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Biostatistics & Statistical Programming /
Novartis Institutes for BioMedical Research

QBW251

CQBW251C12201
ClinicalTrials.gov Identifier: NCT04396366

A randomized, patient- and investigator-blinded, placebo-controlled, parallel group study to assess the safety, tolerability, pharmacokinetics and pharmacodynamics of QBW251 in patients with bronchiectasis

Statistical Analysis Plan (SAP)

Author(s):	Personal Protected Data
Document type:	SAP Documentation – NIBR
Document status:	Final
Release date:	14-Jul-2023
Number of pages:	18

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Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
04-Feb-2021	**Prior to DB lock**	**Creation of initial version**	**N/A - First version**	**NA**
14-Jul-2023	**SAP Amendment**	**Amend for protocol amendment 03 and study termination on 15-JUN-2022**		**Section 1,2,4,5,6,7**

Table of contents

List of tables

1 Introduction

1.1 Scope of document

The reporting and analysis process (RAP) documents contain detailed information to aid the production of Statistics & Programming input into the Clinical Study Report (CSR) for trial **"*CQBW251C12201*".**

The statistical analysis plan (SAP) describes the implementation of the statistical analysis planned in the protocol.

1.2 Study reference documentation

The SAP is developed based on the study protocol v03 dated of 02-Dec-2022.

1.3 Study objectives

Table 1-1 Objectives and related endpoints

Objective(s)	**Endpoint(s)**
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To assess the change on sputum bacterial colonization	• Change from baseline in bacterial load of colony forming units (CFU/mL, 1 CFU/mL = 1 CFU/g) of potentially pathogenic microorganisms in spontaneous sputum with QBW251 compared to placebo at week 12
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To assess the change of QBW251 compared to placebo on sputum bacterial clearance	• Proportion of subjects with absence of any CFU of potentially pathogenic bacteria in sputum culture after 12 weeks of treatment
• To assess the change on patient reported outcomes on bronchiectasis symptom assessment	• Changes from baseline in Quality of Life Questionnaire for Bronchiectasis (QOL-B) (Respiratory symptoms domain) after 12 weeks of treatment.
• To assess the change of fibrinogen plasma concentration	• Change from baseline in fibrinogen plasma concentration after 12 weeks of treatment
• To assess the change in rescue medication use	• Change from baseline in rescue medication use (salbutamol/albuterol) after 12 weeks of treatment.
• To assess the change on lung function.	• Changes from baseline in pre-bronchodilator FEV1, FVC after 12

Objective(s)	Endpoint(s)
	weeks treatment, measured by spirometry
• To assess the change in airway structure and function	• Change from baseline in airway wall and lumen parameters along with extent of global and regional air trapping after 12 weeks of treatment, as measured by HRCT.
• To assess the pharmacokinetics of QBW251 in patients with bronchiectasis	• Assessment of drug exposure (Cmax, AUC) and other PK parameters when feasible on Days 1 and 28 (for a subset of patients at selected sites). Pre- and post- dose concentration (Ctrough and Cmax) on Days 1, 28, 56 and 84 (for all patients).
• To assess the safety and tolerability of QBW251 in patients with bronchiectasis	• All safety endpoints (including adverse events, vital signs, ECG, and safety laboratory changes) during the study
Exploratory objective(s)	**Endpoint(s) for exploratory objective(s)**
• To examine the change from baseline on sputum bacterial colonization after 12 weeks of treatment with QBW251 compared to placebo and at times of potential exacerbation for assessments of pathogens and bacterial load.	• Change from baseline in sputum bacterial colonization after 12 weeks of treatment measured by 16S rRNA PCR

• To assess the change on patient reported outcome	• Changes from baseline in the following PRO after 12 weeks of treatment
	  • St. George's Respiratory Questionnaire (SGRQ)
	  • Euro Quality of Life-5 Dimensions-3 level (EQ-5D-3L)

• To explore the effect of QBW251 on additional HRCT outcome measures	• Change from baseline in HRCT endpoints for distribution of mucus (whole lung and regional), • airway-artery assessments, and scoring after 12 weeks of treatment
• To assess the effect of QBW251 on bronchiectasis exacerbation	• Time to first event, • Annualized rate of exacerbations as defined by EXACT-PRO questionnaire

Objective(s)	Endpoint(s)

