



Clinical trial results:

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

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2016-001412-38 |
| Trial protocol | DE |
| Global end of trial date | 11 July 2018 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 19 June 2019 |
| First version publication date | 19 June 2019 |

Trial information

Trial identification

| | |
|-----------------------|--------------|
| Sponsor protocol code | CQCC374X2201 |
|-----------------------|--------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02927366 |
| 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 | 11 July 2018 |
| Is this the analysis of the primary completion data? | No |

| | |
|----------------------------------|--------------|
| Global end of trial reached? | Yes |
| Global end of trial date | 11 July 2018 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to assess the efficacy of 16 weeks of QCC374 administration in adult subjects with pulmonary arterial hypertension (PAH).

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use <https://www.novctrd.com/CtrdWeb/home.nov> for complete trial results.

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 | 19 September 2017 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety |
| Long term follow-up duration | 2 Years |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-----------------------|
| Country: Number of subjects enrolled | Germany: 3 |
| Country: Number of subjects enrolled | United Kingdom: 3 |
| Country: Number of subjects enrolled | United States: 1 |
| Country: Number of subjects enrolled | Korea, Republic of: 1 |
| Worldwide total number of subjects | 8 |
| EEA total number of subjects | 6 |

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) | 7 |
| From 65 to 84 years | 1 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

This study was conducted in 5 centers in 4 countries: Germany (2), Korea (1), UK (1) and USA (1).

Pre-assignment

Screening details:

Part 1 consisted of 8 subjects, randomized in a 6:2 ratio to QCC374 or placebo. The planned bid dose levels in Part 1 were 0.03 mg, 0.06 mg and 0.12 mg. Subjects began dosing at 0.03 mg bid.

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Overall Study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator |

Arms

| | |
|------------------------------|--------|
| Are arms mutually exclusive? | Yes |
| Arm title | QCC374 |

Arm description:

Adult patients with pulmonary arterial hypertension (PAH) on QCC374

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

Dosage and administration details:

QCC374 capsules for inhalation were supplied to the investigators at dose strengths of 0.015 mg and 0.06 mg.

| | |
|------------------|---------|
| Arm title | Placebo |
|------------------|---------|

Arm description:

Adult patients with pulmonary arterial hypertension (PAH) on matching placebo

| | |
|--|--|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation powder, hard capsule, Capsule |
| Routes of administration | Inhalation use |

Dosage and administration details:

Placebo to match QCC374 capsules for inhalation.

| Number of subjects in period 1 | QCC374 | Placebo |
|---------------------------------------|---------------|------------------|
| Started | 6 | 2 |
| Pharmacodynamic (PD) analysis set | 6 | 2 |
| Pharmacokinetic (PK) analysis set | 4 | 0 ^[1] |
| Completed | 4 | 2 |
| Not completed | 2 | 0 |
| Adverse event, non-fatal | 1 | - |
| Patient schedule | 1 | - |

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: All randomized patients were included in the Safety Analysis Set (SAS) and Pharmacodynamic (PD) analysis set. The PK analysis set (PAS) included 4 subjects with available PK data and no protocol deviations with relevant impact on PK data in the QCC374 treatment arm.

Baseline characteristics

Reporting groups

| | |
|---|---------|
| Reporting group title | QCC374 |
| Reporting group description: | |
| Adult patients with pulmonary arterial hypertension (PAH) on QCC374 | |
| Reporting group title | Placebo |
| Reporting group description: | |
| Adult patients with pulmonary arterial hypertension (PAH) on matching placebo | |

| Reporting group values | QCC374 | Placebo | Total |
|---|--------------|---------------|-------|
| Number of subjects | 6 | 2 | 8 |
| 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) | 5 | 2 | 7 |
| From 65-84 years | 1 | 0 | 1 |
| 85 years and over | 0 | 0 | 0 |
| Age Continuous | | | |
| Units: Years | | | |
| arithmetic mean | 41.0 | 57.5 | |
| standard deviation | ± 14.62 | ± 9.19 | - |
| Sex: Female, Male | | | |
| Units: Subjects | | | |
| Female | 5 | 2 | 7 |
| Male | 1 | 0 | 1 |
| Race/Ethnicity, Customized | | | |
| Units: Subjects | | | |
| Asian | 1 | 0 | 1 |
| White | 5 | 2 | 7 |
| Ethiology of Pulmonary Arterial Hypertension (PAH) | | | |
| Units: Subjects | | | |
| 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 | 2.985 | 9.201 | |
| full range (min-max) | 0.56 to 7.77 | 6.04 to 12.36 | - |

End points

End points reporting groups

| | |
|---|---------|
| Reporting group title | QCC374 |
| Reporting group description: | |
| Adult patients with pulmonary arterial hypertension (PAH) on QCC374 | |
| Reporting group title | Placebo |
| Reporting group description: | |
| Adult patients with pulmonary arterial hypertension (PAH) on matching placebo | |

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

| | |
|---|---|
| End point title | Change from Baseline in Pulmonary Vascular Resistance (PVR) at Week 16 (Day 111) ^[1] |
| End point description: | |
| The efficacy of 16 weeks of QCC374 administration in subjects with Pulmonary Arterial Hypertension (PAH) was assessed by measuring changes from baseline in Pulmonary Vascular Resistance (PVR). PVR is derived from the CO measurement in dyn·s/cm ⁵ and can be calculated as 80 multiplied by (Mean Arterial Pressure - Mean Pulmonary Artery Wedge Pressure) divided by Cardiac Output. A higher negative number in Pulmonary Vascular Resistance indicates improvement. Only descriptive analysis performed. | |
| End point type | Primary |
| End point timeframe: | |
| Baseline, Week 16 (Day 111) | |

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 | QCC374 | Placebo | | |
|--|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 6 | 2 | | |
| Units: dyn*s/cm ⁵ | | | | |
| arithmetic 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) | | |

Statistical analyses

No statistical analyses for this end point

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

| | |
|---|---|
| End point title | Change from Baseline in Six Minute Walk Distance (6MWD) over time |
| 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 |
|----------------|-----------|

End point timeframe:

Baseline, Day 28, Day 56, Day 84 and Day 111

| End point values | QCC374 | Placebo | | |
|--------------------------------------|-------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 6 | 2 | | |
| Units: Meter | | | | |
| arithmetic 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) | | |

Statistical analyses

No statistical analyses for this end point

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

| | |
|-----------------|--|
| End point title | Change from Baseline in Cardiac Output (CO) at Week 16 (Day 111) |
|-----------------|--|

End point description:

The Right Heart Catheterization (RHC) assessment was performed to assess several hemodynamic variables in pulmonary hypertension, including Cardiac Output (CO). All hemodynamic parameters were assessed when the patient was in a stable hemodynamic rest state (as demonstrated by three consecutive CO measurements within 10% of each other) while the patient was breathing ambient air or oxygen. CO was measured in triplicate using the thermodilution technique. Direct Fick could be used only after discussion and approval by the Sponsor. In all cases, the same technique was to be used at baseline and week 16. . A higher positive number in Cardiac Output indicates improvement. Only descriptive analysis performed.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Week 16 (Day 111)

| End point values | QCC374 | Placebo | | |
|--|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 6 | 2 | | |
| Units: L/min | | | | |
| arithmetic 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) | | |

Statistical analyses

No statistical analyses for this end point

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

| | |
|-----------------|--|
| End point title | Change from Baseline in Cardiac Index at Week 16 (Day 111) |
|-----------------|--|

End point description:

The Right Heart Catheterization (RHC) assessment was performed to assess several hemodynamic variables in pulmonary hypertension, including Cardiac Index. All hemodynamic parameters were assessed when the patient was in a stable hemodynamic rest state (as demonstrated by three consecutive CO measurements within 10% of each other) while the patient was breathing ambient air or oxygen. A higher negative number in Cardiac Index indicates improvement. Only descriptive analysis performed.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Week 16 (Day 111)

| End point values | QCC374 | Placebo | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 6 | 2 | | |
| Units: L/min/m2 | | | | |
| arithmetic 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 (± 999) | 999 (± 999) | | |

