STATISTICAL ANALYSIS PLAN

An international, multicenter, open-label, treatment-extension study for subjects who completed a Phase 1 or Phase 2 parental study to continue receiving treatment with SAR245408 or SAR245409 as a monotherapy or as a combination regimen

SAR245408 - SAR245409 - TED12414

STUDY BIOSTATISTICIAN: [redacted]

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TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADI	actual dose intensity
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ATC	anatomical therapeutic chemical
CTCAE	common terminology criteria for adverse events
CR	complete response/remission
DR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
GGT	gamma glutamyltransferase
HLGT	high-level group term
HLT	high-level term
IMP	investigational medicinal product
INR	international normalized ratio
LLT	lower-level term
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
ORR	objective response rate
OS	overall survival
PCSA	potentially clinically significant abnormalities
PD	pharmacodynamics, progressive disease
PFS	progression free survival

PK	pharmacokinetic
PR	partial response
PT	prothrombin time, preferred term
QT	Q wave and T wave in heart's electric cycle
QTcF	QT interval corrected using Fridericia's formula
RDI	relative dose intensity
RR	two R waves in ECG
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOC	system organ class
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
WHO-DD	World Health Organization-Drug Dictionary
β-HCG	Beta-subunit of human chorionic gonadotropin

1 OVERVIEW AND INVESTIGATIONAL PLAN

1.1 STUDY DESIGN AND RANDOMIZATION

This is an open-label, international, multicenter, treatment-extension study, which will enable cancer patients who are currently receiving benefit from either SAR245408, formerly known as XL147, or SAR245409, formerly known as XL765, as a monotherapy or as part of a combination regimen in a Phase 1 or Phase 2 study to continue receiving treatment and further assess safety and tolerability of SAR245408 and SAR245409.

No randomization is implemented in the study.

1.2 OBJECTIVES

1.2.1 Primary objectives

The primary objective is to determine the long-term safety and tolerability of SAR245408 and SAR245409 as a monotherapy or as part of a combination regimen in subjects who are benefiting from treatment.

1.2.2 Secondary objectives

Not applicable.

1.3 DETERMINATION OF SAMPLE SIZE

The sample size of this study will depend on the number of subjects who will continue receiving treatment from the parental studies. It is expected that approximately 100 to 150 subjects will be treated in this study. There is no statistical power consideration for this treatment-extension study, as the study is for investigating the long term safety and tolerability of SAR245408 and SAR245409 as a monotherapy or as part of a combination regimen.

1.4 STUDY PLAN

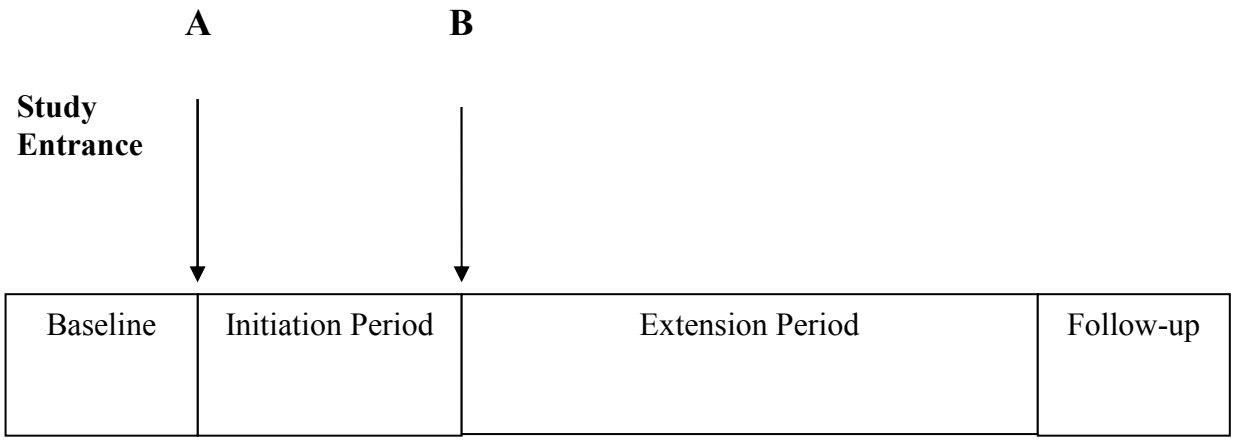
This treatment-extension, open-label, international, multicenter, nonrandomized study is designed to provide continued access to SAR245408 or SAR245409 as a monotherapy or as part of a combination regimen.