• To assess the change on biomarkers of inflammation	• Changes from baseline in blood and sputum after 12 weeks of treatment in markers that may include, but are not limited to:
	  • Serum hsCRP
	  • Blood inflammatory cells e.g. neutrophils, eosinophils
	  • Sputum inflammatory proteins e.g. IL-6, IL-8
	  • Serum protein signatures measured by SomaScan (only measured if primary endpoint is positive)

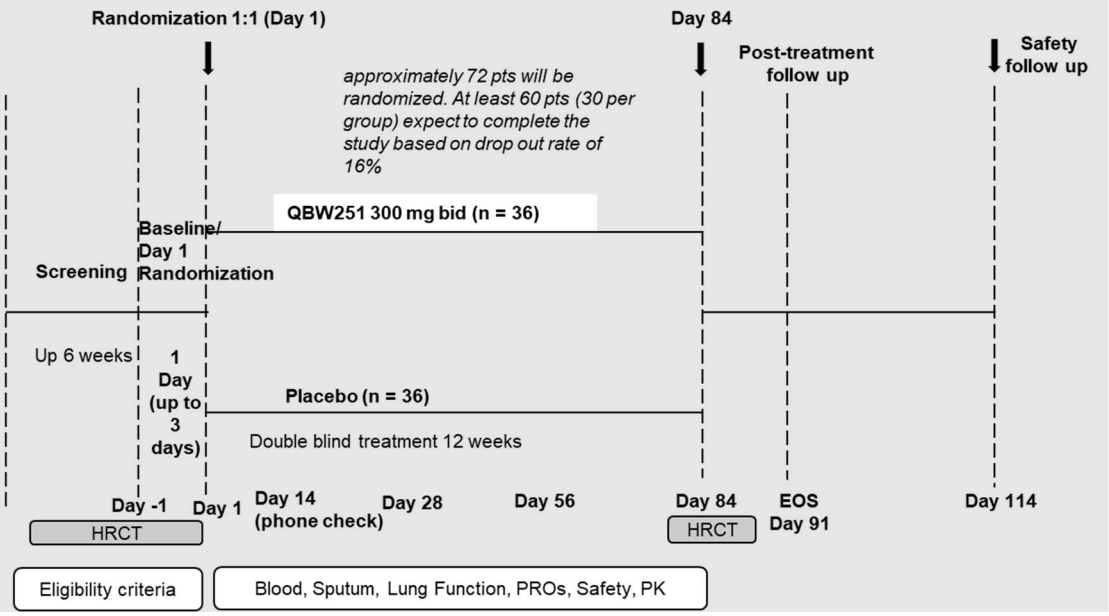
• To perform assessment of bacterial species profile in sputum	• Sputum samples will be biobanked for potential exploration of sputum bacterial profile measured by 16s rRNA gene sequencing
• To perform DNA assessments to examine whether individual genetic variation in genes relating to drug metabolism and transportation or individual genetic variations in CFTR genes or other disease-relevant genetic pathways confer differential response to QBW251 treatment or correlate with disease severity	• Genomic analysis in correlation with exposure to QBW251 or response to QBW251 or disease severity. DNA will be biobanked for potential future analysis of CFTR mutations and for genomic analysis

1.4 Study design and treatment

This is a randomized, patient- and investigator-blinded, placebo-controlled, parallel-group study investigating the preliminary efficacy and safety of QBW251 administered orally for 12 weeks in participants with bronchiectasis. Approximately 72 participants will be randomized in a 1:1 ratio to receive either QBW251 300 mg b.i.d. or placebo in order to achieve 60 participants who complete the treatment period based on the assumption of a 16% dropout rate. The sample size assumptions will be reviewed in an interim analysis in a blinded manner when approximately 14 participants complete the treatment period.

The study consists of the following periods: Screening, baseline/Day 1, treatment period, and end of study assessments (EOS) visit followed by an additional post-treatment safety follow up via phone call. The total duration for each patient in the study is up to approximately 19 weeks.

The study design is described in Figure 3-1 below.



2 First interpretable results (FIR)

First interpretable results (FIR) will not be provided for this trial due to study termination.

3 Interim analyses

A blinded interim analysis is planned for this study when approximately 14 participants will complete Day 84 post treatment assessment. The purpose of this IA is to confirm sample size assumptions while assessing the variability in bacterial colonization of PPMs in this population. If the variability is larger than the variability assumed originally, a re-estimation/adjustment of the sample size may be applied for the rest of the study.

There will be no pause in enrollment at the time of interim analysis, and subjects may continue to be enrolled until the interim analysis is complete.

All enrolled subjects and the participating investigators will remain blinded during the entire study. Only the sponsor may be unblinded at the interim as necessary.

4 Analysis sets

For all analysis sets, subjects will be analyzed according to the study treatment(s) received.

No screen failure data will be presented.

The Safety Set includes all subjects who received at least one dose of study treatment. The safety set will be used in the analysis of all safety variables.

The PK analysis set will include 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 affect PK data. The PK serial sub-group set will include all subjects

with at least one evaluable drug concentration data sample and who consented to participate in the PK serial sub-group.

The PD analysis set will include all subjects with available PD data at both baseline and at least one post-baseline assessment that are not affected by any protocol deviations.

The analysis sets and protocol deviation codes are related as follows:

Table 4-1 Protocol deviation codes and analysis sets

Category Deviation code	Text description of deviation	Data exclusion
Subjects are excluded from Safety analysis in case of these PDs:		**Exclude subject from Safety analysis set**
INCL01	**Informed consent was not obtained before any assessment**	**Y**
Subjects are excluded from PK analysis in case of these PDs:		**Exclude subject from PK analysis set**
INCL01	**Informed consent was not obtained before any assessment**	Y
OTH07	**Patient received incorrect dose**	Y
Subjects are excluded from PD analysis in case of these PDs:		**Exclude subject from PD analysis sets**
INCL01	**Informed consent was not obtained before any assessment**	**Y**

5 Statistical methods for Pharmacokinetic (PK) parameters

5.1 Variables

Summary of PK parameters of all participants in the PK set will include pre-dose concentration Ctrough and Cmax on Day 1, Day 28, Day 56 and Day 84. Summary of PK parameters for participants in the PK serial sub-group will include Cmax, Cmin, Tmax, AUClast, AUC0-12h, and T1/2, eff if feasible on Day 1 and Day 28.

5.2 Descriptive analyses

Plasma concentration data for QBW251 will be listed by treatment, subject and sampling time point. Both scheduled and actual times will be included.

Descriptive statistics of QBW251 plasma concentration data will be provided by treatment and visit/sampling time point, including the number and frequency (n, %) of concentrations below the lower limit of quantification (LLOQ), which will be summarized as zero and reported as BLQ in the listing.

Summary statistics of QBW251 plasma concentration data will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum, and maximum. If zero values occur for the values being summarized due to concentrations below the LLOQ, no geometric mean will be calculated.

All PK parameters of QBW251 will be listed by treatment and subject. Summary statistics will be displayed by treatment, using the same summary statistics as for the PK concentrations. An exception to this is Tmax, where only median, minimum and maximum will be presented.

All summaries will be based on the PK analysis set. For all listings displaying individual data, all subjects will be shown, but subjects not in the PK population and values marked as unreliable by the PK Scientist will be flagged.

In addition, the data from this study may be combined with data from other studies and analyzed by means of population modeling and reported separately.

5.3 Statistical model, assumptions and hypotheses

No model-based statistical analysis will be performed for PK.

6 Statistical methods for Pharmacodynamic (PD) parameters

6.1 Primary objective

The primary objective of the study is to assess the change from baseline of QBW251 compared to placebo on the total number of bacteria over all strains at week 12. The PD Analysis Set will be used for analysis of the primary variable.

6.1.1 Variables

The primary variable of the study is the change from baseline in bacterial load as measured by the number of colony forming units (CFU) of potentially pathogenic microorganisms in sputum at week 12. As bacterial load has been found to follow a log-normal distribution, the analysis will be based on log10-transformed scale.

6.1.2 Descriptive analysis

The baseline CFU (on log10-transformed scale) of potentially pathogenic microorganisms in spontaneous sputum is defined as the bacterial load collected at baseline (on log10-transfromed scale). “No growth” means there is no growth from the sputum specimen for that visit. The maximum measurable CFU from lab culture will be set as 600,000,000. Thus, any CFU data that is higher than 600,000,000 will be considered as 600,000,000 in reporting.

In order to be included in the sputum analysis, a subject must provide a sufficient sputum sample at screening, and/or at baseline and at least one post-baseline visit.

Summary statistics will be provided by treatment group and visit for the primary variable and will include mean, standard deviation (SD), coefficient of variation (CV), median, minimum and maximum.

6.1.3 Statistical model, assumptions and hypotheses,

The planned Bayesian repeated measures model will not be performed due to study termination and in absence of informative data, the original PoC criteria will not be evaluated as well.

The primary analysis will include all available data from subjects in the PD analysis set.

Differences between treatment groups (QBW251 versus placebo) for change from baseline in CFU counts (on log10-transformed scale) will be analyzed using a mixed model for repeated measurements (MMRM). The analysis will be carried out using SAS proc mixed procedure with Unstructured covariance structure, with treatment group and visit as fixed effects, baseline log (CFU count), status of macrolides use at screening as covariates, adjusting for effect of treatment*visit, baseline value*visit. Contrasts for treatment differences will be provided together with two-sided 80% confidence intervals.

6.1.3.1 Handling of missing values/censoring/discontinuations

The CFU counts assessed within 2 weeks after bronchiectasis exacerbations or during or after last dose of antibiotics will not be included in the primary analysis. This is because of the potential confounding effect were expected from the use of antibiotics.

However, the CFU counts at the following visits (if there is no antibiotics use and no bronchiectasis exacerbation) are assumed not to be confounded and will be included in the primary analysis.

Efficacy data collected during intake of rescue medication will be used for analysis, since no confounding effect is expected from the use of rescue medication. Of note, on days of rescue medication intake participants are instructed to fill in the e-diary for that day prior to intake of rescue medication.

Missing on-treatment data related to the primary endpoint will not be explicitly imputed. The repeated measures analysis includes all available information in terms of measurements at all times. If endpoint measurements are missing at random, an analysis of the available data provides consistent estimates of model parameters.

6.1.3.2 Graphical presentation of results

The individual participant total bacterial load of CFU of potentially pathogenic microorganisms in sputum will be presented.

6.1.4 Supportive analysis

The planned supportive/supplementary analysis will not be performed due to study termination.

6.2 Secondary objectives

6.2.1 Variables

The secondary pharmacodynamics and efficacy endpoints are as follows:

- Proportion of subjects with absence of any CFU of potentially pathogenic bacteria in sputum culture.
- Changes from baseline in the Quality of life Questionnaire for Bronchiectasis (QOL-B) (Respiratory symptoms domain).
- Change from baseline in fibrinogen plasma concentration.
- Change from baseline in rescue medication use (salbutamol/albuterol)
- Change from baseline in pre- bronchodilator FEV1, FVC measured by spirometry.
- Change from baseline in airway wall and lumen parameters along with extent of global and

regional air trapping, as measured by HRCT.

6.2.2 Descriptive analyses

Summary statistics of change from baseline for each secondary efficacy endpoint will be provided by treatment group and visit for all secondary endpoints, if data allows.

6.2.1 Statistical model, assumptions and hypotheses

The modeling for secondary pharmacodynamics objectives planned as per protocol will not be performed due to the study termination.

The secondary objective analysis will include all available data from subjects in the PD analysis set.

Baseline secondary efficacy parameters (QOL-B, fibrinogen, FEV1, FVC) is defined as the measurement taken prior to the first dose of study drug (Day 1). If this assessment is missing (or is not confirmed to be pre-dose), then the screening assessment will be considered as baseline.

For spirometry data, only "acceptable" spirometry data will be included for analysis. In case 2 pre-dose spirometry assessments at -45min and -15min are performed, the first attempt (-45min) will be used for analysis if it's acceptable; if the first attempt is not acceptable, then the second attempt (-15min) will be used; if the second attempt is also not acceptable, then there would be no data available for that timepoint.

Changes from baseline in the Quality of life Questionnaire for Bronchiectasis (QOL-B) (Respiratory symptoms domain)

For Quality of Life Questionnaire for Bronchiectasis (QOL-B), the summary statistics for change from baseline in Respiratory Symptoms scale will be reported by treatment group and visit. The Respiratory Symptoms scale scores, with higher scores representing fewer symptoms or better functioning. Refer to Table 6-1 for details of response value and the corresponding scores for QOL-B Questionnaire (Respiratory symptoms domain) during reporting.

Table 6-1 Scoring algorithm for QOL-B Questionnaire (Respiratory symptoms domain)

QUESTION NUMBER	QUESTION SHORT NAME	QUESTION NAME	OPTIONS(CHAR)	OPTIONS(NUMERIC)
29	BQOL129	Congestion in Chest	A lot	1
			A moderate amount	2
			A little	3
			None at all	4
30	BQOL130	Coughing During Day Time	A lot	1
			A moderate amount	2
			A little	3
			None at all	4

31	BQOL131	Cough Up Sputum	A lot	1
			A moderate amount	2
			A little	3
			None at all	4
32	BQOL132	Sputum Observation	Clear	5
			Clear to yellow	4
			Yellowish-green	3
			Brownish-dark	2
			Green with traces of blood	1
			Don't know	0
33	BQOL133	Shortness Breath When Active	Always	1
			Often	2
			Sometimes	3
			Never	4
34	BQOL134	Have You Had Wheezing	Always	1
			Often	2
			Sometimes	3
			Never	4
35	BQOL135	Have You Had Chest Pain?	Always	1
			Often	2
			Sometimes	3
			Never	4
36	BQOL136	Shortness of Breath When Walking	Always	1
			Often	2
			Sometimes	3
			Never	4
37	BQOL137	Woken Up Due to Coughing	Always	1
			Often	2
			Sometimes	3
			Never	4
37	BQOL137	Woken Up Due to Coughing	Always	1
			Often	2
			Sometimes	3
			Never	4

Proportion of subjects with absence of any CFU of potentially pathogenic bacteria in sputum culture.

The number and percentage for participants with no CFU in sputum will be tabulated by treatment arm and visit. Percentages will be based on the number of participants for whom microbiology results exist per visit.

Change from baseline in rescue medication use (salbutamol/albuterol)

Baseline rescue medication use is defined as the average number of puffs per day in the screening period and the morning record at Day 1. All days with data will be used for calculating the baseline value.
The total number of puffs of rescue medication will be divided by the total number of (full or half) days with non-missing rescue data to derive the mean daily number of puffs of rescue medication taken for the patient for each given visit interval. If the number of puffs is missing for part of the day (either morning or evening) then a half day will be used in the denominator. No imputation will be used for missing rescue therapy. Any values >48 for the number of puffs of rescue medication in a 12 hour period will be set to missing. These high numbers are not realistic and could impact the analysis.

If a participant has only 0 to 6 days of data recorded, the baseline will be set to missing. Participants must have at least 7 days of rescue medication data recorded to have a baseline level calculated

The post-baseline treatment period is defined as the period from the evening record of Day 1 up to the morning assessment following the day of the last dose of double-blind treatment. Missing diary data will not be imputed. For the derivations of on-treatment mean weekly and mean monthly number of puffs, only values from Day 1 up to the date of last dose of double-blind treatment will be considered.

The daily number of puffs will be averaged for each week (Week1, Week2, etc). A patient needs to have at least 4 days of data in any week in order for the mean score to be calculated.

Monthly means over a 4-week period will also be calculated. A patient needs to have at least 3 weekly means in that month in order for the monthly mean to be calculated. Mean daily number of puffs will be summarized descriptively by monthly interval.

Changes from Baseline in airway wall and lumen parameters along with extent of global and regional air trapping, as measured by HRCT

The baseline is defined as the HRCT performed after participants have passed all the other screening criteria and prior to randomization. Summary statistics of change from baseline in airway wall and lumen parameters will be provided. Global and region air trapping changes will also be summarized.
Listings for participants' air trapping measured by HRCT will also be provided.

6.2.2 PK/PD relationships

The exploratory analysis of the relationship between pharmacokinetic and pharmacodynamic measures will not be performed because of low sample size resulting from study termination.

6.3 Exploratory objectives

The planned analyses for bronchiectasis exacerbation will not be performed due to study termination.

6.3.1 Variables

The exploratory endpoints are:

- Change from baseline in sputum bacterial colonization measured by 16S rRNA PCR.
- Changes from baseline in SGRQ, and EQ-5D-3L
- Change from baseline in HRCT endpoints for distribution of mucus (whole lung and regional)
- Change from baseline of markers in blood and sputum including:
  - serum hsCRP
  - blood inflammatory cells (e.g. neutrophils, eosinophils)
  - sputum inflammatory proteins (e.g. IL-6, IL-8)

6.3.2 Descriptive analyses

Summary statistics will be provided by treatment group and visit for all exploratory endpoints, if data allows.

7 Statistical methods for safety and tolerability data

For all safety analyses, the safety set will be used. All listings and tables will be presented by treatment group.

Safety summaries include only data from the on-treatment period with the exception of baseline data which will also be summarized where appropriate (e.g. change from baseline summaries). In addition, a separate summary for death including on treatment and post treatment deaths will be provided. In particular, summary tables for adverse events (AEs) will summarize only on-treatment events, with a start date during the on-treatment period (treatment-emergent AEs).

7.1 Variables

Adverse events, vital signs (blood pressure, pulse rate, body temperature), ECG intervals, laboratory measurements, as well as subject demographics, baseline characteristics, and treatment information.

7.2 Descriptive analyses

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented. Day 1 is defined as the date of first study drug administration. Study day is calculated relative to Day 1.

Subject demographics and other baseline characteristics

Demographic, including age, sex, race, ethnicity, and other baseline data including, baseline height, baseline weight, baseline BMI, past medical history including smoking history, history of bronchiectasis exacerbations and current medical conditions including allergies present

before signing the informed consent will be summarized descriptively by treatment group for the Safety set, if data allows.
BMI (kg/m^2) = Weight (kg) / [Height (m) * Height (m)]

All data for background and demographic variables will be listed by treatment group and subject. Summary statistics will be provided by treatment group. Continuous variables will be summarized using descriptive statistics (mean, SD, median, minimum and maximum) and categorical variables will be summarized in terms of the number and percentage of subjects in each category.
Medical history was coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology. History/conditions will be summarized for the safety analysis set, by primary system organ class and preferred term, and overall. Verbatim recorded history/conditions will be listed together with the coded terms, date of diagnosis/surgery and whether the problem was active at the time of first study drug dose.

Subject disposition

A disposition summary will be presented for all subjects in the safety analysis set. This table will present the number and percentage of subjects who randomized, completed and discontinued early, along with the reasons for early discontinuation.

The number and percentage of subjects in each analysis set will be summarized by treatment group. All analysis set results will be presented in listings by subject. A separate listing of all subjects excluded from any analysis set and the reasons for their exclusion will be provided.

All study completion data will be listed by subject.

Treatment

Data for study drug administration, rescue medication and concomitant therapies will be listed by treatment group and subject.

Summary statistics will be provided for the duration of exposure to study treatment using the safety analysis set.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed and summarized according to the Anatomical Therapeutic Chemical (ATC) classification system, by treatment group.

Vital signs

Records taken at baseline visit will be considered as baseline value. Otherwise, records take at Day 1 will be considered as baseline value. Vital sign data for all subjects will be listed by treatment group, subject and visit/time, and abnormalities will be flagged. The normal range of vital signs are:

- Oral body temperature: 36.5-37.5 °C
- Systolic blood pressure: 90-140 mm Hg
- Diastolic blood pressure: 50-90 mm Hg
- Pulse rate: 50 - 100 bpmD

ECG evaluations

ECG data will be collected at scheduled visits in single ECG or triplicate ECGs. If triplicate ECGs are performed, then average of the non-missing values of the 3 measurements will be used in the analysis. ECG data will be listed by treatment, subject and visit/time.
For ECGs, a notable QTc value is defined as a QTcF (Fridericia) interval of ≥ 450 msec for males or ≥ 460 msec for females.

Clinical laboratory evaluations

All laboratory data will be listed by treatment, subject, and visit/time, if normal ranges are available, abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time.

Adverse events

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

Summary tables for adverse events (AEs) will summarize only on-treatment events, with a start date during the on-treatment period (treatment-emergent AEs).

The on-treatment period lasts from the date of first administration of study treatment to 1 week after the last actual administration of any study treatment.

The number (and percentage) of subjects with treatment emergent adverse events (events started after the first dose of study medication or events present prior to start of double-blind treatment but increased in severity based on preferred term) will be summarized by treatment, primary system organ class, preferred term and maximum severity.

Separate summaries will be provided for study medication related adverse events, death including on treatment and post treatment (30 days after the last actual administration of study treatment), serious adverse events, other significant adverse events leading to discontinuation.

A subject with multiple adverse events within a primary system organ class is only counted once towards the total of the primary system organ class. Listings will be provided for all AEs, SAEs and fatal AEs.

For the legal requirements of ClinicalTrials.gov and EudraCT, two required tables on treatment emergent adverse events which are not serious adverse events with an incidence greater than 5% and on-treatment emergent 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.