NOVARTIS

Clinical Development

AMN107/Nilotinib/Tasigna®

AMN107A2409 / NCT01735955

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)-Amendment 2

Document type:	SAP Documentation
Document status:	Final Amendment 2
Release date:	29-Jun-2023
Number of pages:	19

Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
Oct 1, 2018	*Prior to DB lock*	*AMN107A2409 Protocol Amendment v5*	*AEs and Investigator assessed clinical benefit are collected per the new process of Rollover protocol, which are collected in the study following Protocol Amendment version 3.0. SAP is amended to include these new endpoints. Prior to Protocol Amendment version 3.0 only SAEs were being collected.*	*The entire SAP template has been changed in accordance with the new SAP template as compared to the SAP template in 2012. As all the sections have been changed, 'Section and title impacted' are not filled up here.*
29-Jun-2023	*Prior to DB lock*	*Creation of Amendment 2*	*Section 2.1 and 2.8.1: added the statement that AEs were not collected before Protocol Amendment version 3.0. Based on the original protocol only information if SAE (yes/no) occurred since previous visit was collected, further information related to the SAEs were collected only in the safety database.* *Section 2.1.: clarified which data is to be included in the analysis* *Section 2.7 and 5.6: time-windows for analysis of clinical benefit were added.* *Section 2.3.2: added COVID-19 related PDs listing.* *Section 2.3.2: The relevant medical history and current medical conditions listing were added to align with the protocol, TFLs and CRF.* *Section 2.4.1: removed reporting average daily dose and number of dosing days* *Section 2.8.1.1: to align with current process statement that AESIs will be obtained from SAS dataset eCRS in the Novartis computing environment not from Excel spreadsheet in CREDI was added* *Section 2.8.1.1: AESI listing and listing of Case Retrieval Strategy was added.* *Section 2.8.1.2: the section on AE posting requirements was added* *Section 2.8.3: Pregnancy and hepatitis B data listings were added to align with the protocol, TFLs and CRF.* *Section 5.1.1: added one scenario to cover the imputation of the case when both last exposure end date and EOT date are partial*	*2.1, 2.8.1, 2.7, 5.6, 2.3.2, 2.8.1.1, 2.8.1.2, 2.8.3, 2.4.1 and, 5.1.1*

Table of contents

List of abbreviations

AE	Adverse event
ATC	Anatomical Therapeutic Classification
bid	bis in diem/twice a day
CSR	Clinical Study report
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
FAS	Full Analysis Set
eCRF	Electronic Case Report Form
MedDRA	Medical Dictionary for Drug Regulatory Affairs
o.d.	Once Daily
PK	Pharmacokinetics
qd	Qua'que di'e / once a day
SAP	Statistical Analysis Plan
SOC	System Organ Class
TFLs	Tables, Figures, Listings
WHO	World Health Organization

1 Introduction

This statistical analysis plan (SAP) describes all planned analyses for the clinical study report (CSR) of study CAMN107A2409, 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.

The content of this SAP is based on protocol CAMN107A2409 Amendment 5.0. 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

1.1.1 Description of study design

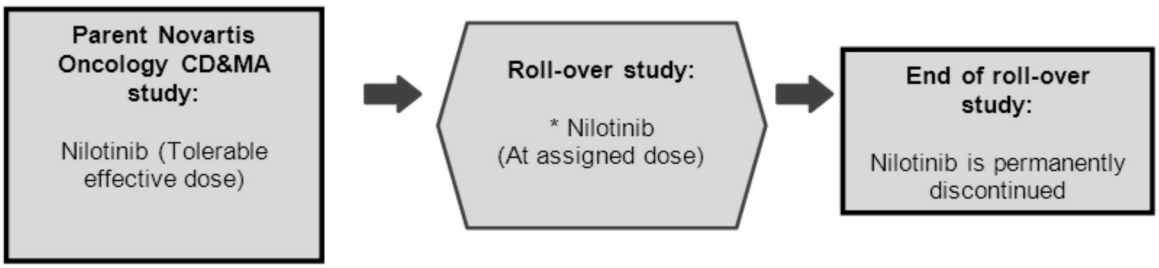
This is a multi-center, open label, phase IV study to better characterize the long-term safety of nilotinib in patients being treated in current Novartis-sponsored, Oncology OGD&GMA studies and who are benefiting from treatment with nilotinib.

There will be no screening period for this study. At the enrollment visit the patient will be consented to the study and eligible patients will start their treatment with nilotinib. At this time, a 3-month supply of nilotinib will be dispensed to the patient/or as per local practice.

Patients must return to the study center on a quarterly basis (12 weeks +/- 1 week), for resupply of study medication at which time limited drug dispensing information will be collected. The patient may return to the clinic at any given time as per standard of care, however, only the quarterly visits will be recorded. All adverse events and serious adverse events will be collected throughout the study. For the safe and effective use of Tasigna, medical monitoring should be performed as clinically indicated at the physician's discretion; this should also include monitoring of cardiovascular risk factors such as serum cholesterol and glucose levels amongst others. Patients will continue to be treated until they are no longer benefiting from nilotinib treatment, develop unacceptable toxicities, withdraw consent, are non-compliant to the protocol, the investigator feels it is no longer in the patient's best interest to continue nilotinib therapy, the patient dies, 10 years after First Patient First Visit into this clinical trial, or until study treatment becomes commercially available and reimbursed in the respective indication, whichever comes first. At every quarterly visit (12 weeks +/- 1 week), the investigator is required to confirm that the patient continues to have clinical benefit and may continue receiving study treatment.

A patient will reach the end of study when nilotinib treatment is permanently discontinued and the end of treatment visit has been performed.
The study is expected to remain open for 10 years from First Patient First Visit, which occurred on 29-Mar-2013, until study treatment becomes commercially available and is reimbursed in the respective indication or until such time that enrolled patients no longer need treatment with nilotinib, whichever comes earlier.

Figure 1-1



1.1.2 Planned number of patients

The total number of patients enrolled will be dependent on the number of patients who enroll in Novartis-sponsored AMN107 studies and meet eligibility for the current study.

1.1.3 Primary analysis time point

This study will only have one analysis, namely final analysis. The analysis cut-off date for the final analysis will be established at the end of the study when all patients have been followed for 30 days after they have either prematurely discontinued from the treatment or completed treatment as per protocol. All analyses will be performed using all data collected in the database up to the data cut-off date.

All events with start date before or on the cut-off date and end date after the cut-off date will be reported as 'continuing at the cut-off date'. 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 reports. For these events, the end date will not be imputed and therefore will not appear in the listings.

It is planned that the data from all centers that participate in this trial will be pooled and analyzed. Unless otherwise specified, qualitative data will be described using frequency and percentages, while quantitative data, will be described using descriptive statistics: n, mean, standard deviation, median, minimum, and maximum.

1.1.4 Timing of interim analyses

No interim analyses are planned.

1.1.5 Definition of end of the study

The end of study is defined as the date when all patients have completed their last assessment per protocol thirty days after end of treatment visit. The last assessment for each patient is the

follow-up assessment that occurs 30 days after the patient's last dose of study treatment. Patients may continue on study treatment until one of the following criteria is met, whichever comes first:

- At least one of the premature patient withdrawal criteria are met (See [Protocol Section 7.1.5 and Section 7.1.5.1])
- 10 years after the First Patient's First Visit into this clinical trial
- Study treatment becomes commercially available and is reimbursed in the respective indication.

Should nilotinib not be commercially available to patients at end of study due to local regulations, Novartis will have a transition plan in place to ensure that patients benefiting from treatment continue to have access to nilotinib without any interruption of treatment.

1.2 Study objectives and endpoints

Objectives and related endpoints are described in Table 1-1 below altogether with the planned analysis of collected data.

Table 1-1

Objective	Endpoint	Analysis
Primary		
To evaluate long term safety data (SAEs and AEs)	Frequency of AEs/SAEs	Frequency and severity of adverse events (AEs) and Frequency of serious adverse events (SAEs)
Secondary		
To evaluate clinical benefit as assessed by the investigator	Clinical benefit as assessed by the investigator at scheduled visits.	Proportion of patients with clinical benefit as assessed by the investigator will be summarized at scheduled visits.

