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QCC374

Clinical Trial Protocol CQCC374X2201E1

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

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Site Operations Manual (SOM)

A Site Operations Manual (SOM) accompanies this protocol, providing the operational details for study conduct. Note: The SOM will not be part of the Clinical Study Report.

Notification of serious adverse events

Dear Investigator,

You must report a serious adverse event (SAE) (initial or follow-up) to Novartis as summarized below. Refer to Section 9.2 of the protocol for SAE criteria and additional requirements. See also page 2 of the Site Operations Manual for further details on the method of reporting a SAE.

- Complete SAE report
- Submit SAE report to Novartis Chief Medical Office and Patient Safety (CMO&PS) **within 24 hours after awareness of the SAE**
- Notify the Novartis Medical Lead
- The fax number(s) and email address(es) are located in the Site Operations Manual.

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List of abbreviations

6MWD	Six Minute Walk Distance
6MWT	Six Minute Walk Test
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
ATS	American Thoracic Society
bid	twice a day
BUN	blood urea nitrogen
C-SSRS	Columbia Suicide Severity Rating Scale
cAMP	cyclic adenosine 3'5' monophosphate
CD-ROM	compact disc – read only memory
CDS	Core Data Sheet (for marketed drugs)
CFR	Code of Federal Regulation
CK	creatinine kinase
CNS	central nervous system
CO	cardiac output
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CV	coefficient of variation
CXR	chest x-ray
DMC	Data Monitoring Committee
ECG	Electrocardiogram
FDA	Food and Drug Administration
FDA	Food and Drug Administration
FEV	forced expiratory volume
FIH	first in human
FVC	forced vital capacity
GCP	Good Clinical Practice
GINA	Global Initiative for Asthma

GLP	Good Laboratory Practice
h	hour
HIV	human immunodeficiency virus
hPaSMc	human pulmonary artery smooth muscle cell
HR	heart rate
HV	healthy volunteer
Hx/Su	Hypoxia/Sugen
i.t.	intra-tracheal
i.v.	intravenous
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IPR	prostacyclin receptor
IRB	Institutional Review Board
IRT	Interactive Response Technology
LDH	lactate dehydrogenase
LLOQ	lower limit of quantification
LV	left ventricular
MAD	multiple ascending dose
MCT	monocrotaline
mg	milligram(s)
mL	milliliter(s)
mPAP	mean pulmonary artery pressure
MTD	maximum tolerated dose
NOAEL	no observed adverse effect level
NT-proBNP	N-terminal prohormone of brain natriuretic peptide
NYHA	New York Heart Association
PA	pulmonary artery
PAH	pulmonary arterial hypertension
PCWP	Pulmonary Capillary Wedge Pressure
PD	pharmacodynamic(s)
PG	pharmacogenetic

PH	pulmonary hypertension
PK	pharmacokinetic(s)
PVR	pulmonary vascular resistance
RA	right atrium
REB	Research Ethics Board
RHC	right heart catheterization
RV	right ventricular
SAD	single ascending dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SOM	Site Operations Manual
SUSAR	Suspected Unexpected Serious Adverse Reactions
TBL	total bilirubin
ULN	upper limit of normal
WHO	World Health Organization

Pharmacokinetic definitions and symbols

Ae0-t	Amount of drug (or defined metabolite) excreted into the urine from time zero to time 't' where t is a defined time point after administration [mass units or % of dose]
AUC0-t	The area under the plasma (or serum or blood) concentration-time curve from time zero to time 't' where t is a defined time point after administration [mass x time / volume]
AUCinf	The area under the plasma (or serum or blood) concentration-time curve from time zero to infinity [mass x time / volume]
AUClast	The area under the plasma (or serum or blood) concentration-time curve from time zero to the time of the last quantifiable concentration [mass x time / volume]
AUCtau	The area under the plasma (or serum or blood) concentration-time curve from time zero to the end of the dosing interval tau [mass x time / volume]
AUCtau,ss	The area under the plasma (or serum or blood) concentration-time curve from time zero to the end of the dosing interval tau at steady state [mass x time / volume]
Cav,ss	The average steady state plasma (or serum or blood) concentration during multiple dosing
CL	The systemic (or total body) clearance from plasma (or serum or blood) following intravenous administration [volume / time]
CL/F	The apparent systemic (or total body) clearance from plasma (or serum or blood) following extravascular administration [volume / time]
CLr	The renal clearance from plasma (or serum or blood) [volume / time]
Cmax	The observed maximum plasma (or serum or blood) concentration following drug administration [mass / volume]
Cmax,ss	The observed maximum plasma (or serum or blood) concentration following drug administration at steady state [mass / volume]
Cmin,ss	The lowest plasma (or serum or blood) concentration observed during a dosing interval at steady state [mass / volume]
F	Bioavailability of a compound. Fabs is the absolute bioavailability, i.e. the fraction (or percentage) of the administered extravascular dose systemically available. Frel is the relative bioavailability, i.e. the bioavailability relative to a reference
MRT	Mean residence time determined as AUMCinf/AUCinf following intravenous administration [time]
Racc	The accumulation ratio
T1/2	The terminal elimination half-life [time]

T1/2,acc	The effective half-life based on drug accumulation at steady state [time]
Tmax	The time to reach the maximum concentration after drug administration [time]
Vss	The volume of distribution at steady state following intravenous administration [volume]
Vz	The volume of distribution during the terminal elimination phase following intravenous administration [volume]
Vz/F	The apparent volume of distribution during the terminal elimination phase following extravascular administration [volume]

Glossary of terms

Assessment	A procedure used to generate data required by the study
Cohort	A specific group of subjects fulfilling certain criteria
Control drug	Any drug (an active drug or an inactive drug, such as a placebo) which is used as a comparator to the investigational drug being tested in the trial
Dosage	Dose of the study treatment given to the subject in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Enrollment	Point/time of subject entry into the study at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Epoch	Interval of time in the planned conduct of a study. An epoch is associated with a purpose (e.g. screening, randomization, treatment, follow-up), which applies across all arms of a study.
Healthy volunteer	A person with no known significant health problems who volunteers to be a study participant
Investigational drug	The study drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and Directive 2001/20/EC and is synonymous with “investigational new drug” or “test substance”
Investigational treatment	All investigational drug(s) whose properties are being tested in the study as well as their associated treatment controls. This includes any placebos, any active controls, as well as approved drugs used outside of their indication/approved dosage or tested in a fixed combination. Investigational treatment generally does not include other treatments administered as concomitant background therapy required or allowed by the protocol when used within approved indication/dosage.
Medication number	A unique identifier on the label of each study drug package in studies that dispense study drug using an IRT system.
Medication pack number	A unique identifier on the label of each drug package in studies that dispense study treatment using an IRT system
Non-investigational medicinal Product (NIMP)	Products which are not the object of investigation (e.g. any background therapy administered to each of the clinical trial subjects, regardless of randomization group, rescue medication, active drug run-ins etc.)
Part	A single component of a study which contains different objectives or populations within that single study. Common parts within a study are: a single dose part and a multiple dose part, or a part in patients with established disease and in those with newly-diagnosed disease.
Patient	An individual with the condition of interest

Period	A minor subdivision of the study timeline; divides phases into smaller functional segments such as screening, baseline, titration, washout, etc.
Premature subject withdrawal	Point/time when the subject exits from the study prior to the planned completion of all study drug administration and assessments; at this time all study drug administration is discontinued and no further assessments are planned.
Randomization number	A unique identifier assigned to each randomized subject, corresponding to a specific treatment arm assignment
Screen Failure	A subject who is screened but is not treated or randomized
Stage	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
Study completion	Point/time at which the subject came in for a final evaluation visit or when study drug was discontinued whichever is later.
Study drug discontinuation	Point/time when subject permanently stops taking study drug for any reason; may or may not also be the point/time of premature subject withdrawal.
Study drug/treatment	Any drug (or combination of drugs) administered to the subject as part of the required study procedures; includes investigational drug, active drug run-ins or background therapy.
Study treatment	Any drug administered to the study participants as part of the required study procedures; includes investigational drug (s), control(s) or non-investigational medicinal product(s)
Study treatment discontinuation	When the subject permanently stops taking study treatment prior to the defined study treatment completion date
Subject	A trial participant (can be a healthy volunteer or a patient)
Subject number	A unique number assigned to each subject upon signing the informed consent. This number is the definitive, unique identifier for the subject and should be used to identify the subject throughout the study for all data collected, sample labels, etc.
Treatment number	A unique identifier assigned in non-randomized studies to each dosed subject, corresponding to a specific treatment arm
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study
Withdrawal of consent (WoC)	Withdrawal of consent from the study is defined as when a subject does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact, and does not allow analysis of already obtained biologic material

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Protocol synopsis

Protocol number	CQCC374X2201E1
Title	Long-term, open label, multicenter, extension study to evaluate the safety and tolerability of QCC374 in patients with pulmonary arterial hypertension (PAH)
Brief title	Long-term extension study of the safety and pharmacokinetics of QCC374 in PAH patients
Sponsor and Clinical Trial Phase	Novartis Phase 2 (Extension Study)
Intervention type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this study, as a long-term open-label safety extension to the Phase 2a study of inhaled QCC374 in adult patients with PAH, is to provide patients with the option to continue receiving QCC374 after completion of the QCC374X2201 trial, and monitor the long-term safety, tolerability and efficacy of QCC374 in patients with PAH.
Primary Objective(s)	To evaluate the safety and tolerability of QCC374 in patients with PAH over a two year period

Secondary Objectives	• To assess the treatment effect of QCC374 in PAH patients not previously dosed with QCC374 (i.e., those subjects previously in the placebo group of QCC374X2201, Arm 2)
	  • Six Minute Walk Distance (6MWD)
	  • Right Ventricular (RV) function with echocardiography
	• To evaluate the pharmacokinetics of QCC374 and its metabolite QCM441 in PAH patients not previously dosed with QCC374 (i.e., subjects previously in the placebo group of QCC374X2201, Arm 2)

Study design	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 screening 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), pulse oximetry, vital signs, weight, spirometry, 6MWD, **Corporate Confidential Information** hematology, blood chemistry, body measurement and urinalysis results from the QCC374X2201 Visit Day 111 visit will be used as the baseline assessments for the extension study.