All subjects in the study will receive SAR245408 or SAR245409; the respective dose will be either the recommended Phase 2 dose (400 mg SAR245408 [tablet formulation polymorph A] once daily or 50 mg SAR245409 [capsule formulation] twice daily) or the subject's established dose either as a monotherapy or in a combination regimen in the parental study.

As shown in Figure 1, subjects who received SAR245408 or SAR245409 for less than 2 cycles in the parental study or who will take a daily dose of SAR245408 or SAR245409 higher than their established dose in the parental study will enter the treatment-extension study on Day 1 of the initiation period (A); subjects who received SAR245408 or SAR245409 for at least 2 cycles in the parental study will enter the treatment-extension study on Day 1 of the extension period (B).

Subjects may continue in the study until disease progression, unacceptable toxicity, withdrawal of consent, or until commercial supplies of SAR245408 or SAR245409 are available to them outside of the clinical trial.

Figure 1 - Graphical study design



A – Subjects who received SAR245408 or SAR245409 for <2 cycles in the parental study or who will take a daily dose of SAR245408 or SAR245409 higher than their established dose in the parental study will enter the treatment-extension study on Day 1 of the initiation period.

B – Subjects who received SAR245408 or SAR245409 for ≥ 2 cycles in the parental study will enter the treatment-extension study on Day 1 of the extension period.

1.5 MODIFICATIONS TO THE STATISTICAL SECTION OF THE PROTOCOL

The statistical section of the protocol was never changed in an amendment.

1.6 STATISTICAL MODIFICATIONS MADE IN THE STATISTICAL ANALYSIS PLAN

Not applicable.

2 STATISTICAL AND ANALYTICAL PROCEDURES

2.1 ANALYSIS ENDPOINTS

2.1.1 Demographic and baseline characteristics

The baseline value is defined as the last value or measurement taken before and up to the first study dose in this study.

All baseline safety parameters are presented along with the on-treatment summary statistics in the safety and efficacy sections (Section 2.4.5 and Section 2.4.4).

Demographic characteristics

Demographic variables are sex (Male, Female), race (Caucasian/white, Black, Asian/Oriental, American Indian or Alaska Native, Native Hawaiian or other Pacific Island, other), age in years (quantitative and qualitative variable : <65, [65 – 75[and ≥75 years), weight, ethnicity (Hispanic, non-Hispanic).

Age in years will be calculated as (Date of Informed Consent – Date of Birth + 1)/365.25.

Cancer diagnosis

Cancer diagnosis is divided into two categories based on tumor type – solid tumor or lymphoma. The following parameters, date of initial diagnosis (years), location of primary tumor and histology type, are collected.

Prior anticancer therapies

Prior anticancer therapies only include parental study drug (SAR245408 or SAR245409) that was administered in the parental study. Any anticancer therapies prior to the parental study drug are not collected in this study. Information about drug per regimen and start/end date are collected.

Vital signs

Vital signs at baseline are weight in kg, height in cm, blood pressure (systolic and diastolic) in mmHg, heart rate, body temperature.

Other baseline measures

Other baseline measures include physical examination, ophthalmologic examination, electrocardiogram (ECG), tumor assessment and Eastern Cooperative Oncology Group (ECOG) performance status.

Any technical details related to computation, dates, and imputation for missing dates are described in Section 2.5.

2.1.2 Prior or concomitant medications (other than anticancer therapies)

All medications taken within 30 days before the first investigational medicinal product (IMP) administration in the current study and until the end of the study are to be reported in the case report form pages.

All medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD) using the version currently in effect at Sanofi at the time of database lock.