2 Statistical methods

This section contains information that will be used to draft CSR Section 9.7 on statistical analysis.

2.1 Data analysis general information

The statistical analysis of these data will be performed by Novartis personnel or designated CRO in accordance with the data analysis section, Section 10, of the study protocol which is available in [Appendix 16.1.1 of the CSR]. SAS version 9.4 or higher will be used in all analyses.

Data included in the analysis

Patients will continue to be treated until they are no longer benefiting from nilotinib treatment, develop unacceptable toxicities, withdraw consent, are non-compliant with the protocol, the investigator feels it is no longer in the patient's best interest to continue nilotinib therapy, 10 years from First Patient First Visit or the patient dies, whichever comes first. A patient will reach the end of study when nilotinib treatment is permanently discontinued and the end of treatment visit has been performed.

All data reported in the database will be included in the analyses.

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

Protocol amendment 3 (PA 3) was approved 07-Apr-2016. In this amendment the scheduled visits were changed from annually to quarterly and the regular data collection was increased.

Additional eCRFs were added to collect data related to

- Study Evaluation Completion
- AEs (based on original protocol only SAE yes/no was collected, and all SAEs were only collected on safety database)
- Relevant medical history/current medical conditions
- Hepatitis screen (only once at next possible visit)
- Confirmation of Clinical Benefit from Study Treatment

However, at the time the PA 3 was approved, 45 patients were enrolled; 28 out of 45 patients were ongoing. Therefore, the additional data is not available for the patients who already discontinued when PA 3 was implemented in the countries, and many of the still ongoing patients only agreed to PA3 in 2017 at their next scheduled visit. Due to this, the data may be underestimated.

Unless otherwise specified, qualitative data will be described using frequency and percentages, while quantitative data, will be described using descriptive statistics: n, mean, standard deviation, median, minimum, and maximum.

2.1.1 General definitions

2.1.1.1 Study Treatment

Study drug and investigation treatment refers to nilotinib. Patients are to use the study treatment based on the parent protocol.

2.1.1.2 Date of first/last administration of study drug

The start date of study drug is defined as the first date when a non-zero dose of study drug was administered and recorded on the Dosage Administration Record (DAR) eCRF.

The date of last administration of study drug is defined as the last date when a non-zero dose of study drug was administered and recorded on DAR eCRF.

2.1.1.3 Treatment period

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

1. on-treatment period: from day of first dose of study medication to 30 days after last dose of study medication
2. post-treatment period: starting at day 30+1 after last dose of study medication.

2.1.1.4 Study day

Definitions will be applied for all situations:

- Study day for post-treatment event = event date – first dose date + 1
- Study day for pre-treatment event = first dose date - event date

The first day of study drug is study day 1.

If duration is to be reported in weeks, duration in days will be divided by 7, likewise if in months, then duration in days will be divided by 30.4375 and if in years, duration in days will be divided by 365.25.

2.2 Analysis sets

The following analysis sets will be used for statistical analysis and data reporting.

2.2.1 Full Analysis Set

Not applicable.

2.2.2 Safety Set

The Safety Set includes all patients who received at least one dose of study medication after enrolling into the roll-over protocol.

2.2.3 Dose-determining analysis set

Not applicable.

2.3 Patient disposition, demographics and other baseline characteristics

2.3.1 Patient disposition

Patient disposition will be summarized using the Safety Set. The following will be tabulated:

- Number (%) of patients, who remained in the trial at the time of data cut-off or final data base lock;
- Number (%) of patients who discontinued the treatment;
- Number (%) of patients by primary reason for end of treatment (based on patient status entered in the ‘END OF TREATMENT DISPOSITION’ page).

Listings will be provided for disposition, protocol deviation using the Safety set. In addition, patients with any COVID-19 related protocol deviation will be listed.

2.3.2 Demographics and other baseline characteristics

Demographic (sex, age, previous study number and women of childbearing potential (WOCBP)) will be summarized descriptively and listed for the Safety Set. The relevant medical history and current medical conditions will be listed. Medical history/current medical conditions are coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The latest MedDRA version available at the time of reporting will be used.