Population	The study population will be comprised of male and female PAH patients who have completed the QCC374X2201 PoC study and wish to participate in the extension study. A total of approximately 38 subjects are planned to be enrolled and randomized in the QCC374X2201 study, with approximately 30 patients expected to complete the study.
Key Inclusion criteria	• Written informed consent must be obtained before any assessment is performed. • Subject was enrolled in the QCC374X2201 study and completed per protocol
Key Exclusion criteria	• Subjects who have started receiving prostacyclin (epoprostenol), prostacyclin analogs (i.e. trepostinil, iloprost, beraprost) or prostacyclin receptor agonists (i.e. selexipag) since the last study drug intake in the QCC374X2201 study. • Females who are pregnant, or who plan to become pregnant during the study, or who are breastfeeding • Any known factor or disease that may interfere with treatment compliance or study conduct (i.e. drug or alcohol dependence) • Subjects who withdrew consent from the study QCC374X2201
Study treatment	• QCC374 0.015 mg • QCC374 0.06 mg
Efficacy/PD assessments	• 6MWD • RV function with echocardiography
Key safety assessments	• Adverse event (AE) monitoring • Physical examinations • Spirometry • ECG • Blood Chemistries, Hematology and Urinalysis
Other assessments	**Corporate Confidential Information** • PK - in those subjects who had not previously received QCC374 in the QCC374X2201 trial **Corporate Confidential Information**
Data analysis	All data for vital signs, ECG evaluations and clinical laboratory evaluations will be listed by subject and visit/time and summarized by descriptive statistics. All information obtained on AEs will be displayed by subject. The number and percentage of subjects with AEs will be tabulated by body system and preferred term and QCC374X2201 study treatment group (QCC374 or placebo). A subject with multiple AEs within a body system is only counted once towards the total of this body system. Baseline and end of study assessments from QCC374X2201 study will be included in the summary tables. Summary statistics will be presented by QCC374X2201 study treatment group. No inferential statistical analysis will be performed.
Key words	Pulmonary Arterial Hypertension

1 Introduction

1.1 Background

Pulmonary arterial hypertension (PAH) is a progressive disease characterized by chronic elevation of mean pulmonary artery pressure (mPAP) and pulmonary vascular resistance (PVR), defined as a mPAP ≥25 mmHg at rest, a PVR > 240 dyn.s.cm^{-5}, and pulmonary capillary wedge pressure (PCWP) < 15 mmHg (Galie et al 2015). The Updated Clinical Classification of Pulmonary Hypertension (Simonneau et al 2013) classifies pulmonary hypertension (PH) into five groups, based on similarities in clinical presentation, pathophysiology, prognosis and therapeutic approach. Within this classification, PAH is classified as Group 1 PH. Most cases of Group 1 PAH are idiopathic (i.e., not associated with known risk factors or conditions), but PAH also occurs in a heritable form and in association with other disorders, including collagen vascular diseases, congenital systemic-to-pulmonary shunts, ingestion of drugs/toxins or other systemic conditions such as HIV infection or portal hypertension.

A variety of arterial abnormalities characterize the pathology of PAH, including intimal hyperplasia, medial hypertrophy, adventitial proliferation, thrombosis in situ, varying degrees of inflammation, and plexiform arteriopathy. These remodeling changes are paramount in the pathogenesis of PAH, resulting in loss of luminal cross-section and increased PVR (Schermuly et al 2011), with only <20% of PAH patients demonstrating a dynamic vasoconstrictive component of their disease (McLaughlin et al 2009). Progressive vascular remodeling and increased PVR results in increased workload for the right ventricle and right ventricular failure, which is the major cause of PAH associated mortality.

Over the last 20 years, significant advances have occurred in the treatment of PAH with the development of marketed therapies targeting three pathways: the endothelin, nitric oxide and prostacyclin pathways. Therapies targeting the prostacyclin pathway include the synthetic prostacyclin epoprostenol, prostacyclin analogs such as iloprost and treprostinil, and the IPR agonist selexipag. Prostacyclins are available via intravenous (epoprostenol, treprostinil), subcutaneous (treprostinil), inhaled (nebulized treprostinil and iloprost) and oral routes (treprostinil, beraprost (Japan only), selexipag). Despite these therapies, however, PAH remains a fatal disease with a median survival from diagnosis of 7 years (Benza et al 2012).

Prostacyclin (Prostaglandin I2, PGI2) is primarily produced by endothelial cells, formed from arachidonic acid via the cyclooxygenase pathway. The prostacyclin receptor (IPR) is widely expressed on multiple cell types, including vascular smooth muscle, fibroblasts, endothelium and various inflammatory cells (Woodward et al 2011). The vasodilatory action of prostacyclins is well validated in the clinic, and there is also growing non-clinical evidence that prostacyclins will impact upon the underlying structural changes that lead to increased vascular resistance, reversing the remodeling of pulmonary vessels. Inhaled iloprost has been shown to reverse vascular remodeling in a monocrotaline (MCT) induced PAH model in the rat (Schermuly et al 2005). In addition to normalization of PVR, iloprost reduced right heart hypertrophy and pulmonary vascular thickening. In another study using the MCT model, selexipag was also able to prevent vascular remodeling (Kuwano et al 2008).

Prostacyclins have also been associated with anti-inflammatory (Hayashi et al 2010) and anti-fibrotic effects (Zhu et al 2010).

Prostacyclins (e.g. epoprostenol, treprostinil, iloprost, selexipag) have been associated with improvements in pulmonary hemodynamics in PAH patients both acutely and following short term chronic dosing (e.g., 12-17 weeks) (Barst el al 1996; McLaughlin et al 2010; Simonneau et al 2002; Simonneau et al 2012). These chronic effects are associated with improvement in exercise capacity (e.g., 6MWD) and functional status. In a 12 week open randomized study, epoprostenol was associated with improved survival in naive, severe Functional Class III/IV patients (Barst et al 1996). Most recently, in a time to clinical worsening (Phase 3 study with 1156 PAH patients treated for up to 4.2 years, selexipag decreased the risk of a worsening event versus placebo by 39%. Currently the effect of prostacyclins (and other PAH therapies) on chronic pulmonary vascular remodeling in the clinic is poorly characterized, in part due to the lack of validated endpoints/biomarkers to represent this process.

All prostacyclins have limitations impacting their safety and potential efficacy profile. Parenteral and oral IPR agonists are associated with on-target dose-limiting adverse events, including headache, jaw pain, nausea, diarrhea and hypotension, and require titration to an individual maximum tolerable dose. Nebulized iloprost and treprostinil are also dose limited by systemic adverse effects and have a relatively short duration of action, with both factors likely contributing to modest efficacy of these agents. As a result of these shortcomings, the initiation of prostacyclin therapy is delayed in some PAH patients, with a clear subsequent negative effect on prognosis (Badagliacca et al 2012).

To address these shortcomings, QCC374 has been designed as a chemically stable, selective inhaled IPR agonist for dry powder inhalation, with long duration of action (via optimized cell membrane affinity) and low systemic exposure (high plasma protein binding, rapid clearance). These characteristics are expected to lead to a considerably improved safety and tolerability profile and potentially increased efficacy compared to other members of the prostacyclin class.

1.2 Nonclinical data

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1.3 Clinical data

The safety, tolerability and pharmacokinetics of QCC374 was evaluated in healthy subjects in the QCC374X2101 study: Part 1 was a single ascending dose (SAD) study; Part 2 was a multiple ascending dose (MAD) study; and Part 3 was a within subject up-titration study in two cohorts. **Corporate Confidential Information**

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1.3.3 Human pharmacodynamic data

There is no human pharmacodynamic data available.

1.4 Study purpose

The purpose of this study, as a long-term open-label safety extension to the Phase 2a study of inhaled QCC374 in adult patients with PAH, is to provide patients with the option to continue receiving QCC374 after completion of the QCC374X2201 trial, and monitor the long-term safety, tolerability and efficacy of QCC374 in patients with PAH.

2 Study objectives and endpoints

2.1 Primary objective(s)

Primary objective(s)	***Endpoints related to primary objective(s)***
• To evaluate the safety and tolerability of QCC374 in patients with PAH over a two year period	• Adverse Events, Serious Adverse Events and all safety assessments

2.2 Secondary objective(s)

Secondary objective(s)	***Endpoints related to secondary objective(s)***
• 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)	• 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.
• 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)	• PK parameters (Cmax, AUClast, AUCtau, Ctrough) of QCC374 and QCM441in plasma

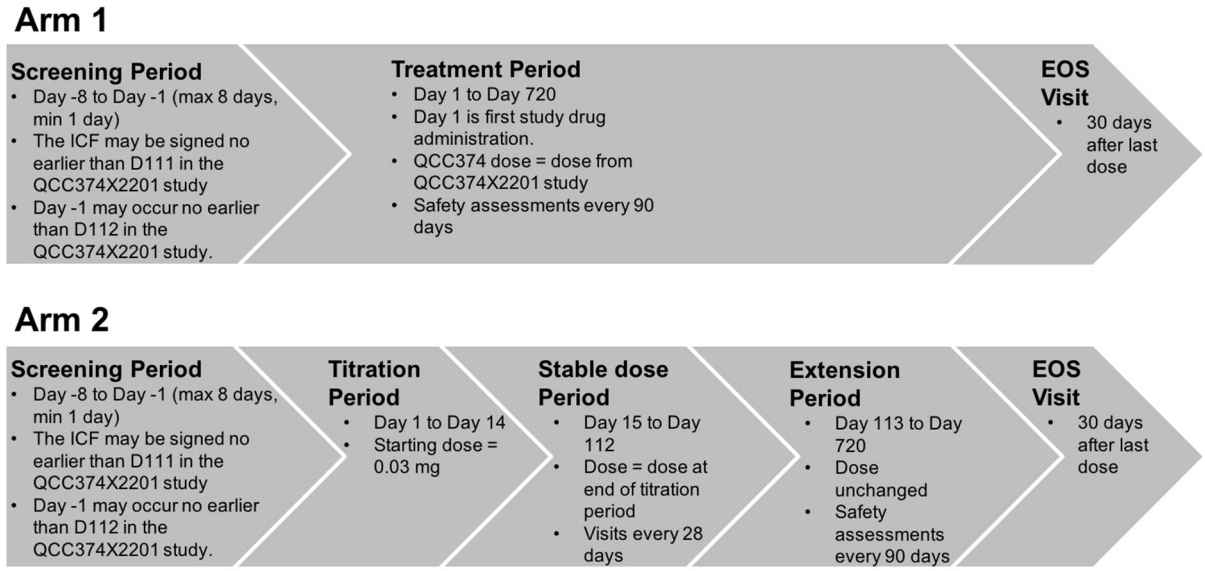
3 Investigational plan

3.1 Study design

This is a multicenter, open label trial to assess the safety, tolerability, pharmacokinetics and efficacy of inhaled QCC374 over a two year period, in subjects with PAH who have completed study QCC374X2201. This study will have two arms (Figure 3-1). In Arm 1, subjects randomized to active in the QCC374X2201 study will continue on QCC374 at their highest stable dose. In Arm 2, the subjects randomized to placebo in the QCC374X2201 study will complete a titration scheme similar to that of the active arm in QCC374X2201 protocol. For subjects in both Arms, the assessments obtained during the Day 111 visit for the companion QCC374X2201 study (including physical examination, vital signs, pulse oximetry, ECG, spirometry, 6MWD, **Corporate Confidential** and laboratory data) will be used as the baseline values for this study. **Information**

This study may be amended in the future to increase the treatment duration period, as additional data emerges for QCC374 in PAH.

Figure 3-1 QCC374X2201E1 Extension Study Design



3.1.1 Study Periods

3.1.1.1 Screening

Arm 1 (patients who received QCC374 in the companion QCC374X2201 study):

The screening period (Day-8 to Day-1, max 8 days, min 1 day) may begin no earlier than Day 111 of the companion QCC374X2201 study. Subjects may be unblinded to the main study treatment allocation and provide informed consent for this study only after all of the Day 111 assessments have been completed for the QCC374X2201 study. Day -1 in the screening period may occur no earlier than Day 112 in the companion QCC374X2201 study. The goal is for patients to continue to receive QCC374 without interruption between the QCC374X2201 study and the extension study; no more than one week (7 days) can elapse between the last dose of study drug administered in the QCC374X2201 study and the first dose of study drug administered in the QCC374X2201E study.

Arm 2 (patients who received placebo in the companion QCC374X2201 study):

The screening period (Day -8 to Day -1, max 8 days, min 1 day) may begin no earlier than Day 111 of the companion QCC374X2201 study. Subjects may be unblinded to the main study treatment allocation and provide informed consent for this study only *after* all of the Day 111 assessments have been completed for the QCC374X2201 study. Day -1 in the screening period may occur no earlier than Day 112 in the companion QCC374X2201 study. No more than one week (7 days) can elapse between the last dose of study drug administered in the QCC374X2201 study and the first dose of study drug administered in the QCC374X2201E study.

3.1.1.2 Treatment Period

Arm 1 (patients who received QCC374 in the companion QCC374X2201 study):

Arm 1 consists of a treatment period of 720 days. Subjects may be dispensed study drug for the extension study no earlier than Day -1. The first study drug administration for the QCC374X2201E extension study will occur on Day 1. The first study drug administration may occur at home if the patient was dispensed study drug on Day -1.

Subjects will continue to receive QCC374 at the same dose that was administered during the proof of concept study (0.06 mg bid or lower if their individual maximum tolerated dose (MTD) if their individual MTD was below 0.06 mg bid). At any point during the treatment period, if a subject is on 0.06 mg and the investigator believes, based on their medical judgement, that the dose should be reduced due to the severity of adverse events, the investigator may reduce the dose to 0.03 mg. The investigator may subsequently increase the dose back to the 0.06 mg dose if the investigator believes this is appropriate based on their medical judgement. A follow-up phone call should be scheduled 7 days after adjustment to review safety and tolerability of the dose adjustment.

Visits will occur every three months during the extension treatment period, but the subject may need to return for drug resupply on a monthly basis. The resupply plan is country and site specific, and the expectations for resupply should be reviewed with the subject prior to the first dispensing of study medication.

Arm 2 (patients who received placebo in the companion QCC374X2201 study):

Arm 2 consists of a treatment period of 720 days, which is further divided into a Titration Period (Day 1 to Day 14), a Stable Dose Period (Day 15 to Day 112), and an Extension Treatment Period (Day 113 to Day 720) (Figure 3-1). Subjects in Arm 2 will be dispensed study drug on Day 1, and the first study drug administration for the QCC374X2201 extension study will occur on Day 1. This study drug administration must occur in the clinic.

Arm 2 Titration Period:

The starting dose of QCC734 for subjects in Arm 2 is 0.03 mg bid.

- On Day 7 the investigator will assess the subject's clinical status, and reported adverse events. The subject's dose will be increased to 0.06 mg unless the investigator believes, based on their medical judgement, that the dose should not be increased due to the severity of typical pharmacological effects of IP-receptor agonists, such as headache, jaw pain, myalgia, flushing and nausea.
- On Day 14 the investigator will assess the subject's clinical status, and reported adverse events. If the subject is not receiving the maximum 0.06 mg bid dose, the dose level will be increased to 0.06 mg, unless the investigator believes, based on their medical judgement, that the dose should not be increased due to the severity of adverse events. If this dosing scenario occurs, the subject is allowed to continue in the trial, and will continue to receive 0.03 mg bid.
- Following the Day 14 visit no further up-titrations above the Day 14 dose are allowed. On Day 21, if the subject was up-titrated on Day 14, a follow-up phone call visit will occur to review safety and tolerability.

Arm 2 Stable Dose Period:

During the stable dose period (Day 15 to Day 112), subjects will continue to receive the QCC374 dose established during the Titration Period (0.06 mg or 0.03 mg). At any point during the stable dose period, if a subject is on 0.06 mg and the investigator believes, based on their medical judgement, that the dose should be reduced due to the severity of adverse events, the investigator may reduce the dose to 0.03 mg. The investigator may subsequently increase the dose back to the 0.06 mg dose if the investigator believes this is appropriate based on their medical judgement. A follow-up phone call should be scheduled 7 days after adjustment to review safety and tolerability of the dose adjustment. During the stable dose period the subject will return for safety assessments every 28 days.

Arm 2 Extension Period:

Once the stable dose period is complete (following Day 112), subjects will continue to receive the same dose of QCC374 throughout the extension treatment period. Visits will occur every three months during the extension treatment period, but the subject may need to return for drug resupply on a monthly basis. The resupply plan is country and site specific and the expectations should be reviewed with the subject prior to the first dispensing of study medication.

3.1.1.3 End of Study Visit

For both Arm 1 and Arm 2, an end of study visit will occur 30 days after the last treatment visit. If a patient stops study medication prematurely, at a minimum a safety evaluation must be completed, and an attempt should be made to complete all assessments indicated at the End of Study Visit.

3.2 Rationale of study design

This open-label safety extension study will offer continuous QCC374 therapy to PAH patients who have completed the study QCC374X2201, and will provide long-term safety, tolerability and efficacy data.

- Open-label: This is a long-term study designed to assess safety and all subjects will receive active treatment
- Dose-titration design: This applies only to subjects in Arm 2 (i.e. those who are initiating treatment with QCC374 at the beginning of the study). All current marketed prostacyclins have an up-titration dosing strategy to increase prostacyclin tolerability. With up-titration significantly higher prostacyclin doses can be tolerated as compared to single dose administration
- Starting dose: This applies only to subjects in Arm 2 (i.e. those who are initiating treatment with QCC374 at the beginning of the study). The starting dose in Arm 2 is 0.03 mg, which is the same as the starting dose in the QCC374X2201 study.
- Eligibility: All subjects who completed QCC374X2201 are eligible to enroll. At the time of enrollment the efficacy of QCC374 in PAH patients will be unknown, as efficacy data from QCC374X2201 will not yet be available. All subjects who completed QCC374X2201 are eligible to enroll in the extension study in order to avoid an interruption in prostacyclin therapy.
- Endpoints: The primary endpoint of this study is the number of participants with adverse events as a measure of safety and tolerability. In addition, there are secondary

Together these assessments are anticipated to inform future, larger studies of QCC374 in PAH.

3.3 Rationale for dose/regimen, route of administration and duration of treatment

There is no comparator in this open-labeled extension study.

3.4 Purpose and timing of interim analyses/design adaptations

3.5 Risks and benefits

Preclinical studies suggest that QCC374 may be of benefit for patients with PAH. However, QCC374 has not been studied previously in PAH patients and as such, the benefit for subjects participating in the study is unknown.

Prostacyclins, including the synthetic prostacyclin epoprostenol, the prostacyclin analogs treprostinil and iloprost, and the IPR agonist selexipag, have been associated a number of unwanted effects, including hypotension, jaw pain, flushing, headaches, an increased risk of bleeding, and gastrointestinal symptoms (nausea, vomiting, abdominal cramps and diarrhea). In addition, inhaled prostacyclin analogs have been associated with an increased risk of bronchospasm. As an inhaled IPR agonist, the potential risks of QCC374 are informed by prostacyclin adverse effects and some of these adverse events (headache, jaw pain, flushing) were observed in the FIH study, as described below. However, due to the QCC374's mode of administration, its high plasma-protein-binding (99.9% in humans) and its fast clearance, the systemic exposure to free QCC374 is very low, which is expected to minimize unwanted effects at the anticipated clinical doses. Furthermore, the data gained from the safety pharmacology and repeated dose toxicity studies, as well as FIH study, suggest a favorable safety and tolerability profile for QCC374.

The risk to subjects in this trial will be minimized by adherence to the eligibility criteria, close clinical monitoring, data review prior to beginning Part 2 and study stopping rules.

There may be unknown risks of QCC374 which may be serious and unforeseen.

3.5.1 Hypotension

In contrast to currently marketed prostacyclin analogs, QCC374 exerts its hemodynamic effects (on pulmonary as well as systemic vasculature) only at considerably higher doses than its antiproliferative effects. Thus, in animal studies considerable reversal of pulmonary vasculature remodeling was achieved in the absence of systemic hypotension.

To further minimize risk in the QCC374X220E1 study, any subjects enrolling in this extension study who are receiving QCC374 for the first time (Arm 2, QCC374X2201 placebo patients) will use the same starting dose as the current starting dose in QCC374X2201 study. In the event of symptomatic hypotension, subjects will be treated with standard of care.

3.5.2 Prostacyclin Associated Adverse Events

As discussed above, all marketed prostacyclins (synthetic prostacyclins, prostacyclin analogs and IPR agonists) are associated with on-target systemic adverse events, including headache, jaw pain, flushing, nausea and diarrhea. Headache, jaw pain and flushing were reported in the FIH study with QCC374. The risk of these adverse events is minimized in early clinical exploratory studies in PAH because subjects are not expected to be titrated to their individual MTD, and the overall systemic exposure is minimized due to inhaled delivery, rapid systemic clearance and high protein binding of QCC374. If a prostacyclin associated adverse event does occur, it is expected to be mild-to-moderate in severity and transient, and the subject will be treated with standard of care (e.g. acetaminophen or ibuprofen analgesia for headache).

3.5.3 Risk of Bronchospasm or Cough

No compound-driven changes in the lung or effects on respiratory function were observed in the animal studies. Reversible alterations of the laryngeal epithelium were seen in the rat inhalation studies; however, similar findings are often observed in rodent inhalation studies and are considered adaptive to extended particle exposure and not test article-specific.

Increased risk of bronchospasm, wheezing and worsening of pre-existing pulmonary edema were reported with the inhaled prostacyclin analogs treprostinil and iloprost.

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Subjects with a history of significant underlying obstructive lung disease will be excluded from early clinical development studies in PAH. Bronchospasm will be monitored by subjective clinical data (i.e., cough, shortness of breath, and chest tightness) and objective clinical data (i.e. spirometry). In the event of clinically apparent airway reactivity/irritation, subjects will be treated with standard of care (i.e., inhaled short acting beta agonist).

Corporate Confidential Information

3.5.4 Hemostasis

Inhibition of platelet aggregation constitutes a major physiological effect of prostacyclin, mediated via the IP receptor and cyclic adenosine monophosphate. Systemic and inhaled prostacyclins are reported to increase the risk of bleeding, particularly in patients with other risk factors for bleeding. Increased bleeding therefore represents a potential risk for QCC374.

Corporate Confidential Information

Throughout early clinical development studies, subjects will be monitored for evidence of increased bleeding or local pulmonary hemorrhage by subjective (shortness of breath, cough, hemoptysis) and objective clinical data (i.e. pulse oximetry, safety laboratory data). Any clinically significant findings are anticipated to be readily reversed with standard of care.

3.5.5 Phototoxicity

QCC374 absorbs UV radiation in the relevant wavelengths of natural sunlight. *In vitro* assessments measuring neutral red uptake in 3T3 cells indicate a possible phototoxic potential. However, given the low expected systemic exposures and lack of specific accumulation in organs associated with phototoxicity (i.e. skin, eyes), the phototoxicity risk is considered to be low under the conditions of intended use for QCC374. Normal precautions to minimize sun exposure should be used throughout the study.

3.5.6 Women of child bearing potential

Women of child bearing potential should be informed that taking the study drug may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the subject will not reliably comply, they should not be entered in the study.

3.5.7 Blood sample volumes

A maximum of 194 mL of blood is planned to be collected over a period of 24 months, from each subject who was an active subject in the QCC374X2201 protocol. A maximum of 331 mL of blood is planned to be collected over a period of 24 months, from each subject who was a placebo subject in the QCC374X2201 protocol. Additional samples for monitoring of any safety findings would be in addition to this. This is not considered to be a risk for this population.

Timings of blood sample collection are outlined in the Assessment Schedule, Section 8.1.

A summary blood log is provided in the Site Operations Manual, together with instructions for all sample collection, processing, storage and shipment information. See Section 8.9 regarding the potential use of residual samples.

4 Population

The study population will consist of male and female patients 18 years or older who have completed the study QCC374X2201. It is expected that all subjects who enrolled and completed the QCC374X2201 study will roll-over into QCC374X2201E1.

4.1 Inclusion criteria

Subjects eligible for inclusion in this study must fulfill **all** of the following criteria:

1. Written informed consent must be obtained before any assessment is performed.
2. Subject was enrolled in the QCC374X2201 study and completed per protocol.
3. For patients enrolling in Arm 2, the spirometry assessed at Visit 111 in the companion QCC374X2201 study must meet ATS criteria for acceptability and reproducibility. If necessary, this assessment can be repeated during the Screening Period.

4.2 Exclusion criteria

Subjects fulfilling any of the following criteria are not eligible for inclusion in this study:

1. Subjects who have started receiving prostacyclin (epoprostenol), prostacyclin analogs (i.e. trepostinil, iloprost, beraprost) or prostacyclin receptor agonists (i.e. selexipag) since the last study drug intake in the QCC374X2201 study.
2. Females who are pregnant, or who plan to become pregnant during the study, or who are breastfeeding
3. Any known factor or disease that may interfere with treatment compliance or study conduct (i.e. drug or alcohol dependence)
4. Subjects who withdrew consent from the study QCC374X2201
5. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using basic methods of contraception during dosing of investigational drug. ***Basic contraception methods include:***
    - Total abstinence from heterosexual intercourse (when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception. For Korea: total abstinence is not an allowed form of basic contraception.
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks before taking investigational drug. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
    - Male sterilization (at least 6 months prior to screening). For female subjects on the study, the vasectomized male partner should be the sole partner for that subject.
    - Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps). For UK: with spermicidal foam/gel/film/cream/vaginal suppository. For Korea: Double barrier method of contraception is required- for example, use of a cervical cap or diaphragm along with a condom.

- Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS)

In case of use of oral contraception women should be stable on the same pill for a minimum of 3 months before taking study drug.

If local regulations deviate from the contraception methods listed above and require more extensive measures to prevent pregnancy, local regulations apply and will be described in the ICF.

Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

6. Subjects who demonstrated a serious protocol deviation, determined by the Sponsor or Investigator, related to subject compliance in the study QCC374X2201.

   No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients.

NOTE: Re-screening of subjects is not allowed for anything other than the Spirometry assessment for inclusion. This assessment will be over read by a central reader and results will need to be communicated from the vendor to the site staff prior to treatment for subjects in Arm 2 in the extension study. If the subject does not meet inclusion from the Day 111 spirometry, the subject is allowed to repeat the assessment during the screening window. The repeat assessment will also need to be over read by the central vendor and the results will need to be confirmed to the site staff.

5 Restrictions for Study Subjects

During recruitment, screening/informed consent review, and baseline visit, the subjects must be informed and reminded of the restrictions outlined in this section.

5.1 Contraception requirements

Women of child bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study, and agree that in order to participate in the study they must adhere to the contraception requirement outlined in the Section 4.2 (Exclusion Criteria). If there is any question that the subject will not reliably comply, they should not be enrolled or continue in the study.

5.2 Prohibited treatment

The use of inhaled, intravenous, subcutaneous or oral prostacyclins (e.g., epoprostenol, treprostinil, iloprost or selexipag) in the 3 months prior to screening, during the screening period or during the treatment period of the trial is not allowed. In the event of a clinically relevant deterioration of the patient's signs or symptoms of PAH, the investigator may consider starting treatment with an alternative prostacyclin. The decision should be based on the investigator's assessment of the patient's well-being and safety, and should be documented in the case report form (CRF). Patients who require prostacyclin therapy must discontinue study treatment.

5.3 Dietary restrictions and smoking

No alcohol for 48 hours prior to all clinic visits and while in the clinic.

On the days when PK is collected, ensure standardized dosing conditions, compound administration will take place 30 min before or after food intake.

5.4 Other restrictions

- For those subjects who were randomized to placebo in the QCC374X2201, there should be no significant change in physical exercise program from the beginning of the study until after the visit has been completed for Day 112. If a subject is participating in a pulmonary rehabilitation program at the time of screening, then participation may continue throughout the study period.
- All subjects should avoid direct sunlight exposure, or, in the event of unavoidable direct sunlight exposure, use topical sun blocking agents

6 Treatment

6.1 Study treatment

Details on the requirements for storage and management of study treatment, and instructions to be followed for subject numbering, prescribing/dispensing and taking study treatment are outlined in the SOM.

6.1.1 Investigational treatment and control drugs

The investigational drug, QCC374 0.015 mg and 0.06 mg will be prepared by Novartis and supplied to the Investigator.

6.2 Treatment arms

All subjects will receive QCC374 during this extension study. Refer to Section 3.1 and Section 3.2 for information on dosing schedule and rationale.

6.3 Treatment assignment and randomization

As this is an open-label extension trial, subjects will maintain the same subject number allocated in the QCC374X2201 protocol. This is not a randomized trial. Additional information for the unblinding of subjects in the QCC374X2201 protocol can be found in the SOM.

6.4 Treatment blinding

As this is an open-label study design, blinding does not apply.

6.5 Treating the subject

QCC374 will be administered to the subject via inhaled administration with the Concept1 dry powder inhaler. Throughout the duration of the extension study, administration will occur at home on an outpatient basis. See the SOM for further details.

Sponsor qualified medical personnel will be readily available to advise on trial related medical questions or problems.

6.6 Permitted dose adjustments and interruptions of study treatment

For patients who are unable to tolerate the preferred protocol-specified dosing scheme, dose adjustments are permitted. The guidelines found in Section 3.1 should be followed.

6.7 Emergency breaking of assigned treatment code

All subjects will receive QCC374 throughout this open label extension study.

6.8 Treatment exposure and compliance

PK parameters (measures of treatment exposure) will be determined in subjects who had not previously received QCC374 (placebo patients from the QCC374X2201 study), as detailed in Section 8.7.

6.9 Recommended treatment of adverse events

Because QCC374 is an inhaled prostacyclin receptor agonist, subjects enrolled in this study may experience typical prostacyclin-associated adverse events, including headache, jaw pain, and flushing. If a subject experiences these adverse events, the subject may use standard of care therapy, including non-opioid analgesics, to relieve any associated symptoms.

In addition, given the inhaled route of administration, there is a risk of local irritation within the airway, including coughing or wheezing. If a subject experiences significant coughing or respiratory symptoms during the study period, the site Investigator should use standard of care therapy, including a short-acting beta-agonist, to relieve symptoms.

Medication used to treat AEs must be recorded on the Concomitant medications/Significant non-drug therapies CRF.

6.10 Rescue medication

Rescue medication is defined as an additional medication, or change in the dose of an existing medication, for the treatment of PAH.

Use of rescue medication must be recorded on the Concomitant medications/Significant non-drug therapies CRF after start of study drug.

6.11 Concomitant treatment

All treatments for PAH are allowed, except for those mentioned in the prohibited treatment section. It is allowed to modify the type or dose of concomitant PAH therapy during the study and these changes should be document in the CRF. The reason for the decision should also be documented.

7 Study completion and discontinuation

7.1 Study completion and post-study treatment

This study will enroll subjects for a planned period of two years. Study completion will either be defined as a voluntary withdrawal or the Sponsor termination of the trial.

All subjects should have a safety follow-up call conducted 30 days after the last clinic visit. The information collected is kept as source documentation. All SAEs reported during this time period must be reported as described in Section 9.2 and the SOM. Documentation of attempts to contact the subject should be recorded in the source documentation.

7.2 Discontinuation of study treatment

Patients may voluntarily discontinue study treatment for any reason at any time. The investigator should discontinue study treatment for a given patient if, on balance, he/she believes that continuation would be detrimental to the patient's well-being.

Study treatment must be discontinued under any of the following circumstances and the reason for discontinuation must be indicated on the CRF:

- Patient withdraws consent.
- Pregnancy (see Section 8.6 (Safety) and Section 9.6 (Pregnancy reporting))
- Clinically significant bronchospasm reflected in spirometry assessments believed to be related to study drug.
- Occurrence of adverse events which the investigator or sponsor judges unacceptable for continuation of participation in the trial.
- Any protocol deviation that results in a significant risk to the patient's safety.
- Use of prohibited treatment (referring to relevant section in the full protocol), including if an investigator decides to initiate therapy with a different prostacyclin analogue or prostacyclin receptor agonist

Patients who discontinue study treatment or who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent. If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, e-mail, and letter) should be made to contact them.

7.3 Withdrawal of informed consent

Subjects may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a subject:

- Does not want to participate in the study anymore, and
- Does not allow further collection of personal data

In this situation, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the subject's decision to withdraw his/her consent and record this information.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the subject are not allowed unless safety findings require communicating or follow-up.

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the subject's study withdrawal should be made as detailed in the assessment table.

Novartis will continue to keep and use collected study information (including any data resulting from the analysis of a subject's samples until their time of withdrawal) according to applicable law.

For US: All biological samples not yet analyzed at the time of withdrawal may still be used for further testing/analysis in accordance with the terms of this protocol and of the informed consent form.

For EU and ROW: All biological samples not yet analyzed at the time of withdrawal will no longer be used, unless permitted by applicable law. They will be stored according to applicable legal requirements.

7.4 Lost to follow-up

For subjects whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator should show "due diligence" by documenting in the source documents steps taken to contact the subject, e.g. dates of telephone calls, registered letters, etc. A subject cannot be formally considered lost to follow-up until his/her scheduled end of study visit would have occurred.

7.5 Study Stopping rules

The study will be placed on hold and no further enrollment of subjects on placebo in QCC374X2201 will occur pending a full safety review if any of the following criteria are met:

- The principle investigator (or his designee) and the sponsor consider that the number and/or severity of adverse events may justify discontinuation of the study
- A safety concern is identified, either during the ongoing safety review conducted by the sponsor in the QCC374X2201 study or the ongoing safety review conducted by the sponsor in this study, which may justifies discontinuation of the study
- The sponsor unilaterally requests it

Any subjects currently being dosed in QCC374X2201 or QCC374X2201E1 will be allowed to continue dosing during the safety review, as long as they have not met an individual discontinuation rule.

7.6 Early study termination by the sponsor

The study can be terminated by Novartis at any time for any reason. This may include reasons related to the benefit/ risk assessment of participating in the study, practical reasons (including slow enrollment), or for regulatory or medical reasons. Should this be necessary, subjects must be seen as soon as possible and treated as a prematurely withdrawn subject. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the subject's interests. The investigator will be responsible for informing IRBs/IECs of the early termination of the trial.

8 Procedures and assessments

8.1 Assessment schedule

Table 8-1 Arm 1 Assessment Schedule (Subjects who completed QCC374X2201 and received QCC374)

Epoch	Extension Screening	Extension-Treatment[5,6]																		
Visit Name	Extension Screening																			
Visit Numbers[1]	301	401	406	408	410	412	413	414	415	416	417	418	419	420	421	422	423	424	425	426
Study Day(s)	-8 to -1 (max 8 days, min 1 day)	1[7]	30 ±5	60 ±5	90 ±5	120 ±5	150 ±5	180 ±5	210 ±5	240 ±5	270 ±5	300 ±5	330 ±5	360 ±5	390 ±5	420 ±5	450 ±5	480 ±5	510 ±5	540 ±5
Time (post-dose)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Informed consent	X[2]																			
Inclusion / Exclusion criteria	X																			
Physical examination					X			X			X			X			X			X
Pulse oximetry					X			X			X			X			X			X
Vital Signs					X			X			X			X			X			X
Pregnancy test	X[3]				X[3]			X[3]			X[3]			X[3]			X[3]			X[3]
Body weight																				
Blood chemistry					X			X			X			X			X			X
Hematology					X			X			X			X			X			X
Urinalysis					X			X			X			X			X			X
Spirometry					X			X			X			X			X			X
ECG evaluation					X			X			X			X			X			X
6-Minute Walk Test					X			X			X			X			X			X
					X			X			X			X			X			X
Corporate Confidential Information					X			X			X			X			X			X
					X															
					X															

Epoch	Extension Screening	Extension-Treatment[5,6]																		
Visit Name	Extension Screening																			
Visit Numbers[1]	301	401	406	408	410	412	413	414	415	416	417	418	419	420	421	422	423	424	425	426
Study Day(s)	-8 to -1 (max 8 days, min 1 day)	1[7]	30 ±5	60 ±5	90 ±5	120 ±5	150 ±5	180 ±5	210 ±5	240 ±5	270 ±5	300 ±5	330 ±5	360 ±5	390 ±5	420 ±5	450 ±5	480 ±5	510 ±5	540 ±5
Time (post-dose)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Corporate Confidential Information					X															
					X															
Echocardiogram																				
Corporate Confidential Information		X																		
Drug dispensation	X[4]	X[4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study drug administration		Study drug administration will be bid - refer to Section 3.1 and Site Operational Manual[7]																		
Concomitant medications		As Required																		
Adverse events		As Required																		
Serious adverse events		As Required																		
Comments		As Required																		
Study/epoch completion information	X																			

Epoch	Extension-Treatment[5,6]						
Visit Name							EOS (30 days post last treatment)
Visit Numbers[1]	427	428	429	430	431	432	433[5]
Study Day(s)	570 ±5	600 ±5	630 ±5	660 ±5	690 ±5	720 ±5	750 ±5
Time (post-dose)	-	-	-	-	-	-	-
Informed consent							
Inclusion / Exclusion criteria							
Physical examination			X			X	X
Pulse oximetry			X			X	X
Vital Signs			X			X	X
Pregnancy test			X[3]			X[3]	X[3]
Body weight							X
Blood chemistry			X			X	X
Hematology			X			X	X
Urinalysis			X			X	X
Spirometry			X			X	X
ECG evaluation			X			X	X
6-Minute Walk Test			X			X	X
			X			X	
			X			X	
						X	
						X	
Corporate Confidential Information						X	
						X	
Echocardiogram							
Corporate Confidential Information	X						
Drug dispensation	X	X	X	X	X	X	
Study drug administration	Study drug administration will be bid - refer to Section 3.1 and Site Operational Manual						

Epoch	Extension-Treatment[5,6]						
Visit Name							EOS (30 days post last treatment)
Visit Numbers[1]	427	428	429	430	431	432	433[5]
Study Day(s)	570 ±5	600 ±5	630 ±5	660 ±5	690 ±5	720 ±5	750 ±5
Time (post-dose)	-	-	-	-	-	-	-
Concomitant medications	As Required						
Adverse events	As Required						
Serious adverse events	As Required						
Comments	As Required						
Study/epoch completion information							X

[1] Visit structure given for internal programming purpose only

[2] The earliest that informed consent can occur is Day 111 in the companion QCC374X2201 study, and informed consent can occur no later than 7 days after Day 111.

[3] Urine Pregnancy Test (females only)

[4] The first drug study dispensation may occur on Day -1 or Day 1.

[5] If a patient stops study medication prematurely, at a minimum, a safety evaluation must be completed. Then an attempt should be made to complete all assessments listed under Visit 433, with the investigator making the determination of what is safe and feasible to complete.

[6] If the subject's dose was altered at any point during the extension treatment period, a follow-up phone call visit should be conducted 7 days post dose change for a review of safety and tolerability.

[7] The goal is for subjects to continue to receive QCC374 without interruption from the QCC374X2201 study, so that no doses are missed. The first study drug administration must occur within 7 days of the last study drug administration in the QCC374X2201 study.

Table 8-2 Arm 2 Assessment Schedule (Subjects who completed QCC374X2201 and received placebo)

Epoch	Extension Screening	Extension-Treatment[8,9]																		
Visit Name	Extension Screening	Titration									Stable Dose Follow Up				Long Term Follow Up					
Visit Numbers[1]	301	401[5]							403	404	405	407	409	411[5]	413	414	415	416	417	418
Study Day(s)	-8 to -1 (max 8 days, min 1 day)	1							7 ±1	14 ±1	28 ±2	56 ±2	84 ±2	112 ±2	150 ±5	180 ±5	210 ±5	240 ±5	270 ±5	300 ±5
Time (post-dose)		0m[6]	5m	15m	30m	2h	4h	-	-	-	-	-	-	-	-	-	-	-	-	-
Informed consent	X[2]																			
Inclusion / Exclusion criteria	X																			
Physical examination		X					X		X	X	X	X	X	X		X			X	
Pulse oximetry		X		X			X		X	X	X	X	X	X		X			X	
Vital Signs		X		X			X		X	X	X	X	X	X		X			X	
Pregnancy test	X[3]													X[3]		X[3]			X[3]	
Body weight																				
Blood chemistry		X[7]									X	X	X	X		X			X	
Hematology		X[7]									X	X	X	X		X			X	
Urinalysis		X[7]									X	X	X	X		X			X	
Spirometry	X[4]					X	X		X	X	X	X	X	X		X			X	
ECG evaluation					X		X		X	X	X	X	X	X		X			X	
6-Minute Walk Test											X	X	X	X		X			X	
											X	X	X	X		X			X	
											X	X	X	X		X			X	
											X	X	X	X						
Corporate Confidential Information														X						
														X						
														X						
Echocardiogram														X						

Epoch	Extension Screening	Extension-Treatment[8,9]																		
Visit Name	Extension Screening	Titration									Stable Dose Follow Up				Long Term Follow Up					
Visit Numbers[1]	301	401[5]							403	404	405	407	409	411[5]	413	414	415	416	417	418
Study Day(s)	-8 to -1 (max 8 days, min 1 day)	1							7 ±1	14 ±1	28 ±2	56 ±2	84 ±2	112 ±2	150 ±5	180 ±5	210 ±5	240 ±5	270 ±5	300 ±5
Time (post-dose)		0m[6]	5m	15m	30m	2h	4h	-	-	-	-	-	-	-	-	-	-	-	-	-
Corporate Confidential Information			X																	
Drug dispensation			X						X	X	X	X	X	X	X	X	X	X	X	X
Study drug administration			Study drug administration will be bid - refer to Section 3.1 and Site Operations Manual																	
PK blood collection		See table below																		
Concomitant medications		As required																		
Adverse events		As required																		
Serious adverse events		As required																		
Comments		As required																		
Study/epoch completion information	X																			

Epoch	Extension-Treatment[8,9]														
Visit Name	Long Term Follow Up														EOS (30 days post last treatment visit)
Visit Numbers[1]	419	420	421	422	423	424	425	426	427	428	429	430	431	432	433[8]
Study Day(s)	330 ±5	360 ±5	390 ±5	420 ±5	450 ±5	480 ±5	510 ±5	540 ±5	570 ±5	600 ±5	630 ±5	660 ±5	690 ±5	720 ±5	750 ±5
Time (post-dose)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Informed consent															
Inclusion / Exclusion criteria															
Physical examination		X			X			X			X			X	X
Pulse oximetry		X			X			X			X			X	X
Vital Signs		X			X			X			X			X	X
Pregnancy test		X[3]			X[3]			X[3]			X[3]			X[3]	X[3]
Body weight															X
Blood chemistry		X			X			X			X			X	X
Hematology		X			X			X			X			X	X
Urinalysis		X			X			X			X			X	X
Spirometry		X			X			X			X			X	X
ECG evaluation		X			X			X			X			X	X
6-Minute Walk Test		X			X			X			X			X	X
		X			X			X			X			X	
Corporate Confidential Information		X			X			X			X			X	
														X	
														X	
														X	
														X	
Echocardiogram															
Corporate Confidential Information	X														

Epoch	Extension-Treatment[8,9]														
Visit Name	Long Term Follow Up														EOS (30 days post last treatment visit)
Visit Numbers[1]	419	420	421	422	423	424	425	426	427	428	429	430	431	432	433[8]
Study Day(s)	330 ±5	360 ±5	390 ±5	420 ±5	450 ±5	480 ±5	510 ±5	540 ±5	570 ±5	600 ±5	630 ±5	660 ±5	690 ±5	720 ±5	750 ±5
Time (post-dose)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Drug dispensation	X	X	X	X	X	X	X	X	X	X	X	X	X		
Study drug administration	Study drug administration will be bid - refer to Section 3.1 and Site Operations Manual														
PK blood collection	See Table 8-3 below														
Concomitant medications	As required														
Adverse events	As required														
Serious adverse events	As required														
Comments	As required														
Study/epoch completion information														X	X

[1] Visit structure given for internal programming purpose only

[2] The earliest that informed consent can occur is Day 111 in the companion QCC374X2201 study, and informed consent can occur no later than 7 days after Day 111.

