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Biostatistics & Statistical Programming /
Novartis Institutes for BioMedical Research

QBW276

CQBW276X2201

A randomized, double blind, placebo-controlled study to assess the safety, tolerability, pharmacokinetics, and pharmacodynamics of multiple doses of inhaled QBW276 in patients with cystic fibrosis

Statistical Analysis Plan (SAP)

Personal Data

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Table of contents

List of tables

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 **"CQBW276X2201".**

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

1.2 Study reference documentation

This SAP has been developed using Clinical Trial Protocol version v02 dated 20-Mar-2017.

1.3 Study objectives

1.3.1 Primary objectives

Primary Objective: Cohort 1 and 2	**Endpoints**

• To assess the safety, tolerability and PK of multiple doses of inhaled QBW276 and its metabolites over 1 or 2 weeks of treatment in patients with CF	• All safety assessments during the cohort period, including:
	  • Physical examination
	  • Hematology
	  • Blood chemistry (central and local labs)
	  • Urinalysis
	  • ECG evaluation
	  • Vital Signs
	  • AEs and SAEs
	• PK measurements

Primary Objective: Cohort 3	**Endpoints**
• To evaluate the response to multiple doses of inhaled QBW276 in lung function (percent of predicted FEV_1) over 4 weeks of treatment compared with placebo in patients with CF that are homozygous for the F508del mutation.	• % predicted FEV_1 (assessed by spirometry)

1.3.2 Secondary objectives

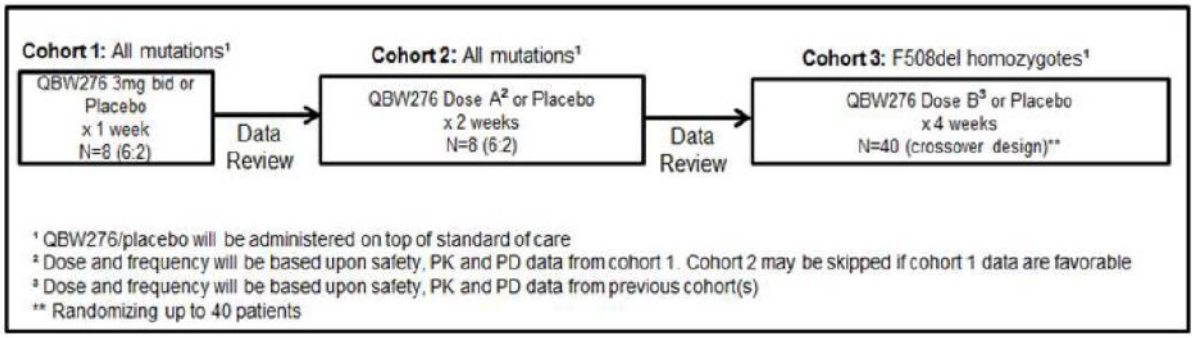
Secondary Objective: Cohort 1 and 2	Endpoints
• To evaluate the response to multiple doses of inhaled QBW276 on change in lung function (percent of predicted FEV_1 and LCI) in patients with CF	• % predicted FEV_1 (assessed by spirometry) • $LCI_{2.5}$ (assessed by Multiple Breath Nitrogen Washout [MBNW]) if FEV_1 at screening is > 80% of predicted
Secondary Objective: Cohort 3	**Endpoints**

• To assess the safety, tolerability, PK and of multiple doses of inhaled QBW276 and its metabolites over 4 weeks of treatment in patients with CF who are homozygous for the F508del mutation	• All safety assessments during the cohort period, including:
	  • Physical examination
	  • Hematology
	  • Blood chemistry
	  • Urinalysis
	  • ECG evaluation
	  • Vital Signs
	  • AEs and SAEs
	• LCI2.5 (assessed by MBNW) if FEV1 at screening is > 80% of predicted
	• PK measurements

1.4 Study design and treatment

This is a study of multiple doses of inhaled QBW276 in patients with CF on top of Standard of Care, Corporate Confidential Information CFTR potentiators and correctors, if applicable. The study will be divided into three cohorts. Cohorts 1 and 2 are designed to be a randomized, double-blind, placebo-controlled, parallel arm multiple ascending dose study of the safety, tolerability, PK and preliminary efficacy of inhaled QBW276 over 1 week (cohort 1) and 2 weeks (cohort 2) in patients with CF regardless of their genotype. The primary rationale for cohorts 1 and 2 will be to assess PK, safety and tolerability in CF. , Cohort 3 is a randomized, double-blind, placebo-controlled, cross-over design multiple dose study of the efficacy,safety, tolerability, and PK of inhaled QBW276 over 4 weeks in patients with CF who are homozygous for the F508del mutation. Corporate Confidential Information