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

2.4.1 Study treatment / compliance

Dose administration data will be summarized using the Safety Set.

2.4.1.1 Dose intensity and exposure

Definition of duration of exposure, includes:

- Duration of exposure (days): last date of study drug − first date of study drug + 1

Duration of exposure to study drug will be summarized descriptively. In addition, the duration of exposure to study drug will be categorized into time intervals; frequency counts and percentages of patients with exposure in each time interval will be presented.

The Dose administration data along with derived parameters will be listed using Safety Set.

2.4.2 Prior, concomitant and post therapies

Not applicable.

2.5 Analysis of the primary objective

The primary objective is to evaluate long term safety as assessed by the occurrence of AEs/SAEs.

2.5.1 Primary endpoint

The assessment of safety will be based mainly on the frequency and severity of AEs and SAEs. See also Section 2.8.

2.5.2 Statistical hypothesis, model, and method of analysis

The primary endpoint (AEs ans SAEs) will be summarized descriptively, and no formal analysis will be performed.

2.5.3 Handling of missing values/censoring/discontinuations

Not applicable.

2.5.4 Supportive analyses

No supportive analysis will be performed.

2.6 Analysis of the key secondary objective

There is no key secondary objective.

2.6.1 Key secondary endpoint

Not applicable.

2.6.2 Statistical hypothesis, model, and method of analysis

Not applicable.

2.6.3 Handling of missing values/censoring/discontinuations

Not applicable.

2.7 Analysis of secondary efficacy objective(s)

The secondary objective of the study was to evaluate clinical benefit as assessed by the investigator. The definition of time windows for the analysis of clinical benefit are provided in the Section 5.6.

2.7.1 Secondary endpoints

Proportion of patients with clinical benefit as assessed by the investigator will be summarized at scheduled visits by using the Safety Set.

2.7.2 Statistical hypothesis, model, and method of analysis

Not applicable.

2.7.3 Handling of missing values/censoring/discontinuations

Not applicable.

2.8 Safety analyses

Safety analyses will be performed on Safety Set. The assessment of safety will be based mainly on the frequency of AEs and SAEs.

2.8.1 Adverse events (AEs)

Treatment emergent AEs are defined as those that started on or after the study medication or those that started before study medication but worsened afterwards up to after 30 days post the last dose of study medication. AEs starting after 30 days post the last dose of study medication are not considered treatment emergent AEs.

Summary tables of adverse events (AEs) have to include only AEs that started or worsened during the on-treatment period, i.e. the treatment-emergent AEs. However, all safety data (including those from the post-treatment periods) will be listed and those collected during the post treatment period are to be flagged.

The incidence of treatment-emergent adverse events (new or worsening from baseline) will be summarized by system organ class and/or preferred term, severity based on CTCAE grades (version 4.03 or higher), type of adverse event, relation to study treatment. The categorical summary will include AEs regardless of study-drug relationship. The same analysis will be repeated for SAEs.

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.

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

AEs were not collected before Protocol Amendment version 3.0. Based on the original protocol only information on whether SAE occurred since previous visit (yes/no) was collected. Further information related to the SAEs were collected only in the safety database. All adverse events ended before Protocol Amendment version 3.0 will be flagged in the listing.

Adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology using the latest available MedDRA version at the time of the analyses and the information of MedDRA version will be specified in the footnote of relevant outputs.

The following selection of AEs will be listed and summarized separately. All these AEs will be summarized for all grades and for grade 3 or 4 side-by-side for Safety Set.

- AEs
- AEs suspected to be study drug related
- AEs reported as serious AEs (SAEs)
- SAEs suspected to be study drug related
- AEs associated with discontinuation of study drug

2.8.1.1 Adverse events of special interest / grouping of AEs

Adverse events of special interest (AESI) are defined as events (serious or non-serious) which are ones of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor may be appropriate. Such events may require further investigation in order to characterize and understand them.

Adverse events of special interest are defined on the basis of an ongoing review of the safety data. AESIs are discussed in detail in the [Investigator Brochure].

