

Biostatistics & Statistical Programming /
Novartis Institutes for BioMedical Research

QCC374

CQCC374X2201

**A randomized, parallel-group, placebo-controlled subject
and investigator blinded study to assess the safety,
tolerability, pharmacokinetics and efficacy of QCC374 in
the treatment of pulmonary arterial hypertension**

Statistical Analysis Plan (SAP)

Personal Data

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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 “**CQCC374X2201**”.

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 objective

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 assess the efficacy of 16 weeks of QCC374 administration in adult patients with PAH 	<ul style="list-style-type: none"> Percentage of the baseline PVR at week 16

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 evaluate the safety and tolerability of multiple doses of QCC374 in patients with PAH 	<ul style="list-style-type: none"> AEs, SAEs and all safety assessments
<ul style="list-style-type: none"> To evaluate the preliminary efficacy of 16 weeks of QCC374 administration in patients with PAH by measuring changes from baseline in: <ul style="list-style-type: none"> <i>Six minute walk distance (6MWD)</i> <i>Hemodynamic parameters other than PVR</i> <i>Right ventricular (RV) function with echocardiography</i> 	<ul style="list-style-type: none"> 6MWD mPAP, PCWP, CO, SVR Key RV function endpoints with echocardiography including 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 patients with PAH 	<ul style="list-style-type: none"> PK parameters of primary interest (C_{max}, T_{max}, AUC_{last}, AUC_{tau}) of QCC374 and QCM441 in plasma

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1.4 Study design and treatment

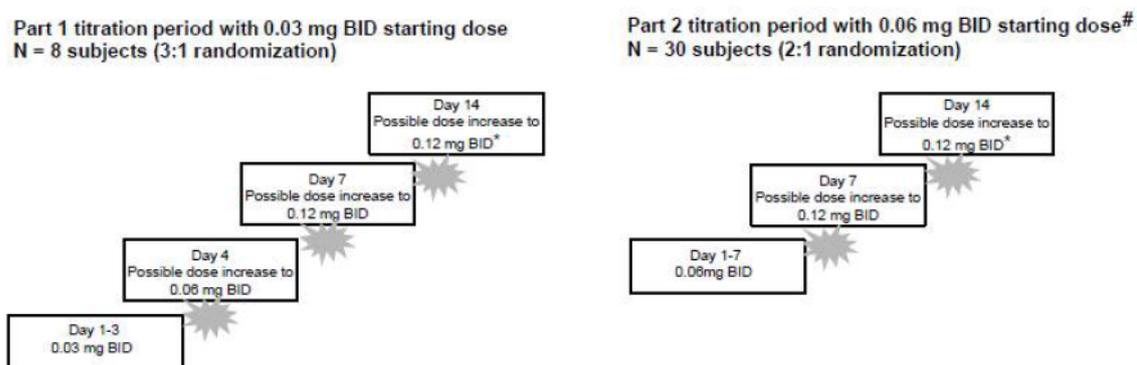
This is a non-confirmatory, randomized, subject and investigator blinded, placebo controlled study of QCC374 in PAH patients. The study will have 2 parts. In Part 1, an initial safety cohort, 8 subjects will be randomized in a 6:2 ratio and the starting dose will be 0.03 mg bid. In Part 2, approximately 30 subjects will be randomized in a 2:1 ratio, with a planned starting dose of 0.06 mg b.i.d. In both parts, subjects will be up-titrated during the first two weeks of

the study to 0.12 mg b.i.d, or to their maximum tolerated dose (MTD) if their individual MTD is below 0.12 mg b.i.d. The treatment duration is 16 weeks.

Figure 1-1: Study Periods



Figure 1-2: Part 1 and Part 2 Dose Evaluation and Titration



= dose evaluation. The investigator will assess an individual subject's clinical status and reported adverse events. The investigator will increase the dose to the next dose level *unless* he/she believes, based on their medical judgement, that the dose should not be increased due to the severity of typical pharmacologic effects of IP-receptor agonists (including headache, jaw pain, myalgia, flushing and nausea).

[#]Part 2 will begin only after a safety evaluation of Part 1, triggered when 8 subjects in Part 1 have completed 2 weeks of dosing. The safety data reviewed will include AE listings, vital signs, spirometry and ECG data. The dosing regimen in Part 2 is subject to change, based on information from Part 1.

*0.12 mg BID is the maximum dose, but a subject may continue in the study at a lower dose if 0.12 mg BID is not reached by Day 14.

2 First interpretable results (FIR)

First interpretable results (FIR) will be provided for this trial.
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FIR will focus on the following analyses:

- Analysis populations (if needed)
- Subject disposition

- Demographics and baseline characteristics. Baseline characteristics include, but 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:
 - Model estimated treatment comparison of PVR at Week 16
 - Raw geometric mean of PVR by treatment over time
 - Model estimated treatment comparison of 6MWD at Week 16
 - Raw arithmetic mean (SD) of 6MWD by treatment over time
 - Group summary plot of Hemodynamic parameters other than PVR by treatment over time
 - Group summary plot of Right ventricular (RV) function parameters with echocardiography (other than PVR) by treatment over time

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.

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. If retrospective review of RHC or echocardiogram data suggests inclusion/exclusion criteria may not have been met, additional subjects may be excluded from the PD analysis set.

Data from the two parts of the study will be pooled for the statistical analysis and treatment groups will be defined as QCC374 and placebo.

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
<i>INCL##</i>	<i>Xxxxxxx</i>	
<i>EXCL##</i>	<i>Xxxxxxx</i>	

Category Deviation code	Text description of deviation	Data exclusion
Subjects are excluded from PD analysis in case of these PDs:		Exclude subject from PD analysis set
<i>INCL##</i>	<i>Xxxxxxx</i>	
<i>EXCL##</i>	<i>Xxxxxxx</i>	
Subjects are excluded from PK and PD analysis in case of these PDs:		Exclude subject from PK and PD analysis sets
<i>INCL##</i>	<i>Xxxxxxx</i>	
<i>EXCL##</i>	<i>Xxxxxxx</i>	

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.

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} 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.

5.2.1 Supportive analyses

A subgroup analysis for smoking status may be performed for selected pharmacokinetic endpoints, if the data permits.

6 Statistical methods for Pharmacodynamic (PD) parameters

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

6.1 Primary objective

The primary objective of this study is to assess the efficacy of 16 weeks of QCC374 administration in adult patients with PAH.

6.1.1 Variables

The primary variable is the PVR (dyn· sec/cm⁵). The PVR is measured at baseline and at 16 weeks. The log transformed PVR is expected to be approximately normally distributed.

6.1.2 Descriptive analyses

The primary variable will be listed by treatment, subject and visit/time, and descriptive statistics will be provided, by treatment and visit/time. Summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum, maximum.

Box plots over time and by treatment will be created.

6.1.3 Statistical model, assumptions and hypotheses

The change from baseline (on log transformed values) will be analyzed using an ANCOVA model with treatment as a factor and log transformed baseline PVR as a covariate. Likelihood based posterior distributions, based on model adjusted means and assuming a t-distribution, will be derived to assess the probability that QCC374 is better than placebo and the probability that the reduction vs placebo is at least 15%.

The following criteria will be assessed as a guide to decision making:

Efficacy criteria at Interim analysis:

- If there is at least 90% probability that the treatment effect of QCC374 is better than placebo in PVR and
 - If there is at least 50% probability that the reduction in PVR is at least 15% (corresponding to a ratio of 0.85) in favor of QCC374 compared to placebo.
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Efficacy criteria at End of Study:

- If there is at least 90% probability that the treatment effect of QCC374 is better than placebo in PVR and
- If there is at least 50% probability that the reduction in PVR is at least 15% in favor of QCC374 compared to placebo.

6.1.3.1 Model checking procedures

The primary analysis of efficacy will be conducted only on complete cases (i.e. patients with baseline and week 16 PVR values), which is considered valid under the missing completely at random (MCAR) assumption.

6.1.3.2 Sensitivity analyses

A sensitivity analyses will be carried out in case of a low percentage of completers, especially when the percentage of completers are different between the two treatment groups. The sensitivity analyses will be performed by imputing missing values following the profile observed in the placebo group, however other sensitivity analyses with alternative missing data mechanisms may also be performed if deemed necessary.

6.1.3.3 Graphical presentation of results

The model estimated geometric mean ratio to placebo with 80% confidence intervals will be used to present the results.

6.2 Secondary objectives

The secondary objective of this study is to evaluate the preliminary efficacy of 16 weeks of QCC374 administration in patients with PAH by measuring changes from baseline in:

- Six minute walk distance (6MWD)
- Hemodynamic parameters other than PVR
- Right ventricular (RV) function with echocardiography

6.2.1 Variables

The secondary variables are:

- Six minute walk distance (6MWD), measured at baseline (defined as the average of the two measurements done prior to start of treatment), 4 weeks, 8 weeks, 12 weeks and 16 weeks.
- Hemodynamic parameters will include mPAP, PCWP, CO, SVR, mVO₂ and CI. CI will be derived as CO divided by body surface area (BSA). BSA is defined as $\sqrt{Weight(kg) * Height(cm)/3600}$. The hemodynamic parameters will be measured at baseline and at 16 weeks. See Table 6.1 for details.
- Right ventricular (RV) function with echocardiography, measured at baseline and at 16 weeks. See Table 6.2 for details.

Table 6-1 Hemodynamic parameters (secondary endpoints)

Hemodynamic parameter	Description	Unit	Directionality
mPAP	Mean pulmonary artery pressure	mmHg	Lower is better
PCWP	Pulmonary capillary wedge pressure	mmHg	Lower is better
CO	Cardiac output	L/min	Higher is better
SVR	Systemic vascular resistance	dyn· sec/cm ⁵	Lower is better
CI	Cardiac index	L/min/m ²	Higher is better
mVO ₂	Myocardial oxygen consumption	mL O ₂ /min	Higher is better

Table 6-2 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

6.2.2 Descriptive analyses

The secondary variables (raw values primarily, and change from baseline where needed) will be listed by treatment, subject and visit/time and descriptive statistics will be provided by treatment 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 treatment as required.

6.2.3 Statistical model, assumptions and hypotheses

Six-minute walk distance (6MWD)

For the 6MWD, change from baseline will be analyzed using a mixed effects model for repeated measures (MMRM). The model will investigate effects for treatment by time interaction and baseline by time interaction. An unstructured residual covariance matrix within subjects will be used if possible. The outcome of interest will be the comparison of QCC374 versus placebo after 16 weeks of treatment.

Hemodynamic parameters and right ventricular (RV) function with echocardiography

The mPAP, PCWP, CO, SVR, and RV function parameters with echocardiography will be analyzed using ANCOVA model with treatment as a factor and baseline value as a covariate. If the distribution of a variable cannot be assumed normal, log-transformation or a non-parametric test will be used.

6.2.3.1 Graphical presentation of results

For 6MWD, the model estimated mean difference to Placebo with 80% confidence intervals will be used to present the results over time.

6.2.4 Supportive analyses

A subgroup analysis for smoking status may be performed for selected pharmacodynamic endpoints, if the data permits. Also a subgroup analysis for PVR change may be performed by monotherapy vs combo therapy, if the data permits. The type of background therapy may be included in the model as a covariate as a supporting analysis, if the data permits.

Although the study is powered for only two treatment groups (QCC374 and Placebo), QCC374 may be separated exploratorily to the dose-levels the subject received in most of the study and the analysis repeated in selected pharmacodynamic endpoints, if the data permits.

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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.

7.1.1 Variables

Adverse events, vital signs (blood pressure, pulse rate, body temperature), ECG intervals, laboratory measurements, spirometry, oximetry, as well as subject demographics, baseline characteristics (including but not limited to etiology of PAH, time from PAH diagnosis, PVR, WHO FC, Borg Dyspnea Score, NT BNP level, background PAH therapy, smoking status, FEV1% predicted, lung volumes, DLco and historic right catheter vs catheter at baseline), 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 group and subject. Summary statistics will be provided by treatment group.

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 treatment group 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.

The proportion of subjects enrolled in the extension study will be summarized by treatment group.

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 treatment and visit/time. Baseline visit will be used as the baseline value.

ECG evaluations

All ECG data will be listed by treatment, subject and visit/time, abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time. Baseline visit will be used as the baseline value.

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 treatment and visit/time. Baseline visit will be used as the baseline value.

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. A subject with multiple adverse events within a body system is only counted once towards the total of this body system and treatment. Separate tables and listings will be presented indicating event severity and study drug relationship. Tables indicating incidence/severity will also be provided with a breakdown by month.

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.

Spirometry

All spirometry data will be listed by treatment, subject and visit/time. Summary statistics will be provided by treatment and visit/time.

Pulse oximetry

Oxygen saturations (%) will be listed by treatment, subject and visit/time. Summary statistics will be provided by treatment and visit/time.

7.1.3 Graphical presentation

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

7.1.4 Supportive analyses

A subgroup analysis for smoking status may be performed for selected safety endpoints, if the data permits.