Statistical analyses

No statistical analyses for this end point

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

| | |
|-----------------|--|
| End point title | Change from Baseline in Pulmonary Capillary Wedge Pressure (PCWP) at Week 16 (Day 111) |
|-----------------|--|

End point description:

The Right Heart Catheterization (RHC) assessment was performed to assess several hemodynamic variables in pulmonary hypertension, including mean Pulmonary Capillary Wedge Pressure (PCWP). All hemodynamic parameters were assessed when the patient was in a stable hemodynamic rest state (as demonstrated by three consecutive CO measurements within 10% of each other) while the patient was breathing ambient air or oxygen. Pressure measurements were made in the PA, PA wedge, right ventricle (RV) and right atrium (RA) and determined at the end of normal expiration. The PCWP was recorded as the mean of three measurements. Only descriptive analysis performed.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Week 16 (Day 111)

| End point values | QCC374 | Placebo | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 6 | 2 | | |
| Units: mmHg | | | | |
| arithmetic 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) | | |

Statistical analyses

No statistical analyses for this end point

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

| | |
|-----------------|---|
| End point title | Change from Baseline in Systemic Vascular Resistance (SVR) at Week 16 (Day 111) |
|-----------------|---|

End point description:

The Right Heart Catheterization (RHC) assessment was performed to assess several hemodynamic variables in pulmonary hypertension, including Systemic Vascular Resistance (SVR). All hemodynamic parameters were assessed when the patient was in a stable hemodynamic rest state (as demonstrated by three consecutive CO measurements within 10% of each other) while the patient was breathing ambient air or oxygen. SVR is derived from the CO measurement in dyn·s/cm⁵ and can be calculated as 80 multiplied by (Mean Arterial Pressure - Mean Venous Pressure or CVP) divided by Cardiac Output. A higher negative number in Mean Systemic Vascular Resistance indicates improvement. Only descriptive analysis performed.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Week 16 (Day 111)

| End point values | QCC374 | Placebo | | |
|--------------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 6 | 2 | | |
| Units: dynes*Sec*cm5 | | | | |
| arithmetic 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) | | |

Statistical analyses

No statistical analyses for this end point

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

| | |
|---|---|
| End point title | Change from Baseline in RV fractional area change and RV Free Wall Average Peak Long Strain at Week 16 (Day 111) using Echocardiography |
| End point description: | |
| Key Right Ventricular (RV) function endpoints such as RV fractional area change (RV FAC) and RV Free Wall Average Peak Long Strain (RV FWPLS) were assessed with echocardiography. Only descriptive analysis performed. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Week 16 (Day 111) | |

| End point values | QCC374 | Placebo | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 5 | 2 | | |
| Units: Percent | | | | |
| arithmetic 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 (± 999) | | |
| RV FWPLS at Baseline (n=5,1) | 12.68 (± 3.534) | 16.30 (± 999) | | |
| RV FWPLS at Day 111 (n=2,0) | 7.85 (± 2.758) | 999 (± 999) | | |

Statistical analyses

No statistical analyses for this end point

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

| | |
|--|--|
| End point title | Change from Baseline in RV Tei Index at Week 16 (Day 111) using Echocardiography |
| End point description: Key Right Ventricular (RV) function endpoints such as RV myocardial performance index or Tei Index were assessed with echocardiography. Only descriptive analysis performed. | |
| End point type | Secondary |
| End point timeframe: Baseline, Week 16 (Day 111) | |

| End point values | QCC374 | Placebo | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 5 | 2 | | |
| Units: Index | | | | |
| arithmetic 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) | | |

Statistical analyses

No statistical analyses for this end point

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

| | |
|--|--|
| End point title | Change from Baseline in Tricuspid Annular Peak Systolic Velocity (TA S') at Week 16 (Day 111) using Echocardiography |
| 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 |
| End point timeframe: Baseline, Week 16 (Day 111) | |

| End point values | QCC374 | Placebo | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 5 | 2 | | |
| Units: cm/s | | | | |
| arithmetic 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 (± 999) | | |