Specific grouping of AEs (AESI) will be obtained from SAS dataset eCRS in the Novartis computing environment. For each specified safety event category, number and percentage of patients with at least one event part of the safety event category will be reported by safety subset and listed. PTs associated with every AESI group will also be listed.

2.8.1.2 Adverse events posting

For the legal requirements of ClinicalTrials.gov and EudraCT, two required tables on on-treatment adverse events which are not serious adverse events with an incidence greater than 5% and on on-treatment serious adverse events and SAE suspected to be related to study treatment will be provided by system organ class and preferred term on the safety set population.

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

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

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

The number of deaths resulting from SAEs suspected to be related to study treatment and SAEs irrespective of study treatment relationship will be provided by SOC and PT. Since the regular AE data collection only started with ICF date for PA3, the table related to SAE will be produced directly from the safety database. And only the table related to non-serious AEs will be programmed using the data from the clinical database.

2.8.2 Deaths

On-treatment deaths which occur within the study or within 30 days after discontinuation from the study will be summarized using n (%) for safety set. All deaths due to any cause at any time in the study, including the follow-up period, will also be summarized using n (%). All deaths will also be listed and post treatment deaths will be flagged.

2.8.3 Laboratory data

All pregnancy monitoring data will be listed. Hepatitis B surface antigen (HBs Ag) and antibodies to hepatitis B core antigen (HBc Ab / anti HBc) data will be listed.

2.8.4 Other safety data

Not applicable.

2.8.4.1 ECG and cardiac imaging data

Not applicable.

2.8.4.2 Vital signs

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 applicable.

3 Sample size calculation

Not applicable.

4 Change to protocol specified analyses

Not applicable.

5 Appendix

5.1 Imputation rules

In this section provide necessary details as needed for imputation.

5.1.1 Study drug

Below mentioned imputation rules will be used in case of missing or partial end date of study drug.

Scenario 1

If the last date of study drug is after the cut-off date or is completely missing and there is no end of treatment eCRF page and no death date the patient should be considered to be ongoing and use the cut-off date for the analysis as the last dosing date

Scenario 2

If the last date of study drug is partial and the end of treatment (EOT) eCRF page is available but partial then the last dosing date will be imputed with the earliest date among the latest visit date, last day of the month of last dose end date, last day of the month of EOT date.

Scenario 3

If the last date of study drug is completely or partially missing and there is EITHER an end of treatment eCRF page OR a death complete date available then imputed last dose date:

= 31DECYYYY, if only Year is available and Year < Year of min (EOT visit date, death date)

= Last day of the month, if both Year and Month are available and Year = Year of min (EOT visit date, death date) and Month < the month of min (EOT visit date, death date)

= min (EOT visit date, death date), for all other cases

The imputed date will be compared with start date of study drug.

If the imputed date < start date of study drug, then last date of study drug is set to start date of study drug; otherwise, use the imputed date.

5.1.2 AE date imputation

Missing date for AE will be handled according to rules specified below. A partial date is simply an incomplete date e.g. DDOCT2001: the days are missing from this DDMMMYYYY date.

There **will be no** attempt to impute the following:

- **Missing** AE start dates
- AE start dates **missing the year**
- Partial/missing AE **end dates**

Table 5-1 AE/Treatment date abbreviations

	Day	Month	Year
Partial AE start date	<not used>	AEM	AEY
Treatment start date (TRTSTD)	<not used>	TRTM	TRTY

The following matrix Table 5-2 describes the possible combinations and their associated imputations. In the light grey boxes the upper text indicates the imputation and the lower text the relationship of the AE start date to the treatment start date (TRTSTD).

Table 5-2 AE partial date imputation algorithm

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

Table 5-3 AE/treatment date relationship and imputation legend

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	
NC/Blank	No convention/imputation
(A)	01MONYYYY

Relationship	
(B)	TRTSTD+1
(C)	15MONYYYY
(D)	01JULYYYY
(E)	01JANYYYY

The following Table 5-4 gives a few examples.

Table 5-4 AE imputation example scenarios

Partial AE start date	Treatment start date	Relationship	Imputation calculation	Imputed date
12mmyyyy	20OCT2001	Uncertain	NC	<blank>
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

5.1.3.1 Prior therapies date imputation

Not applicable

5.1.3.2 Post therapies date imputation

Not applicable

5.1.3.3 Other imputations

Not applicable

5.1.4 Incomplete date for death

All dates must be completed with day, month and year. If the day or month is missing, death will be imputed to the maximum of the last contact date (excluding the date of death) and the following:

- Missing day: 15th of the month and year of death
- Missing day and month: July 1st of the year of death

5.2 AEs coding/grading

Not applicable

5.3 Laboratory parameters derivations

Not applicable.

5.4 Statistical models

5.4.1 Primary analysis

Not applicable.

5.4.2 Key secondary analysis

Not applicable.

5.5 Rule of exclusion criteria of analysis sets

Not applicable.

5.6 Definition of time-windows for analysis of clinical benefit

For clinical benefit, time windows will be used to identify data to be considered for the specific analysis at a specific time point. The time windows are defined so that there are no gaps between the 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. Time windows are defined based on date of first study drug intake (= Study Day 1). Table 5-5 shows the time windows for the analyses of clinical benefit.

Table 5-5 Time windows for analyses of clinical benefit

Planned assessment	Time window
Week 24 (Day 168)	Day 2 to Day 251
Week 48 (Day 336)	Day 252 to Day 419
Week 72 (Day 504)	Day 420 to Day 587
Week 96 (Day 672)	Day 588 to Day 755
Year 3 (Day 1008)	Day 756 to Day 1175
Year xx (Day xx*7*48)	Day ((xx*48 - 24) * 7) to Day ((xx*48 + 24) * 7-1)

xx = Every year until data is available

6 Reference

None.

NOVARTIS

Clinical Development

AMN107/Nilotinib/Tasigna®

AMN107A2409 / NCT01735955

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)
for Novartis Safety database (ARGUS) generated data – Amendment 1

Author: [redacted]

Document type: SAP Documentation

Document status: Final – Amendment 1

Release date: 21-July -2023

Number of pages: 10

Document History - Changes compared to previous final version

Version	Date	Changes
Final 1.0	05-Oct-2022	NA – First version (Prior to DB lock)
Final 1.0 Amendment 1	21-July-2023	Amendment 1 was performed to incorporate changes requested by CTT: • for all outputs clarified that SAEs are coming from ARGUS • Listing 14.3.2-2.1: columns SAE and Grades were removed. Footnote "* More than 30 days after last study treatment." was replaced with "+ = start date is in the pre and post-treatment period." • Table 14.3.1-2.3: replaced title "On-treatment deaths and serious adverse events by system organ class, preferred term and risk group" with "On-treatment deaths and serious adverse events, by system organ class, preferred term". Clarified that for this output deaths are coming from clinical database while SAEs are coming from ARGUS database. • Section 3.1 was updated to reflect that time of SAE is not collected in ARGUS

Table of contents

List of output shells

1 Introduction

This statistical analysis plan (SAP) describes the planned analyses for tables which will be generated from Novartis Safety database (ARGUS) reported in the study CAMN107A2409.

The purpose of this roll-over study CAMN107A2409 is to allow continued use of nilotinib to patients who are on nilotinib treatment in a Novartis-sponsored, Oncology Clinical Development & Medical Affairs (CD&MA) study, have fulfilled all their requirements in the parent study and are benefiting from the treatment as judged by the investigator. As per the initial study protocol dated 11-Oct-2012, the safety reporting requirement was only limited to reporting of all serious adverse events (SAEs) to Novartis Safety database (ARGUS). The collection of all adverse events (including serious and non-serious) in the clinical database was introduced in the protocol amendment version 03 dated 07-Apr-2016 which was approximately 3 years after the First Patient First Visit (29-Mar-2013) in this study. Thus, the tables and listings reflecting the totality of SAEs reported in the entire study period can be generated only based on the data recorded in ARGUS.

This document serves as a complement to the CAMN107A2409 Statistical Analysis Plan for the final clinical study report (CSR) and describes the criteria of the line listings to be retrieved from ARGUS and used by the statistical programming team to generate the above stated tables and listings.

