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QBW251

CQBW251B2202

ClinicalTrials.gov Identifier: NCT04268823

A randomized, subjects- and investigator blinded, placebo - controlled parallel group study to assess the mode-of-action of QBW251 in subjects with Chronic Obstructive Lung disease (COPD).

Statistical Analysis Plan (SAP)

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List of abbreviations

AE	Adverse Event
b.i.d.	twice a day
CASA-Q	Cough and Sputum Assessment Questionnaire
CAT	COPD Assessment Test
CFU	Colony Forming Units
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CV	coefficient of variation
DMS	Document Management System
eCRF	Electronic Case Report Form
EQ-5D-3L	Euro Quality of Life-5 Dimensions-3 Level
FEV1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HRCT	High Resolution Computed Tomography
IA	Interim Analyses
ICS	Inhaled Corticosteroids
LABA	Long-Acting β2-Agonists
LAMA	Long-Acting Muscarinic Antagonists
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Drug Regulatory Affairs
PD	Pharmacodynamics
PK	Pharmacokinetics
PT	Preferred Term
RAP	Reporting & Analysis Process
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SD	Standard deviation
SE	Standard error
SOC	System Organ Class
TFLs	Tables, Figures, Listings
ULOQ	Upper limit of quantification
WHO	World Health Organization

1 Introduction

1.1 Scope of document

The RAP documents contain detailed information to aid the production of Statistics & Programming input into the Clinical Study Report (CSR) for trial ***"CQBW251B2202".***

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

1.2 Study reference documentation

1. Clinical Study Protocol version 02 dated 25-Aug-2021
2. eCRF version 3.0 dated 03-Jul-2020.

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 effect of QBW251 compared to placebo after 12 weeks of treatment on fibrinogen plasma concentration.	• Change from baseline in fibrinogen plasma concentration.
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• **Key secondary objective:** To assess the effect of QBW251 compared to placebo after 12 weeks of treatment on sputum bacterial load.	• Change from baseline in total bacteria load of colony forming units (CFU/mL) of potentially pathogenic microorganisms in sputum.
• **Secondary objectives:** To assess the effect of QBW251 compared to placebo after 12 weeks of treatment on airway structure and function.	• Change from baseline in airway wall and lumen parameters along with extent of global and regional air trapping, as measured by HRCT.
• To assess the effect of QBW251 compared to placebo after 12 weeks of treatment on COPD subjectsubjects symptom burden changes.	• Change from baseline in COPD Assessment Test (CAT) questionnaire.
• To assess the effect of QBW251 compared to placebo after 12 weeks of treatment on health status.	• Changes from baseline in the Euro Quality of Life-5 Dimensions-3 Level (EQ-5D-3L) questionnaire.
• To assess the effect of QBW251 compared to placebo after 12 weeks of treatment on changes in health-related quality of life.	• Change from baseline in St. George's Respiratory Questionnaire (SGRQ) total and domain scores.
• To assess the effect of QBW251 compared to placebo after 12 weeks of treatment on COPD exacerbations.	• Time to first COPD exacerbation • Proportion of subjectsubjects with exacerbations • Annualized rate of exacerbations as defined by EXACT-PRO questionnaire

Objective(s)	Endpoint(s)
• To assess the effect of QBW251 compared to placebo after 12 weeks of treatment on clinical symptoms, cough and sputum.	• Change from baseline in Cough and Sputum Assessment Questionnaire (CASA-Q) domain scores.
• To assess the safety and tolerability of QBW251 in subjects with COPD.	• ECG intervals • Vital signs • Standard clinical laboratory evaluations (hematology, blood chemistry, and urinalysis) • Adverse events
• To assess the effect of QBW251 compared to placebo during and after 12 weeks of treatment on pharmacokinetics.	• Assessment of drug exposure (Ctrough collected at pre-dose and Cmax at post-dose) on Day 1, Day 28, Day 56 and Day 84. Cmax and AUC on Day 1 and Day 28 in subset of subject population (serial samplings up to 8hr).
• To assess the effect of QBW251 compared to placebo after 12 weeks of treatment on spirometry.	• Change from baseline in trough FEV1, FVC, and FEV1/FVC.
Exploratory objective(s)	**Endpoint(s) for exploratory objective(s)**

1.4 Study design and treatment

This is a randomized, subject and investigator blinded, parallel-group, placebo-controlled study investigating the mode of action (MoA) and preliminary efficacy and safety of QBW251 administered orally twice daily (b.i.d.) for 12 weeks in subjects with moderate to very severe COPD (GOLD 2-4). Approximately 100 subjects will be randomized in a 1:1 ratio to either QBW251 or placebo. Based on the assumption of a 15% drop-out rate (% drop out based on completed proof-of-concept COPD study CQBW251X2201), it is expected to have approximately 84 subjects to complete the study. Interim analysis plans were discontinued with strategic decision to stop this trial prior to completion.

The study consists of the following periods (Figure 1-1) : Screening, Baseline / Day 1, Treatment, and End of the Study followed by an additional post-treatment safety phone call. The total duration for each subject in the study is up to approximately 19 weeks.

Figure 1-1 Study design

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Therefore, CQBW251B2202 study drug dose arms are:

- QBW251 CCI
- Placebo b.i.d

2 First interpretable results (FIR)

First interpretable results (FIR) will be provided for this trial.

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3 Interim analyses

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4 Statistical methods: 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 analysis set will include all subjects that received any study drug.

The pharmacokinetic (PK) analysis set will include all subjects with at least one available valid (i.e. not flagged for exclusion) PK concentration measurement, who received QBW251 and experienced no protocol deviations with relevant impact on PK data.

The pharmacodynamic (PD) analysis set will include all subjects with PD data at both baseline and at least one post-baseline assessment which 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

Category Deviation code	Text description of deviation	Data exclusion
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
TRT04	Subject 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

If updates to this table are needed, an amendment to the SAP needs to be implemented prior to DBL.

5 Statistical methods for Pharmacokinetic (PK) parameters

5.1 Variables

The Cmax, Tmax, AUClast, AUC0-8h, T1/2 PK parameters will be derived for QBW251 plasma concentration data for Day 1, Day 28 if feasible in subset of subjects with extensive PK collection.

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 will be provided by treatment and scheduled 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. Concentrations will be expressed in mass per volume unit.

Summary statistics will include mean (arithmetic and geometric), standard deviation (SD), coefficient of variation (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.

Arithmetic mean +/- standard deviations plot of QBW251 plasma concentration will be presented by treatment and using schedule sampling times for Day 1 and 28. An overlaying individual plot will be presented by treatment.

A box plot will be presented by treatment for pre-dose concentrations on Day 1, Day 28, Day 56 and Day 84.

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, including figures of means. For all listings and figures 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.

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 on fibrinogen plasma concentration levels after 12 weeks of treatment with QBW251 compared to placebo.

6.1.1 Variables

The primary estimand, defined below, quantifies a hypothetical effect of 12 weeks treatment that would have been observed if all subjects remained on their treatment for 12 weeks:

- **Target population:** subjects with moderate to severe COPD with features of chronic bronchitis and a history of exacerbations and treated with any of the combinations of LABA, LAMA, or ICS LABA/LAMA, LABA/ICS or LABA/LAMA/ICS along with or without macrolides as background therapy.
- **Variables of interest:** change from baseline in fibrinogen after 12 weeks of treatment.
- **Intercurrent events of interest:**
    1. Discontinuation of study treatment or study participation before 12 weeks of treatment
    2. Intake of antibiotics to treat exacerbations (other than macrolides taken as background medication)
    3. Intake of systemic corticosteroids to treat exacerbations.
    4. Use of rescue medications before 12 weeks of treatment with study drug or placebo is complete
- **Summary measure:** mean difference between treatment groups (QBW251 compared with placebo).

6.1.2 Descriptive analyses

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

6.1.3 Statistical model, assumptions and hypotheses

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

The fibrinogen samples taken within 2 weeks after exacerbation or during or after last dose of antibiotics other than chronically administered macrolide would be set to missing if a valid unscheduled assessment did not happen at that time point for the primary analysis.

The primary analysis will be performed using a one-sided test at alpha=0.1 (two-sided 80% confidence intervals) and estimated treatment difference (QBW251-Placebo) at week 12 will be reported along with the associated 80% confidence intervals.

The comparison of QBW251 to placebo will be evaluated by testing the following null hypothesis (H_0) versus the alternative hypothesis (H_1):

H_0: There is no reduction in fibrinogen from baseline after 12 weeks of treatment in QBW251 compared to placebo.

