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Novartis Institutes for BioMedical Research

QCC374

Clinical Trial Protocol CQCC374X2201

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

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## Site Operations Manual (SOM)

A Site Operations Manual (SOM) accompanies this protocol, providing the operational details for study conduct.

## Notification of serious adverse events

Refer to Section 9.2 of the protocol for definitions and reporting requirements for Serious Adverse Events (within 24 hours after awareness of the SAE to the local Novartis Chief Medical Office and Patient Safety Department and notify the Clinical Trial Leader.).

Contact information is listed 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 |
| bid | twice a day |
| BMI | body mass index |
| BUN | blood urea nitrogen |
| cAMP | cyclic adenosine 3'5' monophosphate |
| CAMPHOR | Cambridge Pulmonary Hypertension Outcome Review |
| CD-ROM | compact disc – read only memory |
| CFR | Code of Federal Regulation |
| CK | creatinine kinase |
| CNS | central nervous system |
| CO | cardiac output |
| $CO_2$ | carbon dioxide |
| CRF | case report/record form (paper or electronic) |
| CRO | contract research organization |
| CV | coefficient of variation |
| CXR | chest x-ray |
| ECG | Electrocardiogram |
| 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 | Pharmacogenetics |
| PH | pulmonary hypertension |
| PK | pharmacokinetic(s) |

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|---|---|
| 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 |
| SVR | systemic vascular resistance |
| TBL | total bilirubin |
| ULN | upper limit of normal |
| WHO | World Health Organization |

## Pharmacokinetic definitions and symbols

| | |
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| 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] |
| 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 |
| 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] |

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| 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

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| Control drug | A study drug used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug. |
| Enrollment | Point/time of subject entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol). |
| 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 is synonymous with "investigational new drug" or "investigational medicinal product". |
| 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. |
| 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 |
| 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. |

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| Subject | An individual who has consented to participate in this study. The term Subject may be used to describe either a healthy volunteer or a patient. |
| Subject number | A number assigned to each subject who enrolls in the study. When combined with the center number, a unique identifier is created for each subject in the study. |
| Variable | Information used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified timepoints. |

## Protocol synopsis

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| **Protocol number** | [CQCC374X2201] |
| **Title** | A randomized, parallel-group, placebo-controlled subject and investigator blinded study to assess the safety, tolerability, pharmacokinetics and efficacy of QCC374 in the treatment of pulmonary arterial hypertension (PAH) |
| **Brief title** | Safety, pharmacokinetics and efficacy study of QCC374 in PAH patients |
| **Sponsor and Clinical Phase** | Novartis<br>Phase II (non-confirmatory) |
| **Intervention type** | Drug |
| **Study type** | Interventional |
| **Purpose and rationale** | This study is designed as a proof of concept study for QCC374, an inhaled prostacyclin receptor (IPR) agonist for the treatment of PAH. The purpose of this study is to assess the safety, tolerability, pharmacokinetics and efficacy of QCC374 in adult patients with PAH to determine if QCC374 has an adequate clinical profile to warrant further clinical development in this indication. |
| **Primary Objective(s)** | To assess the efficacy of 16 weeks of QCC374 administration in patients with PAH by measuring the change from baseline in pulmonary vascular resistance (PVR). |
| **Secondary Objectives** | • To evaluate the safety and tolerability of multiple doses of QCC374 in patients with PAH<br>• To evaluate the preliminary efficacy of 16 weeks of QCC374 administration in patients with PAH by measuring changes from baseline in:<br>  • Six minute walk distance (6MWD)<br>  • Hemodynamic parameters other than PVR<br>  • Right ventricular function with echocardiography<br>• To evaluate the pharmacokinetics of QCC374 and its metabolite QCM441 in patients with PAH |
| **Study design** | This is a non-confirmatory, randomized, subject and investigator blinded, placebo controlled study of QCC374 in PAH patients. The study will have 2 parts. In Part 1, an initial safety cohort, 8 subjects will be randomized in a 6:2 ratio and the starting dose will be 0.03 mg bid. In Part 2, ~ 30 subjects will be randomized in a 2:1 ratio, with a starting dose of 0.03 mg bid. In Part 1, subjects will be up-titrated during the first two weeks of the study to 0.12 mg bid, or to their maximum tolerated dose (MTD) if their individual MTD is below 0.12 mg bid during the first two weeks of the study.<br>In Part 2, subjects will be up-titrated during the first two weeks of the study to 0.06 mg bid, or will remain at the starting dose of 0.03 mg bid if the investigator believes, based on their medical judgement, that the dose should not be increased.<br>The treatment duration is 16 weeks. |
| **Population** | The study population for Parts 1 and 2 will be comprised of male and female adults with symptomatic PAH. A total of approximately 38 patients are planned to be enrolled and randomized, with approximately 30 patients expected to complete the study. The sample size will be re-estimated at the interim analysis and number of randomized patients may be increased up to a maximum of 60. |

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| **Inclusion criteria** | Male and female patients 18 years of age or older with symptomatic PAH.<br><br>Subjects with PAH belonging to one of the following subgroups of the Updated Clinical Classification Group 1 (Nice, 2013):<br>• idiopathic PAH<br>• familial PAH<br>• PAH associated with connective tissue disease, congenital heart disease (surgically repaired at least 12 months prior to screening) or drug or toxin induced (for example, anorexigen use).<br><br>Subjects must have persistent symptoms due to PAH despite therapy with at least one of the following PAH medications: an endothelin receptor antagonist, a soluble guanylate cyclase stimulator or a phosphodiesterase inhibitor. The subjects' PAH medication regimen, with typical medications including endothelin receptor antagonists, soluble guanylate cyclase stimulators and/or phosphodiesterase inhibitors, must have been used at a stable dose and frequency for at least 12 weeks before the screening visit and during the screening period.<br><br>Diagnosis of PAH established according to the standard criteria before the screening visit:<br>• Resting mean pulmonary arterial pressure (mPAP) ≥ 25 mmHg<br>• PVR > 240 dyn·s/cm$^5$<br>• Pulmonary capillary wedge pressure (PCWP) or left ventricular end diastolic pressure ≤ 15 mmHg<br><br>PVR > 400 dyn·s/cm$^5$ at the time of the baseline right heart catheterization (RHC) (if a RHC was completed within one month of the screening visit, that result may be used for inclusion, if data meets criteria outlined in Section 8.5.1).<br><br>6MWD greater than 150 meters at screening. This distance must be confirmed by a second 6MWT prior to randomization. The value of the second 6MWD should be within ± 15% of the value obtained at screening. |
| **Exclusion criteria** | Subjects with clinically unstable right heart failure within the last three months (New York Heart Association (NYHA) Class IV).<br><br>Subjects with PAH associated with portal hypertension, Human Immunodeficiency Virus (HIV) infection or unrepaired congenital systemic to pulmonary shunts<br><br>Subjects who have received or have been scheduled to receive long-term treatment with epoprostenol or any prostacyclin within the three months prior to the screening visit or during the screening period.<br><br>Hypotensive subjects (systemic systolic blood pressure < 85 mmHg)<br><br>Subjects with three or more of the following left ventricular disease/dysfunction risk factors: Body mass index (BMI) > 30 kg/m2 at the screening visit (BMI = Body weight (kg) / [Height (m)]$^2$); History of Essential Hypertension; Diabetes Mellitus – any type; Medical history of significant coronary artery disease (CAD).<br><br>Subjects with left sided heart disease, chronic left sided heart failure, congenital or acquired valvular disease and/or pulmonary venous hypertension.<br><br>Subjects with obstructive (FEV1/FVC < 70% and FEV1 < 70% predicted) or restrictive (total lung capacity < 65% predicted and/or clinically significant abnormality on CXR) lung disease at screening. |

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| **Investigational and reference therapy** | • QCC374 0.015 mg<br>• QCC374 0.06 mg |
| **Efficacy/PD assessments** | • PVR<br>• 6MWD<br>• mPAP, PCWP, Cardiac Output (CO), Systemic Vascular Resistance (SVR)<br>• Right Ventricular (RV) function with echocardiography |
| **Safety assessments** | • Spirometry<br>• Electrocardiogram (ECG)<br>• Chest X-ray (CXR)<br>• Blood Chemistries, Hematology and Urinalysis |
| **Other assessments** | • Pharmacokinetics (PK)<br>Corporate Confidential Information |
| **Data analysis** | Data from the two parts of the study will be pooled for the statistical analysis.<br>The primary variable is PVR. The log transformed PVR is expected to be approximately normally distributed. The change from baseline (on log transformed values) will be analyzed using an Analysis of Covariance (ANCOVA) model with treatment as a factor and log transformed baseline PVR as a covariate. Likelihood based posterior distributions will be derived to assess the probability that QCC374 is better than placebo and the probability that the reduction vs placebo is at least 15%.<br>The efficacy criteria at the end of the study is as follows:<br>• If there is at least 90% probability that the treatment effect of QCC374 is better than placebo in PVR and<br>• If there is at least 50% probability that the reduction in PVR is at least 15% in favor of QCC374 compared to placebo. |
| **Key words** | Pulmonary Arterial Hypertension, Prostacyclin |

# 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 $\geq$ 25 mmHg at rest, a PVR > 240 dyn.s.cm$^{-5}$, and pulmonary capillary wedge pressure (PCWP) $\leq$ 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.