2 Analysis of serious adverse events from ARGUS database

The following SAE summary tables and listing will be generated based on the data from ARGUS.

- Listing of SAEs from ARGUS
- Table of SAEs regardless of study treatment relationship from ARGUS by primary system organ class and preferred term
- Table of SAEs suspected to be study drug related from ARGUS by primary system organ class and preferred term
- Table of on-treatment deaths and treatment-emergent SAEs by system organ class and preferred term (for legal requirements of ClinicalTrials.gov and EudraCT).

The layout of these tables and listing will be similar to the one produced from the clinical database. The corresponding output shells are provided in section 4.

3 Novartis safety database (ARGUS)

3.1 Retrieval of data from ARGUS

A line listing of all SAEs with a case receipt date from First Patient First Visit date (29-Mar-2013) to Last Patient Last Treatment (LPLT) +30 days for Study ID CAMN107A2409 will be generated from the ARGUS by the Novartis Data Science & Analytics team (DS&A).

The line listings will include the following information (column headings). Description of the data field is provided wherever necessary in the Table 3-1 below.

Table 3-1 Data field in ARGUS version 8

Data field in ARGUS version 8	Description
Case Number	Number of the case
Study ID	Trial Number
Center ID	Site ID
Subject number/Patient ID	-
Company Drug code	-
Product Name/Study drug	-
Onset date	Event onset date
Seriousness criteria	Event seriousness criteria
Causality as Reported Source	Causality as Reported by the Investigator or Health Care professional
Causality as Determined Source	Causality as Determined by Novartis
Event Preferred Term	Coded term based on MedDRA version at the time of event reported in ARGUS
Lower Level Term	MedDRA term
HLT name	MedDRA term
HLGT name	MedDRA term
SOC	MedDRA term
Outcome of Event	-
Death Date	-
Death Cause PT	MedDRA term
Product Indication	-
Daily dose with Units	-
Duration of Regimen	-
Action taken	-
De-challenge	-
Re-challenge	-
Country	-
Patient date of birth	-
Description of events	Event verbatim

Data field in ARGUS version 8	Description
End date	Event end date
Lower Level Term Code	MedDRA Code
High Level Term Code	MedDRA Code
High Level Group Term Code	MedDRA Code
Primary System Organ Class Code	MedDRA Code
Preferred Term Code	MedDRA Code
Occurrences	-
Death Flag	-
Deleted/Deactivated case	-
Reason for deletion/deactivation	-

3.2 Transfer of data from Novartis Safety database to GPS tool

The line listings from ARGUS database will be sent via email (Global, Pvdm (Gen) [redacted]) from DS&A to the programming team.

4 Shells for Outputs

The below shells are used for the analysis from adverse event data coming from clinical database. For the analysis of SAEs from ARGUS database the shells may be updated to incorporate the different data structure in ARGUS.

Listing 14.3.2-2.1 Serious adverse events from ARGUS database (Safety set)

Country/ Center/ Patient	Age/ Sex	REPORTED / Preferred term / System organ class	Start date+/ Study day	End date/ Study day	Dur. (days)	Relat. to study drug	Action taken
USA/201/ 0001	55/M /Ca	MILD DIZZINESS / Dizziness (exc vertigo) / Nervous system disorders	1999-09-16/ 9	1999-09-23/ 16	8	Not susp	0
USA/201/ 0008	71/F /Ca	GASTRIC DISTRESS / Abdominal pain upper / Gastrointestinal disorders	1999-09-25/ 93*	1999-09-26/ 94*	2	Susp	0

Action taken: 0=Dose reduced, 1=No Change, 2=Not Applicable, 3=Treatment Discontinued, 4=Treatment Temporary Interrupted.
+ Start date is in the pre or post-treatment period.
MedDRA version <xx.x>, CTCAE version <x.xx>.
Study day is calculated from treatment start date.

Programming Note:
1. *Please note that the output may be updated to incorporate the different data structure in ARGUS.*
2. *Flag those SAEs that occurred more than 30 days after last treatment.*
3. *Display 'Ongoing' under column 'End date/Study Day' if AE is ongoing at final exam / at time of data cut-off.*
4. *All dates should be provided in the format ddmmmyyy as they are in the database.*

5. Oncology standards CSR v3.1 Listing L_AE_303B

Table 14.3.1-2.1 Serious adverse events from ARGUS database, regardless of study drug relationship by primary system organ class and preferred term (Safety Set)

Primary system organ class Preferred term	All patients N=xxx n (%)
Number of patients with at least one event	xxx (xx.x)
Cardiac disorders	xxx (xx.x)
Angina pectoris	xxx (xx.x)
Oedema NOS	xxx (xx.x)
Oedema lower limb	xxx (xx.x)
Bradycardia NOS	xxx (xx.x)
Oedema peripheral	xxx (xx.x)
Sinus bradycardia	xxx (xx.x)
SOC 2	xxx (xx.x)
PT1	xxx (xx.x)
etc.	xxx (xx.x)

Numbers (n) represent counts of patients.
MedDRA version <xx.x>
Includes only on-treatment events.

Programming Note:
1. Sort SOC by alphabetical order, PTs by descending frequency.
2. Include only on-treatment events (as defined in SAP).
3. CSR Oncology standard TLF version 3.1 Table T_AE_301X

Table 14.3.1-2.2 Serious adverse events from ARGUS database, suspected to be study drug related by primary system organ class and preferred term (Safety Set)

Primary system organ class Preferred term	All patients N=xxx n (%)
Number of patients with at least one event	xxx (xx.x)
Cardiac disorders	xxx (xx.x)
Angina pectoris	xxx (xx.x)
Oedema NOS	xxx (xx.x)
Oedema lower limb	xxx (xx.x)
Bradycardia NOS	xxx (xx.x)
Oedema peripheral	xxx (xx.x)
Sinus bradycardia	xxx (xx.x)
SOC 2	xxx (xx.x)
PT1	xxx (xx.x)
etc.	xxx (xx.x)

Numbers (n) represent counts of patients.
MedDRA version <xx.x>
Includes only on-treatment events.

Programming Note:
1. *Sort SOC by alphabetical order, PTs by descending frequency.*
2. *Include only on-treatment events (as defined in SAP) suspected to be study-drug related.*
3. *CSR Oncology standard TLF version 3.1 Table T_AE_301X*

Table 14.3.1-2.3 On-treatment deaths and serious adverse events by system organ class, preferred term (Safety Set)

This is a ClinTrials.gov requirement. This will not be used for the CSR.

Primary system organ class Preferred term	All patients N=xxx
Total number of patients affected	
Patients affected by serious adverse events / exposed (%)	xxx/xxx (xx.xx)
Number of deaths (all causes)	xx
Number of deaths resulting from adverse events*	xx
Infections and infestations	
Pneumonia	
Patients affected / exposed (%)	xxx/xxx (xx.xx)
Occurrences causally related to treatment/all	xx/xx
Deaths causally related to treatment/all	xx/xx
Sepsis	
Patients affected / exposed (%)	xxx/xxx (xx.xx)
Occurrences causally related to treatment/all	xx/xx
Deaths causally related to treatment/all	xx/xx
Investigations	
Platelet count decreased	
Patients affected / exposed (%)	xxx/xxx (xx.xx)
Occurrences causally related to treatment/all	xx/xx
Deaths causally related to treatment/all	xx/xx
etc.	

*Number of deaths resulting from adverse events corresponds to deaths resulting from serious AE throughout the study in safety database (ARGUS) causally related to treatment.
Occurrences causally related to treatment/all: all occurrences are all SAEs occurrences regardless of causality to treatment.
Deaths causally related to treatment/all: all deaths are all SAEs with fatal outcome regardless of causality to treatment.
Includes only on-treatment events.
The on-treatment death data is from the clinical database, and the SAE data is from Argus.
MedDRA version <xx.x>.

Programming Note:
1. *Table used for posting to EudraCT and CT.gov.*
2. *Oncology standards CSR v3.1 Table T_AE_320.*