NOVARTIS

Clinical Trial Results Website

Sponsor

Novartis Pharmaceutical

Generic Drug Name

QCC374

Trial Indication(s)

Pulmonary arterial hypertension.

Protocol Number

CQCC374X2201E1

Protocol Title

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

Clinical Trial Phase

Phase 2

Phase of Drug Development

II

Study Start/End Dates

Study Start Date: February 2018 (Actual)
Primary Completion Date: November 2018 (Actual)
Study Completion Date: November 2018 (Actual)

Reason for Termination (If applicable)

Study Design/Methodology

This was a multicenter, open label trial to assess the safety, tolerability, pharmacokinetics and efficacy of inhaled QCC374 over a two-year period in PAH subjects who completed the core study QCC374X2201. This extension study had two arms: Arm 1, in which subjects who received QCC374 in the QCC374X2201 core study continued at the same dose, and Arm 2, in which subjects who received placebo in the QCC374X2201 core study were now up-titrated with QCC374. Both study arms included four phases: a screening period for up to 8 days, a treatment period of 720 days, an end of study (EOS) visit and a follow-up period. For all subjects the assessments obtained during the Day 112 visit for the core QCC374X2201 study (including physical examination, vital signs, pulse oximetry, ECG, spirometry, 6MWD, WHO functional class and laboratory data) were used as the baseline values for this study.
Subjects in Arm 1 continued to receive QCC374 at the same dose during the core study (0.12 mg bid or lower if their individual maximum tolerated dose (MTD) was below 0.12 mg bid). Subjects in Arm 2, not previously dosed with QCC374, received a QCC374 starting dose of 0.03mg inhaled bid, which was then up-titrated according to the same titration scheme used in the QCC374X2201 core study.
The primary endpoint of this study was the number of participants with adverse events as a measure of safety and tolerability.

Centers

4 centers in 3 countries: Germany(2), United Kingdom(1), United States(1)

Objectives:

Primary:
- To evaluate the safety and tolerability of QCC374 in patients with PAH over a two year period

Secondary:
- To assess the treatment effect of QCC374 in PAH patients not previously dosed with QCC374 (Arm 2: subjects who previously received placebo in QCC374X2201)
- To evaluate the pharmacokinetics of QCC374 and its metabolite QCM441 in PAH patients not previously dosed with QCC374 (Arm 2: subjects who previously received placebo in QCC374X2201)

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. QCC374 was administered to the subject via inhaled administration with the Concept1 dry powder inhaler, twice daily. Throughout the 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 instruction for use.

Statistical Methods

Analysis sets were defined as:
The full analysis set included all subjects that received any study drug.
The safety analysis set included all subjects that received any study drug.
The PK analysis set included all subjects with at least one available valid (i.e. not flagged for exclusion) PK concentration measurement, who received any study drug and experienced no protocol deviations with relevant impact on PK data.
The PD analysis set included all subjects with any available PD data, who received any study drug and experienced no protocol deviations with relevant impact on PD data.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:
• Written informed consent must be obtained before any assessment is performed.
• Subject was enrolled in the QCC374X2201 study and completed per protocol

Exclusion Criteria:
• Subjects who have started receiving prostacyclin (epoprostenol), prostacyclin analogs (i.e. trepostinil, iloprost, beraprost) or prostacyclin receptor agonists (i.e. selexipag) since the last study drug intake in the QCC374X2201 study.
• Females who are pregnant, or who plan to become pregnant during the study, or who are breastfeeding
• Any known factor or disease that may interfere with treatment compliance or study conduct (i.e. drug or alcohol dependence)
• Subjects who withdrew consent from the study QCC374X2201

Participant Flow Table

Overall Study

	Arm 1	Arm 2	Total

Arm/Group Description	Subjects randomized in the QCC374X2201 core study continued on QCC374 at their highest stable dose, in this extension study	Subjects randomized to placebo in the QCC374X2201 core study completed a titration scheme similar to that of the active arm in QCC374X2201 core study protocol	
Started	3	2	5
Completed	0	0	0
Not Completed	3	2	5
Adverse Event	1	0	1
Study Terminated By Sponsor	2	2	4

Baseline Characteristics

	Arm 1	Arm2	Total
Arm/Group Description	Subjects randomized in the QCC374X2201 core study continued on QCC374 at their highest	Subjects randomized to placebo in the QCC374X2201 core study completed a titration scheme similar	

	stable dose, in this extension study 0.12mg - active patients will continue at the dose they finished on the QCC374X2201 study	to that of the active arm in QCC374X2201 core study protocol	
Number of Participants [units: participants]	3	2	5
Age Continuous (units: Years) Mean ± Standard Deviation			
	40.3±4.93	58.0±9.90	47.4±11.41
Sex: Female, Male (units:) Count of Participants (Not Applicable)			
Female	3	2	5
Male	0	0	0
Race/Ethnicity, Customized (units: Participants)			
White	3	2	5

Summary of Efficacy

Primary Outcome Result(s)

Number of Participants Who Experienced Adverse Events (AEs), Serious Adverse Events (SAEs) in patients with PAH over a two year period

(Time Frame: Two years)

	Arm 1	Arm 2
Arm/Group Description	Subjects randomized in the QCC374X2201 core study continued on QCC374 at their highest stable dose, in this extension study 0.12mg - active patients will continue at the dose they finished on the QCC374X2201 study	Subjects randomized to placebo in the QCC374X2201 core study completed a titration scheme similar to that of the active arm in QCC374X2201 core study protocol
Number of Participants Analyzed [units: participants]	3	2
Number of Participants Who Experienced Adverse Events (AEs), Serious Adverse Events (SAEs) in patients with PAH over a two year period (units: Participants)		
Participant with AE	2	2
Participants with serious AE	1	0

Secondary Outcome Result(s)

Maximum Observed Plasma Concentration (Cmax)

(Time Frame: 16 weeks)

	QCC374
Arm/Group Description	placebo patients from QCC374X2201 rolled into extension study will start at 0.03mg b.i.d. or 0.06mg b.i.d. and have the opportunity to up-titrate 0.12mg -active patients will continue at the dose they finished on the QCC374X2201 study
Number of Participants Analyzed [units: participants]	1
Maximum Observed Plasma Concentration (Cmax) (units: pg/mL) Median (Full Range)	
QCC374: Day 1, Dose Level 0.03 mg	82 (82 to 82)
QCC374: Day 112, Dose Level 0.12 mg	664 (664 to 664)

Time to Reach the Maximum Plasma Concentration (Tmax)

(Time Frame: 16 Weeks)

	QCC374

Arm/Group Description	placebo patients from QCC374X2201 rolled into extension study will start at 0.03mg b.i.d. or 0.06mg b.i.d. and have the opportunity to up-titrate 0.12mg -active patients will continue at the dose they finished on the QCC374X2201 study
Number of Participants Analyzed [units: participants]	1
Time to Reach the Maximum Plasma Concentration (Tmax) (units: hour) Median (Full Range)	
QCC374: Day 1, Dose Level 0.03 mg	0.250 (0.250 to 0.250)
QCC374: Day 112, Dose Level 0.12 mg	0.0330 (0.0330 to 0.0330)

Area Under the Plasma Concentration-time Curve From 0 to the Last Measurable Concentration (AUClast)

(Time Frame: 16 weeks)

QCC374

Arm/Group Description	placebo patients from QCC374X2201 rolled into extension study will start at 0.03mg b.i.d. or 0.06mg b.i.d. and have the opportunity to up-titrate 0.12mg -active patients will continue at the dose they finished on the QCC374X2201 study
Number of Participants Analyzed [units: participants]	1
Area Under the Plasma Concentration-time Curve From 0 to the Last Measurable Concentration (AUClast) (units: h*pg/mL) Median (Full Range)	
QCC374: Day 1, Dose Level 0.03 mg	118 (118 to 118)
QCC374: Day 112, Dose Level 0.12 mg	526 (526 to 526)

Area Under the plasma Concentration time Curve From 0 to the end of a dosing interval (AUCtau)

(Time Frame: 16 Weeks)

	QCC374
Arm/Group Description	placebo patients from

	QCC374X2201 rolled into extension study will start at 0.03mg b.i.d. or 0.06mg b.i.d. and have the opportunity to up-titrate 0.12mg -active patients will continue at the dose they finished on the QCC374X2201 study
Number of Participants Analyzed [units: participants]	1
Area Under the plasma Concentration time Curve From 0 to the end of a dosing interval (AUCtau) (units: h*pg/mL) Median (Full Range)	
QCC374: Day 1, Dose Level 0.03 mg	134 (134 to 134)
QCC374: Day 112, Dose Level 0.12 mg	566 (566 to 566)

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

(Time Frame: 16 weeks)

	QCC374
Arm/Group Description	placebo patients from QCC374X2201 rolled into

	extension study will start at 0.03mg b.i.d. or 0.06mg b.i.d. and have the opportunity to up-titrate 0.12mg -active patients will continue at the dose they finished on the QCC374X2201 study
Number of Participants Analyzed [units: participants]	3
Change from Baseline in Six Minute Walk Distance (6MWD) (units: Meter) Mean ± Standard Deviation	
	452 ± 104.65

Change in Tricuspid Annular Peak Systolic Velocity (TA S') at Week 16 (Day 112) using Echocardiography

(Time Frame: Two Years)

	QCC374
Arm/Group Description	placebo patients from QCC374X2201 rolled into extension study will start at 0.03mg b.i.d. or

	0.06mg b.i.d. and have the opportunity to up-titrate 0.12mg -active patients will continue at the dose they finished on the QCC374X2201 study
Number of Participants Analyzed [units: participants]	2
Change in Tricuspid Annular Peak Systolic Velocity (TA S') at Week 16 (Day 112) using Echocardiography (units: cm/s) Mean ± Standard Deviation	10.90 ± NA[1]

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

Change from Baseline in RV Tei Index at Week 16 (Day 112) using Echocardiography

(Time Frame: 16 weeks)

	QCC374
Arm/Group Description	placebo patients from QCC374X2201 rolled into extension study will start at 0.03mg b.i.d. or 0.06mg b.i.d.

	and have the opportunity to up-titrate 0.12mg -active patients will continue at the dose they finished on the QCC374X2201 study
Number of Participants Analyzed [units: participants]	2
Change from Baseline in RV Tei Index at Week 16 (Day 112) using Echocardiography (units: Index) Mean ± Standard Deviation	0.84 ± NA[1]

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

Change from Baseline in RV fractional area change at Week 16 (Day 112) using Echocardiography

(Time Frame: 16 weeks)

	QCC374
Arm/Group Description	placebo patients from QCC374X2201 rolled into extension study will start at 0.03mg b.i.d. or 0.06mg b.i.d. and have the opportunity to

	up-titrate 0.12mg -active patients will continue at the dose they finished on the QCC374X2201 study
Number of Participants Analyzed [units: participants]	2
Change from Baseline in RV fractional area change at Week 16 (Day 112) using Echocardiography (units: Percentage) Mean ± Standard Deviation	
	23.91 ± NA[1]

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

Summary of Safety

Safety Results

All-Cause Mortality

	QCC374 N =	QCC374 Arm 1 N = 3	QCC374 Arm 2 N = 2
Arm/Group Description	placebo patients from QCC374X2201 rolled into extension study will start at 0.03mg b.i.d. or 0.06mg b.i.d. and have the opportunity to up-titrate 0.12mg -active patients will continue at the dose they finished on the QCC374X2201 study	QCC374 Arm 1	QCC374 Arm 2
Total participants affected	---	0 (0.00%)	0 (0.00%)

Serious Adverse Events by System Organ Class

Time Frame	Treatment-emergent adverse events
Source Vocabulary for Table Default	MedDRA (21.0)
Assessment Type for Table Default	Systematic Assessment

	QCC374 N =	**QCC374 Arm 1 N = 3**	**QCC374 Arm 2 N = 2**
Arm/Group Description	placebo patients from QCC374X2201 rolled into extension study will start at 0.03mg b.i.d. or 0.06mg b.i.d. and have the opportunity to up-titrate 0.12mg -active patients will continue at the dose they finished on the QCC374X2201 study	QCC374 Arm 1	QCC374 Arm 2
Total participants affected		1 (33.33%)	0 (0.00%)
Respiratory, thoracic and mediastinal disorders			
Pulmonary arterial hypertension		1 (33.33%)	0 (0.00%)

Other Adverse Events by System Organ Class

Time Frame	Treatment-emergent adverse events
Source Vocabulary for Table Default	MedDRA (21.0)
Assessment Type for Table Default	Systematic Assessment
Frequent Event Reporting Threshold	5%

	QCC374 N =	**QCC374 Arm 1 N = 3**	**QCC374 Arm 2 N = 2**
Arm/Group Description	placebo patients from QCC374X2201 rolled into extension study will start at 0.03mg b.i.d. or 0.06mg b.i.d. and have the opportunity to up-titrate 0.12mg -active patients will continue at the dose they finished on the QCC374X2201 study	QCC374 Arm 1	QCC374 Arm 2
Total participants affected		1 (33.33%)	2 (100.00%)
Blood and lymphatic system disorders			

Lymphopenia	1 (33.33%)	0 (0.00%)
Gastrointestinal disorders		
Abdominal pain upper	0 (0.00%)	1 (50.00%)
Diarrhoea	0 (0.00%)	1 (50.00%)
Nausea	1 (33.33%)	1 (50.00%)
Vomiting	1 (33.33%)	1 (50.00%)
General disorders and administration site conditions		
Asthenia	0 (0.00%)	1 (50.00%)
Fatigue	0 (0.00%)	1 (50.00%)
Infections and infestations		
Nasopharyngitis	1 (33.33%)	2 (100.00%)
Injury, poisoning and procedural complications		
Sunburn	0 (0.00%)	1 (50.00%)
Metabolism and nutrition disorders		
Decreased appetite	0 (0.00%)	1 (50.00%)
Musculoskeletal and connective tissue disorders		
Arthralgia	0 (0.00%)	1 (50.00%)
Pain in extremity	0 (0.00%)	1 (50.00%)
Pain in jaw	0 (0.00%)	2 (100.00%)

Nervous system disorders		
Headache	1 (33.33%)	2 (100.00%)
Respiratory, thoracic and mediastinal disorders		
Cough	0 (0.00%)	1 (50.00%)
Oropharyngeal pain	0 (0.00%)	1 (50.00%)
Vascular disorders		
Flushing	1 (33.33%)	0 (0.00%)

Other Relevant Findings

None

Conclusion:

This study was an open-label safety extension to the Phase 2a study of inhaled QCC374 in adult patients with PAH, to monitor the long-term safety, tolerability and efficacy of QCC374.
The CQCC374X2201E1 study was temporarily halted after five subjects had enrolled in the study when Novartis made the decision to terminate the CQCC374X2201 study and stop further development of QCC374 for strategic reasons. Once the last patient was transitioned to different PAH therapies and reached LPLV, the CQCC374X2201E1 study was terminated early.
This abbreviated clinical study report describes the data obtained from the five adult patients with PAH who enrolled in the study and received QCC374.
No efficacy conclusions can be made from the available data.
The majority of AEs were mild (87%) and occurred in the two subjects who received QCC374 for the first time (77%). No clinically significant findings were identified during the review of the vital sign, EKG, spirometry, laboratory and adverse event data. The safety profile overall was consistent with the known safety of IP agonists and no new safety signals were identified

Date of Clinical Trial Report

16-Jul-2019