

Biostatistics & Statistical Programming /
Novartis Institutes for BioMedical Research

QCC374

CQCC374X2201E1

**Long-term, open label, multicenter, extension study to
evaluate the safety and tolerability of QCC374 in patients
with PAH**

Statistical Analysis Plan (SAP)

Author(s): **Personal Protected Data**
Document type: SAP Documentation – NIBR
Document status: Final
Release date: 04-Dec-2017
Number of pages: 14

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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 “**CQCC374X2201E1**”.

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

1.2 Study reference documentation

Final study protocol (V01) is available at the time of finalization of Statistical Analysis Plan.

1.3 Study objectives

1.3.1. Primary objective(s)

<i>Primary objective(s)</i>	<i>Endpoints related to primary objectives</i>
<ul style="list-style-type: none"> To evaluate the safety and tolerability of QCC374 in patients with PAH over a two year period 	<ul style="list-style-type: none"> Adverse Events, Serious Adverse Events and all safety assessments

1.3.2. Secondary objective(s)

<i>Secondary objective(s)</i>	<i>Endpoints related to secondary objective(s)</i>
<ul style="list-style-type: none"> To assess the treatment effect of QCC374 in PAH patients not previously dosed with QCC374 (Arm 2: those subjects previously in the placebo group of QCC374X2201) 	<ul style="list-style-type: none"> 6MWD Key RV function endpoints with echocardiography will include but not limited to tricuspid annular peak systolic velocity (TA S'), RV Tei index and RV fractional area change.
<ul style="list-style-type: none"> To evaluate the pharmacokinetics of QCC374 and its metabolite QCM441 in PAH patients not previously dosed with QCC374 (Arm 2: subjects previously in the placebo group of QCC374X2201) 	<ul style="list-style-type: none"> PK parameters (C_{max}, AUC_{last}, AUC_{tau}, C_{trough}) of QCC374 and QCM441 in plasma.

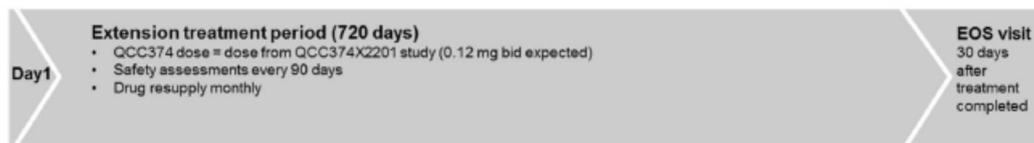
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1.4 Study design and treatment

This is a multicenter, open label trial to assess the safety, tolerability pharmacokinetics and efficacy of inhaled QCC374 over a two year period in patients with PAH who have completed study QCC374X2201. This study will have two arms. In Arm 1, patients who had been randomized to active in the QCC374X2201 study will continue on QCC374 at their highest stable dose. In Arm 2, the patients who had been randomized to placebo will complete a titration scheme similar to that of the active arm in QCC374X2201 protocol.

For both arms the study consists of a Day 1 visit, a treatment period of 720 days, and an EOS visit 30 days after treatment is completed. This study may be amended in the future to increase the treatment duration period, as additional data emerges for QCC374 in PAH.

All patients willing to participate in this trial will roll-over directly from the QCC374X2201 study after their 112 days of participation has been completed. The electrocardiogram (ECG), spirometry, 6MWD, **Corporate Confidential Data** hematology, blood chemistry, body measurement and urinalysis results from the QCC374X2201 Visit Day 112 visit will be used as the Day 1 assessments for the extension study.

Figure 1-1: QCC374X2201E1 extension study design**Arm 1: Subjects who completed QCC374X2201 and received QCC374****Arm 2: Subjects who completed QCC374X2201 and received placebo**

2 First interpretable results (FIR)

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

The study FIR template (mock slides) can be found in CREDI in the study RAP folder.

The template shows the analysis / results to be presented in the FIR. Study outputs required to be created at the time of the FIR will be highlighted in TFL shells document and marked as “Key” in the Programming Deliverables Tracker (PDT) output list.

FIR will focus on the following analyses:

- Analysis populations (if needed)
- Subject disposition
- Demographics and baseline characteristics. Baseline characteristics will be presented both at Core (QCC374X2201) and Extension study (QCC374X2201E1) baseline (subject to data availability at baseline for each study) and will include, but are not limited to:
 - Etiology of PAH
 - Time from PAH diagnosis
 - PVR
 - WHO FC
 - Borg Dyspnea Score
 - NT-proBNP level
 - Background PAH therapy
 - Smoking status
 - FEV1% predicted
 - Lung volumes (TLC % predicted)

- DLco
- Historic right catheter vs catheter at baseline
- Safety results
 - Number and percentage of subjects with adverse events by body system
 - Number and percentage of subjects on different dose levels during stable dose treatment period (0.03, 0.06, 0.12)
- Pharmacodynamic analyses will include, but are not limited to:
 - Raw arithmetic mean (SD) of 6MWD by arm over time

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4 Statistical methods: Analysis sets

For subjects for which the actual treatment received in the Core study (QCC374X2201) does not match the Core study randomized treatment the treatment actually received will be used for the analysis.