H_1: There is a reduction in fibrinogen from baseline after 12 weeks of treatment in favor QBW251 compared to placebo.

The change from baseline in fibrinogen data is assumed to be normally distributed. A MMRM will be fitted to the changes from baseline in fibrinogen for all time points until Day 84 visit including the fixed factors and covariates but are not limited to the following:

- Treatment group
- Visit/Time
- Treatment group by time interaction
- Smoking status
- Baseline fibrinogen value by time interaction.

If normality assumptions are not met, then the fibrinogen data may be log transformed.

Sensitivity analyses:

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Supportive analyses:

Supportive analyses will be performed on subjects whose fibrinogen levels or bacterial load collected at the visits during the study based on the different baseline treatments like LABA, LAMA, or ICS using repeated measures model similar to primary analyses.

6.1.3.1 Model checking procedures

Estimates of the missing values due to intake of rescue medications or antibiotics will be derived by the model under the missing at random (MAR) assumption. Alternative assumptions may be explored to investigate the robustness of the results under plausible non-missing at random situations.

6.1.3.2 Graphical presentation of results

Model based plots will be presented for the fibrinogen data.

6.2 Secondary objectives

The key secondary objective is to assess the effect of QBW251 compared to placebo after 12 weeks of treatment on sputum bacterial load.

6.2.1 Variables

The key secondary objective endpoint is:

- Change from baseline in the logarithm of total number of colony forming units (log_{10}CFU/mL) of potentially pathogenic microorganisms in sputum after 12 weeks of treatment.

The bacterial load samples taken 2 weeks after exacerbation (after antibiotic intake is finished) or during or after last dose of antibiotics would be set to missing if a valid unscheduled assessment did not happen at that time point for the primary analysis.

The other secondary pharmacodynamics and efficacy endpoints are as follows:

- Change from baseline in airway wall and lumen parameters along with extent of global and regional air trapping as measured by HRCT after 12 weeks of treatment.
- Change from baseline in FEV1, FVC and FEV1/FVC ratio measured by spirometry after 12 weeks of treatment.
- Subject reported outcomes and exacerbations
  - Changes from baseline in the Euro Quality of Life-5 Dimensions-3 Level (EQ-5D-3L).
  - Changes from baseline in Cough and Sputum Assessment Questionnaire (CASA-Q) domain scores.
  - Change from baseline in COPD Assessment Test (CAT) questionnaire.
  - COPD exacerbations
    - Time to first COPD exacerbation
    - Proportion of subjects with exacerbations

- Annualized rate of exacerbations as defined by EXACT-PRO questionnaire.
- Change from baseline St. George's Respiratory Questionnaire (SGRQ) total and domain scores.

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.

6.2.2 Descriptive analyses

Summary statistics will be provided by treatment group and visit for total number of colony forming units, all spirometry parameters (FEV1, FVC and FEV1/FVC ratio) and HRCT parameters including regional and global air tapping changes will include arithmetic mean, standard deviation (SD), coefficient of variation (CV), median, minimum and maximum. These will be calculated at all time points as specified in the assessment schedule (Table 8-1) of CSP and specifically at the primary time point of interest (Day 84) considering placebo as the reference treatment.

Summary statistics will be provided by treatment group and visit for Cough and Sputum Assessment Questionnaire (CASA-Q) and St. George's Respiratory Questionnaire (SGRQ) domain scores, COPD assessment test (CAT), EQ-5D-3L and EXACT-PRO questionnaire data.

6.3 Statistical model, assumptions and hypotheses

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

The change from baseline in the logarithm of the total number of colony forming units including all different micro-organisms ($\log_{10}$ CFU) and change from baseline in the secondary efficacy including global air trapping and spirometry parameter will be analyzed using the same model (MMRM) as for the primary variable of interest. Contrasts for treatment differences will be provided together with two-sided 80% Confidence Intervals.

Similarly, other secondary pharmacodynamics and efficacy endpoints (CASA-Q, SGRQ, CAT, EQ-5d-3L and EXACT-PRO) will be analyzed using the same model (MMRM) as for the primary variable of interest.

The following analyses will be performed to explore any differences in the exacerbation events that occur in QBW251 vs placebo:

1. Time to first exacerbation

The time-to-event analyses will be carried out only upon sufficient number of exacerbation events occur during the study to estimate the median in either of the treatment groups.

The time to the first on-treatment exacerbation (event) is defined as the start date of first exacerbation minus the date of randomization +1. Subjects who do not experience an exacerbation or discontinued earlier without an exacerbation will be censored for analyses purposes.

The hazard ratios for QBW251 compared with placebo and their corresponding 80% confidence intervals will be computed using Kaplan-Meier method. The stratification factor may include number of exacerbations in the last 12 months as <=1 and >1.

The Kaplan-Meier estimates of the survival functions for each treatment will be plotted.

A Cox proportional hazards regression model will be applied in time-to-event analyses to test the null-hypothesis H0: λQBW251(t) / λPlacebo(t) = 1, where λ(t) is the hazard function for the failure time of subjects treated with QBW251 dose and Placebo, respectively.
The Cox regression model will be stratified by number of exacerbations in the last 12 months.
The SAS procedure PROC PHREG will be used for analysis. Results will be presented with adjusted hazard ratios for treatment group comparisons and associated 80% confidence intervals.
No check for the validity of proportional hazards assumptions will be done.

2. Annualized rate of COPD exacerbations

The total frequency of COPD exacerbations over the 12-week treatment period will be analyzed using a generalized linear model assuming a negative binomial distribution.

The time at risk for a subject is defined as the length of time the subject is on treatment and the log (length of time) will be used as the offset variable in the model. The model will include treatment, antibiotic use, and the number of exacerbations in the past 12 months prior to screening as categorical variables. An estimate of the rate ratio together with 80% confidence intervals and corresponding p-value will be presented.

3. The percentage of subjects experiencing at least a COPD exacerbation

The proportion of subjects with at least one COPD exacerbation will be analyzed using logistic regression. The model will include treatment, antibiotic use, and the number of exacerbations in the past 12 months prior to screening as categorical variables. The estimated odds ratios will be displayed along with the associated 80% confidence intervals.

6.3.1.1 Graphical presentation of results

The mean (+/- SE) and mean change from baseline plots for total number of colony forming units, all spirometry parameters (FEV1, FVC and FEV1/FVC ratio) and HRCT parameters including regional and global air tapping changes will be presented by treatment. Plot for the estimated treatment differences and associated 80% confidence intervals for change from baseline in total number of colony forming units, all spirometry parameters and HRCT parameters including regional and global air tapping changes.

6.4 Exploratory objectives

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6.4.2 Descriptive analyses

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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 (tables, figures) 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.

Subject demographics and other baseline characteristics

All data for background and demographic variables will be listed by treatment group and subject. Summary statistics will be provided by treatment group for the Safety analysis set.

Other screening/baseline characteristics will be summarized including:

- Smoking Status
- HRCT
- Spirometry (Absolute and percent predicted values of FEV1, FVC)
- hsCRP
- Fibrinogen plasma concentration
- COPD Assessment Test (CAT)
- Sputum bacterial load

Relevant medical histories and current medical conditions at baseline will be summarized by system organ class and preferred term, by treatment group.

Subject disposition

A disposition summary will be presented for all subjects. This table will present the number and percentage of subjects who completed each study epoch and discontinued early for each epoch, along with the reasons for early discontinuation.

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

All study epoch completion data will be listed by treatment group and 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

All vital signs data will be listed by treatment group, subject, and visit/time and if ranges are available, abnormalities (and relevant orthostatic changes) will be flagged. Summary statistics will be provided by treatment and visit/time.

ECG evaluations

All ECG data will be listed by treatment group, subject and visit/time, abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time.

Clinical laboratory evaluations

All laboratory data will be listed by treatment group, subject, and visit/time and if normal ranges are available, abnormalities will be flagged. A separate listing is provided presenting all parameters in a subject with any abnormal values. Summary statistics will be provided by treatment and visit/time. Shift tables using the low/normal/high (low and high) classification will be used to compare baseline to the worst on-treatment value.

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 1week 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 in the following ways:

- by treatment, primary system organ class and preferred term.
- by treatment, primary system organ class, preferred term and maximum severity.
- by treatment, Standardized MedDRA Query (SMQ) and preferred term.

Separate summaries will be provided for study medication related adverse events, death, 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 an individual subject, 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.

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