Statistical analyses

No statistical analyses for this end point

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

| | |
|-----------------|---|
| End point title | Change from Baseline in Tricuspid Annular Plane Sys Excursion (TAPSE) at Week 16 (Day 111) using Echocardiography |
|-----------------|---|

End point description:

Key Right Ventricular (RV) function endpoints such as Tricuspid Annular Plane Sys Excursion (TAPSE) were assessed with echocardiography. Only descriptive analysis performed.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Week 16 (Day 111)

| End point values | QCC374 | Placebo | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 5 | 2 | | |
| Units: cm | | | | |
| arithmetic 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 (± 999) | | |

Statistical analyses

No statistical analyses for this end point

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

| | |
|-----------------|---|
| End point title | Maximum Observed Plasma Concentration (Cmax) for QCC374 and its metabolite QCM441 |
|-----------------|---|

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 |
|----------------|-----------|

End point timeframe:

Day 1, Day 112

| End point values | QCC374 | Placebo | | |
|---|-----------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 4 | 0 ^[2] | | |
| 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 (± 999) | () | | |
| QCC374: Day 112, Dose Level 0.12 mg (n=1,0) | 406 (± 999) | () | | |
| 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 (± 999) | () | | |
| QCM441: Day 112, Dose Level 0.12 mg (n=1,0) | 3610 (± 999) | () | | |

Notes:

[2] - PK sampling only performed in the QCC374 treatment arm

Statistical analyses

No statistical analyses for this end point

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

| | |
|-----------------|--|
| End point title | Time to Reach the Maximum Plasma Concentration (Tmax) for QCC374 and its metabolite QCM441 |
|-----------------|--|

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 |
|----------------|-----------|

End point timeframe:

Day 1, Day 112

| End point values | QCC374 | Placebo | | |
|---|-------------------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 4 | 0 ^[3] | | |
| Units: hour | | | | |
| median (full range (min-max)) | | | | |
| QCC374: Day 1, Dose Level 0.03 mg (n=4,0) | 0.159 (0.0830 to 0.267) | (to) | | |
| QCC374: Day 112, Dose Level 0.06 mg (n=1,0) | 0.00 (0.00 to 0.00) | (to) | | |
| QCC374: Day 112, Dose Level 0.12 mg (n=1,0) | 0.517 (0.517 to 0.517) | (to) | | |
| QCM441: Day 1, Dose Level 0.03 mg (n=4,0) | 3.99 (3.85 to 8.00) | (to) | | |
| QCM441: Day 112, Dose Level 0.06 mg (n=1,0) | 1.00 (1.00 to 1.00) | (to) | | |
| QCM441: Day 112, Dose Level 0.12 mg (n=1,0) | 4.02 (4.02 to 4.02) | (to) | | |

Notes:

[3] - PK sampling only performed in the QCC374 treatment arm

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) for QCC374 and its metabolite QCM441

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

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 |
|----------------|-----------|

End point timeframe:

Day 1, Day 112

| End point values | QCC374 | Placebo | | |
|---|-----------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 4 | 0 ^[4] | | |
| 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 (± 999) | () | | |
| QCC374: Day 112, Dose Level 0.12 mg (n=1,0) | 883 (± 999) | () | | |
| 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 (± 999) | () | | |
| QCM441: Day 112, Dose Level 0.12 mg (n=1,0) | 33800 (± 999) | () | | |

Notes:

[4] - PK sampling only performed in the QCC374 treatment arm

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) for QCC374 and its metabolite QCM441

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

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 |
|----------------|-----------|

End point timeframe:

Day 1, Day 112

| End point values | QCC374 | Placebo | | |
|---|-----------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 4 | 0 ^[5] | | |
| 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 (± 999) | () | | |
| QCC374: Day 112, Dose Level 0.12 mg (n=1,0) | 910 (± 999) | () | | |
| 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 (± 999) | () | | |
| QCM441: Day 112, Dose Level 0.12 mg (n=1,0) | 33800 (± 999) | () | | |

Notes:

[5] - PK sampling only performed in the QCC374 treatment arm

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events and Serious Adverse Events were collected for the maximum duration of participants' treatment exposure plus any follow up period, approximately 5 months.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 21.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Adult patients with pulmonary arterial hypertension (PAH) on matching placebo

| | |
|-----------------------|--------|
| Reporting group title | QCC374 |
|-----------------------|--------|