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

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 PD analysis set will include all subjects with any available PD data, who received any study drug and experienced no protocol deviations with relevant impact on PD 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

Category Deviation code	Text description of deviation	Data exclusion
	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

All subjects within the PK analysis set will be included in the PK data analysis. Only subjects who had been randomized to placebo in the Core study (QCC374X2201) will have blood samples collected.

5.1 Variables

Plasma concentrations of QCC374 and QCM441 will be expressed in the mass per volume unit ng/mL. The following pharmacokinetic parameters of both analytes (where possible/applicable) will be determined using the actual recorded sampling times and non-compartmental method(s) with Phoenix WinNonlin (Version 6.2 or higher):

- Primary: C_{max}, T_{max}, AUC_{last}, AUC_{tau}, R_{acc} for Day 1 and Day 112
- Secondary: T_{last}, T_{1/2}, T_{min}, C_{min}, fluctuation index, C_{av}, V_z/F (QCC374 only) and CL/F (QCC374 only) for Day 1 and Day 112.

Additional parameters may be determined if appropriate. To denote parameters determined at steady state "ss" will be used. The parameters AUC_{last}, AUC_{tau}, and C_{max} will be converted into molar units using the molecular weight of QCC374 (443.58 g/mol) and QCM441 (415.23 g/mol) to enable the exposure comparison between the two analytes in terms of their ratio QCM441/QCC374.

5.2 Descriptive analyses

QCC374 and QCM441 plasma concentrations will be listed by dose-level, subject, and visit/sampling time point. Missing data will be labeled as such in the concentration data listings. Descriptive summary statistics will be provided by dose-level and visit/sampling time point. Summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum and maximum. Concentrations below LLOQ will be treated as zero in summary statistics and for PK parameter calculations. A geometric mean will not be reported if the dataset includes zero values.

Pharmacokinetic parameters for QCC374, QCM441 and their ratio will be listed by dose-level, visit, and subject and summarized by dose-level with descriptive statistics as listed above. Since T_{max} is generally evaluated by a nonparametric method, only median, minimum, and maximum will be reported.

Graphical methods will be employed to show mean and individual concentration-time profiles.

6 Statistical methods for Pharmacodynamic (PD) parameters

All subjects within the PD analysis set will be included in the PD data analysis.

6.1 Secondary objectives

The secondary objective of the study is to assess the treatment effect of QCC374 in PAH patients not previously dosed with QCC374 (Arm 2: those subjects previously in the placebo group).

6.1.1 Variables

The secondary variables are:

- 6MWD
- Right ventricular (RV) function with echocardiography, measured at baseline and at 16 weeks. See Table 6.1 for details.

Table 6-1 Imaging parameters (secondary endpoints)

Imaging parameter (name as in the dataset)	Description	Unit	Directionality
Tvsa	Tricuspid annular peak systolic velocity	cm/sec	Higher is better
tei_index	RV Tei Index	Unitless	Lower is better
Rvfac	RV fractional area change	%	Higher is better
Rvfwls	RV free wall average peak longitudinal strain	%	Lower is better
Tapse	Tricuspid annular plane systolic excursion	cm	Higher is better

The following two definitions of baseline will be used, and where change from baseline will be reported both definitions will be used:

1. Core: Baseline is defined as the Core study (QCC374X2201) baseline visit.
2. Extension: Baseline will be defined as the Extension study (QCC374X2201E1) baseline. The Extension baseline is defined as the Day 112 of the Core study.

6.1.2 Descriptive analyses

The secondary variables (raw values primarily, and change from baseline where needed) will be listed by arm, subject and visit/time and descriptive statistics will be provided by arm and visit/time. Summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum, maximum. A geometric mean will not be reported if the dataset includes zero values.

Graphical methods will be employed to show group summary and individual (spaghetti) plots over time by arm as required.

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7 Statistical methods for safety and tolerability data

All subjects within the Safety analysis set will be included in the safety data analysis.

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 arm and subject. Baseline characteristics will be presented both at Core (QCC374X2201) and Extension study (QCC374X2201E1) baseline. The Extension baseline, is defined, as the Extension study screening visit where the respective measurements are available (as per the assessment schedule) and Day 112 of the Core study where they are not. Summary statistics will be provided by arm.

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

Treatment

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

Summary tables will be used to present the proportion of subjects who reached each QCC374 dose, the proportion of subjects who had their dose reduced due to an adverse event, and the proportion of subjects who completed 16 weeks of treatment by dose subject received most from Day 15 to Day 112. Summary statistics for the number of days at each dose will be provided.

Vital signs

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

ECG evaluations

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

Clinical laboratory evaluations

All laboratory data will be listed by treatment, 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 arm and visit/time.

Adverse events

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

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

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.

Other safety evaluations

Spirometry

All spirometry data will be listed by subject and visit/time. Summary statistics (raw values primarily, and change from baseline) will be provided by QCC374X2201 study arm and visit/time.

Baseline is defined as the Day 112 of the Core study for the subjects who received QCC374 in the Core study, and the Screening visit of the Extension study for the subjects who received placebo in the Core study.

7.3 Graphical presentation

Boxplots to visualize trends in longitudinal safety data (vitals, ECG, lab parameter) will be created. Mean (SD) plots will be used to visualize trends for spirometry.

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