Figure 1-1 Schematic for study design



Cohort 1 will receive 3 mg bid dose (6 mg/day) or placebo over 1 week. Corporate Confidential Information

Upward, downward, or repeat dosing will continue in cohorts 2 and 3, as long as the systemic exposure cap based on pre-clinical data or a clinical maximum tolerated dose (MTD) is not exceeded. Cohorts 1 and 2 will enroll 8 patients each, with 6 patients randomized to receive active drug and 2 patients randomized to receive matching placebo. Cohort 1 will be dosed for 1 week while cohort 2 will be dosed for 2 weeks. Cohort 2 will be initiated only after cohort 1 has completed dosing. Cohort 2 may be skipped if safety, tolerability, PK data from cohort 1 are found favorable to proceed directly to cohort 3. In cohorts 1 and 2, patients may be replaced if they do not complete the study duration for reasons other than safety to obtain 8 completers in each cohort. If a patient has participated in cohort 1, he/she may qualify to participate in cohort 2 contingent upon approval from the sponsor, as long as he/she has been through a 4 week wash-out between dosing in the two cohorts, and has not experienced any significant AEs since enrollment in cohort 1. This will ensure that no patient receives more than 4 weeks of the investigational drug QBW276 in his/her lifetime until further supportive toxicology studies are conducted in the drug's development program.

NOTE: No patient randomized to cohort 1 or 2 will be eligible for cohort 3.

Cohort 1 and 2

Cohorts 1 and 2 will consist of a 21 day screening period followed by a baseline visit and a 7 or 14 day Treatment Period in cohort 1 and 2, respectively Adequate windows will be provided for patient's convenience. QBW276 will be administered on top of the patient's usual standard of care medications.

Study inclusion/exclusion criteria as well as medication use will be assessed at screening. Patients who meet the inclusion/exclusion criteria at screening will report to the study site on Day -1 at a time specified by the investigator, for the baseline assessments. All baseline safety evaluation results must be available prior to dosing on Day 1, hence, Day -1 assessments can be carried out up to 72 hours prior to Day 1 dosing.

Patients who meet all of the inclusion and none of the exclusion criteria at baseline will then report to the study site on Day 1 and will remain in the clinic until at least 6 hours after the first dose in the morning.

On Day 1, pre-dose safety, biomarker, PK blood draw, and urine collection will be performed. Following the pre-dose procedures, subjects will be randomized. Post-dose evaluations will include routine safety evaluations and blood for PK assessments. The patients will be asked to return to the study site for follow-up visits as specified on the respective assessment schedules.

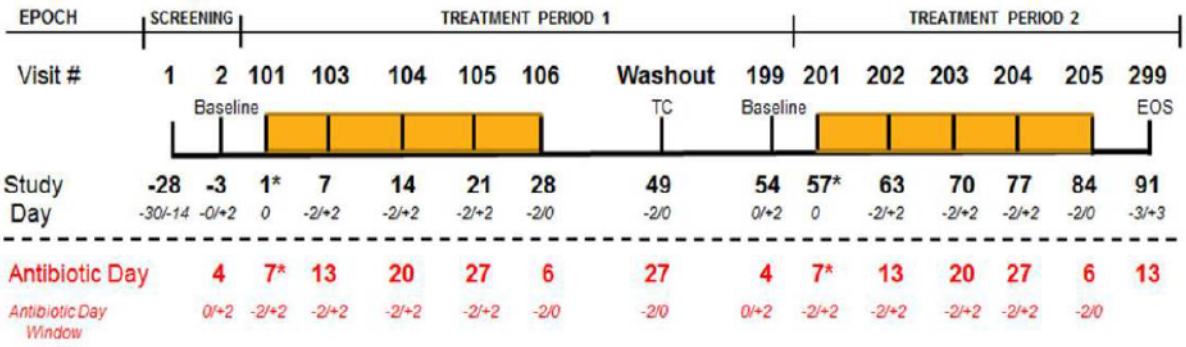
Safety will be monitored by assessment of vital signs, physical examination, ECG, clinical laboratory evaluations (hematology, blood chemistry, and urinalysis), urine electrolytes, aldosterone in plasma, lung function, and monitoring of adverse events (AEs) throughout the study. PK (drug and metabolites) Corporate Confidential Information measured in cohorts 1 and 2 will be compared with data from the healthy volunteer study.