## 1.4 Study purpose

This study is designed as a proof of concept study for QCC374, an inhaled IPR agonist for the treatment of PAH. The purpose of this study is to assess the safety, tolerability, PK and efficacy of QCC374 in adult patients with PAH and determine if QCC374 has an adequate clinical profile to warrant further clinical development in this indication.

# 2 Study objectives and endpoints

## 2.1 Primary objective(s)

| ***Primary objective(s)*** | ***Endpoints related to primary objective(s)*** |
|---|---|
| • To assess the efficacy of 16 weeks of QCC374 administration in adult patients with PAH | • Percentage of the baseline PVR at week 16. |

## 2.2 Secondary objective(s)

| ***Secondary objective(s)*** | ***Endpoints related to secondary objective(s)*** |
|---|---|
| • To evaluate the safety and tolerability of multiple doses of QCC374 in patients with PAH | • AEs, SAEs and all safety assessments |
| • To evaluate the preliminary efficacy of 16 weeks of QCC374 administration in patients with PAH by measuring changes from baseline in:<br>  • Six minute walk distance (6MWD)<br>  • Hemodynamic parameters other than PVR<br>  • Right ventricular (RV) function with echocardiography | • 6MWD<br>• mPAP, PCWP, CO, SVR<br>• Key RV function endpoints with echocardiography including but not limited to tricuspid annular peak systolic velocity (TA S'), RV Tei index and RV fractional area change. |
| • To evaluate the pharmacokinetics of QCC374 and its metabolite QCM441 in patients with PAH | • PK parameters of primary interest (Cmax Tmax, AUClast, AUCtau) of QCC374 and QCM441 in plasma. |

# 3 Investigational plan

## 3.1 Study design

This is a non-confirmatory, randomized, subject and investigator blinded, placebo controlled study of QCC374 in PAH patients. The study will have 2 parts: Part 1, an initial safety cohort with a 0.03 mg bid starting dose, and Part 2, a larger cohort with a 0.03 mg bid starting dose. An unblinded review of all available safety data will be reviewed prior to starting Part 2. The treatment duration is 16 weeks for both parts.

### Study flow and procedures (common to all parts, Figure 3-1):

### Screening Period (up to 28 days)

During this period eligibility will be confirmed. During the screening phase subjects do not receive any study medication.

### Titration Period (2 weeks)

The study dose can be titrated during the initial two week period, as described below for Parts 1 and 2.

### Stable Dose Follow-up (14 weeks)

No further adjustments in dose should occur unless a dose reduction for tolerability or safety reasons is indicated. In the event of a dose reduction, the subject could subsequently be increased back to the dose achieved at the end of the Titration Period, but increases above the dose level reached at the end of the Titration Period are not allowed.

### Safety Follow-up Period:

For all patients stopping study treatment prematurely at any time of the study or who decide not to participate in the long term extension phase study, a safety follow-up visit 28 days after the stop of study medication intake should be performed.

**Figure 3-1 Study Periods**


- Screening Period: up to 28 days
- Titration Period: 2 weeks
- Stable Dose Follow-up Period: 14 weeks
- Safety Follow-up Period: 4 weeks*

*only for patients who do not enter the open label extension trial (there will be a separate protocol for QCC374X2201E1 study) or who stop the study medication prematurely

**General Notes:**

- QCC374 will be administered via inhalation using the Concept1 dry powder inhaler
- At the end of the treatment period of 16 weeks, eligible patients will be given the option to participate in a separate long term extension study, where all patients will be treated with an individual optimal dose of QCC374.
- Patients who complete Visit 108 (Day 111) and do not wish to enroll in the extension study will receive study drug on the morning of Visit 109 (Day 112) and complete PK and indicated safety assessments. These patients will not receive the pm dose of study drug. The last visit for these patients is the End of Study Visit (Visit 202), 28 days after receiving last dose of study drug.

### 3.1.1 Part 1

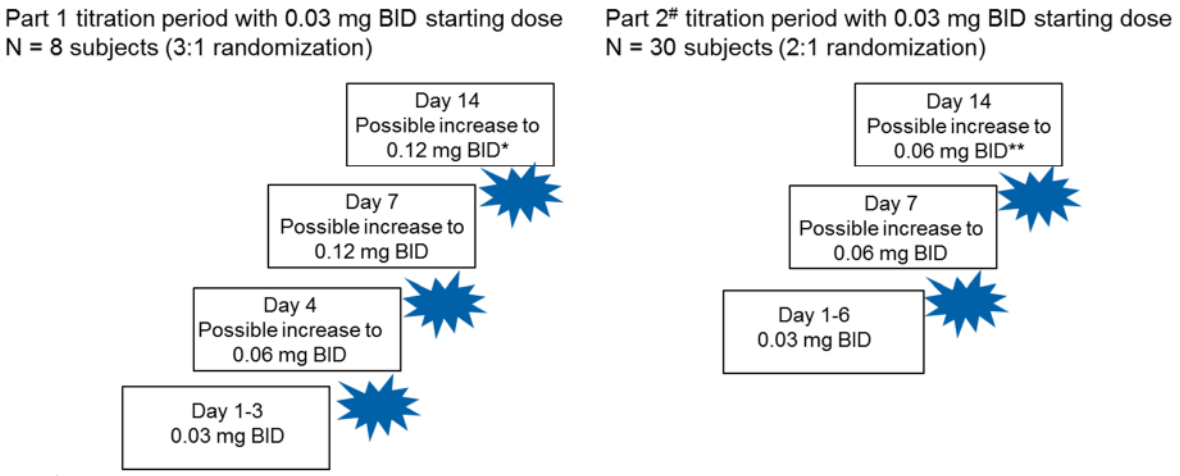
Part 1 (Figure 3-2) will consist of 8 subjects, randomized in a 6:2 ratio to QCC374 or placebo. The planned bid dose levels in Part 1 are 0.03 mg, 0.06 mg and 0.12 mg. Subjects will begin dosing at 0.03 mg bid.

- On Day 4 the investigator will assess an individual subject's clinical status and reported adverse events and confirm that an individual subject can be up-titrated to 0.06 mg bid. This decision, made individually for every subject, will be based on the investigator's assessment of the severity of any adverse events, including adverse events typical of prostacyclins (e.g. headache, jaw pain, myalgia, flushing and nausea).
- On Day 7 the investigator will assess an individual subject's clinical status and reported adverse events and confirm that an individual subject can be up-titrated to the next planned dose level. This decision, made individually for every subject, will be based on the investigator's assessment of the severity of any adverse events, including adverse events typical of prostacyclins.
- On Day 14 the investigator will assess the patient's clinical status and reported adverse events. If the patient is not already receiving the maximum dose of 0.12 mg bid, the investigator will determine whether an individual subject can be up-titrated one dose level.

This decision, made individually for every subject, will be based on the investigator's assessment of the severity of any adverse events, including adverse events typical of prostacyclins.

- Following the Day 14 visit no further up-titrations are allowed. Subjects are allowed to continue in the trial even if their final dose after titration on Day 14 is not 0.12 mg.
- On Day 21, if the subject's dose was up-titrated on Day 14, a follow-up phone call visit will occur to review safety and tolerability.
- At any point during the 16 week treatment period, if the investigator believes, based on their medical judgement, that the dose should be reduced due to the severity of adverse events, the investigator will reduce the dose to the previous tolerated dose. A follow-up phone call should be scheduled 7 days after dose adjustment to review safety and tolerability of adjustment.

**Figure 3-2 Part 1 and Part 2 Dose Evaluation and Titration**




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

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

*0.12 mg BID is the maximum dose in Part 1, but a subject may continue in the study at a lower dose if 0.12 mg BID is not reached by Day 14.

**0.06 mg BID is the maximum dose in Part 2 , but a subject may continue in the study at a lower dose if 0.06 mg BID is not reached by Day 14.

When the 8 subjects in Part 1 have been randomized, and completed 2 weeks of dosing (or discontinued), the sponsor will review all available unblinded safety data for these subjects, including adverse event listings, vital signs, spirometry and ECG data. After receiving feedback from all investigators, and if in the opinion of the sponsor's medical professional there is no evidence of a significant safety finding, dosing in Part 2 will proceed with a 0.06 mg starting dose as described below. If a safety concern is identified by the sponsor's medical physician or by an investigator, or if the sponsor's medical professional believes that the

proposed dosing schedule for Part 2 may not be well-tolerated, the sponsor may decide to adjust the dosing regimen for Part 2, either decreasing the final dose or increasing the interval between up-titrations. There is no plan to pause enrollment between Part 1 and Part 2, but a pause may be implemented if required.

### 3.1.2 Part 2

Part 2 (Figure 3-2) will consist of approximately 30 subjects who will be randomized in a 2:1 ratio, QCC374 or placebo. The planned dose levels in Part 2 are 0.03 mg and 0.06 mg. Subjects will begin dosing at 0.03 mg bid.

- On Day 7 the investigator will assess an individual subject's clinical status and reported adverse events and confirm that an individual subject can be up-titrated to 0.06 mg bid. This decision, made individually for every subject, will be based on the investigator's assessment of the severity of any adverse events, including adverse events typical of prostacyclins (e.g. headache, jaw pain, myalgia, flushing and nausea).
- On Day 14 the investigator will assess the patient's clinical status and reported adverse events. If the patient is not already receiving the maximum dose of 0.06 mg bid, the investigator will determine whether an individual subject can be up-titrated 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.

  This decision, made individually for every subject, will be based on the investigator's assessment of the severity of any adverse events, including adverse events typical of prostacyclins.
- Following the Day 14 visit no further up-titrations are allowed. Subjects are allowed to continue in the trial even if their final dose after titration on Day 14 is not 0.06mg.
- 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.
- At any point during the 16 week treatment period, if the investigator believes, based on their medical judgement, that the dose should be reduced due to the severity of adverse events, the investigator will reduce the dose to the previous tolerated dose. A follow-up phone call should be scheduled 7 days after dose adjustment to review safety and tolerability of adjustment.

## 3.2 Rationale of study design

This study is designed as a randomized, parallel group, placebo-controlled, subject and investigator blinded study, to assess the effect of a 16 week course QCC374 on the change from baseline in PVR as compared to placebo in patients with PAH. The rationales for key elements of the study design are as follows:

- Randomization: Decreases the chance of an imbalance in subject characteristics between treatment groups
- Subject and Investigator Blinding: Decreases the risk of bias of investigators or subjects in assessing subjective readouts such as adverse events*

- Placebo controlled: Provides a comparison group for efficacy and safety/tolerability assessments. The placebo group will receive the standard of care therapy for PAH, as QCC374 and placebo are being studied in addition to standard of care therapy.
- Dose Titration Design: 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.



- Lower starting dose for 8 subjects in Part 1: Because QCC374 has not previously been tested in PAH patients, a lower starting dose is proposed for the first 8 subjects to monitor for any signals suggesting unanticipated, acute hemodynamic effects.
- Part 2 starting dose: As a result of the Safety Review of the 8 patients enrolled in Part 1, the starting dose of 0.03 mg was maintained for subjects enrolling in Part 2.
- Endpoints: PVR has been used by clinical studies in PAH previously to assess the pharmacodynamic effect of therapies on pulmonary pressures. In addition to PVR, several complementary endpoints will be used to assess efficacy, including additional pulmonary hemodynamic measurements, the 6MWD and echocardiographic assessments. Together these assessments are anticipated to provide a comprehensive view of the effect of QCC374 on PAH and inform future, larger studies.

*If a patient is considering enrollment in the separate long-term extension study (QCC374X2201E1), then the investigators may be unblinded only after all of the assessments on Day 111 (Visit 108) are completed; unblinding is necessary so that the appropriate dosing regimen can be selected for the extension study – either maintenance of the individual QCC374 dose for subjects randomized to QCC374 in this study, or initiation of QCC374 titration for subjects randomized to placebo.

## 3.4 Rationale for choice of comparator

Placebo will be used as a comparator to QCC374 to provide an unbiased control for assessing and interpreting safety data as well as clinical efficacy data generated from patients exposed to QCC374.

## 3.5 Rationale for choice of background therapy

QCC374 will be studied on top of standard of care therapy (endothelin receptor antagonist/soluble guanylate cyclase stimulator AND/OR a phosphodiesterase inhibitor) for PAH. Subjects will continue on their stable background therapy as established prior to study entry (Section 6.11), thereby justifying potential treatment with placebo. In addition, subjects will be maintained on their pre-existing stable medical regiment for treatment of any additional pre-existing medical conditions.

## 3.7 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.

### 3.7.1 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.



### 3.7.2 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).

### 3.7.3 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).

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### 3.7.4 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

### 3.7.5 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.

### 3.7.6 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.

### 3.7.7 Blood sample volumes

A maximum of 242 mL of blood (231,2 ml in South Korea and Taiwan) is planned to be collected over a period of 20 weeks, from each subject as part of the study. 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.

# 4 Population

## 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. Able to communicate well with the investigator, to understand and comply with the requirements of the study.
3. Male and female patients 18 years of age or older with symptomatic PAH (WHO Functional Class II or III).
4. Subjects with PAH belonging to one of the following subgroups of the Updated Clinical Classification Group 1 (Nice, 2013):
   - Idiopathic PAH
   - familial PAH
   - PAH associated with connective tissue disease, congenital heart disease (surgically repaired at least 12 months prior to screening) or drug or toxin induced (for example, anorexigen use).

5. Subjects must have persistent symptoms due to PAH despite therapy with at least one of the following PAH medications: an endothelin receptor antagonist, a soluble guanylate cyclase stimulator or a phosphodiesterase inhibitor. The subjects' PAH medication regimen, with typical medications including endothelin receptor antagonists, soluble guanylate cyclase stimulators and/or phosphodiesterase inhibitors, must have been used at a stable dose and frequency for at least 12 weeks before the screening visit and during the screening period.
6. Diagnosis of PAH established according to the standard criteria before the screening visit:
    1. Resting mPAP $\geq$ 25 mmHg.
    2. PVR > 240 dyn·s/cm$^5$.
    3. PCWP or left ventricular end diastolic pressure $\leq$15 mmHg
7. A PVR > 400 dyn·s/cm$^5$ at the time of the baseline RHC (if a RHC was completed within one month of the screening visit, that result may be used for inclusion if data meets criteria outlined in Section 8.5.1)
8. 6MWD greater than 150 meters at screening. This distance must be confirmed by a second 6MWT prior to randomization. The value of the second 6MWD must be within ± 15% of the initial value.

## 4.2 Exclusion criteria

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

1. Subjects with clinically unstable right heart failure (NYHA Class IV) or with more than one unplanned hospital admission for the treatment of PAH within the three months prior to screening.
2. Subjects with PAH associated with portal hypertension, Human Immunodeficiency Virus (HIV) infection or unrepaired congenital systemic to pulmonary shunts, or subjects with PAH responsive to high dose calcium channel blockers.
3. Subjects who have received or have been scheduled to receive treatment with a prostacyclin (prostacyclin analog or IPR agonist) within the three months prior to the screening visit or during the screening period.
4. Hypotensive subjects (systemic systolic blood pressure < 85 mmHg) at the screening visit or at the baseline visit.
5. Subjects with left sided heart disease, chronic left sided heart failure, congenital or acquired valvular disease and/or pulmonary venous hypertension, as determined by history or echocardiogram at baseline visit.
6. Subjects with three or more of the following left ventricular disease/dysfunction risk factors:
    1. Body mass index (BMI) > 30 kg/m$^2$ at the screening visit. BMI = Body weight (kg) / [Height (m)]$^2$.
    2. History of Essential Hypertension
    3. Diabetes Mellitus – any type
    4. Medical history of significant coronary artery disease (CAD), including a history of myocardial infarction or chronic stable angina, a history of percutaneous intervention or coronary artery surgery, prior angiographic evidence of CAD, or a positive stress test with imaging.

7. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test.
8. Use of other investigational drugs at the time of enrollment, or within 5 half-lives of enrollment, or within 30 days, whichever is longer; or longer if required by local regulations.
9. History of hypersensitivity to any of the study drugs or to drugs of similar chemical classes.
10. History of drug or alcohol abuse within the 12 months prior to dosing, or evidence of such abuse as indicated by the laboratory assays conducted during screening.
11. Subjects with a history of a ventilation-perfusion lung scan or pulmonary angiography indicative of thromboembolic disease
12. Subjects with obstructive (FEV1/ FVC < 70% and FEV1 < 70% predicted) or restrictive (total lung capacity < 65% predicted and/or clinically significant abnormality on CXR) lung disease at screening.
13. Subjects with moderate or severe hepatic impairment (Child-Pugh B and C)
14. Subjects with clinically significant chronic renal insufficiency at screening visit (estimated creatinine clearance < 30 mL/minute, or serum creatinine > 2.5 mg/dL).
15. Subjects unable to perform the 6MWT due to disability from another condition, e.g. musculoskeletal disorder or arthritis
16. A history of immunodeficiency diseases, including a positive HIV test result.
17. Chronic infection with Hepatitis B (HBV) or Hepatitis C (HCV) at screening. A positive HBV surface antigen (HBsAg) test excludes a subject. Subjects with a positive HCV antibody test at screening should have HCV RNA levels measured and confirmed by the central lab prior to their baseline visit. Subjects with positive (detectable) HCV RNA should be excluded.
18. Patients with a history of moderate or severe asthma (as diagnosed by the Global Initiative for Asthma (GINA) Guidelines 2016)
19. 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.

Subjects who failed to meet inclusion/exclusion criteria for temporary reasons can be rescreened once. Please refer to the Site Operations Manual for additional details.

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

# 5 Restrictions for Study Subjects

During recruitment, screening/informed consent review, and baseline visit, the subjects must be informed and reminded of the following restrictions:

## 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 entered 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, to ensure standardized dosing conditions, compound administration will take place 30 min before or after food intake.

## 5.4 Other restrictions

- 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 patient is participating in a pulmonary rehabilitation program at the time of screening, then participation may continue throughout the study period.
- 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 storage and management of study medication, randomization and instructions for prescribing 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, and matching placebo will be prepared by Novartis and supplied to the Investigator in blinded subject packs.

## 6.2 Treatment arms

Subjects will be assigned to either the QCC374 or Placebo treatment arms in a ratio of 3:1 in Part 1 and ratio of 2:1 in Part 2. Refer to Section 3.1 and Section 3.2 for information on dosing schedule and rationale.

## 6.3 Treatment assignment and randomization

Randomized treatment will be assigned to individual subjects by way of a randomization number, which will be in the range of 5101-5108 for Part 1 and 5201-5252 for Part 2. The availability of 60 randomization numbers is chosen here as the sample size may be increased at the IA.

The randomization number is only used to identify which treatment the patients have been randomized to receive. The Subject number assigned to a subject at screening remains the unique identifier for the subject throughout the study. For information on subject numbering, please see ‘Subject numbering’ section in the SOM.

All eligible subjects will be randomized via Interactive Response Technology (IRT) to one of the treatment arms. The investigator or his/her delegate will use the IRT system after confirming that the subject fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the subject, which will be used to link the subject to a treatment arm, and will specify a unique medication number for the first package of investigational treatment to be dispensed to the subject.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from subjects and investigator staff. A subject randomization list will be produced by the IRT provider using a validated system that automates the random assignment of subject numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automates the random assignment of medication numbers to packs containing the investigational drug(s).

The randomization scheme for subjects will be reviewed and approved by a member of the Randomization Office. Follow the details outlined in the SOM regarding the process and timing of treatment assignment and randomization of subjects.

## 6.4 Treatment blinding

This is a subject and investigator blinded study. Subjects and investigators will remain blinded to study treatment throughout the study, except where indicated below. If the subject is eligible for the optional extension study (QCC374X2201E1) and is considering participation, the blind for the investigator and subject can be broken only after all assessments on Day 111 (Visit 108) have been completed.

The identity of the treatments will be concealed by the use of study drugs that are all identical in packaging, labeling, schedule of administration, appearance, and odor.

Unblinding a single subject at site for safety reasons (necessary for subject management) will occur via an emergency system in place at the site (see Section 6.7).

## 6.5 Treating the subject

QCC374 will be administered to the subject via inhaled administration with the Concept1 dry powder inhaler. Throughout the 16-week treatment period, the majority of 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

Emergency unblinding should only be undertaken when it is essential to treat the subject safely and efficaciously. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study subject who presents with an emergency condition. Emergency treatment code breaks are performed using the IRT. When the investigator contacts the system to break a treatment code for a subject, he/she must provide the requested subject identifying information and confirm the necessity to break the treatment code for the subject. The investigator will then receive details of the investigational drug treatment for the specified subject and a fax or email confirming this information. The system will automatically inform the study monitor for the site and the study team that the code has been broken. The local Novartis CPO (or any entity to which there has been delegation for the emergency code breaks) needs to be contacted. It is the investigator's responsibility to ensure that there is a procedure in place to allow access to the IRT in case of emergency. If appropriate, the investigator will inform the subject how to contact his/her backup in cases of emergency when he/she is unavailable.

An assessment will be done by the appropriate site personnel and the sponsor after an emergency unblinding to assess whether or not study drug should be discontinued for a given subject and, if applicable, whether the subject can continue into the next trial phase (e.g, the extension study).

## 6.8 Treatment exposure and compliance

PK parameters (measures of treatment exposure) will be determined in all subjects treated with QCC374, as detailed in Section 8.7.

## 6.9 Recommended treatment of adverse events

Since 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. A clinical worsening of PAH requiring a change in dose of an existing PAH specific medication, or the addition of a new PAH specific medication, is criteria for discontinuation for study treatment as described in Section 7.2. PAH specific medications include: all endothelin receptor antagonists, phosphodiesterase 5

inhibitors, soluble guanylate cyclase inhibitors and oral, intravenous or subcutaneous prostacyclins.

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

## 6.11 Concomitant treatment

All prescription medications, over-the-counter drugs and significant non-drug therapies (including physical therapy and blood transfusions) administered or taken within the timeframe defined in the entry criteria prior to the start of the study and during the study, must be recorded on the Concomitant medications/Significant non-drug therapies section of the CRF.

Medication entries should be specific to trade name, the single dose and unit, the frequency and route of administration, the start and discontinuation date and the reason for therapy.

If present for at least 3 months before screening and during the screening period, at a stable dose, which should remain unchanged during the study, the following treatments for PAH are allowed:

- Oral phosphodiesterase inhibitors (e.g., sildenafil) or soluble guanylate cyclase inhibitor (riociguat)
- Endothelin receptor antagonists

It is not allowed to modify the dose or type of concomitant PAH therapy during the screening period or treatment period of the study. In the event of a clinically relevant deterioration of the patient's signs or symptoms of PAH, the investigator should determine whether a change to the concomitant PAH therapy is indicated based on the patient's well-being and safety. If so, the reason for this decision should be documented in the CRF. An adjustment in the dose of a diuretic is allowed and should be documented as described in Section 6.10. Calcium channel blockers are allowed, but patients with PAH responsive to high dose calcium channel blockers should not be enrolled as described in exclusion criterion #2. Patients who require a modification of their concomitant PAH therapy during the screening or treatment period must discontinue study treatment.

# 7 Study completion and discontinuation

## 7.1 Study completion and post-study treatment

Each subject will be required to complete the study in its entirety and thereafter the subject will have the opportunity to enroll in the QCC374X2201E1 extension study protocol. Study completion for this trial is defined as when the last subject completes their end of study (EOS) visit, and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator, or in the event of an early study termination decision, the date of that decision. If the subject wishes to continue into the extension study, the subject's last visit is on Day 112.

Patients who agree to participate in the extension study may be unblinded on Study Day 111. For those patients who are on placebo, the completion of PK assessment on Study Day 112 is required in order to conduct bioanalysis to confirm lack of drug exposure and also have exposure data to explain if there are any drug-related safety findings in the subject

For subjects who do not wish to participate in the extension study protocol, at a minimum, they will be contacted for safety evaluations during the 30 days following the Study Completion visit, including a final post-study safety contact at the 30-day point. Documentation of attempts to contact the subject should be recorded in the source documentation. All SAEs reported during this time period must be reported as described in the SOM.

## 7.2 Discontinuation of study treatment

Subjects may voluntarily discontinue study treatment for any reason at any time.