[3] Urine Pregnancy Test (females only)

[4] Spirometry assessment during screening is only required if the spirometry testing session for V111 in the QCC374X2201 study did not meet ATS criteria for acceptability and reproducibility.

[5] Domiciling is optional. The subject should remain in the clinic until all assessments are complete.

[6]Assessments to be completed immediately prior to first QCC374 administration.

[7] Assessments to be repeated prior to dosing if more than 4 days have elapsed since the D111 QCC374X2201 assessments.

[8] If a patient stops study medication prematurely, at a minimum, a safety evaluation must be completed. Then an attempt should be made to complete all assessments listed under Visit 433, with the investigator making the determination of what is safe and feasible to complete.

[9] If the subject's dose was altered at any point during the extension treatment period, a follow-up phone call visit should be conducted 7 days post dose change for a review of safety and tolerability.

Table 8-3 Arm 2 PK blood collection (Subjects who completed QCC374X2201 and received placebo)

Epoch	Visit Name	Visit Numbers	Day	Time (post-dose)	PK blood collection
Extension Screening	Extension Screening	301	1	0m	X
Extension-Treatment	Titration	401	1	5m	X
				15m	X
				30m	X
				1h	X
				2h	X
				4h	X
				8h	X
	Stable Dose Follow Up	411	112 -2 +2	0m	X
				5m	X
				15m	X
				30m	X
				1h	X
				2h	X
				4h	X
				8h	X

NOTE: Additional visit information can be found in Table 8-2

8.2 Informed consent procedures

Eligible subjects may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC-approved informed consent.

Novartis will provide to investigators a proposed informed consent form that complies with the ICHE6 GCP guideline and regulatory requirements and is considered appropriate for this study. **Corporate Confidential Information**

Any changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC.

Information about common side effects already known about the investigational drug can be found in the Investigator's Brochure (IB). This information will be included in the subject informed consent and should be discussed with the subject during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated as appropriate, for example, via an Investigator Notification or an Aggregate Safety Finding. New information might require an update to the informed consent and then must be discussed with the subject.

A copy of the approved version of all consent forms must be provided to the Novartis monitor after IRB/IEC approval.

8.3 Subject screening

Subjects are only allowed to participate in the trial if they have successfully completed the QCC374X2201 study and have signed consent for this trial. Additional information can be found in the SOM.

8.4 Subject demographics/other baseline characteristics

Subject demographic and baseline characteristic data will be collected on all subjects. Relevant medical history/current medical conditions data will also be collected until signature of informed consent. Details are outlined in the SOM.

Investigators have the discretion to record abnormal test findings on the medical history CRF, if in their judgment, the test abnormality occurred prior to the informed consent signature.

8.5 Efficacy / Pharmacodynamics

Pharmacodynamic (PD) samples will be collected at the time points defined in the Assessment schedule, Section 8.1. Follow instructions outlined in the SOM regarding sample collection, numbering, processing and shipment.

In order to better define the PD profile, the timing of the sample collection may be altered based on emergent data. The number of samples/blood draws and total blood volume collected will not exceed those stated in the protocol. PD samples will be obtained and evaluated in all subjects at all dose levels.

8.5.1 Echocardiogram

In this trial, this assessment will only be completed for subjects who were randomized to placebo in the QCC374X2201 study, (Arm 2). For the assessment of the impact of QCC374 on right and left heart structure and function, echocardiography will be performed based on the clinical practice and local regulation. All imaging will be performed where possible using the same ultrasound scanner. The methods for assessment and recording are specified in the imaging manual/charter.

The coded medical images will be used primarily for analysis as described in this protocol; however, the images may also be used for the development and evaluation of new analysis methods directly related to the area of research that this study covers.

8.5.2 6-Minute Walk Test

A standardized 6MWT will be performed in accordance with ATS guidelines (ATS 2002). The 6MWT measures how many meters a person can walk in 6 minutes. Repeated measurement of the 6MWT over time has been used in studying numerous musculoskeletal, pulmonary, and cardiovascular conditions and is a validated outcome in investigational drug trials.

For the Borg score component, the patient will answer questions on a scale of one to ten in order to determine the patient's shortness of breath during the 6MWT. During the 6MWT the patient will be connected to a portable pulse oximeter via a finger probe and oximetry results will be monitored. As soon as the test is complete, the patient will be asked to sit down and the SaO2, HR and Borg score values will be recorded.

Patients resting values of oxygen saturation (%), heart rate (b/min), blood pressure and Borg score will be recorded in the CRF before the test, at the end of the test and two minutes after the end of the test. Total distance walked (meters), the number and duration of any stops and whether the patient completed the test will also be recorded in the CRF.

Requirement of rescue medication including oxygen therapy and any adverse events occurring during the 6MWT will be recorded. If the patient is on chronic oxygen therapy, oxygen should be given at the standard rate (and at the same rate during each 6MWT procedure) or as directed by the investigator.

Additional information on this assessment can be found in the SOM.

8.6 Safety

Safety assessments are specified below; methods for assessment and recording are specified in the SOM, with the Assessment Schedule (Section 8.1) detailing when each assessment is to be performed.

8.6.1 Spirometry

Spirometry testing will be performed according to the American Thoracic Society guidelines (Miller et al 2005) as detailed in the Assessment Schedule (Section 8.1).

The spirometry equipment will be supplied for the study. The same spirometry equipment should be used for all assessments performed by a subject. A limited number of staff, as designated by the investigator, will evaluate all patients at all visits throughout the entire trial. Where possible the same technician should perform all maneuvers for an individual subject. All staff conducting the spirometry tests must have received appropriate training which must be documented. Information on the procedures can be found in the SOM.

8.6.2 Physical Examination

Information can be found in the SOM.

8.6.3 Vital Signs

At multiple time points referenced in the Assessment Schedule (Section 8.1), Blood Pressure, Pulse and Body Temperature will need to be recorded.

8.6.4 Pulse Oximetry

Oxygen saturations (%) will be measured by pulse oximetry using a SpO2 finger sensor. The timing of the assessments can be found in the Assessment Schedule (Section 8.1) and results will be recorded in the CRFs.

8.6.5 Body weight

Weight will need to be recorded as referenced in the Assessment Schedule (Section 8.1).

8.6.6 Laboratory Evaluations

Clinically relevant deviations of laboratory test results occurring during or at completion of the study must be reported and discussed with Novartis personnel. The results should be evaluated for criteria defining an adverse event and reported as such if the criteria are met. Repeated evaluations are mandatory until normalization of the result(s) or until the change is no longer clinically relevant. In case of doubt, Novartis personnel should again be contacted.

Hematology

Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential and platelet count will be measured. In addition, aPTT and PT/INR will be assessed.

Clinical chemistry

Sodium, potassium, creatinine, urea, uric acid, chloride, albumin, calcium, alkaline phosphatase, total bilirubin, LDH, GGT, AST, ALT, aPTT, CK, glucose, total cholesterol, triglycerides. If the total bilirubin concentration is increased above 1.5 times the upper limit of normal, direct and indirect reacting bilirubin should be differentiated.

Urinalysis

Urine test by dipstick e.g. Combur9: leucocytes, nitrite, pH, protein, glucose, ketones, urobilinogen, bilirubin, blood/ hemoglobin

If the dipstick result is positive for protein, nitrite, leucocytes and/or blood, the sample will be sent for microscopic analysis of WBC, RBC and casts.

8.6.7 Pregnancy and Assessment of Fertility

All pre-menopausal women who are not surgically sterile will have pregnancy testing. See the Assessment schedule (Section 8.1), for timing of the protocol required pregnancy testing; additional pregnancy testing may be performed to meet local requirements. A positive urine pregnancy test must be immediately confirmed with a serum β-hCG, and if the serum β-hCG is found to be positive, study treatment must be discontinued.

Refer to Section 9.6 for details on Reporting Pregnancy.

8.6.8 ECG

ECGs will be assessed locally. Full details of all procedures relating to the ECG collection and reporting are contained in the SOM.

8.7 Pharmacokinetics

Only those subjects who had been randomized to placebo in the PoC study (QCC374X2201) will have blood samples collected outlined in Table 8-3. Blood sampling times need to be adhered to sampling schedules.

In order to better define the PK profile, the timing of the PK sample collection may be altered based on emergent data. The number of samples/blood draws and total blood volume collected will not exceed those stated in the protocol.

Further details on sample collection, numbering, processing and shipment can be found in the SOM.

8.7.1 PK Sample Collection

All samples will be given a unique sample number and a collection number. Each site is to ensure the correct sample number is reflected on the respective tube. The actual sample collection time will be entered on the PK blood collection page of the CRF. Sampling problems will be commented in the CRFs provided to the site.

Further details on sample collection, numbering, processing and shipment can be found in the SOM.

8.7.2 Bioanalytical Method

QCC374 and QCM441 concentrations in plasma samples will be determined by a validated LC-MS/MS method; the Lower Limit of Quantification (LLOQ) is 5 pg/mL for QCC374 and 20 pg/mL for QCM441. Biofluid concentrations will be expressed in mass per volume units and referring to the free base. Missing data will be labelled as such in the concentration data listings. Concentrations below LLOQ will be treated as zero in summary statistics for concentration data as well as for calculation of PK parameters.

PK samples remaining after completion of the determination of QCC374 and QCM441 may be used for exploratory assessment of metabolites or other bioanalytical purposes (e.g. cross check between different sites, stability assessment). Given the exploratory nature of the work, the analytical method used for those assessments will not be validated and results will not be reported in the CSR.

8.7.3 Calculation of PK Parameters

For standard pharmacokinetic abbreviations and definitions see the list provided at the beginning of this protocol.

The following pharmacokinetic parameters of QCC374 and QCM441 (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: Cmax, Tmax, AUClast, AUCtau for Day 1 and Day 112

Secondary: Tlast, T1/2, Tmin, Cmin, fluctuation index, Cav, Vz/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 AUClast, AUCtau, and Cmax will be transferred 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.

The linear trapezoidal rule will be used for AUC calculation. Regression analysis of the terminal plasma elimination phase for the determination of T1/2 will include at least 3 data points after Cmax. If the adjusted R^2 value of the regression analysis of the terminal phase will be less than 0.75 and the extrapolated AUC will be greater than 20%, no values will be reported for AUCtau, T1/2, CL/F, and Vz/F.

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9 Safety monitoring

9.1 Adverse events

An AE is any untoward medical occurrence (i.e., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject or clinical investigation subject *after providing written informed consent* for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

The occurrence of adverse events should be sought by non-directive questioning of the subject at each visit during the study. AEs also may be detected when they are volunteered by the subject during or between visits or through physical examination, laboratory test, or other assessments.

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms,
- they are considered clinically significant,
- they require therapy.

Clinically significant abnormal laboratory values or test results should be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in patients with underlying disease. Investigators have the responsibility for managing the safety of individual subject and identifying adverse events. Alert ranges for liver related events are included in Section 9.3.

Adverse events must be recorded on the Adverse Events CRF for subjects that have been randomized into the study. The adverse events should be reported according to the signs, symptoms or diagnosis associated with them, and accompanied by the following information:

- The severity grade:
  - mild: usually transient in nature and generally not interfering with normal activities
  - moderate: sufficiently discomforting to interfere with normal activities
  - severe: prevents normal activities
- Relationship to the study treatment
- Duration (start and end dates) or if the event is ongoing, an outcome of not recovered/not resolved should be reported.
- Whether it constitutes a serious adverse event (SAE). See Section 9.2 for definition of SAE.
- Action taken regarding study treatment. All adverse events should be treated appropriately. Treatment may include one or more of the following:
  - no action taken (i.e. further observation only)
  - study treatment dosage adjusted/temporarily interrupted
  - study treatment permanently discontinued due to this adverse event
  - concomitant medication given
  - non-drug therapy given
  - subject hospitalized/subject's hospitalization prolonged
- Outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown).

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

Information about common side effects already known about the investigational drug can be found in the Investigator Brochure (IB) or will be communicated between IB updates in the form of Investigator Notifications (IN). This information will be included in the subject informed consent and should be discussed with the subject during the study as needed.

The investigator should also instruct each subject to report any new adverse event (beyond the protocol observation period) that the subject, or the subject's personal physician, believes might reasonably be related to study treatment. This information should be recorded in the investigator's source documents, however, if the AE meets the criteria of an SAE, it must be reported to Novartis.

9.2 Serious adverse event reporting

9.2.1 Definition of SAE

An SAE is defined as any adverse event (appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s) or medical conditions(s) which meets any one of the following criteria:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - elective or pre-planned treatment for a pre-existing condition (that is unrelated to the indication under study) and has not worsened since the start of study drug
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
  - social reasons and respite care in the absence of any deterioration in the patient's general condition
- is medically significant, i.e. defined as an event that jeopardizes the subject or may require medical or surgical intervention.

Life-threatening in the context of a SAE refers to a reaction in which the subject was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe.

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse.

All AEs (serious and non-serious) are captured on the CRF and SAEs also require individual reporting to the Drug Safety and Epidemiology Department as per Section 9.2.2.

9.2.2 SAE reporting

To ensure subject safety, every SAE, regardless of causality, occurring after the subject has provided informed consent and until 30 days after the last study visit must be reported to Novartis within 24 hours of learning of its occurrence as described below. Any SAEs experienced after this should only be reported to Novartis if the investigator suspects a causal relationship to study treatment.

Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode, regardless of when the event occurs. This report must be submitted within 24 hours of the investigator receiving the follow-up information. An SAE that is considered completely unrelated to a previously reported one should be reported separately as a new event.

SAEs (initial and follow-up) that are recorded electronically in the Electronic Data Capture system should be entered, saved and e-signed within 24 hours of awareness of the SAE or changes to an existing SAE. These data will automatically be submitted to Novartis Drug Safety & Epidemiology immediately after investigator signature or 24 hours after entry, whichever occurs first. Study site personnel must also inform the Clinical Trial Leader.

Follow- up information provided should describe whether the event has resolved or continues, if and how it was treated, whether the treatment code was broken or not and whether the subject continued or withdrew from study participation. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the investigational treatment a Drug Safety and Epidemiology Department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same investigational treatment that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

Note: SAEs reported by subjects deemed to be screen failures must be reported to Novartis as outlined here with appropriate information also captured in the CRFs as specified in the SOM.

9.3 Liver safety monitoring

To ensure subject safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of liver events has to be followed.

Please refer to Table 15-1-Appendix 1 for complete definitions of liver events.

Follow-up of liver events

Every liver event defined in Table 15-1-Appendix 1 should be followed up by the investigator or designated personnel at the trial site, as summarized below. Additional details on actions required in case of liver events are outlined in Table 15-2-Appendix 1.

- Repeating liver chemistry tests (ALT, AST, TBL, PT/INR, ALP and γGT) to confirm elevation within 48-72 hours.

These LFT repeats should be performed using the central laboratory if possible. If this is not possible, then the repeats can be performed at a local laboratory to monitor the safety of the patient. Repeats laboratory should then be performed at central laboratory as soon as possible. If a liver event is subsequently reported, any local LFTs previously conducted that are associated with this event should be reported on the appropriate CRF pages.

- If the initial elevation is confirmed, close observation of the subject will be initiated, including consideration of treatment interruption if deemed appropriate.
- Discontinuation of the investigational drug (refer to Section 7.2 Discontinuation of study treatment if appropriate)
- Hospitalization of the subject if appropriate
- Causality assessment of the liver event
- Thorough follow-up of the liver event should include:
    - Repeating liver chemistry tests two or three times weekly. Testing should include ALT, AST, ALP, PT/INR, and γGT. If total bilirubin is elevated > 2 x ULN, fractionation into direct and indirect bilirubin is required. To rule out muscular origin of transaminase elevations, CPK should be measured along with liver chemistry tests. Frequency of retesting can decrease to once a week or less if abnormalities stabilize or the study drug has been discontinued and the subject is asymptomatic. Retesting should be continued up to resolution.
    - Obtaining a more detailed history of symptoms and prior or concurrent diseases.
    - Obtaining a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets.
    - Exclusion of underlying liver disease, as specified in Table 15-3.
    - Imaging such as abdominal US, CT or MRI, as appropriate
    - Obtaining a history of exposure to environmental chemical agents.
    - Considering gastroenterology or hepatology consultations.

All follow-up information, and the procedures performed must be recorded as appropriate in the CRF.

9.4 Renal safety monitoring

Every renal laboratory trigger or renal event must be followed up by the investigator or designated personnel at the trial site. Recommended follow-up assessments are listed in Appendix 2.

9.5 Reporting Medication errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, patient/subject or consumer (EMA definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

All study treatment errors and uses outside of what is foreseen in the protocol will be collected in the dose administration record (DAR) CRF. Study treatment errors are only to be reported to Novartis Drug Safety and Epidemiology department if the treatment error is associated with an SAE.

All instances of misuse or abuse must be documented in the adverse event (AE) CRF irrespective of the misuse/abuse being associated with an AE/SAE. In addition, all instances of misuse or abuse must be reported to Novartis Drug Safety and Epidemiology. As such, instances of misuse or abuse are also to be reported using the SAE form/CRF. Table 9-1 summarizes the reporting requirements.

Table 9-1 Summary of reporting requirements for medication errors

Treatment error type	Document in Dose Administration (DAR) CRF	Document in AE CRF	Complete SAE form/CRF
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes	Yes, even if not associated with a SAE

For more information on AE and SAE definition and reporting requirements, please see Section 9.1 and Section 9.2, respectively.

9.6 Pregnancy reporting

To ensure patient safety, each pregnancy in a subject on study drug must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. The study drug must be discontinued, though the subject may stay in the study, if she wishes to do so. All assessments that are considered as a risk during pregnancy must not be performed. The subject may continue all other protocol assessments. Pregnancy must be recorded on a Pharmacovigilance Pregnancy Form and reported by the investigator to the local Novartis Drug Safety and Epidemiology Department. Pregnancy

follow-up should be recorded on the same form and should include an assessment of the possible relationship to the Novartis study drug of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on an SAE Report Form

9.7 Prospective suicidality assessment

The Investigator will monitor adverse events in an ongoing manner and inform the Sponsor of any clinically relevant observations.

When two or more clinical site(s) are participating in the clinical study, the Sponsor will advise the Investigator(s) at all sites in writing (e-mail) (and by telephone if possible) of any new, clinically relevant safety information reported from another site during the conduct of the study in a timely manner

10 Data review and database management

10.1 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and CRFs with the investigators and their staff. During the study Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The monitor will visit the site to check the completeness of subject records, the accuracy of entries on the CRFs, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study drug is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the monitor during these visits.

The investigator must maintain source documents for each subject in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the subject's file. The investigator must also keep the original informed consent form signed by the subject (a signed copy is given to the subject).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the CRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the eligibility criteria, documentation of SAEs, and the recording of data that will be used for all primary and safety variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the subjects will be disclosed.

10.2 Data collection

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms using fully validated software that conforms to 21 CFR Part 11 requirements. Designated investigator site staff will not be given access to the electronic data capture system until they have been trained. Automatic validation programs check for data discrepancies and, by generating appropriate error messages, allow the data to be confirmed

or corrected before transfer of the data to the CRO working on behalf of Novartis. The Investigator must certify that the data entered into the Electronic Case Report Forms are complete and accurate. After database lock, the investigator will receive a CD-ROM or paper copies of the subject data for archiving at the investigational site.

Data not requiring a separate written record will be defined in the SOM and Assessment Schedule and can be recorded directly on the CRFs. All other data captured for this study will have an external originating source (either written or electronic) with the CRF not being considered as source.

10.3 Database management and quality control

All data should be recorded, handled and stored in a way that allows its accurate reporting, interpretation and verification.

The CRO working on behalf of Novartis will review the data entered into the eCRFs by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions. Queries are sent to the investigational site using an electronic data query. Designated investigator site staff is required to respond to the query and confirm or correct the data. If the electronic query system is not used, a paper Data Query Form will be faxed to the site. Site personnel will complete and sign the faxed copy and fax it back to CRO working on behalf of Novartis who will make the correction to the database.

Concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Laboratory samples will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

ECG readings and Spirometry will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

All data in reference to dispensing of study drug(s) to the subject and all IRT recorded dosage changes will be tracked using Interactive Response Technology (IRT). The system will be supplied by a vendor, who will also manage the database. The database will be sent electronically to Novartis (or a designated CRO).

The occurrence of any protocol deviations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked and the treatment codes will be unblinded and made available for data analysis. Any changes to the database after that time can only be made by joint written agreement between the Global Head of Clinical Information Sciences and the Clinical Franchise Head.

10.4 Data Monitoring Committee

This study will not be using a Data Monitoring Committee (DMC), as this is an open label study. However, the QCC374X2201 trial will be using a DMC, which will have a charter completed prior to the FPFV and will meet on a regular basis. A Data Monitoring Committee (DMC) is a group of professionals, experienced in clinical care and/or clinical research, assembled to provide additional safety oversight to a clinical study. The QCC374X2201 DMC will consist of four members, with one member being a statistician.

10.5 Adjudication Committee

Not required

11 Data analysis

The analysis will be conducted on all subject data at the time the trial ends. Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

11.1 Analysis sets

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

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 with no protocol deviations that impact on PK data.

The PD analysis set will include all subjects with available PD data and no protocol deviations with relevant impact on PD data.

11.2 Subject demographics and other baseline characteristics

All data for background and demographic variables will be listed by subject.

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

11.3 Treatments

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

11.4 Analysis of the primary variable(s)

The primary aim of the study is to evaluate safety and tolerability of QCC374 in patients with PAH over a two year period.

11.4.1 Variable(s)

Safety and tolerability assessments include vital signs, ECG evaluations, clinical laboratory evaluations and AEs.

11.4.2 Statistical model, hypothesis, and method of analysis

All data for vital signs, ECG evaluations and clinical laboratory evaluations will be listed by subject and visit/time and summarized by descriptive statistics.

All information obtained on AEs will be displayed by subject. The number and percentage of subjects with AEs will be tabulated by body system and preferred term and QCC374X2201 study treatment group (QCC374 or placebo). A subject with multiple AEs within a body system is only counted once towards the total of this body system.

Baseline and end of study assessments from QCC374X2201 study will be included in the summary tables. Summary statistics will be presented by QCC374X2201 study treatment group.

No inferential statistical analysis will be performed.

11.4.3 Handling of missing values/censoring/discontinuations

All patients who received study drug will be included in the safety and tolerability evaluation.

11.4.4 Summary statistics of safety

Vital signs

All vital signs data will be listed by subject, and visit/time and if ranges are available abnormalities (and relevant orthostatic changes) will be flagged. Summary statistics will be provided by QCC374X2201 study treatment and visit/time.

ECG evaluations

All ECG data will be listed by subject and visit/time, abnormalities will be flagged. Summary statistics will be provided by QCC374X2201 study treatment and visit/time.

Clinical laboratory evaluations

All laboratory data will be listed by subject and visit/time and if normal ranges are available abnormalities will be flagged. Summary statistics will be provided by QCC374X2201 study treatment and visit/time.

Adverse events

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

The number and percentage of subjects with adverse events will be tabulated by body system and preferred term with a breakdown by QCC374X2201 study treatment. A subject with multiple adverse events within a body system is only counted once towards the total of this body system.

Other safety evaluations

All spirometry data will be listed by subject and visit/time. Summary statistics will be provided by QCC374X2201 study treatment and visit/time.

11.4.5 Sensitivity analyses

Not applicable.

11.5 Analysis of secondary variable(s)

11.5.1 Efficacy / Pharmacodynamics

Data from 6MWD and RV structure and function with echocardiography will be listed by subject and visit/time and summarized descriptively. Baseline and end of study assessments from QCC374X2201 study will be included in the summary tables.

No inferential statistical analysis will be performed.

11.5.2 Pharmacokinetics

QCC374 and its metabolite QCM441 plasma concentration data will be listed by subject, and visit/sampling time point. Descriptive summary statistics will be provided by visit/sampling time point, including the frequency (n, %) of concentrations below the LLOQ and reported as zero.

Summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum and maximum. An exception to this is Tmax where median, minimum and maximum will be presented. 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 will be calculated as described in Section 8.7 and will be listed by subject.

11.5.3 Pharmacokinetic / pharmacodynamic interactions

Not Applicable.

11.5.4 Other assessments

There will be no other assessments than what has been previously documented.

11.7 Sample size calculation

As this is an open-label extension of a previous study (QCC374X2201), no sample size calculation is done.

11.8 Power for analysis of key secondary variables

Not applicable.

12 Ethical considerations

12.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US Code of Federal Regulations Title 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

12.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g. advertisements) and any other written information to be provided to subjects. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and

records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

For multi-center trials, a Coordinating Investigator will be selected by Novartis around the time of Last Patient Last Visit to be a reviewer and signatory for the clinical study report.

12.3 Publication of study protocol and results

The key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

13 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of subjects should be administered as deemed necessary on a case by case basis. Under no circumstances is an investigator allowed to collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs under the protocol.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and health authorities, where required, it cannot be implemented.

13.1 Protocol Amendments

Any change to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC prior to implementation.

Amendments that are intended to eliminate an apparent immediate hazard to subjects may be implemented immediately, provided the Health Authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any subject included in this study, even if this action represents a deviation from the protocol. In such cases, the reporting requirements identified in Section 9 (Safety Monitoring) must be followed and the Study Lead informed.

14 References

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15 Appendix 1: Liver Event Definitions and Follow-up Requirements

Table 15-1 Liver Event Definitions

Definition	Thresholds
Potential Hy's law cases	• ALT or AST > 3 × ULN and TBL > 2 × ULN without initial increase in ALP to > 2 × ULN
ALT or AST elevation with coagulopathy	• ALT or AST > 3 × ULN and INR > 1.5 (in the absence of anticoagulation)
ALT or AST elevation accompanied by symptoms	• ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash, or eosinophilia
Isolated ALT or AST elevation	• ALT or AST > 8 × ULN • 5 x ULN < ALT/AST £ 8 x ULN • 3 x ULN < ALT/AST £ 5 x ULN
Isolated ALP elevation	• ALP > 2 × ULN (in the absence of known bone pathology)
Others	• Any clinical event of jaundice (or equivalent term) • Any adverse event potentially indicative of liver toxicity

Table 15-2 Actions required for Liver Events

Criteria	Actions required
Potential Hy's Law case ALT or AST elevation with coagulopathy ALT or AST elevation accompanied by symptoms Isolated ALT or AST elevation > 8 × ULN Jaundice	• Discontinue the study treatment immediately • Hospitalize, if clinically appropriate • Establish causality • Complete CRFs per liver event guidance
Isolated ALT or AST elevation > 5 to ≤ 8 × ULN	• If confirmed, consider interruption or discontinuation of study drug • If elevation persists for more than 2 weeks, discontinue the study drug • Establish causality • Complete CRFs per liver event guidance
Isolated ALT or AST elevation > 3 to ≤ 5 × ULN (patient is asymptomatic)	• Monitor liver chemistry tests two or three times weekly
Isolated ALP elevation	• Repeat liver chemistry tests within 48-72 hours • If elevation is confirmed, measure fractionated ALP; if >50% is of liver origin, establish hepatic causality • Complete CRFs per liver event guidance
Any AE potentially indicative of liver toxicity	• Consider study treatment interruption or discontinuation • Hospitalize if clinically appropriate • Complete CRFs per liver event guidance

Table 15-3 Exclusion of underlying liver disease

Disease	Assessment
Hepatitis A, B, C, E	• IgM anti-HAV; HBSAg, IgM anti-HBc, HBV DNA; anti-HCV, HCV RNA, IgM & IgG anti-HEV, HEV RNA
CMV, HSV, EBV infection	• IgM & IgG anti-CMV, IgM & IgG anti-HSV; IgM & IgG anti-EBV
Autoimmune hepatitis	• ANA & ASMA titers, total IgM, IgG, IgE, IgA
Alcoholic hepatitis	• Ethanol history, gGT, MCV, CD-transferrin
Nonalcoholic steatohepatitis	• Ultrasound or MRI
Hypoxic/ischemic hepatopathy	• Medical history: acute or chronic CHF, hypotension, hypoxia, hepatic venous occlusion. Ultrasound or MRI.
Biliary tract disease	• Ultrasound or MRI, ERCP as appropriate.
Wilson disease	• Caeruloplasmin
Hemochromatosis	• Ferritin, transferrin
Alpha-1-antitrypsin deficiency	• Alpha-1-antitrypsin

16 Appendix 2: Specific Renal Alert Criteria and Actions

Table 16-1 Specific Renal Alert Criteria and Actions

Criteria	Action required
Serum creatinine (sCr) increase 25 – 49% compared to baseline	• Consider causes and possible interventions • Follow up within 2-5 days
Serum creatinine increase ≥ 50%	• Consider causes and possible interventions • Repeat assessment within 24-48h if possible • Consider drug interruption or discontinuation unless other causes are diagnosed and corrected • Consider hospitalization and specialized treatment
Protein-creatinine or albumin-creatinine ratio increase ≥ 2-fold or new onset dipstick proteinuria ≥ 1+ or Albumin-creatinine ratio (ACR) ≥ 30 mg/g or ≥ 3 mg/mmol; or Protein-creatinine ratio (PCR)≥ 150 mg/g or >15 mg/mmol	• Consider causes and possible interventions • Assess serum albumin & serum protein • Repeat assessment to confirm • Consider drug interruption or discontinuation unless other causes are diagnosed and corrected
New onset glucosuria on urine dipstick (unless related to concomitant treatment, diabetes)	Assess & document: • Blood glucose (fasting) • Serum creatinine • Urine albumin-creatinine ratio
New hematuria on dipstick	Assess & document: • Urine sediment microscopy • Assess sCr and urine albumin-creatinine ratio • Exclude infection, trauma, bleeding from the distal urinary tract/bladder, menstruation • Consider bleeding disorder

Additional specialized assessments are available to assess renal function or renal pathology. (Note: In exceptional cases when a nephrologist considers a renal biopsy, it is strongly recommended to make specimen slides available for evaluation by Novartis to potentially identify project-wide patterns of nephrotoxicity.)

Whenever a renal event is identified, a detailed subject history and examination are indicated to identify, document and potentially eliminate risk factors that may have initiated or contributed to the event:

- Blood pressure assessment (after 5 min rest, with an appropriate cuff size)
- Signs and symptoms such as fever, headache, shortness of breath, back or abdominal pain, dysuria, hematuria, dependent or periorbital edema
- Changes in blood pressure, body weight, fluid intake, voiding pattern, or urine output
- Concomitant events or procedures such as trauma, surgical procedures, cardiac or hepatic failure, contrast media or other known nephrotoxin administration, or other potential causes of renal dysfunction, e.g., dehydration, hemorrhage, tumor lysis

Table 16-2 Follow-up of renal events

Action	Follow up
Assess*, document and record in the Case Report Form (CRF) or via electronic data load. Review and record possible contributing factors to the renal event (co-medications, other co-morbid conditions) and additional diagnostic procedures (MRI etc) in the CRF.	• Urine dipstick and sediment microscopy • Blood pressure and body weight • Serum creatinine, electrolytes (sodium, potassium, phosphate, calcium), bicarbonate and uric acid • Urine output
Monitor subject regularly (frequency at investigator's discretion) until:	• Event resolution: (sCr within 10% of baseline or protein-creatinine ratio within 50% of baseline) or • Event stabilization: sCr level with ±10% variability over last 6 months or protein-creatinine ratio stabilization at a new level with ±50% variability over last 6 months.

* Urine osmolality: in the absence of diuretics or chronic kidney disease this can be a very sensitive metric for integrated kidney function that requires excellent tubular function. A high urinary osmolality in the setting of an increase in sCr will point toward a "pre-renal" cause rather than tubular toxicity.