A blinded review of data will be conducted after completion of each cohort prior to initiation of the next cohort. The Sponsor (medically qualified representative) in conjunction with the designated site Investigator(s) will review blinded data (including lung function, AEs, vital signs, safety laboratory parameters including aldosterone values, and PK). An external data monitoring committee (DMC) will also be assembled to monitor study safety data as per an approved charter. After the first 4 patients in Cohort 1 have completed the Day 7 study assessments, the PK data may be reviewed by the study pharmacokineticist to compare exposure levels with previously observed data in healthy patients.

Cohort 3

Dosing in cohort 3 will not commence until the Sponsor (medically qualified representative) in conjunction with the designated site Investigator(s) have reviewed all available safety, tolerability, PK, data from cohorts 1 and/or 2. Endorsement for the dose selected for cohort 3 will also be sought from the DMC members per the DMC charter.

Figure 1-2 Schematic for Cohort 3 study design



*For patients on inhaled antibiotics, the study drug will be started on the 7th day (+/- 2 days) of inhaled antibiotic use during their 28 day antibiotic cycle.

For Cohort 3, patients will be randomized to one of two treatment sequences: QBW276 in Period 1 and Placebo in Period 2 or Placebo in Period 1 and QBW276 in Period 2. Based on drop-out rates observed during conduct of the study, up to 40 patients will be randomized to ensure that at least 24 patients complete the study. After a 4 week screening period, patients who meet all selection criteria will receive drug for 4 weeks and placebo for 4 weeks, separated by a 4 week wash out period, or vice versa. QBW276 will be administered on top of the patient's usual standard of care medications. Periods 1 and 2 will commence on day 7 (+/- 2) of the patient's standard of care cyclic inhaled antibiotic regimen.

Screening and baseline visits for cohort 3 will be similar to the respective visits in cohorts 1 and 2. On Day 1 of cohort 3, pre-dose safety, efficacy and biomarker collection will be performed. Following the pre-dose procedures eligible patients will be dosed for up to 28 days. Post-dose evaluations will include routine safety evaluations and blood for PK assessments. The patients will be asked to return to the study site for follow-up visits on Days 7, 14, 21, and 28 after which they will undergo a 4 week wash-out period prior to cross-over to the opposite arm, and follow a similar visit schedule until End of Study assessment approximately 7 days after the last visit in the second period. All patients will undergo the same assessments regardless of their dose.

Efficacy will be evaluated by spirometry, multiple breath nitrogen washout (if FEV1 at screening is > 80% of predicted), lung volume measurements, and responses to the CFQ-R. Safety will be monitored by assessment of vital signs, physical examination, ECG, clinical laboratory evaluations (hematology, blood chemistry, and urinalysis), urine electrolytes, aldosterone in plasma, and monitoring of adverse events (AEs) throughout the study.

Randomization will be stratified by Corporate Confidential Information concomitant medication in Cohort 3 only. This is because improvement in lung function after treatment with QBW276 may or may not be synergistic Corporate Confidential Information based on their mechanism of action, Corporate Confidential Information

If a maximum tolerated dose for patients with CF (MTD) is identified in cohorts 1 or 2 on the basis of dose-limiting toxicity, the predicted exposure at the maximum planned dose in cohort 3 shall not exceed the exposure at the MTD. If an MTD is not defined in cohorts 1 and 2, the

maximum planned dose in cohort 3 shall not exceed the systemic exposure cap based on pre-clinical data.

2 First interpretable results (FIR)

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

Corporate Confidential Information

4 Statistical methods: Analysis sets

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

The safety analysis set will include all subjects that received any study drug.

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 experienced no protocol deviations with relevant impact on PK data.

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 PK analysis in case of these PDs:		Exclude subject from PK analysis set
Subjects are excluded from PD analysis in case of these PDs:		Exclude subject from PD analysis set
Subjects are excluded from PK and PD analysis in case of these PDs:		Exclude subject from PK and PD analysis sets

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 parent compound QBW276 and the hydrolysis products QBP545 and QBV697 will be determined in whole blood.

The following pharmacokinetic parameters for all three analytes will be determined for Day 1 and Day 7 or 14 in Cohorts 1 and 2 using the actual recorded sampling times and noncompartmental methods: Cmax, Tmax, and AUCtau on Day 1 and Cmax,ss, Tmax,ss, and AUCtau,ss on Day 7 for cohort 1 and Day 14 for cohort 2. Half-lives will be calculated by log-linear regression on the terminal portion of the concentration-time profile if enough concentrations are available (minimum 3). Racc will be derived as the ratio of AUCtau,ss from Day 14 divided by the AUCtau from Day 1.