- Prior medications are any medications (except the study medications in the parental study) taken by patients within 30 days prior to the first IMP intake. Prior medications can be discontinued before first administration or can be ongoing during treatment phase.
- Concomitant medications are any treatments received by the patient concomitantly with the IMPs, from the start of the first study drug dose to the last study drug dose + 30 days. A given medication can be classified both as a prior medication and as a concomitant medication. Concomitant medications do not include medications started during the post-treatment period (as defined in the observation period in Section 2.1.4).

Any technical details related to computation, dates, imputation for missing dates are described in Section 2.5.

2.1.3 Efficacy endpoints

This treatment-extension study is for investigating the long term safety and tolerability of SAR245408 and SAR245409 as a monotherapy or as part of a combination regimen, and thus there is no primary or secondary efficacy endpoint. All the efficacy variables and analyses are exploratory.

2.1.3.1 Primary efficacy endpoint(s)

Not applicable.

2.1.3.2 Secondary efficacy endpoint(s)

Not applicable.

2.1.4 Safety endpoints

Safety endpoints include AEs (including deaths), vital signs, physical examination, ophthalmologic examination, ECG, and laboratory data.

Observation period

The observation of safety data will be as follows:

- **Pre-treatment period**: the pre-treatment period is defined from the date the subjects give informed consent to the first study treatment intake in the current study.
- **Treatment period**: the treatment period is defined from the date of the first dose of any study drug up to 30 days after the last dose of any study drug.
- **Post-treatment period**: post-treatment period is defined as the time from the day after the end of treatment period to end of the study (study cut-off date) specified in the protocol.
- **On-study period**: the on-study period is defined as the time from the first dose of any study drug until the end the study.

2.1.4.1 Adverse event (AE) variables

Adverse event observation period

The AE observations are per the on-study observation periods defined above, and will include all treatment-emergent AE (TEAE), serious AE, AE of special interest (AESI), AE leading to death, AE that causes dose reduction and/or delay, AE that causes treatment interruption, AE that causes treatment discontinuation, and AE related to treatment. AEs which occur after the first dose of any study drug in this study will be reported to this study regardless of the timing of the last dose of study drug in the parental study.

Treatment-emergent AE is defined as any AE that is new, worsened in severity or becomes serious during the on treatment period.

All AEs (including serious AEs and AESI) will be coded to a lower-level term (LLT), preferred term (PT), high-level term (HLT), high-level group term (HLGT), and associated primary system organ class (SOC) using the version of Medical Dictionary for Regulatory Activities (MedDRA) currently in effect at Sanofi at the time of database. All AEs are graded using the NCI CTCAE v4.03.

Adverse events of special interests (AESI)

An AESI (serious or non-serious) is one of scientific and medical concern specific to Sanofi product or program, for which ongoing monitoring and rapid communication by the Investigator to Sanofi may be appropriate. Such events may require further investigation in order to characterize and understand them and may require follow-up beyond the planned time of study completion.

- Grade ≥2 increase in ALT (for SAR245409 only)
- Pregnancy
- Symptomatic overdose with IMP/NIMP
- Asymptomatic overdose with IMP/NIMP
- Skin toxicities ≥ Grade 2 (SAR245408 and SAR245409).

2.1.4.2 Deaths

- The death observations are per the observation periods defined above.

2.1.4.3 Laboratory safety variables

The laboratory parameters will be classified as follows:

- Hematology

  WBC (including neutrophils, lymphocytes, monocytes, eosinophils, basophils), platelet, hemoglobin, hematocrit, glycosylated hemoglobin

- Serum chemistry

  Sodium, potassium, calcium, phosphorus, magnesium, glucose, creatinine, chloride, carbon dioxide, total proteins, albumin, amylase, aspartate aminotransferase (AST), alkaline phosphatase, alanine aminotransferase (ALT), total bilirubin, blood urea nitrogen, gamma glutamyltransferase (GGT), lipase

- Coagulation

  Prothrombin time/international normalized ratio (PT/INR), activated partial thromboplastin time (aPTT)

- Urinalysis

  Proteins, glucose, bilirubin, occult blood

- Others

  hemoglobin A1c (HbA1c), serum pregnancy test (β-HCG)

2.1.4.4 Vital signs variables

Vital signs include: blood pressure (systolic and diastolic; mmHg), heart rate (bpm), temperature and weight in kg.

