-off date

- If a patient discontinues study treatment prior to experiencing an event, then the patient will be censored at the date of last assessment prior to the date of discontinuation.

5. **To evaluate quality of life of 300mg nilotinib BID therapy**
   Refer to Section 2.11 for details.

2.7.4 Handling of missing values/censoring/discontinuations

For MMR and CCyR assessment at a specific time point, only patients with response which occurs or is sustained at the specific time point are considered responders; e.g. a patient who achieves MMR before 12 months but is no longer in MMR at 12 months (or progressed), will be considered as a non-responder at 12 months. The same applies for all time points and response variables. Patients dropping out early or not providing sufficient data for any other reason will be considered as early discontinuation or not evaluable, respectively, and will be included in the analysis set as non-responders.

2.8 Safety analyses

All the safety analyses will be based on the Safety Set Population.

2.8.1 Adverse events (AEs)

Adverse events (AE) will be coded using the MedDRA dictionary that provides the system organ class and preferred term information. CTCAE version 4.0 will be used for reporting AE severity. Treatment-emergent AEs starting on or after the date of first study medication (including AEs that start after the discontinuation of the study medication regardless of the number of days after discontinuation) will be reported and summarized. Treatment Emergent Adverse Events are those, which start in on-treatment period, or which start in pre-treatment period but worsen in on-treatment period, last day of treatment + 30 days.

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.

Adverse events will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. If CTCAE grading does not exist for an AE, the severity of mild, moderate, severe, and life-threatening, corresponding to Grades 1 to 4, will be used. CTCAE Grade 5 (death) will not be used in this study.

The following selection of AEs will be summarized separately.

- AEs, by toxicity grade
- AEs suspected to be study drug related
- AEs reported as serious AEs (SAEs)
- AEs reported as non-serious
- AEs associated with discontinuation of study drug
- AEs requiring dose adjustment or study drug interruption

Deaths will also be also be summarized similarly by MedDRA System Organ Class and Preferred Term. Listings for all AEs, SAEs and deaths will also be provided.

2.8.1.1 Adverse events of special interest / grouping of AEs

The crude incidence for SPP risks will be summarized. In addition, listings will be provided presenting which subjects experienced which risk.
The incidence of following AEs of special interest will be summarized by MedDRA System Organ Class and Preferred Term...

- 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

2.8.2 Deaths

Deaths which occurred, within the treatment phase of the study, or within 30 days after discontinuation of the treatment phase of the study will be summarized and listed.

2.8.3 Laboratory data

Laboratory values analyzed using the CTCAE grades version 4.03. Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used.

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

The following summaries will be generated separately for hematology and clinical chemistry:

- Summary statistics for change from baseline for the parameters will be presented;
- Number and percentage of patients with laboratory abnormalities, by parameter and worst post-baseline CTCAE grade. Each patient will be counted only for the worst grade observed post-baseline, regardless of the baseline status;
- Shift tables using CTCAE grades to compare baseline to the worst on treatment value;
- Listing of all laboratory data with values flagged to show the corresponding CTCAE grades and the classifications relative to the laboratory normal ranges.

Newly observed or worsened laboratory abnormalities with grade 3 or 4 will be presented separately. Any laboratory toxicity will be defined as being newly occurring or worsening grade 3/4 if:

- patients have baseline result missing or a grade 0, 1 or 2 and then develop grade ≥ 3, or
- patients have baseline result of a grade 3 and then develop grade 4.

Summary statistics will be presented for urinalysis at screening and serum pregnancy test results by visit.

2.8.4 Other safety data

2.8.4.1 European Society of Cardiology (ESC) Risk Score

Calculated ESC Risk score will be summarized descriptively by visit.

2.8.4.2 Smoking Status

Following variables will be summarized for smoking status using safety set:

- Subject's usage status(Never/Current/ Former)
- Number of cigarettes smoked everyday
- Years as smoker
- Estimated amount consumed on average (Pack year(s))

2.8.4.3 ECG and cardiac imaging data

The following quantitative variables will be summarized:

- Fridericia (QTcF) corrections (msec),
- maximum heart rate (beats/min),
- PR interval duration (msec),
- QT duration (msec)
- QRS Duration (msec)

Summary statistics will be presented for ECG variables by visit.

In addition, shift tables comparing baseline ECG interpretation (normal, abnormal, not available, total) with the worst on-study interpretation (normal, abnormal, not available, total) will be provided.

A listing of all newly occurring or worsening abnormalities will be provided, as well as a by-subject listing of all quantitative ECG parameters.

2.8.4.4 Vital signs

Following vital signs will be summarized:

- Weight (kilogram)
- Temperature (Celsius)
- Sitting Pulse (Beats/ Min)
- Systolic Blood Pressure (mmHg)
- Diastolic Blood Pressure (mm Hg)

Analysis in vital sign measurement using descriptive summary statistics for the change from baseline for each post-baseline visit will be performed. These descriptive summaries will be

presented by vital sign and treatment group. Change from baseline will only be summarized for patients with both baseline and post-baseline values and will be calculated as:

change from baseline = post-baseline value – baseline value

The number and percentage of patients with newly occurring notable vital signs will be presented. Criteria for notable vital sign abnormalities are provided in section 5.3.1

2.8.4.5 ECOG performance status

For ECOG performance status, shift tables will be provided comparing baseline with post-baseline assessment at end of study.

2.9 Pharmacokinetic endpoints

Not applicable.

2.10 PD and PK/PD analyses

Not applicable.

2.11 Patient-reported outcomes

The following PROs will be summarized using FAS.

EORTC QLQ-C30 in combination with the EORTC Quality of Life Questionnaire (QLQ)-CML 24 questionnaire

EORTC QLQ-CML 24 is an internationally developed disease specific health-related quality of life (HRQOL) questionnaire for CML patients, together with the EORTC-QLQ C30 questionnaire. The QLQ-CML 24 has been developed according to the EORTC guidelines involving a large sample of patients (655 CML patients in 10 countries). The questionnaire is composed of four multi-item scales and two single-item scales. The module consists of 24 items assessing symptom burden, impact on daily life and on worry/mood, body image problems, and satisfaction with care and social life. The items are measured on four levels: not at all, a little, quite a bit and very much. The EORTC QLQ-CML 24 is a supplement to the EORTC-QLQ C30 and intended to be used in conjunction (Efficace et al., 2014, Aaronson et al., 1993).

Mean and standard deviation will be provided for the EORTC QLQ-C30 scales in combination with the EORTC QLQ-CML 24 questionnaire up to the end of study at Baseline/Screening(within 7 days prior to study inclusion), and at 3, 6, 12, 18, 24 months. No total score is calculated on the EORTC QLQ questionnaire. Each item will be scored as the proportion of patients who select each response option.

Descriptive statistics for baseline and change from baseline in EORTC QLQ-C30 and EORTC QLQ CML 24 will be provided at each visit. In addition to this, Descriptive statistics for baseline and change from baseline will be provided for EORTC QLQ-CML24 scales by response to molecular response at each visit

Score procedure for EORTC QLQ-C30 and EORTC QLQ CML 24.

For Mapping item to the EORTC QLQ-C30 and EORTC QLQ CML 24 scale use table 2.11.1 and 2.11.2 respectively.

Table 2.11.1: Scoring the QLQ-30 version 3.0

Table 2.11.2: Scoring the QLQ- CML 24

EORTC QLQ CML 24: First four scale (Symptom burden, Impact on worry/mood, Impact on daily life and Body image problems) will be considered under Symptom scale/item. Last two scale or item (Satisfaction with care and information and Satisfaction with social life) will be derived as Function scale. Range for all scale/item will be 3 (4-1);

For all scales, the *RawScore*, *RS*, is the mean of the component items:

$$RawScore = RS = (I_1 + I_2 + ... + I_n)/n$$

Then for **Functional scales**:

$$Score = \left\{1 - \frac{(RS - 1)}{range}\right\} \times 100$$

and for **Symptom scales / items** and **Global health status / QoL:**

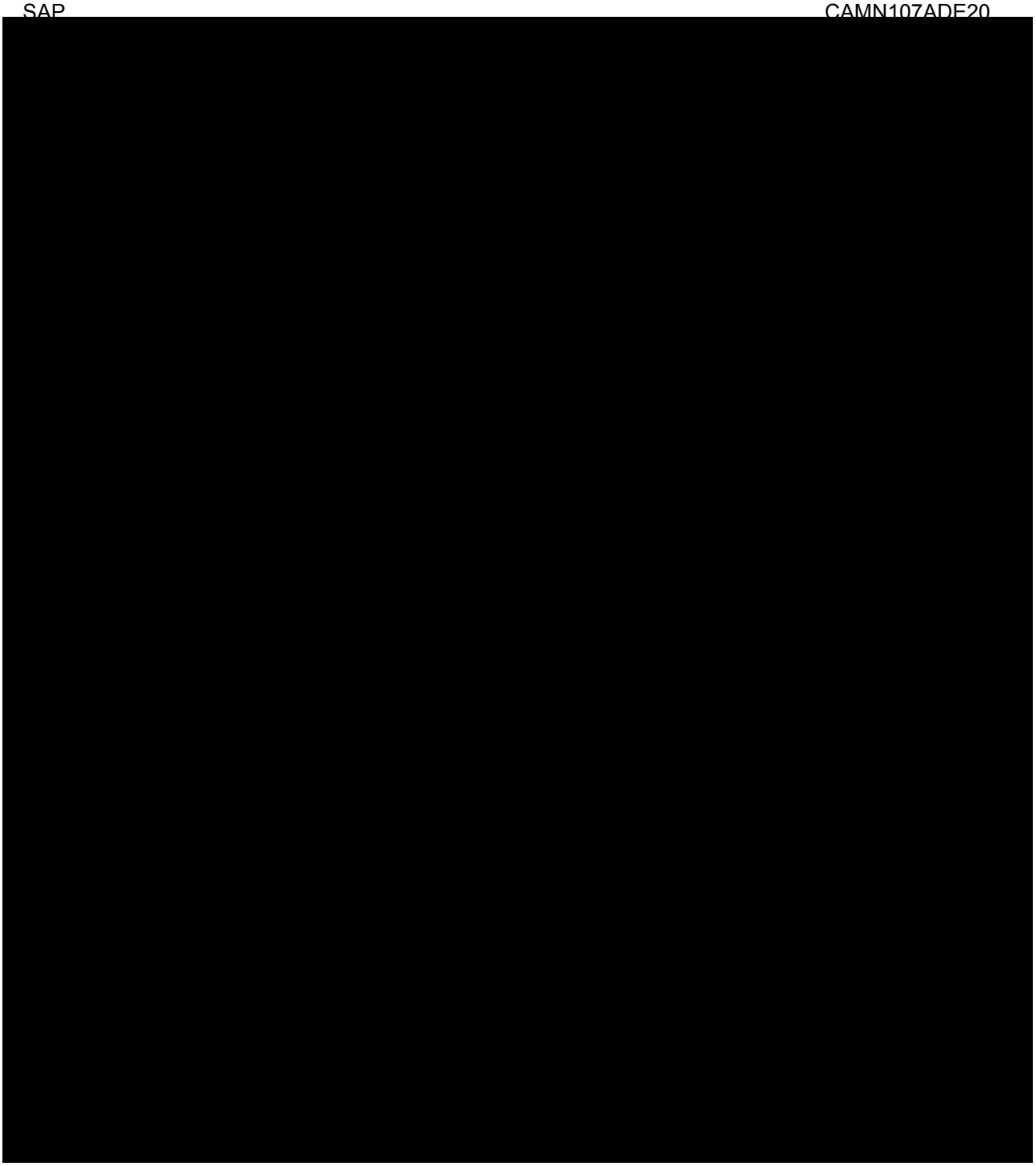
$$Score = \{(RS - 1)/range\} \times 100$$

Refer SC manual for more detail explanation.

2.12 Absolute change from baseline will also be provided by visit. Biomarkers

Not applicable

[redacted]



2.14 Mutational Analysis

A listing will be provided for patients who undergo mutational analysis and assessments are recorded “Mutational Analysis – Summary” CRF page.

2.15 Interim analysis

An interim analysis of baseline and follow-up data is planned after the first 38 patients included in the study reach the end of month 6 visit, as of April 2017 in order to evaluate the integrity of the collected data. No evaluation of the primary endpoint will be conducted and therefore no adjustments with regard to the alpha level will be made. The rational for interim analysis is to check the integrity of the data.

The interim analysis will be purely descriptive in nature and include patient characteristics, vital signs, Sokal risk score, EUTOS score, ESC risk score, ECOG performance status, hematologic and blood chemistry laboratory values, RQ-PCR results, medical history and adverse events. These parameters are described in panels DM, ZC, VS, SRS, QSEUT, QSESC, QSECOG, LBLGH, B2, B1, MH, FACM, SU, EG, LBLGC, AE and LBLGU. For panel VS, QSESC, LBLGH, B2, B1, FACM, SU, EG, LBLGC, AE and LBLGU analysis will be performed for initial visit and all sub sequential visits till end of month 6.

3 Sample size calculation

The aim of the current study is to confirm the MR4.5 rates of nilotinib in a broad population using the EUTOS MR4.5 (‘European Treatment and Outcome Study for CML’) standardized molecular laboratories.

Therefore, the sample size is based on the precision of estimate computation; i.e. the 95% confidence interval of the proportion of patients with MR4.5 at month 24.

Assuming a MR4.5 rate at 24 months to be 25%, a total of 171 patients will allow for a precision of +/- 6.5 %.

4 Change to protocol-specified analyses

5 Appendix

5.1 Imputation rules

This section will be used later for drafting CSR Appendix 16.1.9.

5.1.1 Study drug

Not applicable.

5.1.2 AE date imputation

5.1.2.1 AE Start Date Imputation

Imputation is based only on a comparison of the partial AE start date to the treatment start date as mentioned in the Table 5.1-2 below.

1. If the AE start date year value is missing, the date uncertainty is too high to impute a rational date. Therefore, if the AE year value is missing, the imputed AE start date is set to NULL.
2. If the AE start date year value is less than the treatment start date year value, the AE started before treatment. Therefore:
    a. If the AE year is less than the treatment year and the AE month is missing, the imputed AE start date is set to the mid-year point (01JulYYYY).
    b. Else if the AE year is less than the treatment year and the AE month is not missing, the imputed AE start date is set to the mid-month point (15MONYYYY).
3. If the AE start date year value is greater than the treatment start date year value, the AE started after treatment. Therefore:
    a. If the AE year is greater than the treatment year and the AE month is missing, the imputed AE start date is set to the year start point (01JanYYYY).
    b. Else if the AE year is greater than the treatment year and the AE month is not missing, the imputed AE start date is set to the month start point (01MONYYYY).
4. If the AE start date year value is equal to the treatment start date year value:
    a. And the AE month is missing or the AE month is equal to the treatment start month, the imputed AE start date is set to one day after treatment start.
    b. Else if the AE month is less than the treatment start month, the imputed AE start date is set to the mid-month point (15MONYYYY).
    c. Else if the AE month is greater than the treatment start month, the imputed AE start date is set to the start month point (01MONYYYY).

Table 5.1-2: AE date imputation

	MON	**MON < CFM**	**MON = CFM**	**MON > CFM**
	MISSING			
YYYY MISSING	NULL	NULL	NULL	NULL
	Uncertain	Uncertain	Uncertain	Uncertain
YYYY < CFY	(D) = 01JULYYYY	(C)= 15MONYYYY	(C)= 15MONYYYY	(C)= 15MONYYYY
	Before Treatment Start	Before Treatment Start	Before Treatment Start	Before Treatment Start
YYYY = CFY	(B)= TRTSTD+1	(C)= 15MONYYYY	(A)= TRTSTD+1	(A)= 01MONYYYY
	Uncertain	Before Treatment Start	Uncertain	After Treatment Start

YYYY > CFY	(E)= 01JANYYYY	(A)= 01MONYYYY	(A)= 01MONYYYY	(A)= 01MONYYYY
	After Treatment Start	After Treatment Start	After Treatment Start	After Treatment Start
Before Treatment Start		Partial indicates date prior to Treatment Start Date		
After Treatment Start		Partial indicates date after Treatment Start Date		
Uncertain		Partial insufficient to determine relationship to Treatment Start Date		
LEGEND:				
(A)		MAX(01MONYYYY,TRTSTD+1)		
(B)		TRTSTD+1		
(C)		15MONYYYY		
(D)		01JULYYYY		
(E)		01JANYYYY		

5.1.2.2 AE End Date Imputation

Rules for imputing the AE end date:

- Rules for imputing the AE end date:
- If AE day is missing but year and month are available, then the AE end date is set to minimum of (end date of follow-up period (treatment end date + 30 days), last day of the month, date of death, cutoff date).
- If AE month and day are missing but year is available, then it is set to minimum of (end date of follow-up period, Dec-31 of the year, date of death, cutoff date).
- If AE year is missing the end date will not be imputed.
- If complete (imputed) AE end date is available and the imputed AE start date is greater than the (imputed) AE end date, then imputed AE start date should be set to the (imputed) AE end date. If patient has not yet started study treatment, no imputation will be done for AE end date.

5.1.3 Concomitant medication date imputation

Concomitant medication (CMD) date imputation uses both a comparison of the partial CMD start date to the treatment start date, and the value of the CMDTYP1C flag (1, 2, or 3). Event date comparisons to treatment start date are made based on the year and month values only (any day values are ignored) in Table 5.1-3 below.

1. If the CMD start date year value is missing, the date will be imputed based on the CMDTYP1C flag value. If the flag value is 1 or 3, the imputed CMD start date is set to one day before the treatment start date. Else, if the flag value is missing or 2, the imputed CMD start date is set to one day after the treatment start date. (Note that for some legacy

data, the CMDTYP1C variable may not exist in the data. When this happens and the CMD start date year value is missing, the imputed date value will be NULL.)

2. If the CMD start date year value is less than the treatment start date year value, the CMD started before treatment. Therefore:
    a. if the CMD year is less than the treatment year and the CMD month is missing, the imputed CMD start date is set to the mid-year point (01JulYYYY).
    b. Else if the CMD year is less than the treatment year and the CMD month is not missing, the imputed CMD start date is set to the mid-month point (15MONYYYY).

If the CMD start date year value is greater than the treatment start date year value, the CMD started after treatment. Therefore:

    a. If the CMD year is greater than the treatment year and the CMD month is missing, the imputed CMD start date is set to the year start point (01JanYYYY).
    b. Else if the CMD year is greater than the treatment year and the CMD month is not missing, the imputed CMD start date is set to the month start point (01MONYYYY).

3. If the CMD start date year value is equal to the treatment start date year value:
    a. and the CMD month is missing or the CMD month is equal to the treatment start month,
        i. If the flag value is 1 or 3, the imputed CMD start date is set to one day before the treatment start date.
        ii. Else, if the flag value is missing or 2, the imputed CMD start date is set to one day after the treatment start date.
    a. Else if the CMD month is less than the treatment start month, the imputed CMD start date is set to the mid-month point (15MONYYYY).
    b. Else if the CMD month is greater than the treatment start month, the imputed CMD start date is set to the start month point (01MONYYYY).

Table 5.1-3: CMD date imputation

	MON MISSING	**MON < CFM**	**MON = CFM**	**MON > CFM**
YYYY MISSING	**(F)**	**(F)**	**(F)**	**(F)**
	Uncertain	Uncertain	Uncertain	Uncertain
YYYY < CFY	**(D)=01JULYYYY**	**(C)=15MONYY**	**(C)=15MONYY**	**(C)=15MONYY**
	Before Treatment Start	Before Treatment Start	Before Treatment Start	Before Treatment Start
YYYY = CFY	**(B)**	**(C)=15MONYY**	**(B)**	**(A)=01MONYYYY**
	Uncertain	Before Treatment Start	Uncertain	After Treatment Start
YYYY > CFY	**(E)= 01JANYYYY**	**(A)=01MONYYYY**	**(A)=01MONYYYY**	**(A)=01MONYYYY**
	After Treatment Start	After Treatment Start	After Treatment Start	After Treatment Start

Before Treatment Start	Partial indicates date prior to Treatment Start Date
After Treatment Start	Partial indicates date after Treatment Start Date
Uncertain	Partial insufficient to determine relationship to Treatment Start Date
LEGEND:	
(A)	MAX(01MONYYYY,TRTSTD+1)
(B)	IF CMDTYP1C IN (1,3) THEN TRTSTD-1 ELSE IF CMDTYP1C in(. , 2) THEN TRTSTD+1
(C)	15MONYYYY
(D)	01JULYYYY
(E)	01JANYYYY
(F)	IF CMDTYP1C IN (1,3) THEN TRTSTD-1 ELSE IF CMDTYP1C in (. , 2) THEN TRTSTD+1

5.1.3.1 Prior therapies date imputation

Not applicable.

5.1.3.2 Post therapies date imputation

Not applicable.

5.1.3.3 Other imputations

Not applicable.

5.2 AEs coding/grading

The verbatim term recorded on CRF will be identified as adverse event and will be coded by primary system organ class and preferred term using MedDRA version 18.1 and above.

5.3 Laboratory parameters derivations

5.3.1 Criteria for notable vital sign abnormalities

	Very high risk Patient	High risk Patient	Moderate Patient	Low risk patient
Normal sbp	<140	<140	<140	<140
			<160 If (all “ESC Risk related medical history/conditions”) are marked as “NO”	<160 If (all “ESC Risk related medical history/conditions”) are marked as “NO”
Normal DBP	<90	**<90**	<90	<90
	<85 if (Diabetes mellitus (type 1 or type 2) but without CV risk factors or target organ damage , Diabetes mellitus (type 1 or type 2) with one or more CV risk factors and/or target organ damage (such as microalbuminuria: 30-300 mg/24 h)) are “YES”	<85 if (Diabetes mellitus (type 1 or type 2) but without CV risk factors or target organ damage , Diabetes mellitus (type 1 or type 2) with one or more CV risk factors and/or target organ damage (such as microalbuminuria: 30-300 mg/24 h)) are “YES”		
Normal ldl	<70mg/dl / <1.8mmol/l	<100mg/dl / <2.6mmol/l	<115mg/dl / <3.0mmol/l	<115mg/dl / <3.0mmol/l
Normal HbA1C	<7	<7	<7	<7
	<8 (if very old age (age >=65))	<8 (if very old age (age >=65))	<8 (if very old age (age >=65))	<8 (if very old age (age >=65))

5.4 Statistical models

5.4.1 Primary analysis

5.4.1.1 Clopper-Pearson CI for response rate

The 100 × (1 – alpha level) % Pearson-Clopper CI for the proportion of responders (binary outcome = 1 or “Yes”), for a given treatment group X, is obtained from the following:

```
proc freq data = dataset;
where treatment group = X;
```

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

When there are no responders for treatment group X, 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:

- LCLLEVEL="Yes" (%) = 100% - UCLLEVEL="No" (%)
- UCLLEVEL="Yes" (%) = 100% - LCLLEVEL="No" (%)

5.4.2 Secondary analysis

5.4.2.1 Log-rank test

The log-rank test will be conducted for selected time to event analyses. The p-value for this test is obtained from the following:

```
proc lifetest data = dataset;
where treatment group = X or Y;
strata <group> / group = treatment group;
time time to event * censor(1);
```

5.4.2.3 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 linear transformation, is obtained from the following:

```
proc lifetest data = dataset alpha = estimated rate alpha level alphaqt
= estimated median alpha level conftype = linear;
where treatment group = X;
time time to event * censor(1);
```

Note that all these codes are for reference purpose.

5.5 Rule of exclusion criteria of analysis sets

Table 5.5.1 Protocol deviations that cause subjects to be excluded

Deviation Id	Deviation description	Exclusion from analyses	Severity code	Major or Minor
INCL01	Subject is less than 18 years or age is missing	Defined individually	Refer DRM minutes	To be categorized individually case by case
INCL02	Subject is not having ECOG as 0,1 or 2	Include in everything	0	Minor
INCL03	Patients within 6 months of diagnosis of CML in chronic phase with cytogenetic confirmation of Ph positive [t(9,22) translocation]	Include in everything	0	Minor
INCL04	Subject does not meet the criteria defined for Chronic phase CML	Defined individually	Refer DRM minutes	To be categorized individually case by case
INCL05	Patients must be previously untreated for CML with the exception of 6 months treatment with hydroxyurea and a maximum of 6 weeks treatment with imatinib.	Exclude from PPS	4	Major
INCL06	Adequate end organ function as defined in protocol	Include in everything	0	Minor
INCL07	Serum level to be greater than or equal to lower limit of normal or corrected to normal by supplements for potassium, magnesium, total calcium or phosphorus prior to first dose of study medication	Include in everything	0	Minor
INCL08	Subject did not provided Informed Consent prior to any study related procedures	Include in everything	0	Minor
EXCL01	Contraindication to excipients in study medication	Include in everything	0	Minor
EXCL02	Known impaired cardiac function as per protocol	Include in everything	0	Minor

EXCL03	History of acute (within 1 year of starting study medication) or chronic pancreatitis	Include in everything	0	Minor
EXCL04	Severe and/or uncontrolled concurrent medical conditions that in the opinion of the investigator could cause unacceptable safety risks or compromise compliance with the protocol	Include in everything	0	Minor
EXCL05	Impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of study drug	Exclude from PPS	4	Major
EXCL06	History of significant congenital or acquired bleeding disorder unrelated to cancer	Include in everything	0	Minor
EXCL07	Patients on strong CYP3A4 inhibitors and or inducers or medications with potential to prolong QT interval not discontinued before start of study drug	Include in everything	0	Minor
EXCL08	Patients who have not recovered from prior surgery	Include in everything	0	Minor
EXCL09	Pregnant, Breast feeding, Childbearing potential without a -ve pregnancy test prior to baseline and female of childbearing potential unwilling to use contraceptive precautions throughout the trial	Include in everything	0	Minor
EXCL10	Patients with history of another primary malignancy that is currently clinically significant or currently requires active intervention with exception of previous or concomitant basal cell skin cancer	Include in everything	0	Minor
EXCL11	Treatment with other investigational agents within 30 days of Day 1	Defined individually	Refer DRM minutes	To be categorized individually case by case

EXCL12	Patients not able to understand and to comply with study instructions and requirements	Include in everything	0	Minor
TRT01	Subject should start study drug with a dose of 300 mg BID	Defined individually	Refer DRM minutes	To be categorized individually case by case
TRT02	Subject not compliant with prescribed study drug dose and regimen	Defined individually	Refer DRM minutes	To be categorized individually case by case
TRT03	Subject took total daily dose of Nilotinib less than 450 mg	Defined individually	Refer DRM minutes	To be categorized individually case by case
TRT04	Subject took dose of Nilotinib=>450 mg and regimen 2 times per dayfor more than 28 days or Subject took dose of Nilotinib>600 mg and regimen 1times per day for more than 28 days	Defined individually	Refer DRM minutes	To be categorized individually case by case
TRT06	Drug supply method changed due to COVID-19	Include in everything	0	Minor
TRT07	Treatment not given due to COVID-19	Include in everything	0	Minor
TRT08	Subject took dose of Nilotinib greater than 600mg daily dose for more than 28 days	Defined individually	Refer DRM minutes	To be categorized individually case by case
OTH01	Hepatitis assessment not performed for the subject	Include in everything	0	Minor
OTH02	Subject enrolled in the study without completing key assessments per protocol eligibility criteria	Include in everything	0	Minor
OTH03	Subject completed Screening assessments prior to signing ICF	Include in everything	0	Minor
OTH04	Missed Visit due to COVID-19	Include in everything	0	Minor

OTH05	Assessment related to assessing Inclusion criteria and Exclusion criteria not performed	Include in everything	0	Minor
OTH06	Visit not done at Study site due to COVID-19	Include in everything	0	Minor
OTH07	Assessment / procedure changed due to COVID-19	Include in everything	0	Minor
OTH08	Discontinuation due to COVID-19	Include in everything	0	Minor
COMD01	Use of anticancer agents including chemotherapy and biologic agents	Defined individually	Refer DRM minutes	To be categorized individually case by case
COMD02	Subject took concomitant medication excluded as per protocol during study treatment	Defined individually	Refer DRM minutes	To be categorized individually case by case

Table 5.5.2 Analysis set exclusions based on population codes

Analysis set	Population codes that cause a subject to be excluded
RAN	NA
SAF	2, 3
FAS	1, 3
PPS	4

Table 5.5.3 Population code text

Population Code	Population code text
0	INCLUDE IN EVERYTHING
1	EXCLUDE FROM FULL ANALYSIS SET (FAS)
2	EXCLUDE FROM SAFETY SET (SAF)
3	EXCLUDE FROM FAS AND SAF
4	EXCLUDE FROM PPS

Unless otherwise stated, summary tables, figures and listings will be on all subjects included in the analysis set under consideration.

6 Reference

1. Study protocol: Oncology study protocol CAMN107ADE20.