In cohort 3, exposure from 15-minute sample after start of inhalation of the morning dose on selected days will be monitored.

Other PK parameters maybe calculated in all cohorts if deemed necessary.

5.2 Descriptive analyses

The concentrations will be listed by treatment, patient and visit/sampling time point. Descriptive statistics will be provided by treatment and visit/sampling time point. Summary statistics will include mean (arithmetic and geometric), SD, and CV (arithmetic and geometric), median, minimum and maximum.

Concentrations below the LLOQ will be treated as zero in summary statistics. A geometric mean and CV will not be reported if the dataset includes zero values.

Pharmacokinetic parameters in Cohorts 1 and 2 will be calculated as described in Section 5.1 and will be listed by treatment and patient. Descriptive summary statistics will include mean (arithmetic and geometric), SD, and CV (arithmetic and geometric), median, minimum and maximum. An exception to this is Tmax and Tmax,ss where median, minimum and maximum will be presented.

5.2.1 Statistical model, assumptions and hypotheses

An exploratory statistical analysis analysis of the accumulation ratio of Day 7 vs Day 1 for cohort 1, Day 14 vs Day 1 for cohort 2 and Day 28 vs Day 1 for cohort 3 may be carried out for the parameters AUCtau and Cmax for each dose level. A mixed linear model will be fitted to the log-transformed observations. This model will include day as a factor ("Day 7/14/28" and "Day 1"), log-dose as a covariate, and subject as a random effect. The mean difference between Day 7/14/28 and Day 1 for each dose-level, together with 90% confidence limits, will be calculated from this model. These will be back-transformed to provide an estimate of the accumulation ratio (Day 7/14/28 vs. Day 1) with corresponding 90% CI for both parameters. Due to the small number of subjects in cohorts 1 and 2 there may be convergence issues with the mixed model. In case of convergence issues, alternative covariance structures will be considered and compared using standard fit statistics (AIC).

5.2.2 Graphical presentation of results

Individual concentration-time profiles and mean profiles with SD bars will be presented for Days 1 and 7 (cohort 1) and Days 1 and 14 (cohort 2) and Period 1 and 2 (cohort 3).

6 Statistical methods

6.1 Primary objective

The primary variable is occurrence of an adverse event for cohort 1 and cohort 2 and evaluate response as reflected in percent of predicted FEV1 for cohort 3 of multiple doses of inhaled QBW276 in CF patients.

6.1.1 Variables

6.1.2 Descriptive analyses

Summary statistics of absolute and change from baseline values of percent of predicted FEV1 and all other spirometry parameters will be presented by treatment group and time.

Baseline is defined as the following:

- Cohorts 1 and 2: Result on day 1
- Cohort 3: Last Result before treatment in each period

6.1.3 Statistical model, assumptions and hypotheses

Percent of predicted FEV1 values measured on Day 7, Day 14, Day 21 and Day 28 of each treatment period at the study site for cohort 3 will be analyzed using a mixed effects model for repeated measurements. The model will include fixed effects for period, time (Days 7, 14, 21, 28 as appropriate), treatment and treatment by time. Subject will be included as a random effect and time will be repeated within each patient by period interaction term. Subject-average baseline and period-adjusted baseline will be fitted as covariates. An unstructured covariance matrix will be applied. In case of the analysis fails to converge, compound symmetric covariance structure will be used in the first instance and if further alterations to the model are necessary the significance of the covariates will be explored. Kenward Roger options will be used to calculate the degrees of freedom in all Proc Mixed analysis.

The subject average baseline will be derived as the average of their pre-dose assessments from each period. Period adjusted baseline will be calculated for each subject and for each period, as the difference between the period baseline and the subject average baseline, i.e. value of period baseline - value of average baseline.

The final model estimates will include the LSmean for each treatment together with standard error (SE), the adjusted mean difference between treatments, and 80% two-sided confidence intervals and P-value for the differences. These will be calculated at all time points, and specifically at the primary time point of interest (Day 28) using Placebo as the reference treatment.

No adjustments for multiplicity will be applied for this exploratory study. Missing data is assumed to be Missing At Random (MAR).

Additional summaries of frequencies of responder rates will be presented. A subject will be considered a responder where improvements are seen such that FEV1 >5% or LCI >1 unit.