2.1.4.5 Electrocardiogram variables

ECG parameters include heart rate, PR, QRS, QT, corrected QTc and RR. QTc will be calculated based on Fridericia's formula ($QTcF=QT/RR^{0.33}$) if possible. Both reported and calculated QTcF will be summarized.

2.1.4.6 Other safety endpoints

Results from physical examination and ophthalmologic examination will be used for the safety analyses. Ophthalmologic examinations are required at extension visit only for subjects administered SAR245409.

2.1.5 Pharmacokinetic variables

Not applicable.

2.1.6 Pharmacodynamic/genomics endpoints

Not applicable.

2.1.7 Quality-of-life endpoints

Not applicable.

2.1.8 Health economic endpoints

Not applicable.

2.2 DISPOSITION OF PATIENTS

Safety population is defined to be all treated subjects (safety population) are those who took at least one dose of the study drug.

For patient study status, the total number of patients in each of the following categories will be presented in the clinical study report using a summary table:

- Treated patients (safety population)
- Patients who discontinued study treatment with reason for treatment discontinuation.

For all categories of patients percentages will be calculated. Reasons for treatment discontinuation will be supplied in tables giving numbers and percentages by treatment group (SAR245408 and SAR 245409).

2.2.1 Randomization and drug dispensing irregularities

Not applicable.

2.2.2 Protocol deviations

During the blinded review of the database, compliance with the protocol will be examined with regard to inclusion and exclusion criteria, treatment, prohibited therapies, and timing and availability of planned assessments. Protocol deviations will be identified by the study team before database lock and listed in the Data Review Report, including missing data and study drug discontinuations, and classified as minor, major or critical deviations.

Important protocol deviations will be derived adequately (algorithmically and/or following medical review from data listings) and determination of deviations will be finalized prior to database lock.

Following are potentially important protocol deviations to be considered:

- Inclusion/exclusion deviations
- The first dose administration date is before the date of informed consent
- Dose interruption/delay for more than 7 days that is not due to AE
- IMP symptomatic overdose
- Used prohibited medications during the study

All important deviations will be listed and summarized as appropriate.

2.3 ANALYSIS POPULATIONS

2.3.1 Efficacy populations

Efficacy population is not defined because efficacy analysis is exploratory.

2.3.1.1 Intent–to-treat/Modified intent-to-treat population

Not applicable.

2.3.2 Safety population

The safety population is defined as: All treated subjects (safety population) are those who took at least one dose of the study drug.

2.4 STATISTICAL METHODS

Continuous data will be summarized using the number of available data, mean, standard deviation (SD), median, minimum, and maximum for each treatment group. Categorical and ordinal data will be summarized using the number and percentage of patients in each treatment group.

P-values on demographic and baseline characteristic data will not be calculated

2.4.1 Demographics and baseline characteristics

Demographic characteristics and other baseline characteristics described in Section 2.1.1 will be summarized by treatment groups using descriptive statistics.

Parameters such as age, height and weight will be summarized as continuous data. Age group, sex, race, ethnicity, ECOG performance status and cancer history will be summarized as categorical/ordinal data.

2.4.2 Prior or concomitant medications (other than anticancer therapies)

The prior and concomitant medications will be presented on the safety population and summarized by treatment group (SAR245408 Monotherapy, SAR245408 Combination regimen, SAR245409 Monotherapy and SAR245409 Combination regimen)according to the WHO-DD dictionary, considering the first digit of the anatomic category (ATC) class (anatomic category) and the first 3 digits of the ATC class (therapeutic category). All ATC codes corresponding to a medication will be summarized, and patients will be counted once in each ATC category (anatomic or therapeutic) linked to the medication. Therefore patients may be counted several time for the same medication.

The table for prior and concomitant medications will be sorted by decreasing frequency of ATC followed by all other therapeutic classes based on the overall incidence across treatment groups (SAR245408 and SAR245409). In case of equal frequency regarding ATCs, alphabetical order will be used.

2.4.3 Extent of study treatment exposure

The extent of study treatment exposure will be assessed and summarized by treatment group (SAR245408 Monotherapy, SAR245408 Combination regimen, SAR245409 Monotherapy and SAR245409 Combination regimen) within the safety population (Section 2.3.2).

2.4.3.1 Extent of study treatment exposure

The extent of study treatment exposure will be assessed by the duration (in days) of IMP exposure, and actual dose information.

Duration of study drug exposure is defined as last dose date – first dose date + 1 day, regardless of unplanned intermittent discontinuations (see Section 2.5.4 for calculation in case of missing or incomplete data). The first and last study dose administration is any dose of first and last administration of study drug recorded on CRF pages.

Dose information will be assessed by the following variables:

- Total number of cycles administered
- Cumulative dose: sum of all doses administered for all cycles while the subject is on treatment
- The actual dose intensity (ADI) is defined as the cumulative dose divided by duration of study drug exposure in terms of the number of weeks on study
- The relative dose intensity is (RDI) defined as the ratio of the actual dose intensity to the planned dose intensity.
- Dose reduction

Dose information variables will be summarized descriptively (number, mean, SD, median, minimum, and maximum).

2.4.3.2 Compliance

Not applicable because no additional analysis is planned for compliance.

2.4.4 Analyses of efficacy endpoints

2.4.4.1 Analysis of primary efficacy endpoint(s)

Not applicable.

2.4.4.2 Analyses of secondary efficacy endpoints

Not applicable.

2.4.4.3 Multiplicity issues

Not applicable since no statistical test will be performed in the study.

2.4.4.4 Analyses of exploratory efficacy endpoints

The efficacy analysis will be exploratory. Listings of tumor response and subgroup efficacy analyses may be performed by parental study, monotherapy and combination therapy, when appropriate.

2.4.5 Analyses of safety data

All safety analyses will be performed on the safety population as defined in Section 2.3.2, by treatment group (SAR245408 Monotherapy, SAR245408 Combination regimen, SAR245409 Monotherapy and SAR245409 Combination regimen) unless otherwise specified, using the following common rules:

- The baseline value is defined as the last available non-missing measurement prior to the first dose of study treatment
- The analysis of the safety variables will be essentially descriptive and systematic testing is planned.

2.4.5.1 Analyses of adverse events

Generalities

The primary focus of AE reporting will be on TEAE. Pretreatment and post-treatment AEs will be described separately.

If an AE date/time of onset (occurrence, worsening, or becoming serious) is incomplete, an imputation algorithm will be used to classify the AE as pretreatment, treatment-emergent, or post-treatment. The algorithm for imputing date/time of onset will be conservative and will classify an AE as treatment-emergent unless there is definitive information to determine it is pretreatment or post-treatment.

Adverse event incidence tables will present by SOC, HLGT, HLT, and PT, sorted in alphabetical order for each treatment group, the number (n) and percentage (%) of patients experiencing an AE. Multiple occurrences of the same event in the same patient will be counted only once in the tables within a treatment phase. The denominator for computation of percentages is the safety population within each treatment group.

The grade will be taken into account in the summary. For patients with multiple occurrences of the same event, the maximum grade is used.

Analysis of all TEAEs

The following TEAE summaries will be generated for the safety population.

- Overview of TEAEs, summarizing number (%) of patients with any
  - Treatment-emergent AE
  - Grade 3-4 TEAE
  - Treatment-emergent SAE (TESAE)
  - Grade 3-4 TESAE
  - Treatment-related TEAE
  - Treatment related grade 3-4 TEAE
  - Treatment related grade3-4 TESAE
  - Treatment-emergent AE leading to death
  - Treatment-emergent AE leading to permanent treatment discontinuation
  - Treatment-emergent AE leading to dose reduction or interruption
- All TEAEs by primary SOC, HLGT, HLT, and PT, showing number (%) of patients with at least 1 TEAE sorted by the SOC internationally agreed order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order
- All TEAEs by primary SOC and PT, showing the number (%) of patients with at least 1 TEAE, sorted by the internationally agreed SOC order and by decreasing incidence of PTs within each SOC.

