NOVARTIS

Clinical Development

LOU064

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CLOU064E12201

An adaptive Phase 2 randomized double-blind, placebo-controlled multi-center study to evaluate the safety and efficacy of multiple LOU064 doses in patients with moderate to severe Sjögren's Syndrome (LOUiSSe).

Commercially Confidential Information (CCI)

Statistical Analysis Plan (SAP)

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List of abbreviations

AE	Adverse Event
AUC	Area under the curve
Bid	Twice a day (for latin: “bis in die”)
CRF	Case Report Form
CSR	Clinical Study Report
DMS	Document Management System
ECG	Electrocardiogram
EoS	End of Study
EQ-5D	EuroQual 5 dimensions (Standard instrument to measure the health-related quality of life)
ESSDAI	EULAR Sjögren’s Syndrome Disease Activity Index
ESSPRI	EULAR Sjögren's Syndrome Patient Reported Index
FACIT-F	Functional Assessment of Chronic Illness Therapy-Fatigue
FAS	Full Analysis Set
IA	Interim Analyses
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MedDRA	Medical Dictionary for Drug Regulatory Affairs
MMRM	Mixed effect Model Repeat Measurement
PhGA	Physician global assessment scale
PK	Pharmacokinetics
PPS	Per-Protocol Set
PRO	Patient-reported Outcomes
RAP	Reporting & Analysis Process
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SjS	Sjögren's Syndrome
TFLs	Tables, Figures, Listings
ULN	Upper Limit of Normal
WHO	World Health Organization

1 Introduction

The purpose of this Statistical Analysis Plan (SAP) is to describe the implementation of the statistical analyses for CCI "***CLOU064E12201***" trial. This SAP will be used in executing the CSR CCI for this study.

Study protocol amendment (v04), IA SAP (v03) and full study SAP (initial) are available at the time of finalization of SAP.

1.1 Study design

This is a randomized, double-blind, placebo-controlled, multicenter, CCI study to evaluate the safety and efficacy of multiple LOU064 doses in patients with moderate to severe Sjögren's Syndrome (SjS).

Commercially Confidential Information In CCI the study, the CCI dose (100 mg LOU064) is being tested in two different treatment regimen: *qd* and *bid*, and compared to a Placebo arm. A total of approximately 72 subjects will be equally randomized to these three treatment groups for an expected sample size of 24 subjects per group.

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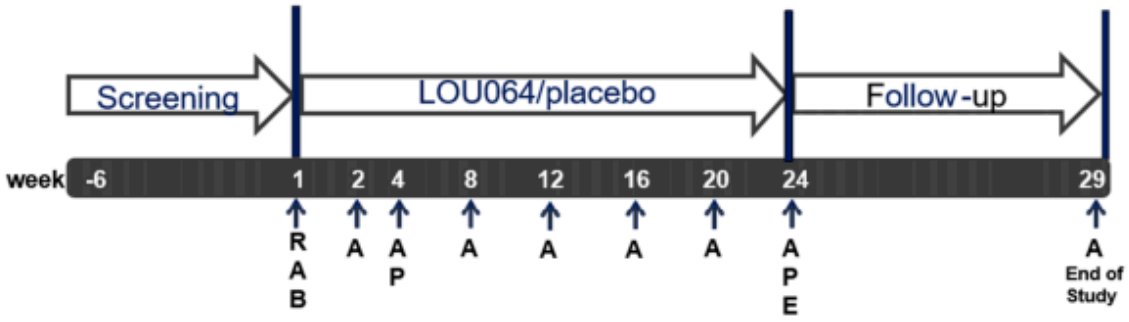
Each individual study subject will first undergo a screening prior of up to 6 weeks, a treatment duration of 24 weeks and a follow-up period of approximately 30 days post last administration of study treatment, before the End of Study (EoS) visit. The total duration for each subject in the study, including screening, will be up to 35 weeks, as shown in Figure 1-2.

Figure 1-2: Study flow chart and visit schedule



Key: **B**: Baseline; **R**: Randomization; **A:** Assessments; **P:** PK sampling; **E**: end of treatment

1.2 Study objectives, endpoints and estimands

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• Commercially Confidential Information	• Change from baseline in ESSDAI at Week 24

Secondary objective(s)	Endpoint(s) for secondary objective(s)
• To evaluate the efficacy of LOU064 compared to placebo with respect to change from baseline on patient and physician-reported outcomes over time	• Change from baseline in ESSPRI, FACIT-F ,EQ-5D and PhGA over time
• Commercially Confidential Information	• Change from baseline in ESSPRI at Week 24
• To evaluate the efficacy of LOU064 compared to placebo with respect to change from baseline in ESSDAI over time	• Change from baseline in ESSDAI over time
• To evaluate the safety and tolerability of LOU064	• Safety endpoints will include • Occurrence of treatment emergent adverse events (both serious and non-serious) during the study

Objective(s)	Endpoint(s)
	• Occurrence of treatment emergent abnorml vital signs, laboratory and ECG during the study
• To assess PK parameters of LOU064	• PK parameters AUC, Cmax, Tmax and if feasible MRT and others as needed

Exploratory objective(s)	Endpoint(s) for exploratory objective(s)

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1.2.1 Primary estimand(s) CCI

The following estimand framework is adopted for the primary analysis CCI .

- Population: The subjects in the FAS; data up to Week 24 visit are included.
- Variable of interest: Change from baseline in ESSDAI total score after 24 weeks of study drug administration. This will be defined as the Week 24 visit ESSDAI value minus the baseline ESSDAI value with negative values indicating improvement in disease status.
- Treatment of interest: The randomized treatment (LOU064 or placebo) on top of allowed concomitant medication
- Intercurrent events: Regardless whether early termination from the study, interruption of study treatment, or intensified concomitant treatment (local and systemic) has occurred
- Summary measure: Difference in mean change from baseline in ESSDAI total score at Week 24 visit between placebo and LOU064 (100mg *qd* and *bid* averaged).

2 Statistical methods

2.1 Data analysis general information

Blinded analyses using dummy treatment codes will be produced by ClinBAY statisticians and programmers according to this SAP, using SAS version 9.4 or higher (SAS Institute, Cary NC). Programs and datasets will then be provided to and run by ClinBAY Statistician and Programmer using the true treatment codes to provide the unblinded TLFs in electronic format for discussion. Details of these analyses are outlined in this document.

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Descriptive statistics (unless otherwise specified) on continuous data will include number of non-missing observations (n) mean (arithmetic), standard deviation (SD), median, Q1 (25th percentile), Q3 (75th percentile), minimum and maximum, while for categorical variables frequencies and percentages will be reported.

Graphical presentations of individual and summary data will be provided, as applicable.

- Inferential modelling for primary and key secondary variables will include
- stratification factor baseline ESSDAI score <10 or ≥10. The stratification factor baseline ESSDAI score will be based on the data in the database and not on the IRT data.

If not otherwise specified, p-values will be presented as two-sided p-values and two-sided confidence intervals will be displayed.

2.1.1 General definitions

The term ***'study treatment'*** or ***'study drug'*** refers to the Novartis investigational drug, LOU064 or placebo, dispensed by the investigators during the study. Specifically, the following grouping scheme will be used for reporting of summaries:

Placebo

LOU064 100 mg *qd*

LOU064 100 mg *bid*

Any LOU064 (i.e. LOU064 100 mg *qd* and 100 mg *bid* combined)

The term ***'date of first administration of study drug/treatment'*** refers to the date on which the study drug/treatment was given for the first time in the CLOU064E12201 study.

The term ***'date of last administration of study drug/treatment'*** refers to the date on which the study drug/treatment was given for the last time in the CLOU064E12201 study.

The term ***'study day'*** refers to the Analysis Relative Day, Relative Start Day or Relative End Day, as applicable. Day 1 is defined as the date of first dose of study drug (LOU064 or placebo). Study day is defined as the number of days since the date of first dose of study treatment (Day 1).

Therefore, for a particular date, study day will be calculated as follows:

- for dates on or after the first administration of study treatment,

  Study day = Assessment date – Date of first dose of study treatment +1

- for dates prior to the date of first administration of study treatment,

  Study day = Assessment date – Date of first dose of study treatment.

The term ***'baseline'*** refers to the last assessment performed prior to administration of the first dose of study treatment. In case the scheduled baseline assessment value is missing, the screening value if available will be used instead.

The term ***'treatment-emergent adverse event'*** refers to any adverse event (AE) started after the first dose of study treatment, or events present prior to the first dose of study treatment but increased in severity (based on preferred term (PT).

Visit windowing

For the efficacy analysis, when visit windows are used, all visits will be re-aligned, i.e. they will be mapped into one of the visit windows. For example, if the Week 4 visit of a subject is delayed and occurs on Day 46 in stead of Day 29, it will be re-aligned to visit window Week 8. In the case of major deviations from the visit schedule, or due to unscheduled visits, several assessments of a subject may fall in a particular visit window (either scheduled or unscheduled). The rules to derive the visit windows are given in the Appendix.

2.2 Analysis sets

The following analysis sets will be used in this trial:

Full Analysis Set (FAS): will include all randomized subjects, except those who were mis-randomized. Mis-randomized subjects are defined as those subjects who were mistakenly randomized into the IRT prior to the site confirming all eligibility criteria had been met and to whom no study medication was given. Mis-randomized subjects are treated as screen failures.

Following to the intent-to-treat principle, subjects will be analyzed according to the treatment assigned at randomization, but actual stratum.

Safety Set (SS): includes all subjects who received at least one dose of study drug. Subject will be analyzed according to treatment received and the stratum they actually belong to in case of misallocation of strata during the randomization process. The safety set will be used in the analysis of all safety variables.

PK Analysis Set: includes all subjects with at least one available valid (i.e. not flagged for exclusion) PK concentration measurement, who received any study drug and with no protocol deviations that impact on PK data.

2.2.1 Subgroup of interest

Subgroups of interest are listed below. These will not necessarily be applied to all analyses but used as specified in the protocol or this SAP.

- stratification factor baseline ESSDAI score <10 or ≥10

2.3 Patient disposition, demographics and other baseline characteristics

The FAS analysis set will be used for the analyses below.

2.3.1 Patient disposition

The subject disposition will be summarized by treatment group and overall and listed by treatment group and subject.

The number and percent of subjects screened, randomized, completed and discontinued from the study will be summarized with reasons for discontinuation.

2.3.2 Demographics and other baseline characteristics

Demographic (gender, age, race, ethnicity, weight, height, BMI and disease duration) and other baseline characteristics (ESSDAI and number of subjects per ESSDAI stratum (the actual stratum), ESSPRI, PhGA, EQ-5D, FACIT-F, unstimulated salivary flow, CCI use of DMARDs (split by type), and percentage of subjects with history of prior biologics treatment use) will be summarized descriptively for all subjects and by treatment group.

Relevant medical history, current medical conditions, results of laboratory screens, drug tests and any other relevant information will be listed by treatment group and subject.

2.3.3 Protocol deviations

Protocol deviations will be summarized by treatment group by protocol deviation category and protocol deviation term.

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

The safety analysis set will be used for the analyses below.

2.4.1 Study treatment / compliance

The duration of exposure to study treatment will be summarized by treatment group. In addition, the number of patients with exposure of at least certain thresholds (e.g. any exposure, 0 - <1, ≥1 - <2, ≥2 – 4, etc) will be displayed.

Duration of exposure of a treatment is defined as following:

Duration of exposure (days) = end of treatment date – date of first dose + 1

Duration of exposure (weeks) = duration of exposure (days)/7

2.4.2 Prior, concomitant and post therapies

Prior medications are defined as treatments taken and stopped prior to first dose of study treatment. Any medication given at least once between the day of first dose of randomized study treatment and the date of the last study visit will be a concomitant medication, including those which were started pre-baseline and continued into the period where study treatment is administered.

Prior and concomitant medications will be listed and summarized in separate tables. Medications will be presented in alphabetical order, by Anatomical Therapeutic Classification (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. Prohibited medications (listed in Appendix 5.7) will be summarized separately using a frequency summary table, by treatment group.

The number and percentage of subjects receiving systemic therapies for SjS as prior and concomitant background medication will be presented separately by preferred term.

In addition, a descriptive frequency table of the use of DMARDs will be presented separately by DMARDs terms.

2.5 Analysis supporting primary objective(s)

All subjects within the FAS analysis set will be included for the primary analyses.

2.5.1 Primary endpoint

The ESSDAI score is obtained by summation of the twelve domain scores. Each domain score is obtained by multiplying the activity level with the domain weight. The maximum theoretical ESSDAI score is 123. For details on ESSDAI calculation, please refer to Appendix 5.5.1.

The ESSDAI score will be listed by treatment group, subject and visit/time. Descriptive statistics will be provided by treatment group and visit/time on both raw and change from baseline values.

Spaghetti plots of ESSDAI up to Week 24 will be provided by treatment over time.

2.5.2 Statistical hypothesis, model, and method of analysis

The change from baseline in ESSDAI is assumed to be normally distributed.

A mixed effect model for repeated measurements (MMRM) will be fitted to the changes from baseline in ESSDAI for all post-baseline time points up to (and including) Week 24 visit including the following fixed factors

- treatment group (LOU064 100 mg *qd*, LOU064 100mg *bid*, placebo)
- visit
- treatment group by visit interaction

- stratification factor using baseline ESSDAI score <10 or ≥10

and baseline ESSDAI as a continuous covariate. An unstructured variance-covariance matrix will be fitted to model the dependency between repeated observations. Graphical checks on the model assumptions of normality of the data will be provided.

Both unadjusted and adjusted mean values of change from baseline will be presented along with standard error. The difference in the mean change from baseline in ESSDAI at each visit between LOU064 (*qd* and *bid* averaged) and placebo will be estimated from the model and presented together with the associated 95% confidence intervals and one-sided p-value. In addition, the difference in the mean change from baseline in ESSDAI at each visit between LOU064 dosing regiments (qd vs bid) will presented along with the associated 95% confidence intervals.

The following two criteria will be used to assess treatment efficacy

- a statistically significant decrease in ESSDAI at Week 24 on LOU064 compared to placebo (at one-sided alpha level at 0.10) and
- an estimated mean change in ESSDAI at Week 24 on LOU064 compared to placebo.

2.5.3 Handling of intercurrent events

The primary analysis will include data from participants regardless whether early termination from the study, interruption of study treatment, or intensified concomitant treatment (local and systemic) has occurred.

2.5.4 Handling of missing values not related to intercurrent event

Missing baseline value

If the baseline ESSDAI total score is missing, the screening value (if available) will be used to impute the baseline value. If neither the ESSDAI total score at baseline nor the ESSDAI total score at screening can be calculated due to missing domain scores, then the baseline ESSDAI total score is calculated using combination of baseline visit domain scores (where those are not missing) and screening domain scores (where the baseline analogs are missing) if they are available, and otherwise the baseline ESSDAI total score is set to missing.

Other missing data

For post-dose time points with missing data in one of the domains of the ESSDAI, the ESSDAI total score will be set to missing.

The MMRM utilized for the primary analysis implicitly imputes missing data under a missing at random assumption.

2.5.5 Sensitivity analyses

N/A.

2.5.6 Supplementary analyses

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2.6 Analysis supporting secondary objectives

The FAS analysis set will be used for the analysis described here.

2.6.1 Secondary endpoint(s)

Secondary endpoints of interest are the following:

- ESSPRI
    - The total score of ESSPRI is defined as the mean of the three domains (pain, fatigue and dryness). If at least one of the domains is missing, then the total score of ESSPRI will not be derived for the corresponding subject.
- FACIT-F
    - The total score of FACIT-F will be used to assess the impact on fatigue. The FACIT-F contains 13 questions, where each has a scale from 0 to 4, where 0 is for “Not at all”, 1 is for “A little bit”, 2 is for “Somewhat”, 3 is for “Quite a bit” and 4 is for “Very much”. For details on total score of FACIT-F calculation, please refer to Appendix 5.5.2.
- EQ-5D
    - The EQ-5D consists of a descriptive system and the EQ VAS scale.

      The descriptive system comprises five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. This can be used as a quantitative measure of health outcome that reflects the patient’s own judgement. The scores on these five dimensions can be presented as a health profile or can be converted to a single summary index number (utility) reflecting preferability compared to other health profiles.

      The EQ VAS records the patient’s self-rated health on a vertical visual analogue scale with 0 representing 'Worst imaginable Health State' and 100 'Best imaginable Health State'.
- PhGA

- The physician's global assessment scale is used for the Investigator to rate the disease activity of their patient using 100 mm VAS ranging from "no disease activity" (0) to "maximal disease activity" (100).

where similar estimand framework as for the primary endpoint described in Section 2.5.1, will be adopted.

All secondary endpoints may be listed by treatment group, subject and visit/time. Descriptive statistics on raw and change from baseline for the continuous data (total scores) as well as for the categorical variables (individual scores of EQ-5D) will be provided by treatment group and visit/time.

Spaghetti plots (except EQ-5D) up to Week 24 will be provided by treatment over time.

2.6.2 Statistical hypothesis, model, and method of analysis

The change from baseline for ESSPRI, FACIT-F, EQ VAS and PhGA VAS are assumed to be normally distributed.

A mixed effect model for repeated measurements (MMRM) will be fitted, similar to the primary analysis described in Section 2.5.2, to the changes from baseline for each secondary endpoint, for all post-baseline time points up to (and including) Week 24 visit including the following fixed factors

- treatment group (LOU064 100 mg *qd*, LOU064 100mg *bid*, placebo)
- visit
- treatment group by visit interaction
- stratification factor baseline ESSDAI score <10 or ≥10

and baseline corresponding secondary endpoint fitted, as a continuous covariate. An unstructured variance-covariance matrix will be fitted to model the dependency between repeated observations. Graphical checks on the model assumptions of normality of the data will be provided.

Both unadjusted and adjusted mean values of change from baseline will be presented along with standard error. The difference in the mean change from baseline of each secondary endpoint, at each visit between LOU064 (*qd* and *bid* averaged) and placebo will be estimated from the model and presented together with the associated 95% confidence intervals and one-sided p-value. In addition, the difference in the mean change from baseline of each secondary endpoint, at each visit between LOU064 dosing regiments (qd vs bid) will presented along with the associated 95% confidence intervals.

2.6.3 Handling of missing values not related to intercurrent event

Missing data will not be imputed. If missing data occurs in a domain, the corresponding total measurement will be set to missing. If a baseline assessment is missing (and there is no screening value available to replace it), the corresponding change from baseline value will be missing.

The MMRM utilized for the analysis implicitly imputes missing data under a missing at random assumption.

2.6.4 Supplementary analyses

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2.7 Analysis supporting exploratory objectives

The FAS analysis set will be used for the analysis described here.

2.7.1 Exploratory endpoint(s)

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2.7.2 Statistical hypothesis, model and method of analysis.

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2.8 Safety analyses

All subjects within the SAF analysis set will be included for the safety analyses.

2.8.1 Adverse events (AEs)

All information obtained on adverse events will be displayed by treatment group and subject.

The treatment emergent adverse events (TEAEs) will be summarized by treatment group, primary system organ class, preferred term and by maximum severity (separately). A subject with multiple adverse events within a body system is only counted once towards the total of this body system. TEAEs will be also summarized by preferred term suspected to be related to treatment.

Serious TEAEs will be also summarized by treatment group preferred term and causality.

Graphical methods (such as bar plots) will be used to present the infections by severity and treatment groups and the number of subjects with infections by severity and treatment groups.

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2.8.1.1 Adverse events of special interest / grouping of AEs

The number (and proportion) of subjects with AEs of special Interest (AESI) will be summarized by treatment group and risk level. List of AESI can be found in Appendix 5.2.1.

2.8.2 Deaths

All information obtained on deaths will be displayed by treatment group and subject.

Separate summary statistics will be provided for deaths, serious adverse events and other significant AEs leading to discontinuation, by treatment group.

2.8.3 Laboratory data

Laboratory data with any abnormal values will be listed by treatment group and subject; in case of any value outside the normal range in a parameter in a subject, all records of this parameter will be presented. Summary statistics will be provided by treatment and visit/time.

The number and percentage of subjects with newly occurring clinically notable post-baseline laboratory results will be presented for all assessments performed. Clinically notable laboratory values can be found in Appendix 5.3.

Newly occurring liver enzyme abnormalities will be tabulated by treatment and timepoint.

Spaghetti plots will be provided by treatment group and visit/time.

2.8.4 Other safety data

2.8.4.1 ECG and cardiac imaging data

Triplicate measurements on ECG are scheduled for some visits. For numeric measurements, the mean of the triplicate measurements will be used.

PR, QRS, QT, QTcF, and RR intervals will be obtained from 12-lead ECGs for each subject during the study. ECG values with any abnormal values will be listed by treatment group and subject.

Summary statistics will be provided by visit/time by treatment group. In addition the number and percentage of subjects with clinically notable post-baseline ECG abnormalities on QT and QTcF intervals and with noteworthy PR, QRS and Heart Rate interval or changes from baseline will be presented. Details in regards to notable intervals can be found in Appendix 5.3.

Spaghetti plots will be provided by treatment group and visit/time.

2.8.4.2 Vital signs

Vital signs values outside normal range will be listed by treatment group and subject.

Summary statistics will be provided by visit/time by treatment group. The number and percentage of subjects with clinically notable post-baseline vital signs will be presented. Details in regards to notable intervals can be found in Appendix 5.3.

Spaghetti plots will be provided by treatment group and visit/time.

2.9 Pharmacokinetic endpoints

All subjects within the PK analysis set will be included for the PK analyses.

LOU064 plasma concentration data will be listed by treatment group, subject and visit/sampling time point. Descriptive summary statistics for PK concentration data will be provided by treatment group and sampling time point, including the frequency (n, %) of concentrations below the lower limit of quantification (LLOQ) and reported as zero. Summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum and maximum. Commercially Confidential Information

PK parameters will be listed by treatment group, visit/time and subject. Descriptive summary statistics for pharmakokinetic parameters will be provided by treatment. Summary statistics include mean (arithmetic and geometric), SD, and CV (arithmetic and geometric), median, minimum, and maximum. An exception to this is Tmax where median, minimum, and maximum will be presented.

Arithmetic mean (SD) and geometric mean (95% CI) plasma concentration data will be plotted across time, with separate line types for treatment.

Table 2-1 Non-compartmental pharmacokinetic parameters

AUClast and AUC0-4h	The AUC from time zero to the last measurable concentration sampling time (t_{last}) (ng x h/mL). As the proposed sampling time is up to 4 hr AUClast will be equivalent to AUC0-4 hr if blood concentrations can be measured up to 4 hr
AUC_{tau}	The AUC calculated/extrapolated to the end of a dosing interval (tau) at steady-state (ng x h/mL).
C_{max}	The maximum (peak) observed blood, or other body fluid drug concentration after single dose administration (ng/mL)
T_{max}	The time to reach maximum (peak) blood or other body fluid drug concentration after single dose administration (h)
MRT	Mean residence time of the analyte in the central compartment (h)
$T_{1/2}$ if possible	The elimination half-life (if calculation is feasible)

The PK profile of LOU064 will be characterized but not limited to the PK parameters listed above.

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2.11 Patient-reported outcomes

N/A.

2.12 Biomarkers

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2.13 Interim analysis

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3 Sample size calculation

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4 Change to protocol specified analyses

No changes from protocol specified analysis were made.

5 Appendix

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