6.1.3.1 Model checking procedures

The repeated measures analysis includes all available information in terms of measurements at all times. If missing measurements are missing at random, an analysis of the available data provides consistent estimates of model parameters. Reasons for dropouts will be explored.

Where data has values below and above limits of quantification then the following rule will apply.

In the summary tables, the frequency (n, %) of values below the LLOQ and above the ULOQ, respectively, will be included.

Any values below the limit of quantification will be analyzed as 0.5*the lower limit, both in the descriptive and the model analysis. Any values above the limit of quantification will be analyzed as 1.0*the upper limit, both in the descriptive and the model analysis.

No other imputation of missing data is allowed.

6.1.3.2 Graphical presentation of results

Individual time profiles and Mean (SD) plots of absolute and change from period baseline of percent of predicted FEV1 and all spirometry parameters will be presented by treatment group and time.

The results of statistical analysis will also be presented in a graphical representation showing the estimated mean differences to placebo and their confidence intervals per time point.

6.2 Secondary objectives

6.2.1 Variables

parameters to be analyzed are all spirometry and LCI parameters and CFQ-R PRO questionnaire.

6.2.2 Descriptive analyses

Absolute and change from baseline for all spirometry and LCI parameters will be listed by cohort, treatment, patient and visit/time and summarized by treatment group and dose level.

Summary statistics of these endpoints will be performed, split by the stratification of LCI results based on baseline $FEV_1 > 80\%$ of predicted.

6.2.3 Statistical model, assumptions and hypotheses

The primary model described for percent of predicted FEV_1 in Section 6.1.3 will be used for all secondary parameters of interest (separate model for each parameter) for cohort 3. Treatment contrasts and their 80% two-sided confidence intervals will be derived at Day 7, Day 14, Day 21 and Day 28.

6.2.3.1 Graphical presentation of results

Individual time profiles and Mean (SD) plots of absolute and change from baseline for all spirometry and LCI parameters will be presented by treatment group and dose level.

Correlation of change from baseline at each timepoint between spirometry and LCI endpoints will be presented.

6.2.5 Lung volumes and small airway measurements

Lung Volume parameters include:

- FRC, RV/TLC, difference between SVC and FVC

Small airway measurements parameters include:

- FEV3, 1-FEV3, FEV6, FEV3/FVC, 1-FEV3/FVC, FEV3/FEV6, 1-FEV3/FEV6, FEV1/FEV6 (assessed by spirometry)

Parameters obtained from spirometry and Pulse oximetry at each time-point and changes from baseline will be summarized by treatment group. In cohort 3 summary stats will be provided by time within period.

7 Statistical methods for safety and tolerability data

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

Subject demographics and other baseline characteristics

All data for background and demographic variables will be listed by treatment group (treatment sequence for cohort 3) and subject. Summary statistics will be provided by treatment in cohorts 1 and 2 and overall (by sequence) in cohort 3.

Relevant medical history, current medical conditions, results of laboratory screens, drug tests and any other relevant information will be listed by treatment group (treatment sequence for cohort 3) and subject.

Treatment

Data for study drug administration (rescue medication) and concomitant therapies will be listed by treatment group (treatment sequence for cohort 3) and subject.

Vital signs

All vital signs data will be listed by cohort, treatment group (treatment sequence for cohort 3), subject, and visit/time and if ranges are available abnormalities (and relevant orthostatic changes) will be flagged. Summary statistics will be provided by treatment group and visit/time. In cohort 3 summary stats will be provided by time within period (Days 1,7,14,21,28)

ECG evaluations

All ECG data will be listed by cohort, treatment group (treatment sequence for cohort 3), subject and visit/time, abnormalities will be flagged. Summary statistics will be provided by treatment group and visit/time. In cohort 3 summary stats will be provided by time within period (Days -1,14,28)

Clinical laboratory evaluations

All laboratory data will be listed by cohort, treatment group (treatment sequence for cohort 3), 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 group and visit/time. In cohort 3 summary stats will be provided by time within period (Days -1,14,28)

Adverse events

All information obtained on adverse events will be displayed by cohort, treatment group (treatment sequence for cohort 3) and subject.

The number and percentage of subjects with adverse events will be tabulated by body system and preferred term with a breakdown by treatment. A subject with multiple adverse events within a body system is only counted once towards the total of this body system and treatment.

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.

7.3 Graphical presentation

Boxplots to visualize trends in longitudinal safety data (vitals, ECG, lab parameter) will be created.

9 References