Sponsor

Novartis Pharmaceuticals

Generic Drug Name

QCC374

Trial Indication(s)

Pulmonary arterial hypertension

Protocol Number

CQCC374X2201

Protocol 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

Clinical Trial Phase

Phase 2

Phase of Drug Development

Phase II

Study Start/End Dates

Study Start Date: September 2017 (Actual)
Primary Completion Date: June 2018 (Actual)
Study Completion Date: June 2018 (Actual)

Reason for Termination (If applicable)

The decision for early termination was based on changes in Novartis strategy, and was not based on any safety concerns regarding QCC374. Only Part 1 of the study was completed and the review of safety data from Part 1 of study CQCC374X2201 indicated that QCC374 is safe.

Study Design/Methodology

This was a non-confirmatory, randomized, placebo controlled, subject and investigator blinded study of QCC374 in PAH subjects. The study was planned to 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 0.06 mg bid starting dose. However, due to early study termination following Part 1, Part 2 was not completed. Both study parts were comprised of four phases: a screening period for up to 28 days, a titration period of 2 weeks, a stable dose period of 14 weeks and safety follow-up period for 28 days. At the end of the treatment period of 16 weeks, eligible patients were given the option to participate in a separate long-term extension study (CQCC374X2201E1), where all patients were treated with an individual optimal dose of QCC374.

During the screening period, no study medication was administered. The planned bid dose levels in Part 1 were 0.03 mg, 0.06 mg and 0.12 mg. The study dose was titrated during the initial two week titration period. Subjects were planned to begin dosing at 0.03 mg bid (Day 1-3), then increase to 0.06 mg bid (Day 4) and finally increase to 0.12 mg bid (Day 7-14.)

Once the titration was completed, no further adjustments in dose occurred unless a dose reduction for tolerability or safety reasons was indicated. In the event of a dose reduction, the subject was allowed to increase 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 were not allowed.

For all subjects who stopped study treatment prematurely or who decided not to participate in the long-term extension phase study, a safety follow-up visit occurred 28 days after the stop of study medication.

Centers

5 centers in 4 countries: United Kingdom(1), Germany(2), United States(1), Korea, Republic of(1)

Objectives:

Primary:

- To assess the efficacy of 16 weeks of QCC374 administration in adult subjects with pulmonary arterial hypertension (PAH)

Secondary:

- To evaluate the safety and tolerability of multiple doses of QCC374 in subjects with PAH
- To evaluate the preliminary efficacy of 16 weeks of QCC374 administration in subjects with PAH by measuring changes from baseline in six minute walk distance (6MWD), hemodynamic parameters other than pulmonary vascular resistance (PVR) and right ventricular (RV) function with echocardiography
- To evaluate the pharmacokinetics of QCC374 and its metabolite QCM441 in subjects with PAH

Test Product (s), Dose(s), and Mode(s) of Administration

QCC374 capsules for inhalation were supplied to the investigators at dose strengths of 0.015 mg and 0.06 mg. Placebo capsules were also supplied. QCC374 was administered to the subject via inhaled administration with the Concept1 dry powder inhaler, twice daily. Throughout the 16-week treatment period, the majority of administration occurred at home on an outpatient basis. Stepwise instructions for use of the capsules and inhalation using the Concept1 dry powder inhaler were provided in the instructions for use.

Statistical Methods

For all analysis sets, subjects were analyzed according to the study treatments received.

The safety analysis set (SAS) included all subjects that received any study drug.

The PK analysis set (PAS) included subjects with available PK data and no protocol deviations with relevant impact on PK data.

The PD analysis set included all subjects who received any study drug and have no protocol deviations with relevant impact on PD data.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:
• Male and female patients 18 years of age or older with symptomatic PAH.
• 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).
• Subjects must have persistent symptoms due to PAH despite therapy with at least one of the following PAH medications: an endothelin receptor antagonist, asoluble guanylate cyclase stimulator or a phosphodiesterase inhibitor. The subjects' PAH medication regimen, with typical medications including calcium channel blockers, 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.
• Diagnosis of PAH established according to the standard criteria before the screening visit:
• Resting mean pulmonary arterial pressure > 25 mmHg.
• PVR > 240 dynes s/cm5.
• Pulmonary capillary wedge pressure or left ventricular end diastolic pressure < 15 mmHg
• PVR > 400 dynes s/cm5 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).
• 6-minute walk distance 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).
• Subjects with PAH associated with portal hypertension, Human Immunodeficiency Virus (HIV) infection or unrepaired congenital systemic to pulmonary shunts
• 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.
• Hypotensive subjects (systemic systolic blood pressure < 85 mmHg)
• Subjects with a history of left sided heart disease, chronic left sided heart failure, congenital or acquired valvular disease and/or pulmonary venous hypertension.
• Subjects with significant obstructive (forced expiratory volume in one second [FEV1]/forced vital capacity [FVC] < 70% predicted) or restrictive (total lung capacity < 70% predicted) lung disease at screening.

Participant Flow Table

Overall Study

	QCC374	Placebo	Total
Arm/Group Description	Adult patients with pulmonary arterial hypertension (PAH) on QCC374	Adult patients with pulmonary arterial hypertension (PAH) on matching placebo	
Started	6	2	8
Pharmacodynamic (PD) analysis set	6	2	8
Pharmacokinetic (PK) analysis set	4	0	4
Completed	4	2	6
Not Completed	2	0	2
Adverse Event	1	0	1
Patient schedule	1	0	1

Baseline Characteristics

	QCC374	Placebo	Total
Arm/Group Description	Adult patients with pulmonary arterial hypertension	Adult patients with pulmonary arterial hypertension (PAH) on	

	(PAH) on QCC374	matching placebo	
Number of Participants [units: participants]	6	2	8
Age Continuous (units: Years) Mean ± Standard Deviation			
	41.0±14.62	57.5±9.19	45.1±14.93
Sex: Female, Male (units: Participants) Count of Participants (Not Applicable)			
Female	5	2	7
Male	1	0	1
Race/Ethnicity, Customized (units: Participants)			
Asian	1	0	1
White	5	2	7
Ethiology of Pulmonary Arterial Hypertension (PAH) (units: Participants) Count of Participants (Not Applicable)			
Family PAH	1	0	1
Idiopathic PAH	4	1	5
PAH associated with Connective Tissue Disease	1	0	1
PAH induced by Drug/Toxin	0	1	1
Time from Pulmonary Arterial Hypertension (PAH) diagnosis (units: Years) Median (Full Range)			

2.985 (0.56 to 7.77)	9.201 (6.04 to 12.36)	4.966 (0.56 to 12.36)

Summary of Efficacy

Primary Outcome Result(s)

Change from Baseline in Pulmonary Vascular Resistance (PVR) at Week 16 (Day 111)

(Time Frame: Baseline, Week 16 (Day 111))

	QCC374	Placebo
Arm/Group Description	Adult patients with pulmonary arterial hypertension (PAH) on QCC374	Adult patients with pulmonary arterial hypertension (PAH) on matching placebo
Number of Participants Analyzed [units: participants]	6	2
Change from Baseline in Pulmonary Vascular Resistance (PVR) at Week 16 (Day 111) (units: dyn*s/cm5) Mean ± Standard Deviation		
PVR at Screening-Ratio to Baseline (n=6,2)	1.00 ± 0.000	1.00 ± 0.000
PVR at Day 111-Ratio to Baseline (n=4,2)	1.07 ± 0.274	1.05 ± 0.073

Secondary Outcome Result(s)

Change from Baseline in Six Minute Walk Distance (6MWD) over time

(Time Frame: Baseline, Day 28, Day 56, Day 84 and Day 111)

	QCC374	Placebo
Arm/Group Description	Adult patients with pulmonary arterial hypertension (PAH) on QCC374	Adult patients with pulmonary arterial hypertension (PAH) on matching placebo
Number of Participants Analyzed [units: participants]	6	2
Change from Baseline in Six Minute Walk Distance (6MWD) over time (units: Meter) Mean ± Standard Deviation		
Baseline (n=6,2)	443.83 ± 47.942	458.50 ± 111.723
Chge from BL at Day 28 (n=6,2)	-7.17 ± 20.651	9.75 ± 13.789
Chge from BL at Day 56 (n=5,2)	-11.60 ± 19.562	14.50 ± 19.799
Chge from BL at Day 84 (n=4,2)	-4.25 ± 21.956	12.50 ± 16.971
Chge from BL at Day 111 (n=4,2)	13.25 ± 25.002	14.00 ± 9.192

Change from Baseline in Cardiac Output (CO) at Week 16 (Day 111)

(Time Frame: Baseline, Week 16 (Day 111))

	QCC374	Placebo
Arm/Group Description	Adult patients with pulmonary arterial hypertension (PAH) on QCC374	Adult patients with pulmonary arterial hypertension (PAH) on matching placebo
Number of Participants Analyzed [units: participants]	6	2
Change from Baseline in Cardiac Output (CO) at Week 16 (Day 111) (units: L/min) Mean ± Standard Deviation		
Average Cardiac Output at Baseline (n=6,2)	4.33 ± 1.527	3.61 ± 0.085
Average Cardiac Output at Day 111 (n=4,2)	4.46 ± 0.937	3.79 ± 0.191
Cardiac Output 1 at Baseline (n=6,2)	4.38 ± 1.491	3.61 ± 0.127
Cardiac Output 1 at Day 111 (n=4,2)	4.58 ± 1.002	3.69 ± 0.311
Cardiac Output 2 at Baseline (n=5,2)	3.96 ± 1.588	3.60 ± 0.000
Cardiac Output 2 at Day 111 (n=3,2)	4.33 ± 0.993	3.89 ± 0.233
Cardiac Output 3 at Baseline (n=5,2)	3.98 ± 1.340	3.61 ± 0.127
Cardiac Output 3 at Day 111 (n=3,2)	4.40 ± 1.238	3.79 ± 0.028

Change from Baseline in Cardiac Index at Week 16 (Day 111)

(Time Frame: Baseline, Week 16 (Day 111))

	QCC374	Placebo
Arm/Group Description	Adult patients with pulmonary arterial hypertension (PAH) on QCC374	Adult patients with pulmonary arterial hypertension (PAH) on matching placebo
Number of Participants Analyzed [units: participants]	6	2
Change from Baseline in Cardiac Index at Week 16 (Day 111) (units: L/min/m2) Mean ± Standard Deviation		
Cardiac Index at Baseline (n=6,2)	2.45 ± 0.794	2.15 ± 0.070
Cardiac Index at Day 111 (n=1,0)	2.54 ± NA[1]	

[1] NA: Not estimable due to insufficient number of participants with events

Change from Baseline in Pulmonary Capillary Wedge Pressure (PCWP) at Week 16 (Day 111)

(Time Frame: Baseline, Week 16 (Day 111))

	QCC374	Placebo
Arm/Group Description	Adult patients with pulmonary arterial hypertension (PAH) on QCC374	Adult patients with pulmonary arterial hypertension (PAH) on

		matching placebo
Number of Participants Analyzed [units: participants]	6	2
Change from Baseline in Pulmonary Capillary Wedge Pressure (PCWP) at Week 16 (Day 111) (units: mmHg) Mean ± Standard Deviation		
PCWP at Baseline (n=6,2)	8.67 ± 1.366	9.50 ± 0.707
PCWP at Day 111 (n=4,2)	11.75 ± 5.188	9.50 ± 0.707

Change from Baseline in Systemic Vascular Resistance (SVR) at Week 16 (Day 111)

(Time Frame: Baseline, Week 16 (Day 111))

	QCC374	**Placebo**
Arm/Group Description	Adult patients with pulmonary arterial hypertension (PAH) on QCC374	Adult patients with pulmonary arterial hypertension (PAH) on matching placebo
Number of Participants Analyzed [units: participants]	6	2
Change from Baseline in Systemic Vascular Resistance (SVR) at Week 16 (Day 111) (units: dynes*Sec*cm5) Mean ± Standard Deviation		
SVR at Baseline (n=5,2)	1133.31 ± 410.336	1425.89 ± 633.723
SVR at Day 111 (n=2,2)	1285.50 ± 465.983	1240.00 ± 274.357

Change from Baseline in RV fractional area change and RV Free Wall Average Peak Long Strain at Week 16 (Day 111) using Echocardiography

(Time Frame: Baseline, Week 16 (Day 111))

	QCC374	Placebo
Arm/Group Description	Adult patients with pulmonary arterial hypertension (PAH) on QCC374	Adult patients with pulmonary arterial hypertension (PAH) on matching placebo
Number of Participants Analyzed [units: participants]	5	2
Change from Baseline in RV fractional area change and RV Free Wall Average Peak Long Strain at Week 16 (Day 111) using Echocardiography (units: Percent) Mean ± Standard Deviation		
RV FAC at Baseline (n=4,2)	20.17 ± 8.717	30.05 ± 7.050
RV FAC at Day 111 (n=2,1)	20.70 ± 5.091	26.20 ± NA[12]
RV FWPLS at Baseline (n=5,1)	12.68 ± 3.534	16.30 ± NA[12]
RV FWPLS at Day 111 (n=2,0)	7.85 ± 2.758	

[1] NA: Not estimable due to insufficient number of participants with events
[2] NA: Not estimable due to insufficient number of participants with events

Change from Baseline in RV Tei Index at Week 16 (Day 111) using Echocardiography

(Time Frame: Baseline, Week 16 (Day 111))

	QCC374	Placebo
Arm/Group Description	Adult patients with pulmonary arterial hypertension (PAH) on QCC374	Adult patients with pulmonary arterial hypertension (PAH) on matching placebo
Number of Participants Analyzed [units: participants]	5	2
Change from Baseline in RV Tei Index at Week 16 (Day 111) using Echocardiography (units: Index) Mean ± Standard Deviation		
RV Tei Index at Baseline (n=4,2)	0.92 ± 0.260	0.88 ± 0.361
RV Tei Index at Day 111 (n=2,2)	0.89 ± 0.099	0.89 ± 0.078

Change from Baseline in Tricuspid Annular Peak Systolic Velocity (TA S') at Week 16 (Day 111) using Echocardiography

(Time Frame: Baseline, Week 16 (Day 111))

	QCC374	Placebo
Arm/Group Description	Adult patients with pulmonary arterial hypertension (PAH) on QCC374	Adult patients with pulmonary arterial hypertension (PAH) on matching placebo

Number of Participants Analyzed [units: participants]	5	2
Change from Baseline in Tricuspid Annular Peak Systolic Velocity (TA S') at Week 16 (Day 111) using Echocardiography (units: cm/s) Mean ± Standard Deviation		
TA S' at Baseline (n=4,2)	11.23 ± 1.723	9.50 ± 0.990
TA S' at Day 111 (n=3,1)	9.73 ± 1.069	13.20 ± NA[1]

[1] NA: Not estimable due to insufficient number of participants with events

Change from Baseline in Tricuspid Annular Plane Sys Excursion (TAPSE) at Week 16 (Day 111) using Echocardiography

(Time Frame: Baseline, Week 16 (Day 111))

	QCC374	Placebo
Arm/Group Description	Adult patients with pulmonary arterial hypertension (PAH) on QCC374	Adult patients with pulmonary arterial hypertension (PAH) on matching placebo
Number of Participants Analyzed [units: participants]	5	2
Change from Baseline in Tricuspid Annular Plane Sys Excursion (TAPSE) at Week 16 (Day 111) using Echocardiography (units: cm) Mean ± Standard Deviation		
TAPSE at Baseline (n=4,2)	1.88 ± 0.313	1.27 ± 0.170
TAPSE at Day 111 (n=3,1)	1.79 ± 0.511	1.76 ± NA[1]

[1] NA: Not estimable due to insufficient number of participants with events

Maximum Observed Plasma Concentration (Cmax) for QCC374 and its metabolite QCM441

(Time Frame: Day 1, Day 112)

	QCC374	Placebo
Arm/Group Description	Adult patients with pulmonary arterial hypertension (PAH) on QCC374	Adult patients with pulmonary arterial hypertension (PAH) on matching placebo
Number of Participants Analyzed [units: participants]	4	0
Maximum Observed Plasma Concentration (Cmax) for QCC374 and its metabolite QCM441 (units: pg/mL) Geometric Mean (Geometric Coefficient of Variation)		
QCC374: Day 1, Dose Level 0.03 mg (n=4,0)	101 (15.7%)	
QCC374: Day 112, Dose Level 0.06 mg (n=1,0)	461 (NA%)[1234]	
QCC374: Day 112, Dose Level 0.12 mg (n=1,0)	406 (NA%)[1234]	
QCM441: Day 1, Dose Level 0.03 mg (n=4,0)	346 (32.4%)	
QCM441: Day 112, Dose Level 0.06 mg (n=1,0)	2350 (NA%)[1234]	
QCM441: Day 112, Dose Level 0.12 mg (n=1,0)	3610 (NA%)[1234]	

[1] NA: Not estimable due to insufficient number of participants with events
[2] NA: Not estimable due to insufficient number of participants with events
[3] NA: Not estimable due to insufficient number of participants with events

[4] NA: Not estimable due to insufficient number of participants with events

Time to Reach the Maximum Plasma Concentration (Tmax) for QCC374 and its metabolite QCM441

(Time Frame: Day 1, Day 112)

	QCC374	Placebo
Arm/Group Description	Adult patients with pulmonary arterial hypertension (PAH) on QCC374	Adult patients with pulmonary arterial hypertension (PAH) on matching placebo
Number of Participants Analyzed [units: participants]	4	0
Time to Reach the Maximum Plasma Concentration (Tmax) for QCC374 and its metabolite QCM441 (units: hour) Median (Full Range)		
QCC374: Day 1, Dose Level 0.03 mg(n=4,0)	0.159 (0.0830 to 0.267)	
QCC374: Day 112, Dose Level 0.06 mg (n=1,0)	0.00 (0.00 to 0.00)	
QCC374: Day 112, Dose Level 0.12 mg (n=1,0)	0.517 (0.517 to 0.517)	
QCM441: Day 1, Dose Level 0.03 mg (n=4,0)	3.99 (3.85 to 8.00)	
QCM441: Day 112, Dose Level 0.06 mg (n=1,0)	1.00 (1.00 to 1.00)	
QCM441: Day 112, Dose Level 0.12 mg (n=1,0)	4.02 (4.02 to 4.02)	

Area Under the Plasma Concentration-time Curve From 0 to the Last Measurable Concentration (AUClast) for QCC374 and its metabolite QCM441

(Time Frame: Day 1, Day 112)

	QCC374	Placebo
Arm/Group Description	Adult patients with pulmonary arterial hypertension (PAH) on QCC374	Adult patients with pulmonary arterial hypertension (PAH) on matching placebo
Number of Participants Analyzed [units: participants]	4	0
Area Under the Plasma Concentration-time Curve From 0 to the Last Measurable Concentration (AUClast) for QCC374 and its metabolite QCM441 (units: h*pg/mL) Geometric Mean (Geometric Coefficient of Variation)		
QCC374: Day 1, Dose Level 0.03 mg (n=4,0)	128 (14.3%)	
QCC374: Day 112, Dose Level 0.06 mg (n=1,0)	638 (NA%)[1234]	
QCC374: Day 112, Dose Level 0.12 mg (n=1,0)	883 (NA%)[1234]	
QCM441: Day 1, Dose Level 0.03 mg (n=4,0)	2590 (22.8%)	
QCM441: Day 112, Dose Level 0.06 mg (n=1,0)	17700 (NA%)[1234]	
QCM441: Day 112, Dose Level 0.12 mg (n=1,0)	33800 (NA%)[1234]	

[1] NA: Not estimable due to insufficient number of participants with events
[2] NA: Not estimable due to insufficient number of participants with events
[3] NA: Not estimable due to insufficient number of participants with events
[4] NA: Not estimable due to insufficient number of participants with events

Area Under the plasma Concentration time Curve From 0 to the end of a dosing interval (AUCtau) for QCC374 and its metabolite QCM441

(Time Frame: Day 1, Day 112)

	QCC374	Placebo
Arm/Group Description	Adult patients with pulmonary arterial hypertension (PAH) on QCC374	Adult patients with pulmonary arterial hypertension (PAH) on matching placebo
Number of Participants Analyzed [units: participants]	4	0
Area Under the plasma Concentration time Curve From 0 to the end of a dosing interval (AUCtau) for QCC374 and its metabolite QCM441 (units: h*pg/mL) Geometric Mean (Geometric Coefficient of Variation)		
QCC374: Day 1, Dose Level 0.03 mg (n=4,0)	148 (15.5%)	
QCC374: Day 112, Dose Level 0.06 mg (n=1,0)	638 (NA%)[1234]	
QCC374: Day 112, Dose Level 0.12 mg (n=1,0)	910 (NA%)[1234]	
QCM441: Day 1, Dose Level 0.03 mg (n=4,0)	2600 (40.6%)	
QCM441: Day 112, Dose Level 0.06 mg (n=1,0)	17700 (NA%)[1234]	

QCM441: Day 112, Dose Level 0.12 mg (n=1,0)	33800 (NA%)[1234]

[1] NA: Not estimable due to insufficient number of participants with events
[2] NA: Not estimable due to insufficient number of participants with events
[3] NA: Not estimable due to insufficient number of participants with events
[4] NA: Not estimable due to insufficient number of participants with events

Summary of Safety

Safety Results

All-Cause Mortality

	QCC374 N = 6	Placebo N = 2
Arm/Group Description	Adult patients with pulmonary arterial hypertension (PAH) on QCC374	Adult patients with pulmonary arterial hypertension (PAH) on matching placebo
Total participants affected	0 (0.00%)	0 (0.00%)

Serious Adverse Events by System Organ Class

Time Frame	Adverse Events and Serious Adverse Events were collected for the maximum duration of participants' treatment exposure plus any follow up period, approximately 5 months.
Source Vocabulary for Table Default	MedDRA (21.0)

Assessment Type for Table Default	Systematic Assessment

	QCC374 N = 6	**Placebo N = 2**
Arm/Group Description	Adult patients with pulmonary arterial hypertension (PAH) on QCC374	Adult patients with pulmonary arterial hypertension (PAH) on matching placebo
Total participants affected	1 (16.67%)	0 (0.00%)
Nervous system disorders		
Syncope*	1 (16.67%)	0 (0.00%)

* Non-systematic Assessment

Other Adverse Events by System Organ Class

Time Frame	Adverse Events and Serious Adverse Events were collected for the maximum duration of participants' treatment exposure plus any follow up period, approximately 5 months.
Source Vocabulary for Table Default	MedDRA (21.0)
Assessment Type for Table Default	Systematic Assessment
Frequent Event Reporting Threshold	5%

	QCC374 N = 6	**Placebo N = 2**

Arm/Group Description	Adult patients with pulmonary arterial hypertension (PAH) on QCC374	Adult patients with pulmonary arterial hypertension (PAH) on matching placebo
Total participants affected	6 (100.00%)	1 (50.00%)
Gastrointestinal disorders		
Dental Caries*	0 (0.00%)	1 (50.00%)
Diarrhoea*	2 (33.33%)	0 (0.00%)
Dyspepsia*	1 (16.67%)	0 (0.00%)
Gastrointestinal Disorder*	1 (16.67%)	0 (0.00%)
Gastrooesophageal Reflux Disease*	1 (16.67%)	0 (0.00%)
Nausea*	3 (50.00%)	0 (0.00%)
Vomiting*	1 (16.67%)	0 (0.00%)
General disorders		
Hangover*	0 (0.00%)	1 (50.00%)
Infections and infestations		
Gastroenteritis*	1 (16.67%)	0 (0.00%)
Nasopharyngitis*	2 (33.33%)	1 (50.00%)
Otitis Media*	1 (16.67%)	0 (0.00%)
Musculoskeletal and connective tissue disorders		

Pain In Extremity*	1 (16.67%)	0 (0.00%)
Pain In Jaw*	2 (33.33%)	0 (0.00%)
Nervous system disorders		
Dysgeusia*	1 (16.67%)	0 (0.00%)
Head Discomfort*	1 (16.67%)	0 (0.00%)
Headache*	5 (83.33%)	0 (0.00%)
Skin and subcutaneous tissue disorders		
Erythema*	1 (16.67%)	0 (0.00%)
Vascular disorders		
Flushing*	3 (50.00%)	0 (0.00%)

* Non-systematic Assessment

Other Relevant Findings

None

Conclusion:

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

Novartis terminated the study at the end of Part 1 for strategic reasons. The review of safety data from Part 1 indicated that QCC374 is safe, and the decision for early termination was not based on any safety concerns. Due to limited available data, no inferential analyses were performed and only descriptive analysis of primary and secondary endpoints were presented. No efficacy related conclusions could be drawn between treated and the placebo groups due to the small sample size.

Subjects who received QCC374 in this study demonstrated typical AEs associated with prostacyclins, including headache (83%), flushing (50%), nausea (50%), diarrhea (33%) and pain in jaw (33%). The majority of these AEs were mild. There were no deaths during the study. One SAE was reported (syncope) resulting in study discontinuation, but the SAE was not suspected to be the study drug related. One subject experienced gastro-intestinal disorder (not suspected to be study drug related, clinical assessment of Norovirus) which resulted in the subject missing ~20% of doses and subsequently the subject completed the study at a lower dose (0.06mg). No clinically significant findings were identified during the review of the vital sign, ECG, spirometry, laboratory and adverse event data. Overall, the safety profile was consistent with the known safety of IPR agonists and no new safety signals were identified.

Date of Clinical Trial Report

06-May-2019