Reporting group description:

Adult patients with pulmonary arterial hypertension (PAH) on QCC374

| Serious adverse events | Placebo | QCC374 | |
|---|---------------|----------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 6 (16.67%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Nervous system disorders | | | |
| Syncope | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 6 (16.67%) | |
| 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 | Placebo | QCC374 | |
|---|----------------|-----------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 1 / 2 (50.00%) | 6 / 6 (100.00%) | |
| Vascular disorders | | | |
| Flushing | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 3 / 6 (50.00%) | |
| occurrences (all) | 0 | 3 | |
| Nervous system disorders | | | |

| | | | |
|---|---------------------|---------------------|--|
| Dysgeusia subjects affected / exposed occurrences (all) | 0 / 2 (0.00%) 0 | 1 / 6 (16.67%) 1 | |
| Head Discomfort subjects affected / exposed occurrences (all) | 0 / 2 (0.00%) 0 | 1 / 6 (16.67%) 1 | |
| Headache subjects affected / exposed occurrences (all) | 0 / 2 (0.00%) 0 | 5 / 6 (83.33%) 8 | |
| General disorders and administration site conditions Hangover subjects affected / exposed occurrences (all) | 1 / 2 (50.00%) 1 | 0 / 6 (0.00%) 0 | |
| Gastrointestinal disorders Dental Caries subjects affected / exposed occurrences (all) | 1 / 2 (50.00%) 1 | 0 / 6 (0.00%) 0 | |
| Diarrhoea subjects affected / exposed occurrences (all) | 0 / 2 (0.00%) 0 | 2 / 6 (33.33%) 3 | |
| Dyspepsia subjects affected / exposed occurrences (all) | 0 / 2 (0.00%) 0 | 1 / 6 (16.67%) 2 | |
| Gastrointestinal Disorder subjects affected / exposed occurrences (all) | 0 / 2 (0.00%) 0 | 1 / 6 (16.67%) 1 | |
| Gastrooesophageal Reflux Disease subjects affected / exposed occurrences (all) | 0 / 2 (0.00%) 0 | 1 / 6 (16.67%) 1 | |
| Nausea subjects affected / exposed occurrences (all) | 0 / 2 (0.00%) 0 | 3 / 6 (50.00%) 4 | |
| Vomiting subjects affected / exposed occurrences (all) | 0 / 2 (0.00%) 0 | 1 / 6 (16.67%) 1 | |
| Skin and subcutaneous tissue disorders | | | |

| | | | |
|---|---|---|--|
| Erythema subjects affected / exposed occurrences (all) | 0 / 2 (0.00%) 0 | 1 / 6 (16.67%) 1 | |
| Musculoskeletal and connective tissue disorders Pain In Extremity subjects affected / exposed occurrences (all) Pain In Jaw subjects affected / exposed occurrences (all) | 0 / 2 (0.00%) 0 0 / 2 (0.00%) 0 | 1 / 6 (16.67%) 2 2 / 6 (33.33%) 3 | |
| Infections and infestations Gastroenteritis subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all) Otitis Media subjects affected / exposed occurrences (all) | 0 / 2 (0.00%) 0 1 / 2 (50.00%) 1 0 / 2 (0.00%) 0 | 1 / 6 (16.67%) 1 2 / 6 (33.33%) 3 1 / 6 (16.67%) 1 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 27 February 2017 | Amendment 1: The primary purpose of this amendment was to clarify inclusion/exclusion criteria, and study design (including the addition of a study design figure), based on investigator and health authority feedback. In addition, minor changes were made to align this protocol with an amendment to the companion QCC374X2201E1 protocol. The completion of this amendment was prior to enrolling any subjects in the study. |
| 07 May 2018 | Amendment 2: As the study was terminated early and part 2 was not completed, this amendment was written and distributed, but was not implemented. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Due to the limited number of subjects with the available data at Week 16 (Day 111), for the primary and secondary efficacy endpoints, it is not possible to draw any meaningful treatment comparisons.

Notes: