



Clinical trial results:

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

Summary

EudraCT number	2016-001411-20
Trial protocol	GB DE
Global end of trial date	06 November 2018

Results information

Result version number	v1 (current)
This version publication date	20 November 2019
First version publication date	20 November 2019

Trial information

Trial identification

Sponsor protocol code	CQCC374X2201E1
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02939599
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	06 November 2018
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	06 November 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 February 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 2
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	United States: 1
Worldwide total number of subjects	5
EEA total number of subjects	4

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	5
From 65 to 84 years	0

85 years and over	0
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Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The screening period (Day-8 to Day-1, max 8 days, min 1 day) began no earlier than Day 111 of the companion QCC374X2201 study. The goal is for patients to continue to receive QCC374 without interruption between the QCC374X2201 study and the extension study.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm 1

Arm description:

Subjects randomized in the QCC374X2201 core study continued on QCC374 at their highest stable dose, in this extension study

Arm type	Experimental
Investigational medicinal product name	QCC374
Investigational medicinal product code	QCC374
Other name	QCC374
Pharmaceutical forms	Inhalation powder, hard capsule
Routes of administration	Inhalation use

Dosage and administration details:

0.015 mg and 0.06mg

Arm title	Arm 2
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Arm description:

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

Arm type	Experimental
Investigational medicinal product name	QCC374
Investigational medicinal product code	QCC374
Other name	QCC374
Pharmaceutical forms	Inhalation powder, hard capsule
Routes of administration	Inhalation use

Dosage and administration details:

0.015 mg and 0.06 mg.

Number of subjects in period 1	Arm 1	Arm 2
Started	3	2
Completed	0	0
Not completed	3	2
Adverse event, non-fatal	1	-
Study Terminated By Sponsor	2	2

Baseline characteristics

Reporting groups

Reporting group title	Arm 1
Reporting group description:	
Subjects randomized in the QCC374X2201 core study continued on QCC374 at their highest stable dose, in this extension study	
Reporting group title	Arm 2
Reporting group description:	
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	

Reporting group values	Arm 1	Arm 2	Total
Number of subjects	3	2	5
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	3	2	5
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous			
Units: years			
arithmetic mean	40.3	58	-
standard deviation	± 4.93	± 9.90	-
Sex: Female, Male			
Units: Subjects			
Female	3	2	5
Male	0	0	0
Race/Ethnicity, Customized			
Units: Subjects			
Germany	1	1	2
United kingdom	1	1	2
United States	1	0	1

Subject analysis sets

Subject analysis set title	Arm2
Subject analysis set type	Safety analysis
Subject analysis set description:	
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	
Subject analysis set title	Arm 1
Subject analysis set type	Safety analysis

Subject analysis set 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

Reporting group values	Arm2	Arm 1	
Number of subjects	2	3	
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age Continuous Units: years			
arithmetic mean	58.0		
standard deviation	± 9.90	±	
Sex: Female, Male Units: Subjects			
Female	2		
Male	0		
Race/Ethnicity, Customized Units: Subjects			
Germany United kingdom United States			

End points

End points reporting groups

Reporting group title	Arm 1
Reporting group description: Subjects randomized in the QCC374X2201 core study continued on QCC374 at their highest stable dose, in this extension study	
Reporting group title	Arm 2
Reporting group description: 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	
Subject analysis set title	Arm2
Subject analysis set type	Safety analysis
Subject analysis set description: 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	
Subject analysis set title	Arm 1
Subject analysis set type	Safety analysis
Subject analysis set 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	

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

End point title	Number of Participants Who Experienced Adverse Events (AEs), Serious Adverse Events (SAEs) in patients with PAH over a two year period ^[1]
End point description: Patients with all (serious and non-serious) adverse events, serious adverse events and death were reported, Only descriptive analysis performed	
End point type	Primary
End point timeframe: Two years	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive analysis performed.

End point values	Arm 1	Arm 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	2		
Units: Participants				
Participant with AE	2	2		
Participants with serious AE	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Plasma Concentration (Cmax)

End point title	Maximum Observed Plasma Concentration (Cmax)
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End point description:

Cmax is the maximum (peak) observed plasma drug concentration after single dose administration. PK parameters were calculated from plasma concentration-time data using non-compartmental methods. Only descriptive analysis performed

End point type	Secondary
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End point timeframe:

16 weeks

End point values	Arm 1			
Subject group type	Subject analysis set			
Number of subjects analysed	1			
Units: pg/mL				
median (full range (min-max))				
QCC374: Day 1, Dose Level 0.03 mg	82 (82 to 82)			
QCC374: Day 112, Dose Level 0.12 mg	664 (664 to 664)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Reach the Maximum Plasma Concentration (Tmax)

End point title	Time to Reach the Maximum Plasma Concentration (Tmax)
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End point description:

Tmax is the time to reach maximum plasma concentration after single dose administration. PK parameters were calculated from plasma concentration-time data using non-compartmental methods. Only descriptive analysis performed.

End point type	Secondary
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End point timeframe:

16 Weeks

End point values	Arm 1			
Subject group type	Subject analysis set			
Number of subjects analysed	1			
Units: hour				
median (full range (min-max))				
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)			

Statistical analyses

No statistical analyses for this end point

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

End point title	Area Under the Plasma Concentration-time Curve From 0 to the Last Measurable Concentration (AUClast)
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End point description:

AUClast is the area under the plasma concentration-time curve from time zero to the last measurable concentration sampling time. PK parameters were calculated from plasma concentration-time data using non-compartmental methods. Only descriptive analysis performed.

End point type	Secondary
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End point timeframe:

16 weeks

End point values	Arm 1			
Subject group type	Subject analysis set			
Number of subjects analysed	1			
Units: h*pg/mL				
median (full range (min-max))				
QCC374: Day 1, Dose Level 0.03 mg	118 (118 to 118)			
QCC374: Day 112, Dose Level 0.12 mg	526 (526 to 526)			

Statistical analyses

No statistical analyses for this end point

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

End point title	Area Under the plasma Concentration time Curve From 0 to the end of a dosing interval (AUCtau)
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End point description:

AUCtau is the area under the plasma concentration-time curve from time zero to the end of the dosing interval. PK parameters were calculated from plasma concentration-time data using non-compartmental methods. Only descriptive analysis performed

End point type	Secondary
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End point timeframe:

16 Weeks

End point values	Arm 1			
Subject group type	Subject analysis set			
Number of subjects analysed	1			
Units: h*pg/mL				
median (full range (min-max))				
QCC374: Day 1, Dose Level 0.03 mg	134 (134 to 134)			
QCC374: Day 112, Dose Level 0.12 mg	566 (566 to 566)			

Statistical analyses

No statistical analyses for this end point

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

End point title	Change from Baseline in Six Minute Walk Distance (6MWD) ^[2]
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End point description:

The Six Minute Walk Test measures the distance an individual is able to walk over a total of six minutes on a hard, flat surface. The goal is for the individual to walk as far as possible in six minutes. The individual is able to self-pace and rest as needed as they traverse back and forth along a marked walkway. Only descriptive analysis performed.

End point type	Secondary
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End point timeframe:

16 weeks

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only descriptive analysis performed.

End point values	Arm 1			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: meter				
least squares mean (standard deviation)	452 (± 104.65)			

Statistical analyses

No statistical analyses for this end point

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

End point title	Change in Tricuspid Annular Peak Systolic Velocity (TA S') at Week 16 (Day 112) using Echocardiography ^[3]
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End point description:

Key Right Ventricular (RV) function endpoints such as Tricuspid Annular Peak Systolic Velocity (TA S') were assessed with echocardiography. Only descriptive analysis performed.

End point type	Secondary
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End point timeframe:

Two Years

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only descriptive analysis performed.

End point values	Arm 1			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: cm/s				
arithmetic mean (standard deviation)	10.90 (± 999)			

Statistical analyses

No statistical analyses for this end point

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

End point title	Change from Baseline in RV Tei Index at Week 16 (Day 112) using Echocardiography ^[4]
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End point description:

Key Right Ventricular (RV) function endpoints such as Tei Index were assessed with echocardiography. The RV Tei index is using both systolic and diastolic time intervals to evaluate the overall global dysfunction of the right ventricle in PAH patients. A lower number in RV Tei Index indicates an improvement. Only descriptive analysis performed.

End point type	Secondary
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End point timeframe:

16 weeks

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only descriptive analysis performed.

End point values	Arm 1			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: Index				
arithmetic mean (standard deviation)	23.91 (± 999)			

Statistical analyses

No statistical analyses for this end point

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

End point title	Change from Baseline in RV fractional area change at Week 16 (Day 112) using Echocardiography ^[5]
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End point description:

Key Right Ventricular (RV) function endpoints such as Tei Index were assessed with echocardiography. The RV Tei index is using both systolic and diastolic time intervals to evaluate the overall global dysfunction of the right ventricle in PAH patients. A lower number in RV Tei Index indicates an improvement. Only descriptive analysis performed.

End point type	Secondary
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End point timeframe:

16 weeks

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Only descriptive analysis performed.

End point values	Arm 1			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: Percentage				
arithmetic mean (standard deviation)	0.84 (± 999)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment-emergent adverse events

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	21.0
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Reporting groups

Reporting group title	QCC374 Arm 2
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Reporting group description:

QCC374 Arm 2

Reporting group title	QCC374 Arm 1
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Reporting group description:

QCC374 Arm 1

Serious adverse events	QCC374 Arm 2	QCC374 Arm 1	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary arterial hypertension			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	QCC374 Arm 2	QCC374 Arm 1	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 2 (100.00%)	1 / 3 (33.33%)	
Injury, poisoning and procedural complications			
Sunburn			
subjects affected / exposed	1 / 2 (50.00%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Vascular disorders			

Flushing subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0	1 / 3 (33.33%) 1	
Nervous system disorders Headache subjects affected / exposed occurrences (all)	2 / 2 (100.00%) 3	1 / 3 (33.33%) 1	
Blood and lymphatic system disorders Lymphopenia subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0	1 / 3 (33.33%) 1	
General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all) Fatigue subjects affected / exposed occurrences (all)	1 / 2 (50.00%) 1 1 / 2 (50.00%) 1	0 / 3 (0.00%) 0 0 / 3 (0.00%) 0	
Gastrointestinal disorders Abdominal pain upper subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	1 / 2 (50.00%) 1 1 / 2 (50.00%) 3 1 / 2 (50.00%) 1 1 / 2 (50.00%) 4	0 / 3 (0.00%) 0 0 / 3 (0.00%) 0 1 / 3 (33.33%) 1 1 / 3 (33.33%) 1	
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Oropharyngeal pain	1 / 2 (50.00%) 1	0 / 3 (0.00%) 0	

subjects affected / exposed occurrences (all)	1 / 2 (50.00%) 1	0 / 3 (0.00%) 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 2 (50.00%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Pain in extremity			
subjects affected / exposed	1 / 2 (50.00%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Pain in jaw			
subjects affected / exposed	2 / 2 (100.00%)	0 / 3 (0.00%)	
occurrences (all)	2	0	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	2 / 2 (100.00%)	1 / 3 (33.33%)	
occurrences (all)	2	1	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 2 (50.00%)	0 / 3 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 February 2017	The primary purpose of this amendment was to clarify language around the study design (including the addition of a study design figure) based on health authority feedback. Specifically, the starting dose for subjects enrolling in the QCC374X2201E1 study who were randomized to placebo in the companion QCC374X2201 study was further clarified throughout the protocol.
07 May 2018	The purpose of this amendment is to: (1) lower the dose of QCC374 based on emerging data from the companion QCC374X2201 study, (2) to clarify the transition from the companion QCC374X2201 study to this extension study based on investigator feedback, and (3) to remove 12 hours post-dose PK samples on Day 1 and D112. In the companion QCC374X2201 study, a planned safety review occurred at the end of Part 1, to review the tolerability of the selected QCC374 titration regimen. No clinically significant findings were identified during the review of vital signs, ECG, spirometry and laboratory data. The majority of AEs were mild and consistent with expected prostacyclin adverse events (headache, jaw pain, flushing, nausea). Considering the incidence of expected prostacyclin adverse events, and after receiving feedback from site Investigators, the companion QCC374X2201 study and this study are being amended to make two changes to the dosing regimen: (1) the starting dose will be maintained at 0.03 mg bid for all subjects and (2) the maximum dose with titration will be 0.06 mg bid. In regards to the transition from the QCC374X2201 study to the extension study, the text has been modified to clarify the alignment of the extension study screening period with the companion QCC374X2201 study, as well as further clarify the screening period duration and what assessments need to be completed during screening. To reduce patient burden, the 12 hours post-dose PK collections on Day 1 and Day 112 have been removed with this amendment, and the steady state AUC_{tau,ss} will be calculated using predose values at steady state

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported