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An open label, multi-center nilotinib roll-over protocol for patients who have completed a previous Novartis sponsored nilotinib study and are judged by the investigator to benefit from continued nilotinib treatment

Statistical Analysis Plan (SAP)

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Time point	Reason for update	Outcome for update	Section and title impacted (Current)
Prior to DB lock	Creation of final version	N/A - First version	NA
Prior to DB lock	Protocol amendment	Modified the follow up period from 5 years to 10 years.	Section 1.1 Study design
	Protocol amendment	Removed all changes to protocol specified analyses.	Section 4
	Use of common word	Renamed “pre-study period” to “pre-treatment period” and “on-study period” to “on-treatment period”	Section 2.1.1
	Mandatory for CSR	Added analysis to summarize demographics data	Section 2.3
	Analysis for final CSR	Removed the number of patients who are on-going and add the number of patients who completed study treatment	Section 2.3.1
	Not mandatory for analysis of AESI	Removed analysis for AESI	Section 2.8.1.1
	Mandatory for the study registered in CT.gov	Added analysis for death, serious AE and non-serious AE.	Section 2.8.1

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List of abbreviations

AE	Adverse event
AESI	Adverse Event of Special Interest
CSR	Clinical Study report
CTCAE	Common Terminology Criteria for Adverse Events
DI	Dose Intensity
EOT	End of Treatment
FAS	Full Analysis Set
eCRF	Electronic Case Report Form
MedDRA	Medical Dictionary for Drug Regulatory Affairs
NMQ	Novartis MedDRA Queries
PDI	Planned dose intensity
PK	Pharmacokinetics
PPS	Per-Protocol Set
PT	Preferred Term
RDI	Relative Dose Intensity
SAP	Statistical Analysis Plan
SMQ	Standardized MedDRA Queries
SOC	System Organ Class

1 Introduction

This statistical analysis plan (SAP) describes all planned analyses for the clinical study report (CSR) of study CAMN107A1201, an open label, multi-center nilotinib roll-over protocol for Japanese patients who have completed a previous Novartis sponsored nilotinib study and are judged by the investigator to benefit from continued nilotinib treatment.

The content of this SAP is based on protocol CAMN107A1201 Amendment version 3. All decisions regarding final analysis, as defined in the SAP document, have been made prior to database lock of the study data.

1.1 Study design

This is an open label, multi-center, phase II study to collect and assess long term safety of nilotinib in Japanese patients being treated in current Novartis-sponsored, clinical studies and who are benefiting from treatment with nilotinib.
Frequency and nature of Adverse Events (AEs) are the primary endpoints in this study.
The final analysis will be performed when all patients discontinued the trial or 10-year follow-up was completed, whichever comes earlier.

1.2 Study objectives and endpoints

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

Table 1-1 Objectives and related endpoints

Objective	Endpoint
Primary To collect and assess long-term safety of nilotinib to patients receiving nilotinib in a Novartis-sponsored clinical study which has reached its objectives and who are benefiting from treatment with nilotinib.	Frequency and nature of AEs

2 Statistical methods

2.1 Data analysis general information

The final analysis will be performed by Novartis and/or a designated CRO. SAS version 9.4 or later software will be used to perform all data analyses and to generate tables, figures and listings.

General analysis conventions

Pooling of center: Unless specified otherwise, data from all study centers will be pooled for the analysis. Due to expected small size of centers, no center effect will be assessed.
Qualitative data will be summarized by means of contingency tables by treatment group; 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.
Quantitative data will be summarized by appropriate descriptive statistics (i.e. mean, standard deviation, median, minimum, and maximum) by treatment group.

2.1.1 General definitions

Study treatment

Study treatment will refer to Nilotinib in this study.

Date of first administration of study treatment in this study

The date of first administration of study treatment is derived as the first date in this rollover study when a nonzero dose of study treatment was administered as per the Dosage Administration CRF. The date of first administration of study treatment will also be referred as start of study treatment.

Date of last administration of study treatment in this study

The date of last administration of study treatment is defined as the last date in this rollover study when a nonzero dose of study treatment was administered as per Dose Administration eCRF.

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 is the start of treatment in this particular study.

The study day will be displayed in the data listings. If an event starts before the reference start date, the study day displayed on the listing will be negative.

Baseline

For safety and efficacy evaluations, the last available assessment on or before the date of start of study treatment in this particular study is defined as “baseline” assessment.

If patients have no value as defined above, the baseline result will be considered as missing.

On-treatment assessment/event and observation periods

The overall observation period will be divided into three mutually exclusive segments:

1. ***pre-treatment period***: before first administration of study treatment in this rollover study
2. ***on-treatment period***: from date of first administration of study treatment in this study to 30 days after date of last actual administration of any study treatment (including start and stop date)
3. ***post-treatment period***: starting at day 30+1 after last administration of study treatment.

Summary tables for adverse event (AEs) will summarize on-treatment period events as described in the point (2) above. However, all safety data (including those from the pre-treatment and post-treatment period) will be listed and those collected during the pre-treatment and post-treatment period are to be flagged.

2.2 Analysis sets

Full Analysis Set

No Full Analysis Set (FAS) is defined for this trial.

Per protocol set (PPS)

No Per-Protocol Set (PPS) is defined for this trial.

Safety Set

The Safety Set includes all patients who received at least one dose of Nilotinib in this study. All the analyses will be conducted by Safety Set.

Patient Classification:

Patients may be excluded from the analysis populations defined above based on the protocol deviations entered in the database and/or on specific subject classification rules defined in Table 2-2.

Table 2-1 Subject classification based on protocol deviations and non-protocol deviation criteria

Analysis set	Protocol deviations leading to exclusion	Non protocol deviation leading to exclusion
Safety set	No written inform consent	No dose of study medication in this study

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 data sets. The date on which a patient withdraws full consent is recorded in the eCRF.

2.3 Patient disposition, demographics and other baseline characteristics

Patient demographics and baseline characteristics at entry in this rollover study, such as age will be listed by patient.

Basic demographic and background data

All demographic data will be summarized and listed.

2.3.1 Patient disposition

The number (%) of patients who are enrolled in this study, who are still on treatment, who discontinued the study phases and the reason for discontinuation will be presented. This analysis will be presented for enrolled patients.

The following summaries will be provided: % based on the total number of patients in safety set:

- Number (%) of patients who completed treatment ("Treatment duration completed as per protocol" was selected in the 'End of Treatment' page)
- Number (%) of patients who discontinued the study treatment phase (any reason aside from "Treatment duration completed as per protocol" was selected in the 'End of Treatment' page)
- Primary reason of study treatment phase discontinuation for patients who discontinued the study treatment (based on the 'End of Treatment' page)

All primary reason for end of treatment will be listed.

Protocol deviations

Since the number of patients will be limited, so all protocol deviations will be provided as listings, but no summery will be provided.

Analysis sets

The number (%) of patients in each analysis set (defined in Section 2.2) will be summarized.

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

2.4.1 Study treatment / compliance

The duration of exposure to Nilotinib in the current study will be calculated for each patient, and will be summarized.

The dose intensity defined as the ratio of the cumulative dose to the duration of exposure may be calculated and summarized.

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 in this particular study:

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

The last date of exposure to study treatment is the latest of the last dates of exposure to study treatment. The duration of exposure to study treatment will not be summarized. It will be used for dose intensity.

Cumulative dose

Cumulative dose of a study treatment is defined as the total dose given during the study treatment exposure and will be summarized. The actual cumulative dose refers to the total actual dose administered, over the duration for which the patient 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.

The planned cumulative dose for a study treatment component is the total planned dose as per the protocol up to the last date of study treatment administration. The planned cumulative dose will not be summarized. It will be used for relative dose intensity calculations.

For the study treatment which is administered daily the planned cumulative dose is the planned starting dose summed over the duration of exposure.

Dose intensity and relative dose intensity

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

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

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 / days) = Planned Cumulative dose (mg) / Duration of exposure (days).

Relative dose intensity (RDI) is defined as follows:

RDI = DI (mg / days) / PDI (mg / days).

DI and RDI will be summarized.

Dose change

The change and the reason will be listed.

'Dose change' fields from the Dosage Administration CRF pages (DAR) will be used to determine the dose change.

2.4.2 Prior, concomitant and post therapies

Not applicable.

2.5 Analysis of the primary objective

Primary objective of this trial is to collect and assess the long-term safety of Nilotinib in patients receiving nilotinib in Novartis-sponsored clinical studies which has reached its objectives and who are benefiting from treatment with Nilotinib.

2.5.1 Primary endpoint

The primary endpoint of the study is frequency and nature of AEs.

2.5.2 Statistical hypothesis, model, and method of analysis

No null hypothesis test and statistical modeling are planned. Method of analysis is referred to Section 2.8.1.

2.5.3 Handling of missing values/censoring/discontinuations

Not applicable.

2.5.4 Supportive analyses

Not applicable.

2.6 Analysis of the key secondary objective

Not applicable.

2.7 Analysis of secondary efficacy objective(s)

Not applicable.

2.8 Safety analyses

An AE is defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) that occur after patient's signed informed consent has been obtained.

All AE data (including those from pre-study and post-treatment period) will be listed by patient and those collected during the pre-treatment and post-treatment are to be flagged. The incidence of AE will be summarized by system organ class and or preferred term, severity (based on CTCAE grades), type of AE, relation to study drug. CTCAE Grade 5 (death) was not used in this study; rather, information about deaths will be collected at the End of Treatment.

Note that AEs from pre-treatment will not be analyzed.

Deaths reportable as SAEs and non-fatal serious AEs will be listed by patient.

2.8.1 Adverse events (AEs)

AE summaries will include all AEs occurring during on-treatment period. All AEs collected in the AE eCRF page will be listed along with the information collected on those AEs e.g. AE relationship to study drug, AE outcome etc. AEs with start date outside of on-treatment period will be flagged in the listings.

AEs will be summarized by number and percentage of subjects having at least one AE, having at least one AE in each primary system organ class (SOC) and for each preferred term (PT) using MedDRA coding. A subject with multiple occurrences of an AE will be counted only once in the respective AE category. A subject with multiple CTCAE grades for the same preferred term will be summarized under the maximum CTCAE grade recorded for the event.

In AE summaries, the primary system organ class will be presented alphabetically and the preferred terms will be sorted within primary SOC in descending order of AE frequencies.

The following adverse event summaries will be produced; AEs by SOC and PT, severity, relationship, leading to treatment discontinuation, serious AEs and non-serious AEs.

2.8.2 Deaths

On treatment deaths will be summarized. All deaths will be listed.

2.8.3 Laboratory data

Not applicable.

2.8.4 Other safety data

Not applicable.

2.9 Pharmacokinetic endpoints

Not applicable.

2.10 PD and PK/PD analyses

Not applicable.

2.11 Patient-reported outcomes

Not applicable.

2.12 Biomarkers

Not applicable.

2.13 Other Exploratory analyses

Not applicable.

2.14 Interim analysis

Not interim analysis is planned.

3 Sample size calculation

No formal sample size calculation is required for this trial since only Japanese patients who are still on treatment in Novartis-sponsored clinical studies will be enrolled in this trial.

4 Change to protocol specified analyses

Table 4-1 summarizes the changes to protocol-specified analyses and associated rationale for inclusion in Appendix 16.1.9 (Documentation of Statistical Methods) of the CSR.

Table 4-1 Changes to protocol specified analysis or descriptions and rationale

Protocol section	Protocol description	Change	Rationale
10.2 Patient demographics/other baseline characteristics	Patient demographics and baseline characteristics such as age will be listed by patient	Patient demographics and baseline characteristics such as age will be summarized and listed by patient	Summary table for demographics is necessary for CSR.

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

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

If the dose end date is completely or partially missing and the EOT page is available:

Case 1: The dose end date is completely missing, and the EOT completion date is complete, then this latter date should be used.

Case 2: Only Year(yyyy) of the dose end date is available and yyyy < the year of EOT date:

Use Dec31yyyy

Case 3: Only Year(yyyy) of the dose end date is available and yyyy = the year of EOT date:

Use EOT date

Case 4: Both Year(yyyy) and Month (mm) are available for dose end date, and yyyy = the year of EOT date and mm < the month of EOT date:

Use last day of the Month (mm)

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

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

Use the treatment start date

Patients with missing start dates are to be considered missing for all study treatment component related calculations and no imputation will be made. If start date is missing then end-date should not be imputed.

5.1.2 AE date imputation

The following missing dates will not be imputed

- Partial/missing AE end dates

For other type of missing dates, rules specified in Tables 5-1 to 5-3 will be used

Table 5-1 AE/Treatment Date Abbreviations

	Day	Month	Year
Partial Adverse Event Start Date	<not used>	AEM	AEY

	Day	Month	Year
Treatment Start Date (TRTSTD)	<not used>	TRTM	TRTY

Table 5-2 describes the possible combinations and their associated imputations. The upper text indicates the imputation (A, B, C etc.) and the lower text the relationship of the AE start date to the treatment start date (TRTSTD).

Table 5-2 Imputation algorithm

	AEM MISSING	AEM < TRTM	AEM = TRTM	AEM > TRTM
AEY MISSING	(B) Uncertain	(B) Uncertain	(B) Uncertain	(B) Uncertain
AEY < TRTY	(D) Before TRTSTD	(C) Before TRTSTD	(C) Before TRTSTD	(C) Before TRTSTD
AEY = TRTY	(B) Uncertain	(C) Before TRTSTD	(B) Uncertain	(A) After TRTSTD
AEY > TRTY	(E) After TRTSTD	(A) After TRTSTD	(A) After TRTSTD	(A) After TRTSTD

The legend to the above table is shown in Table 5-3.

Table 5-3 Imputation algorithm legends

Relationship	
Before TRTSTD	Indicates AE start date prior to Treatment Start Date
After TRTSTD	Indicates AE start date after Treatment Start Date
Uncertain	Insufficient to determine the relationship of AE start date to Treatment Start Date
Imputation calculation	
(A)	01MONYYYY
(B)	TRTSTD+1
(C)	15MONYYYY
(D)	01JULYYYY
(E)	01JANYYYY

Few examples are shown in Table 5-4.

Table 5-4 Example scenarios

Partial AE start date	Treatment start date	Relationship with TRTSTD	Imputation Calculation	Imputed Date
ddmmmyyyy	20OCT2001	Uncertain	(B)	21OCT2001
ddmmm2000	20OCT2001	Before	(D)	01JUL2000
ddmmm2002	20OCT2001	After	(E)	01JAN2002
ddmmm2001	20OCT2001	Uncertain	(B)	21OCT2001
ddSEP2001	20OCT2001	Before	(C)	15SEP2001
ddOCT2001	20OCT2001	Uncertain	(B)	21OCT2001
ddNOV2001	20OCT2001	After	(A)	01NOV2001

5.1.3 Concomitant medication date imputation

Not applicable.

5.2 AEs coding/grading

Adverse events were coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

AEs were assessed by the investigator according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

The CTCAE represents a comprehensive grading system for reporting the acute and late effects of cancer treatments. CTCAE grading is by definition a 5-point scale generally corresponding to mild, moderate, severe, life threatening, and death. This grading system inherently places a value on the importance of an event, although there is not necessarily proportionality among grades (a grade 2 is not necessarily twice as bad as a grade 1). The CTCAE grade of 5 (death) is not used; rather, 'fatal' is collected as AE outcome and death information is also collected on a separate eCRF page.

5.3 Laboratory parameters derivations

Not applicable.

5.4 Statistical models

No null hypothesis test and statistical modeling were planned.

6 Reference

No reference.