Analysis of all TESAE(s)

- All TESAEs by primary SOC and PT (all grade, grade 3-4), showing the number (%) of patients with at least 1 TESAE, sorted by the internationally agreed SOC order and by decreasing incidence of PTs within each SOC.
- Listing of all SAEs with onset date, grade, relationship and outcome.

Analysis of all TEAE(s) leading to treatment discontinuation

- All TEAEs leading to treatment discontinuation, by primary SOC and PT (all grade, grade 3-4), showing the number (%) of patients sorted by the internationally agreed SOC order and by decreasing incidence of PTs within each SOC.

Analysis of all TEAE(s) leading to dose modification

- All TEAEs leading to dose reduction, by primary SOC and PT, showing the number (%) of patients, sorted by the internationally agreed SOC order and by decreasing incidence of PTs within each SOC.
- All TEAEs leading to dose interruption, by primary SOC and PT, showing the number (%) of patients, sorted by the internationally agreed SOC order and by decreasing incidence of PTs within each SOC.

Analysis of AESI

- All AESIs, by PT, showing the number (%) of patients, sorted by decreasing incidence of PTs.

Analysis of TEAE(s) based on Sanofi-defined grouping method

- TEAEs based on sanofi-defined grouping method

Analysis of pretreatment and post-treatment AEs

- All post-treatment AEs by primary SOC and PT, showing the number (%) of patients with at least 1 post-treatment AE, sorted by the internationally agreed SOC order and decreasing incidence of PTs within each SOC
- Listing of all pre-treatment and post-treatment AEs.

2.4.5.2 Deaths

The following summaries of deaths will be generated for the safety population.

- Number (%) of patients who died by study period (pre-treatment, on study, post-study as appropriate)
- Listing of death
- Treatment-emergent AEs leading to death, by primary SOC and PT showing number (%) of patients sorted by internationally agreed SOC order and by decreasing incidence of PTs within each SOC. This table may be replaced by a listing if number of deaths is smaller than or equal to 5.

2.4.5.3 Analyses of laboratory variables

Clinical laboratory values will be analyzed after conversion into standard international units. International units will be used in all listings and tables. Hematological and clinical biochemistry toxicities will be assessed from selected laboratory test parameters including hematological and serum chemistry parameters. Each test results will be graded by the NCI CTCAE v4.03 as appropriate. The number of patients with abnormal laboratory tests at baseline will be presented by grade. The frequency of patients in each grade of laboratory tests during treatment will be summarized. When appropriate, the summary table will present the frequency of patients with any grade of abnormal laboratory tests.

Possible drug induced liver toxicity will be assessed using AST, ALT, ALP and total bilirubin. The frequency and percentage of subjects by worst NCI CTCAE v4.03 post-baseline grade will be presented for these parameters. Summarization and listing of possible Hy's Law cases identified with either ALT/AST >3 x ULN and total bilirubin >2 x ULN will display ALT, AST, ALP and total bilirubin.

2.4.5.4 Analyses of vital sign variables

The incidence of potentially clinically significant abnormalities (PCSA, defined in Appendix A) at any time during the TEAE period will be summarized by treatment group.

2.4.5.5 Analyses of electrocardiogram variables

The incidence of PCSAs (defined in Appendix A) at any time during the TEAE period will be summarized by treatment group irrespective of the baseline level and/or according to the following baseline status categories:

- Normal/missing
- Abnormal according to PCSA criterion or criteria

2.4.5.6 Other safety analyses

Ophthalmologic examination results will be summarized by number and percentage of subjects with abnormality by treatment group any time during the treatment-emergent period.

Abnormalities in prothrombin time/international normalized ratio, HbA1c will be described in data listings as needed.

Subgroup safety analyses will be performed by parental study, monotherapy and combination therapy, when appropriate. In addition, cumulative incidence combining parental and extension studies may be provided for TEAEs, SAEs, AESIs, etc., as appropriate.

2.4.6 Analyses of pharmacokinetic and pharmacodynamic variables

Not applicable as subjects have been exposed to the IMP in parental studies.

