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QVA149

CQVA149A2325

A randomized, double-blind, placebo-controlled, two-period crossover study to assess the effect of inhaled QVA149 on global and regional lung function and gas exchange in patients with moderate to severe COPD

Statistical Analysis Plan (SAP)

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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 ***"CQVA149A2325".***

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

1.2 Study reference documentation

Final Study protocol is available at the time of finalization of this Statistical Analysis Plan

1.3 Study objectives

1.3.1 Primary objectives

- To assess global ventilated lung volume after treatment with QVA149 compared to placebo

1.3.2 Secondary objective(s)

- To assess regional lung ventilated volume after treatment with QVA149 compared to placebo
- To evaluate physiologic measures of lung function after treatment with QVA149 compared to placebo to provide a measure of assay sensitivity for this study
- To assess small airway function after treatment with QVA149 compared to placebo

1.4 Study design and treatment

This is a double-blind, randomized, placebo-controlled, two-period, cross-over study in patients with moderate to severe COPD.

The study will consist of a 2-week screening period, a 7-9 day run-in, a baseline visit, a double-blind up to 10 day treatment Period 1 followed by a washout period before crossing over to a double-blind up to 10-day treatment Period 2, and an end-of-study visit. At the Run-In visit study subjects will be taken off medications (Refer protocol: section 5.2 of Table 5-2)

and will receive rescue medication. The investigator will need to assess whether subjects can tolerate being off long-acting bronchodilators prior to baseline assessments.

To minimize patient burden, MRI and lung function assessments (spirometry, MBNW/lung volumes, DLCO) will not be scheduled for the same day. Subjects will have two MRI sessions – approximately 20 mins for He^3 MRI and 10 mins for proton MRI for a total of 30-45 mins per session that includes the setup and completion of 4-5 sequences. Actual MRI assessments will commence 2 hours after subject dosing at the site. Assessments for evaluation of MRI endpoints will be done on Day 7 and all other assessments, in particular spirometry, MBNW/lung volumes, and DLCO will be done on the day following MRI assessments i.e. Day 8 of treatment during Period 1 and Period 2.

If for important operational reasons MRI assessments cannot be performed on Day 7 of the respective treatment period, treatment in this period may be extended by up to 3 days. If MRI assessments cannot be performed on Day 7, then Day 7 and Day 8 assessments can be flexibly scheduled in any order (i.e. Day 7 assessments can be performed before or after Day 8 assessments and vice-versa) between Day 7 and Day 10, with all efforts made to minimize total days of treatment.

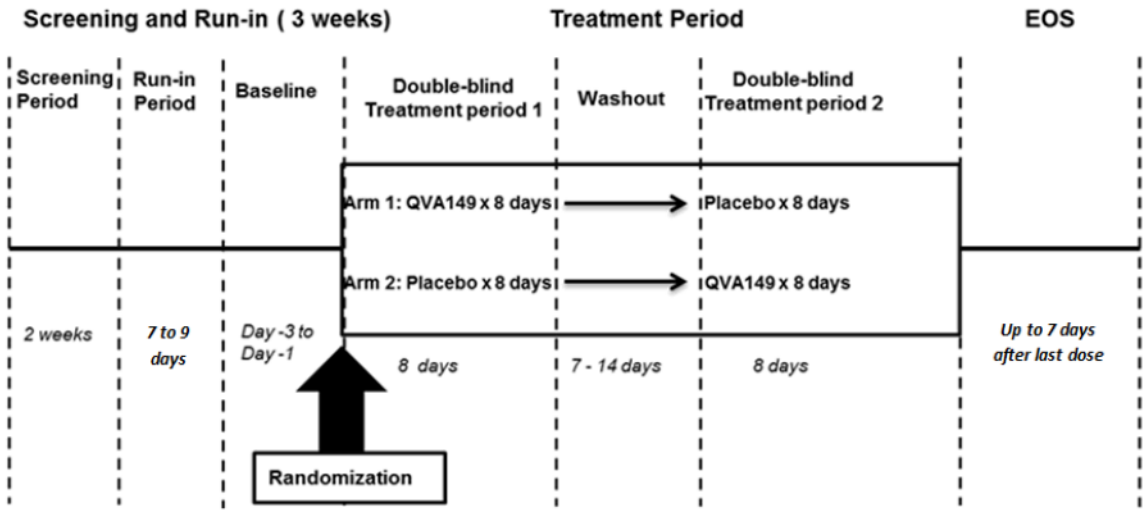
If the Day 7 or Day 8 assessments are scheduled on Day 8, 9 or 10 the subject will continue dosing until the day of the last assessment with a maximum 10 day dosing period. Sites will be requested to maintain the same sequence of MRI and lung function assessments for both treatment periods.

Study drug should be taken on each assessment day in the presence of and under the guidance of study site personnel. The assessment days are Day 1, Day 7 (MRI) and Day 8 (lung function tests) for each treatment period. Deviations within the time-frame given above are permissible. At all other times the subjects will take the drug at home and note date and time in the provided patient diary along with information about rescue medication use.

Randomization takes place on Day 1 of Treatment Period 1. Each treatment period consists of a once daily dose of QVA149 or placebo over 8 days (dosing is allowed for up to 10 days). The treatment will be administered by oral inhalation using the Concept 1 inhalation device.

A wash-out period of at least 7 days, but no more than 14 days, will separate the two treatment periods.

Safety assessments will include physical examinations, ECGs, vital signs, standard clinical laboratory evaluations (hematology, blood chemistry and urinalysis), adverse event and serious adverse event monitoring.



2 First interpretable results (FIR)

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

3 Interim analyses

Interim analyses may be conducted to support decision making concerning the current clinical study, the sponsor's clinical development projects in general or in case of any safety concerns. In this case, this interim analysis may be performed by the study statistician. The purpose of this IA is to confirm the sample size assumptions while assessing the variability in the primary end point in this population.

There will be no pause in enrollment at the time of interim analysis.

4 Statistical methods: Analysis sets

For subjects for which the actual treatment received does not match the randomized treatment the treatment actually received will be used for the analysis.

For subjects for which the actual sequence of treatments received does not match the randomized sequence of treatments, the actual sequence will be used for analysis involving a sequence component (e.g. ANOVAs with a sequence effect) if the actual sequence is one of the sequences planned in the study design. If the actual sequence is not one of the sequences planned in the study design, the randomized sequence will be used for analysis involving a

sequence component but data points from periods in which the subject has not received the randomized treatment will be excluded from the analysis.

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

The primary population of interest is the PD population, all the patients with evaluable PD parameter data and no major protocol deviations impacting PD data will be included in the PD data analysis "PD population". Any PD data less than 6 hours after rescue medication use or within 7 days of systemic corticosteroid will be set to missing.

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 all *(safety)* analysis in case of these PDs:		Exclude subject completely from all ***(safety)*** analysis sets
INCL01	Deviation from inclusion criteria: Written informed consent was not obtained before any study assessment was performed	Yes
Subjects are excluded from PD analysis in case of these PDs:		Exclude subject from PD analysis set
INCL01	Deviation from inclusion criteria: Written informed consent was not obtained before any study assessment was performed	Yes

Only PDs which impacts in subject's exclusion are mentioned above.

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

5 Statistical methods for Pharmacokinetic (PK) parameters

Not applicable.

5.1 Variables

Not applicable.

5.2 Descriptive analyses

Not applicable.

5.3 Statistical model, assumptions and hypotheses

Not applicable.

5.3.1 Model checking procedures

Not applicable.

5.3.2 Graphical presentation of results

Not applicable.

6 Statistical methods for Pharmacodynamic (PD) parameters

6.1 Primary objective

6.1.1 Variables

The primary variable is the percent of global lung ventilation volume as determined by 3He lung MRI to evaluate the pharmacodynamic response on day 7 after once daily treatment with QVA149 compared to placebo.

6.1.2 Descriptive analyses

Results for percent of global lung ventilation volume will be presented in summary table by treatment and time, and graphically as arithmetic mean and boxplots by treatment over time and as individual graphs (individual data for each patient over time, separate for each treatment). All results will also be listed by treatment group, subject, and time-point.

6.1.3 Statistical model, assumptions and hypotheses

A comparison of QVA149 vs. placebo on percent of global lung ventilation volume is of primary interest to investigate the effect of QVA149 on global and regional lung ventilation using MRI hyperpolarized gas imaging to enhance the understanding of QVA149 pharmacology in COPD patients.

The percent of global ventilation volume on day 7 will be analyzed using a mixed effects model. The model will include sequence, period and treatment as fixed effects. Patient factor will be included as a random effect. The within-patient correlation will be modeled using the unstructured covariance matrix. Restricted maximum likelihood method will be used. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. In case of the analysis fails to converge, compound symmetric covariance structure will be used. No adjustment for multiplicity is planned.

The final model estimates will include the LSmean for each treatment (QVA149 and placebo) together with standard error (SE), the adjusted mean difference between QVA149 and placebo, and corresponding 90% two-sided confidence intervals and P-value for the differences using placebo as the reference treatment.

6.1.3.1 Model checking procedures

Missing data will not be imputed for the primary analysis. Subjects withdrawn for any reason other than safety and tolerability may be replaced.

6.1.3.2 Graphical presentation of results

Refer section 6.1.2

6.2 Secondary objectives

6.2.1 Variables

Secondary pharmacodynamic variables are Forced Expiratory Volume in 1 second (FEV1), Forced Vital Capacity (FVC), FEV1/FVC ratio measured by spirometry, Lung Clearance Index measured by Multiple Breath Nitrogen Washout, Percent of regional ventilation defects volume measured by MRI using hyperpolarized helium (^{3}He), Pulmonary perfusion (ml/g/min) using Standard ^{1}H MRI with gadolinium enhancement.

6.2.2 Descriptive analyses

Results for all secondary parameters will be presented in summary tables by treatment and time, and graphically as mean plots and boxplots by treatment over time and as individual graphs (individual data for each patient over time, separate for each treatment). All results will also be listed by treatment sequence, subject, and time-point. Summary statistics will include arithmetic mean, SD, CV (arithmetic), median, minimum and maximum.

6.2.3 Statistical model, assumptions and hypotheses

The primary model described for percent of global ventilation volume in Section 6.1.3 will be fit to all secondary parameters of interest (separate model for each parameter). For spirometry parameters, the model will include fixed effects for time (15 min, 1 hour and 2 hours post dose) and treatment by time interaction term. Time will be repeated within each patient*period interaction and subject-average baseline and period-adjusted baseline as covariates in addition to the factors added to the primary analysis. An unstructured variance unstructured covariance matrix will be applied.

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 baseline will be defined as the average of -45 min and -15 min pre-dose assessments. This gives a more robust estimate of pre-dose values for the calculation of subject average baseline.

Sensitivity analysis for LCI, Lung volumes and DLCO as described in Section 6.1.3 may be repeated with a mixed effects model as described for primary variable by adding screening visit as covariate.

6.2.3.1 Model checking procedures

Refer section 6.1.3.1

6.2.3.2 Graphical presentation of results

Refer section 6.2.2

6.3 Exploratory objectives

6.3.1 Variables

6.3.2 Descriptive analyses

Results for all exploratory parameters will be presented in summary tables by treatment and time, and graphically as boxplots by treatment over time and as individual graphs (individual data for each patient over time, separate for each treatment). All results will also be listed by treatment sequence, subject, and time-point. Summary statistics will include arithmetic mean, SD, CV (arithmetic), median, minimum and maximum.

Correlations between MR imaging parameters, spirometry, MBNW/ lung volumes and DLCO at baseline and end of each period for QVA149 and Placebo will be presented, and all end points will be summarized graphically and in tables.

HRCT results will be listed by subject and visit.

Refer section 6.2.3 for statistical analysis of the exploratory end points.

7 Statistical methods for safety and tolerability data

7.1.1 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.

7.1.2 Descriptive analyses

Subject demographics and other baseline characteristics

All data for background and demographic variables will be listed by treatment sequence and subject. Summary statistics will be provided for all subjects, as well as for each treatment sequence.

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

Treatment

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

Vital signs

All vital signs data will be listed by treatment sequence, 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 sequence, 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 sequence, 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.

Adverse events

All information obtained on adverse events will be displayed by treatment 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. An adverse event starting in one period and continuing into the next period is counted only in the onset period. A subject with multiple adverse events within a body system and treatment period is only counted once towards the total of this body system and treatment.

The number and percentage of subjects with adverse events by maximum severity of adverse events will be tabulated by body system and preferred term with a breakdown by treatment.

The number and percentage of subjects with adverse events classified as related to study drug will be tabulated by body system and preferred term with a breakdown by treatment.

7.1.3 Graphical presentation

Boxplots to visualize trends in longitudinal safety data (vital signs) will be created.

8 Statistical methods for Biomarker data

Not applicable.