The investigator must discontinue study treatment for a given patient if, on balance, he/she believes that continuation would be detrimental to the subject'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:

- Subjects 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 study
- Non-compliance with the conditions of the trial and/or instructions by the investigator which could jeopardize the subject's safety or integrity of study results
- Use of prohibited treatment as per Section 5.2.
- Clinical worsening of PAH:
    - A persistent decrease in 6MWD of more than 15% from baseline, confirmed by two tests on different days, believed to be due to worsening of underlying PAH*
    - Hospitalization due to persistent worsening of PAH*
    - The need for new PAH specific treatment or an adjustment in dose or type of an existing specific PAH treatment (PAH specific medications include: all endothelin receptor antagonists, phosphodiesterase 5 inhibitors, soluble guanylate cyclase inhibitors and oral, intravenous or subcutaneous prostacyclins.)*

*In the event of clinical deterioration the investigator must carefully assess if the deterioration of the subject's condition is related to the underlying pulmonary hypertension or can be explained by an alternative cause (e.g. transient infection, surgical or medical intervention other than PH related, musculoskeletal disease) and document this determination in the CRF.

The appropriate personnel from the site and Novartis will assess whether study treatment should be discontinued for any patient whose treatment code has been broken inadvertently for any reason.

Subjects 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 (see Section 7.3). If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, e-mail, letter) should be made to contact them as specified in Section 7.4.

## 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 ans 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 should not 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 will occur pending a full safety review if any of the following criteria are met:

- The principal 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 of this study or for the extension study QCC374X2201E1, which may justify 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 at any time for any reason by Novartis. Should this be necessary, subjects should 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 Part 1 Assessment Schedule**

| Epoch | Screening | | Treatment[4] | | | | | | | | | | | | | | Post Treatment Follow Up | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit Name | Screening | Baseline | Titration | | | | | | | | Stable Dose Follow Up | | | | | | Termination Visit | EOS Visit (28 days post last treatment) |
| Visit Numbers[1] | 1 | 2[2] | 101[2] | | | | | 102 | 103 | 104[3] | 105 | 106 | 107 | 108[2] | 109[2,5] | | 201[6] | 202[7] |
| Study Day(s) | -28 to -2 | -1 | 1 | | | | | 4 | 7 ±1 | 14 ±1 | 28 ±2 | 56 ±2 | 84 ±2 | 111 ±2 | 112 ±2 | | 113 | 140 |
| Time (post-dose) | - | - | 0m | 15m | 30m | 2h | 4h | - | - | - | - | - | - | - | 0m | 12h | - | - |
| Informed consent | X | | | | | | | | | | | | | | | | | |
| Corporate Confidential Information | X | | | | | | | | | | | | | | | | | |
| Medical history/current medical conditions | X | | | | | | | | | | | | | | | | | |
| Demography | X | | | | | | | | | | | | | | | | | |
| Inclusion / Exclusion criteria | X | X | X | | | | | | | | | | | | | | | |
| Randomization | | | X | | | | | | | | | | | | | | | |
| Physical examination | X | X | X | | | | X | X | X | X | X | X | X | X | X | | X | X |
| Pulse oximetry | X | X | X | X | | | X | X | X | X | X | X | X | X | X | | X | X |
| Vital Signs | X | X | X | X | | | X | X | X | X | X | X | X | X | X | | X | X |
| Body height | X | | | | | | | | | | | | | | | | | |
| Body weight | X | X | | | | | | | | | | | | | | | X | |
| Hepatitis screen | S[8] | | | | | | | | | | | | | | | | | |
| HIV screen | S[8] | | | | | | | | | | | | | | | | | |
| Alcohol Test, Drug Screen, and Cotinine Test | S[8] | | | | | | | | | | | | | | | | | |

| Epoch | Screening | | Treatment[4] | | | | | | | | | | | | | | Post Treatment Follow Up | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit Name | Screening | Baseline | Titration | | | | | | | | Stable Dose Follow Up | | | | | | Termination Visit | EOS Visit (28 days post last treatment) |
| Visit Numbers[1] | 1 | 2[2] | 101[2] | | | | | 102 | 103 | 104[3] | 105 | 106 | 107 | 108[2] | 109[2,5] | | 201[6] | 202[7] |
| Study Day(s) | -28 to -2 | -1 | 1 | | | | | 4 | 7 ±1 | 14 ±1 | 28 ±2 | 56 ±2 | 84 ±2 | 111 ±2 | 112 ±2 | | 113 | 140 |
| Time (post-dose) | - | - | 0m | 15m | 30m | 2h | 4h | - | - | - | - | - | - | - | 0m | 12h | - | - |
| Pregnancy test | X[9] | X[10] | | | | | | | | | | | | | | | X[10] | |
| 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[11] | X | X | X | X | X | X | X | X | X | | X | |
| Lung Volumes/DLCO | X | | | | | | | | | | | | | | | | | |
| ECG evaluation | X | X | | | X | | X | X | X | X | X | X | X | X | X | | X | |
| 6-Minute Walk Test | X[12] | | | | | | | | | | X | X | X | X | | | | |
| Corporate Confidential Information | X | | | | | | | | | | X | X | X | X | | | | |
| | X | X | | | | | | | | | X | X | X | X | | | | |
| | | X | | | | | | | | | | | | X | | | | |
| Chest X-ray | | X[13] | | | | | | | | | | | | X[14] | | | | |
| Corporate Confidential Information | | X | | | | | | | | | X | X | X | X | | | | |
| | | X | | | | | | | | | | | | X | | | | |
| | | X | | | | | | | | | | | | X | | | | |
| | | X | | | | | | | | | | | | X | | | | |
| Echocardiogram | | X[15] | | | | | | | | | | | | X | | | | |
| Corporate Confidential Information | | X | | | | | | | | | | | | | | | | |
| Right heart catheterization | X[16] | | | | | | | | | | | | | X | | | | |
| Drug dispensation | | | 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 | | | | | | | | | | | | | | | |

| Epoch | Screening | | Treatment[4] | | | | | | | | | | | | | Post Treatment Follow Up | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit Name | Screening | Baseline | Titration | | | | | | | Stable Dose Follow Up | | | | | | Termination Visit | EOS Visit (28 days post last treatment) |
| Visit Numbers[1] | 1 | 2[2] | 101[2] | | | | | 102 | 103 | 104[3] | 105 | 106 | 107 | 108[2] | 109[2,5] | 201[6] | 202[7] |
| Study Day(s) | -28 to -2 | -1 | 1 | | | | | 4 | 7 ±1 | 14 ±1 | 28 ±2 | 56 ±2 | 84 ±2 | 111 ±2 | 112 ±2 | 113 | 140 |
| Time (post-dose) | - | - | 0m | 15m | 30m | 2h | 4h | - | - | - | - | - | - | - | 0m | 12h | - | - |
| Corporate Confidential Information | | | X[17] | | | | | | | | | | | | | | | |
| PK blood collection[18] | See Table 8-2 below | | | | | | | | | | | | | | | | | |
| Study/Epoch completion information | | X | | | | | | | | | | | | | | X | | X |
| Concomitant medications | As Required | | | | | | | | | | | | | | | | | |
| Adverse events | As Required | | | | | | | | | | | | | | | | | |
| Serious adverse events | As Required | | | | | | | | | | | | | | | | | |
| Comments | As Required | | | | | | | | | | | | | | | | | |

[1] Visit structure given for internal programming purpose only
[2] Domiciled in Clinic (optional)
[3] If the subject was up-titrated at the Day 14 visit, a phone call for follow-up on subject safety and tolerability should be conducted 7 days later.
[4] If a patient needs to stop study medication prematurely (for example, due to worsening of underlying PAH), then an attempt should be made to complete the Day 113 assessments, including a Blood Chemistry, Blood Hematology and Echocardiogram (unless these assessments were completed on Day 111). The investigator is responsible for making determination of what is safe and feasible. At a minimum, a safety evaluation must be completed.
[5] Visit 109 (Day 112) must occur 1 day after Visit 108 (Day 111)
[6] This visit is only for subjects who have completed the study treatment (Day 112) and do not wish to participate in Extension Study, or for subjects who discontinue study treatment early.
[7] This 28 days post last treatment follow up visit is for those subjects who have either prematurely stopped study treatment, or those subjects who completed the study treatment, but do not wish to participate in the extension study.
[8] The results of this assessment will only be recorded in the source data
[9] Serum Pregnancy Test
[10] Urine Pregnancy Test
[11] Within 2 hours after dose.
[12] During screening at least two 6MWT must be performed at least 2 hours apart. The two values must be within 15% of one another. Additional 6MWT may be performed until two consecutive 6MWDs are within 15% of on another (maximum of 4 tests performed).
[13] Chest X-ray needs to be completed prior to randomization, but Chest X-ray post RHC can be used (if part of standard of care follow-up)
[14] This to be completed post RHC
[15] Echocardiogram can be completed any time during Day -21 to Day -1
[16] The baseline RHC can be completed any time from Day -28 to Day -1. If the subject has a historical RHC within one month of the screening visit, this result can be used



For all follow-up visits, the PK sample collection will take place during the visit, but the subject must record time of morning dose.

**Table 8-2 Part 1 PK blood collection**

| Epoch | Visit Name | Visit Numbers | Day | Time (post-dose) | PK blood collection |
|---|---|---|---|---|---|
| Treatment | Titration | 101 | 1 | 0m | X |
| | | | | 5m | X |
| | | | | 15m | X |
| | | | | 30m | X |
| | | | | 1h | X |
| | | | | 2h | X |
| | | | | 4h | X |
| | | | | 8h | X |
| | | | | 12h | X |
| | Stable Dose Follow Up | 109 | 112<br>-2 +2 | 0m | X |
| | | | | 5m | X |
| | | | | 15m | X |
| | | | | 30m | X |
| | | | | 1h | X |
| | | | | 2h | X |
| | | | | 4h | X |
| | | | | 8h | X |
| | | | | 12h | X |

NOTE: Additional visit information can be found in Table 8-1

**Table 8-3 Part 2 Assessment Schedule**

| Epoch | Screening | | Treatment[4] | | | | | | | | | | | | | Post Treatment Follow Up | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit Name | Screening | Baseline | Titration | | | | | | | Stable Dose Follow Up | | | | | | Termination Visit | EOS Visit (28 days post last treatment) |
| Visit Numbers[1] | 1 | 2[2] | 101[2] | | | | | 103 | 104[3] | 105 | 106 | 107 | 108[2] | 109[2,5] | | 201[6] | 202[7] |
| Study Day(s) | -28 to -2 | -1 | 1 | | | | | 7 ±1 | 14 ±1 | 28 ±2 | 56 ±2 | 84 ±2 | 111 ±2 | 112 ±2 | | 113 | 140 |
| Time (post-dose) | - | - | 0m | 15m | 30m | 2h | 4h | - | - | - | - | - | - | 0m | | - | - |
| Informed consent | X | | | | | | | | | | | | | | | | |
| Corporate Confidential Information | X | | | | | | | | | | | | | | | | |
| Medical history/current medical conditions | X | | | | | | | | | | | | | | | | |
| Demography | X | | | | | | | | | | | | | | | | |
| Inclusion / Exclusion criteria | X | X | X | | | | | | | | | | | | | | |
| Randomization | | | X | | | | | | | | | | | | | | |
| Physical examination | X | X | X | | | | X | X | X | X | X | X | X | X | | X | X |
| Pulse oximetry | X | X | X | X | | | X | X | X | X | X | X | X | X | | X | X |
| Vital Signs | X | X | X[19] | X[19] | | | X | X | X | X | X | X | X | X | | X | X |
| Body height | X | | | | | | | | | | | | | | | | |
| Body weight | X | X | | | | | | | | | | | X | | | X | |
| Hepatitis screen | S[8] | | | | | | | | | | | | | | | | |
| HIV screen | S[8] | | | | | | | | | | | | | | | | |
| Alcohol Test, Drug Screen, and Cotinine Test | S[8] | | | | | | | | | | | | | | | | |
| Pregnancy test | X[9] | X[10] | | | | | | | | | | | | X[10] | | X[10] | |
| 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[11] | X | X | X | X | X | X | X | X | | X | |

| Epoch | Screening | | Treatment[4] | | | | | | | | | | | | | Post Treatment Follow Up | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit Name | Screening | Baseline | Titration | | | | | | | Stable Dose Follow Up | | | | | | Termination Visit | EOS Visit (28 days post last treatment) |
| Visit Numbers[1] | 1 | 2[2] | 101[2] | | | | | 103 | 104[3] | 105 | 106 | 107 | 108[2] | 109[2,5] | | 201[6] | 202[7] |
| Study Day(s) | -28 to -2 | -1 | 1 | | | | | 7 ±1 | 14 ±1 | 28 ±2 | 56 ±2 | 84 ±2 | 111 ±2 | 112 ±2 | | 113 | 140 |
| Time (post-dose) | - | - | 0m | 15m | 30m | 2h | 4h | - | - | - | - | - | - | 0m | | - | - |
| Lung Volumes/DLCO | X | | | | | | | | | | | | | | | | |
| ECG evaluation | X | X | | | X | | X | X | X | X | X | X | X | X | | X | |
| 6-Minute Walk Test | X[12] | | | | | | | | | X | X | X | X | | | | |
| Corporate Confidential Information | X | | | | | | | | | X | X | X | X | | | | |
| | X | X | | | | | | | | X | X | X | X | | | | |
| | | X | | | | | | | | | | | X | | | | |
| Chest X-ray | | X[13] | | | | | | | | | | | X[14] | | | | |
| Corporate Confidential Information | | X | | | | | | | | X | X | X | X | | | | |
| | | X | | | | | | | | | | | X | | | | |
| | | X | | | | | | | | | | | X | | | | |
| | | X | | | | | | | | | | | X | | | | |
| | | X[15] | | | | | | | | | | | X | | | | |
| Echocardiogram Corporate Confidential Information | | X | | | | | | | | | | | | | | | |
| Right heart catheterization | X[16] | | | | | | | | | | | | X | | | | |
| Drug dispensation | | | X | | | | | X | X | X | X | X | | | | | |
| Study drug administration[20] | | | Study Drug Administration will be bid - refer to Section 3.1 and Site Operations Manual | | | | | | | | | | | | | | |
| Corporate Confidential Information | | | X[17] | | | | | | | | | | | | | | |
| PK blood collection[18] | See Table 8-4 below | | | | | | | | | | | | | | | | |

| Epoch | Screening | | Treatment[4] | | | | | | | | | | | | Post Treatment Follow Up | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit Name | Screening | Baseline | Titration | | | | | | | Stable Dose Follow Up | | | | | Termination Visit | EOS Visit (28 days post last treatment) |
| Visit Numbers[1] | 1 | 2[2] | 101[2] | | | | | 103 | 104[3] | 105 | 106 | 107 | 108[2] | 109[2,5] | 201[6] | 202[7] |
| Study Day(s) | -28 to -2 | -1 | 1 | | | | | 7 ±1 | 14 ±1 | 28 ±2 | 56 ±2 | 84 ±2 | 111 ±2 | 112 ±2 | 113 | 140 |
| Time (post-dose) | - | - | 0m | 15m | 30m | 2h | 4h | - | - | - | - | - | - | 0m | - | - |
| Study/Epoch completion information | | X | | | | | | | | | | | | X | | X |
| Concomitant medications | As required | | | | | | | | | | | | | | | |
| Adverse events | As required | | | | | | | | | | | | | | | |
| Serious adverse events | As required | | | | | | | | | | | | | | | |
| Comments | As required | | | | | | | | | | | | | | | |

[1] Visit structure given for internal programming purpose only
[2] Domiciled in Clinic (optional)
[3] If the subject was up-titrated at the Day 14 visit, a phone call for follow-up on subject safety and tolerability should be conducted 7 days later.
[4] If a patient needs to stop study medication prematurely (for example, due to worsening of underlying PAH), then an attempt should be made to complete the Day 113 assessments, including a Blood Chemistry, Blood Hematology and Echocardiogram (unless these assessments were completed on Day 111). The investigator is responsible for making determination of what is safe and feasible. At a minimum, a safety evaluation must be completed.
[5] Visit 109 (Day 112) must occur 1 day after Visit 108 (Day 111)
[6] This visit is only for subjects who discontinue study treatment early.
[7] This 28 days post last treatment follow up visit is for those subjects who have either prematurely stopped study treatment, or those subjects who completed the study treatment, but do not wish to participate in the extension study.
[8] The results of this assessment will only be recorded in the source data
[9] Serum Pregnancy Test
[10] Urine Pregnancy Test
[11] Within 2 hours after dose.
[12] During screening at least two 6MWT must be performed at least 2 hours apart. The two values must be within 15% of one another. Additional 6MWT may be performed until two consecutive 6MWDs are within 15% of on another (maximum of 4 tests performed).
[13] Chest X-ray needs to be completed prior to randomization, but Chest X-ray post RHC can be used (if part of standard of care follow-up)
[14] This to be completed post RHC
[15] Echocardiogram can be completed any time during Day -21 to Day -1
[16] The baseline RHC can be completed any time from Day -28 to Day -1. If the subject has a historical RHC within one month of the screening visit, this result can be used



For all follow-up visits, the PK sample collection will take place during the visit, but the subject must record time of morning dose.

[19] Blood pressure should be collected in the sitting position and then repeated after 3 minutes in the standing position.

[20] For patients who performed Visit 108 (Day 111) and do not wish to continue into the extension study, the last dose administration will be the morning dose on Visit 109, with no dose administration in the afternoon.

**Table 8-4 Part 2 PK blood collection**

| Epoch | Visit Name | Visit Numbers | Day | Time (post-dose) | PK blood collection |
|---|---|---|---|---|---|
| Treatment | Titration | 101 | 1 | 0m | X |
| | | | | 5m | X |
| | | | | 15m | X |
| | | | | 30m | X |
| | | | | 1h | X |
| | | | | 2h | X |
| | | | | 4h | X |
| | | | | 8h | X |
| | | | | | |
| | Stable Dose Follow Up | 109 | 112<br>-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 8-3

## 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.

The date of signing of informed consent (and withdrawal, if later withdrawn) should be documented in the CRF.

Novartis will provide to investigators a proposed informed consent form that complies with the ICH Good Clinical Practice (GCP) guideline and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC.



In the event that Novartis wants to perform testing on the samples that are not described in this protocol, additional Institutional Review Board and/or Ethics Committee approval will be obtained.

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

Information on screening procedures and data collected for Screen Failures can be found in the Study Operational Manual. In general it may be allowed to re-screen a subject once if s/he fails the initial screening; however, each case must be discussed and agreed with the Sponsor on a case-by-case basis.

## 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 includes data until signature of informed consent. Details are outlined in the SOM. When possible, diagnoses and not symptoms should be recorded. Investigators have the discretion to record abnormal test findings on the medical history CRF whenever in their judgment, the test abnormality occurred prior to the informed consent signature.

## 8.5 Efficacy / Pharmacodynamics

Pharmacodynamic assessments are specified below, with the methods for assessment and recording specified in the SOM. Assessments will be performed/samples collected at the time point(s) defined in the Assessment schedule (Section 8.1).

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.

### 8.5.1 Right Heart Catheterization

The RHC assessment is performed to assess several hemodynamic variables in pulmonary hypertension, including mPAP, PCWP, CO, PVR and Systemic Vascular Resistance (SVR).

- RHC will be performed according to the local hospital procedures.
- Concomitant PAH medications that could affect hemodynamic measurements, including endothelin receptor antagonists, phosphodiesterase inhibitors, soluble guanylate cyclase inhibitors and diuretics, will be taken on a standard schedule relative to the timing of the RHC. When possible, these medications should be taken at least 60 minutes prior to the start of the procedure. Exact timing of dosing should be recorded in the source document for catheterization. The timing of a patient's concomitant medication relative to catheterization should be the same for the subsequent catheterization.
- The Week 16 RHC should occur after the QCC374 morning dose (2-4 hours post dose)
- The following hemodynamic parameters will be assessed when the patient is in a stable hemodynamic rest state (as demonstrated by three consecutive CO measurements within 10% of each other) while the patient is breathing ambient air or oxygen:
    - RA, mPAP, PCWP, systolic and diastolic blood pressure, HR
    - CO (measured in triplicate by the thermodilution technique)
    - Mixed venous blood gas measurement
- Thermodilution is the preferred technique for measurement of hemodynamic parameters. The direct Fick technique may be used only with prior discussion and written approval from the Sponsor. In all cases, the same technique must be used for the baseline and week 16 RHC measurements.
- The following parameters will be derived from the CO measurement:
    - SVR in $dyn \cdot s/cm^5$
    - PVR in $dyn \cdot s/cm^5$

Additional instructions for RHC procedures can be found in the SOM.

### 8.5.2 Echocardiography

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. The duration between an acceptable baseline scan and initiation of dosing will be less than 21 days. In all patients, the baseline and follow-up 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.

### 8.5.3 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.

During screening at least two 6MWT must be performed at least 2 hours apart. The two values must be within 15% of one another. Additional 6MWT may be performed until two consecutive 6MWDs are within 15% of on another (maximum of 4 tests performed).

The site should record the values of both qualifying 6MWT in the CRF. The average of the two consecutive qualifying tests will be used as the baseline.

After screening, single 6MWTs will be performed according the Assessment schedule (Section 8.1). Every attempt should be made to conduct the 6MWT at about the same time of day.

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) at screening to assess patients' eligibility for the study and 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 Chest X-ray

Standard CXR will be performed except for those who have had a valid X-ray done within 6 months of the screening visit to confirm eligibility. During the trial, there may be standard CXRs completed at the time of the RHC (if part of site's standard of care follow-up).

### 8.6.3 Physical examination

Information can be found in the SOM.

### 8.6.4 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.

### 8.6.5 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.

### 8.6.6 Height and weight

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

### 8.6.7 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 and INR will be assessed.

### Clinical chemistry

Sodium, potassium, creatinine, urea, uric acid, chloride, albumin, calcium, alkaline phosphatase, total bilirubin, LDH, GGT, AST, ALT, 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, hemoglobin

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

### 8.6.8 Pregnancy and assessments 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.

### 8.6.9 Lung Volumes and DLCO

Lung volumes and DLCO measurements will be determined according to ATS guidelines (Wanger et al 2005, MacIntyre et al 2005). Detailed procedures for lung volume and DLCO acquisition are provided in the SOM.

### 8.6.10 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

All subjects who receive QCC374 (or matching placebo) will have blood samples collected as outlined in Table 8-2 and Table 8-4 (Section 8.1). 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.

### 8.7.1 PK Sample Collection

All samples will be given a unique sample number and a collection number (as listed in Table 8-2 and Table 8-4, Section 8.1). 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. Any problems with sampling will be documented within the CRFs.

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.

Untreated samples (placebo) will not be analyzed.

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 clinical study report (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.

# 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:

1. 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
2. Relationship to the study treatment
3. Duration (start and end dates) or if the event is ongoing, an outcome of not recovered/not resolved should be reported.
4. Whether it constitutes a serious adverse event (SAE). See Section 9.2 for definition of SAE.
5. 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
6. 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 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 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, 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 but should not be applicable in this single dose study where treatment is administered under supervision of site staff.

All study treatment errors and uses outside of what is foreseen in the protocol will be collected in the dose administration record. 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 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 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 Early phase safety monitoring

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 CRF 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 contract research organization (CRO) working on behalf of Novartis. The Investigator must certify that the data entered into the CRFs 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 (Section 8.1) 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 CRFs 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).

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

Randomization codes and 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).

Each occurrence of a code break via IRT will be reported to the clinical team and monitor. The code break functionality will remain available until study shut down or upon request of Novartis.

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

The study will be using a Data Monitoring Committee (DMC). A 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 DMC will consist of four members, with one member being a statistician. The DMC will have a charter completed prior to FPFV and will meet on a regular basis to review safety.

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

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

The PD analysis set will include all subjects who received any study drug and have no protocol deviations with relevant impact on PD data. If retrospective review of RHC or echocardiogram data suggests inclusion/exclusion criteria may not have been met, additional subjects may be excluded from the PD analysis set.

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

## 11.2 Subject demographics and other baseline characteristics

All data for background and demographic variables will be listed by treatment group and subject. Summary statistics will be provided by treatment group.

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

## 11.3 Treatments

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

## 11.4 Analysis of the primary variable(s)

The primary objective of this study is to assess the efficacy of 16 weeks of QCC374 administration in patients with PAH. The primary endpoint is the percentage of the baseline PVR at week 16.

### 11.4.1 Variable(s)

The primary variable is the PVR. The log transformed PVR is expected to be approximately normally distributed.

### 11.4.2 Statistical model, hypothesis, and method of analysis

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



### 11.4.3 Handling of missing values/censoring/discontinuations

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

### 11.4.4 Sensitivity analyses

Sensitivity analyses will be carried out if the assumption of missing completely at random values is not appropriate.

## 11.5 Analysis of secondary variable(s)

### 11.5.1 Efficacy / Pharmacodynamics

For the 6MWD, mPAP, PCWP, CO, SVR, and RV function with echocardiography, the raw data and change from baseline will be listed by treatment, subject and visit/time. Summary statistics will be provided by treatment and visit/time.

For the 6MWD, change from baseline will be analyzed using a mixed effects model for repeated measures. The model will investigate effects for treatment by time interaction and baseline by time interaction. The outcome of interest will be the comparison of QCC374 versus placebo after 16 weeks of treatment.

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

### 11.5.2 Safety

#### Vital signs

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

#### ECG evaluations

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

#### Clinical laboratory evaluations

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

#### Adverse events

All information obtained on AEs will be displayed by treatment and subject.

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

#### Spirometry

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

**Pharmacokinetics**

QCC374 and QCM441 plasma concentration data will be listed by dose-level, subject, and visit/sampling timepoint. Missing data will be labeled as such in the concentration data listings.

Descriptive summary statistics will be provided by dose-level and visit/sampling time point, 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. Concentrations below LLOQ will be treated as zero in summary statistics as well as for calculation of PK parameters. 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 dose-level, study day and subject. Descriptive summary statistics will be provided including mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum and maximum. An exception to this are Tmax, Tmin, and Tlast where only median, minimum and maximum will be presented. A geometric mean will not be reported if the dataset includes zero values.

### 11.5.3 Pharmacokinetic / pharmacodynamic interactions

Not applicable for this study.

### 11.5.4 Other assessments

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

## 11.7 Sample size calculation

We assume around 20% dropout, which should provide complete PVR data from around 30 patients (approximately 10 on placebo and approximately 20 on QCC374), if approximately 38 patients are randomized.




If the true effect is 20% over placebo, then the probability to meet the efficacy criteria is 80%. If the drug effect over placebo is 0, then there is 40% chance of declaring futility at the IA. If the drug effect over placebo is 0, then the chance of declaring efficacy is 9% at the end of the study.



## 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 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 should 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

Novartis assures that 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 should an investigator collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs.

Investigators must apply due diligence to avoid protocol deviations. If the 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/REB it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

## 13.1 Protocol Amendments

Any change or addition 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.

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

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 clinical trial leader should be informed and (serious) adverse event reporting requirements (Section 9) followed as appropriate.

# 14 References

ATS Statement: Guidelines for the Six-Minute Walk Test (2002) Am J Respir Crit Care Med 166:111-117.

Badagliacca R, Pezzuto B, Poscia R, et al (2012) Prognostic factors in severe pulmonary hypertension patients who need parenteral prostanoid therapy: The impact of late referral. J Heart Lung Transplant. 31: 364–72

Barst RJ, Rubin LJ, Long WA, et al (1996) A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension: The Primary Pulmonary Hypertension Study Group. N Engl J Med; 334: 296-301.

Benza R, Miller DP, Barst RJ, et al (2012) An evaluation of long-term survival from time of diagnosis in pulmonary arterial hypertension from the REVEAL Registry. Chest; 142:448-56.

Galie N, Humbert M, Vachiery JL, et al (2015) 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Respir J; 46: 903-975.

Global Initiative for Asthma (2016) Pocket Guide for the Diagnosis and Management of Asthma. www.ginaasthma.org, accessed 31 August 2016.

Hayashi M, Koya T, Kawakami H, et al (2010) A prostacyclin agonist with thromboxane inhibitory activity for airway allergic inflammation in mice. Clin Exp Allergy; 40, 317-326.

Kuwano K, Hashino A, Noda K, et al (2008) A long-acting and highly selective prostacyclin receptor agonist prodrug, 2-{4-[(5,6-diphenylpyrazin-2-yl)(isopropyl)amino]butoxy}-N-(methylsulfonyl)acetamide (NS-304), ameliorates rat pulmonary hypertension with unique relaxant responses of its active form, {4-[(5,6-diphenylpyrazin-2-yl)(isopropyl)amino]butoxy}acetic acid (MRE-269), on rat pulmonary artery. J Pharm Exp Ther; 326, 691-699.

MacIntyre N, Crapo RO, Viegi G, et al (2005) Standardisation of the single-breath determination of carbon monoxide uptake in the lung. Eur Respir J; 26:720-735.

McLaughlin VV, Archer SL, Badesh DB, et al (2009) ACCF/AHA 2009 Expert Consensus Document on Pulmonary Hypertension: A Report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association Developed in Collaboration With the American College of Chest Physicians; America Thoracic Society, Inc.; and the Pulmonary Hypertension Association. J Am Coll Cardiol 53: 1573-1619.

McLaughlin VV, Benza RL, Rubin LJ, et al (2010) Addition of inhaled treprostinil to oral therapy for pulmonary arterial hypertension: a randomized controlled clinical trial. J Am Coll Cardiol; 55(18): 1915-22.

Miller MR, Hankinson J, Brusasco V, et al (2005) Standardization of spirometry. Eur Respir J; 26:319-338.

Schermuly RT, Yilmaz H, Ghofrani HA, et al (2005) Inhaled iloprost reverses vascular remodeling in chronic experimental pulmonary hypertension. Am J Resp Crit Care; 172, 358-63.

Schermuly RT, Ghofrani HA, Wilkins MR, et al (2011) Mechanisms of disease: pulmonary arterial hypertension. Nat Rev Cardiol; 8(8): 443-55.

Simonneau G, Barst RJ, Galie N, et al (2002) Continuous subcutaneous infusion of treprostinil, a prostacyclin analog, in patients with pulmonary arterial hypertension: a double-blind, randomized, placebo-controlled trial. Am J Respir Crit Care Med.; 165(6):800-4.

Simonneau G, Torbicki A, Hoeper MM, et al (2012) Selexipag, an oral, selective IP receptor agonist for the treatment of pulmonary arterial hypertension. Eur Respir J; 40: 874–880.

Simonneau G, Gatzoulis M, Adatia I, et al (2013) Updated Clinical Classification of Pulmonary Hypertension. J Am Coll Cardiol; 62:25_S.

Wanger J, Clausen JL, Coates G, et al (2005) Standardization of the measurement of lung volumes. Eur Respir J; 26:511-522.

Woodward DF, Jones RL, Narumiya S (2011) International Union of Basic and Clinical Pharmacology. LXXXIII: Classification of Prostanoid Receptors, Updating 15 Years of Progress. Pharm Rev; 63, 471-538.

Zhu Y, Liu Y, Zhou W, et al (2010) A prostacyclin analog, iloprost, protects from bleomycin-induced pulmonary fibrosis in mice. Respir Res; 11:34.

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

**Table 15-1 Liver Event Definitions**

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

**Table 15-2 Actions required for Liver Events**

| Criteria | Actions required |
|---|---|
| Potential Hy's Law case<br>ALT or AST elevation with coagulopathy<br>ALT or AST elevation accompanied by symptoms<br>Isolated ALT or AST elevation > 8 × ULN<br>Jaundice | • Discontinue the study treatment immediately<br>• Hospitalize, if clinically appropriate<br>• Establish causality<br>• Complete CRFs per liver event guidance |
| Isolated ALT or AST elevation > 5 to ≤ 8 × ULN | • If confirmed, consider interruption or discontinuation of study drug<br>• If elevation persists for more than 2 weeks, discontinue the study drug<br>• Establish causality<br>• 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<br>• If elevation is confirmed, measure fractionated ALP; if >50% is of liver origin, establish hepatic causality<br>• Complete CRFs per liver event guidance |
| Any AE potentially indicative of liver toxicity | • Consider study treatment interruption or discontinuation<br>• Hospitalize if clinically appropriate<br>• 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<br>• Follow up within 2-5 days |
| Serum creatinine increase ≥50% | • Consider causes and possible interventions<br>• Repeat assessment within 24-48h if possible<br>• Consider drug interruption or discontinuation unless other causes are diagnosed and corrected<br>• Consider hospitalization and specialized treatment |
| Protein-creatinine or albumin-creatinine ratio increase ≥ 2-fold<br>or<br>new onset dipstick proteinuria ≥ 1+<br>or<br>Albumin-creatinine ratio (ACR) ≥ 30 mg/g or ≥ 3 mg/mmol;<br>or<br>Protein-creatinine ratio (PCR )≥ 150 mg/g or >15 mg/mmol | • Consider causes and possible interventions<br>• Assess serum albumin & serum protein<br>• Repeat assessment to confirm<br>• 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:<br>• Blood glucose (fasting)<br>• Serum creatinine<br>• Urine albumin-creatinine ratio |
| New hematuria on dipstick | Assess & document:<br>• Urine sediment microscopy<br>• Assess sCr and urine albumin-creatinine ratio<br>• Exclude infection, trauma, bleeding from the distal urinary tract/bladder, menstruation<br>• Consider bleeding disorder |

Additional specialized assessments are available to assess renal function or renal pathology. 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
- hanges 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<br>• Blood pressure and body weight<br>• Serum creatinine, electrolytes (sodium, potassium, phosphate, calcium), bicarbonate and uric acid<br>• 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)<br>or<br>• 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.