2.4.7 Analyses of quality of life/health economics variables

Not applicable.

2.5 DATA HANDLING CONVENTIONS

2.5.1 General conventions

Some general rules of data handling conventions and analyses are provided in this section.

Baseline variables

The baseline demographics variables were recorded in the demography CRF page. For laboratory parameters and vital signs, the baseline values will be based on the last non-missing value prior to the first study drug day in the rollover study.

2.5.2 Study day calculation

In some cases such as AEs or laboratory safety presentation, days relative to IMP would be needed, this will be defined as the date of the event – 1st IMP date in rollover study + 1 if the event occurred on or after 1st study drug date. Otherwise, it was defined as the date of event- 1st study drug date.

2.5.3 Data handling conventions for secondary efficacy variables

Not applicable.

2.5.4 Missing data

For categorical variables, patients with missing data are not included in calculations of percentages unless otherwise specified. When relevant, the number of patients with missing data is presented.

The analyses and summaries for variables with continuous scales will be based on the observed data only. The number of patients with non-missing observations will be provided.

Handling of computation of treatment duration if IMP end of treatment date is missing

For the calculation of the treatment duration, the date of the last dose of IMP is equal to the date of last administration reported on the end-of-treatment case report form page. If this date is missing, the exposure duration should be left as missing.

Handling of medication missing/partial dates

No imputation of medication start/end dates or times will be performed. If a medication date or time is missing or partially missing and it cannot be determined whether it was taken prior or concomitantly, it will be considered a prior, concomitant, and follow-up medication.

Handling of AEs with missing or partial date/time of onset

Missing or partial AE onset dates and times will be imputed so that if the partial AE onset date/time information does not indicate that the AE started prior to treatment or after the TEAE period, the AE will be classified as treatment-emergent. No imputation of AE end dates/times will be performed. These data imputations are for categorization purpose only and will not be used in listings. No imputation is planned for date/time of AE resolution.

Handling of AEs when date and time of first investigational medicinal product administration is missing

When the date and time of the first IMP administration is missing, all AEs that occurred on or after the day the subject entered into the study should be considered as TEAEs. The exposure duration should be kept as missing.

Handling of missing assessment of relationship of AEs to investigational medicinal product

If the assessment of the relationship to IMP is missing, then the relationship to IMP has to be assumed and the AE considered as such in the frequency tables of possibly related AEs, but no imputation should be done at the data level.

Handling of missing severity/grades of AEs

If the severity/grade is missing for 1 of the treatment-emergent occurrences of an AE, the maximal severity on the remaining occurrences will be considered. If the severity is missing for all the occurrences, a "missing" category will be added in the summary table as appropriate.

Handling of potentially clinically significant abnormalities

For PCSAs with 2 conditions, 1 based on a change from baseline value or a normal range and the other on a threshold value, the first condition being missing, the PCSA will be based only on the second condition.

For PCSAs based on a threshold and/or a normal range, it will be derived using the threshold if the normal range is missing.

Measurements flagged as invalid vy the laboratory will not be summarized nor will they be taken into account in the computation of PCSA values.

2.5.5 Windows for time points

Summaries by cycles focusing on laboratory data will be tabulated based on cycles as recorded in the case report form. For specific measurements such as vital signs, a window defined around the date of treatment may be considered.

2.5.6 Unscheduled visits

When appropriate, unscheduled visit measurements of laboratory data, vital signs, and ECG will be used for computation of baseline and worst values and/or grades. For the purpose of descriptive analyses of AE data, no distinction will be made between scheduled and unscheduled assessment. All data collected will be presented in the data listings. All data will be considered in the descriptive data summaries unless otherwise specified in this SAP.

2.5.7 Pooling of centers for statistical analyses

Not applicable.

2.5.8 Statistical technical issues

Not applicable.

3 INTERIM ANALYSIS

No interim analysis is planned.

4 DATABASE LOCK

The database is planned to be locked within 4 to 8 weeks from the last subject last visit.

5 SOFTWARE DOCUMENTATION

All summaries and statistical analyses will be generated using SAS version 9.2 or higher.

6 REFERENCES

Not applicable.