



Clinical trial results:

A Randomised, Multicentre, Double-Blind, Placebo-Controlled Study Of Ambrisentan In Subjects With Inoperable Chronic Thromboembolic Pulmonary Hypertension (CTEPH).

Summary

| | |
|--------------------------|----------------------|
| EudraCT number | 2012-001646-18 |
| Trial protocol | ES AT DE GB IT CZ NL |
| Global end of trial date | 30 March 2015 |

Results information

| | |
|--------------------------------|--|
| Result version number | v3 (current) |
| This version publication date | 23 March 2017 |
| First version publication date | 01 April 2016 |
| Version creation reason | • Correction of full data set Changes required. |

Trial information

Trial identification

| | |
|-----------------------|--------|
| Sponsor protocol code | 115811 |
|-----------------------|--------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01884675 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | GlaxoSmithKline |
| Sponsor organisation address | 980 Great West Road, Middlesex, Brentford, United Kingdom, |
| Public contact | GSK Response Center, GlaxoSmithKline, +1 8664357343, |
| Scientific contact | GSK Response Center, GlaxoSmithKline, +1 8664357343, |

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 | 26 August 2015 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 30 March 2015 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

It is hypothesised that ambrisentan may provide benefit to subjects with inoperable chronic thromboembolic pulmonary hypertension (CTEPH). This Phase III, randomized, double-blind placebo controlled parallel group, 16 week study will compare the safety and efficacy of ambrisentan 5 milligrams (mg) versus placebo in subjects with inoperable CTEPH. The study will enroll 160 subjects, to assure at least 72 evaluable subjects per treatment arm, based on 10% drop-out rate.

Protection of trial subjects:

NA

Background therapy: -

Evidence for comparator: -

| | |
|---|-------------------|
| Actual start date of recruitment | 12 September 2013 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-----------------------|
| Country: Number of subjects enrolled | China: 11 |
| Country: Number of subjects enrolled | Czech Republic: 2 |
| Country: Number of subjects enrolled | Germany: 3 |
| Country: Number of subjects enrolled | Japan: 5 |
| Country: Number of subjects enrolled | Mexico: 2 |
| Country: Number of subjects enrolled | Russian Federation: 2 |
| Country: Number of subjects enrolled | Spain: 6 |
| Country: Number of subjects enrolled | United Kingdom: 1 |
| Country: Number of subjects enrolled | Netherlands: 1 |
| Worldwide total number of subjects | 33 |
| EEA total number of subjects | 13 |

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) | 19 |
| From 65 to 84 years | 14 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

A total of 160 participants were planned to be enrolled, however only 33 participants were randomized in the study.

Pre-assignment

Screening details:

This was a double-blind study which included clinic visits at Screening, Baseline visit, Weeks 4, 8, 12 and 16. A Follow-up visit was scheduled approximately 30 days after the Week 16 visit for those participants not continuing into study AMB116457 (Open-label extension study).

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, Monitor, Data analyst, Carer, Assessor |

Arms

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

Arm description:

Participants received a matching placebo tablet once daily for a period of 16 weeks.

| | |
|--|----------|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

5mg round, white, film-coated, immediate-release tablets, once daily

| | |
|------------------|-----------------|
| Arm title | Ambrisentan 5mg |
|------------------|-----------------|

Arm description:

Participants received an ambrisentan 5milligram (mg) tablet, once daily for a period of 16 weeks.

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | Ambrisentan |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

5mg round, white, film-coated, immediate-release tablets, once daily

| Number of subjects in period 1 | Placebo | Ambrisentan 5mg |
|---------------------------------------|---------|-----------------|
| Started | 16 | 17 |
| Completed | 13 | 15 |
| Not completed | 3 | 2 |
| Study terminated | 3 | 2 |

Baseline characteristics

Reporting groups

| | |
|---|-----------------|
| Reporting group title | Placebo |
| Reporting group description: | |
| Participants received a matching placebo tablet once daily for a period of 16 weeks. | |
| Reporting group title | Ambrisentan 5mg |
| Reporting group description: | |
| Participants received an ambrisentan 5milligram (mg) tablet, once daily for a period of 16 weeks. | |

| Reporting group values | Placebo | Ambrisentan 5mg | Total |
|---|----------------|-----------------|-------|
| Number of subjects | 16 | 17 | 33 |
| Age categorical Units: Subjects | | | |
| Age continuous Units: years arithmetic mean standard deviation | 59.8 ± 8.99 | 61.2 ± 13.38 | - |
| Gender categorical Units: Subjects | | | |
| Female | 10 | 8 | 18 |
| Male | 6 | 9 | 15 |
| RaceEthnicityOther Units: Subjects | | | |
| Asian - East Asian Heritage | 6 | 5 | 11 |
| Asian - Japanese Heritage | 4 | 1 | 5 |
| White - White/Caucasian/European Heritage | 6 | 11 | 17 |

End points

End points reporting groups

| | |
|---|-----------------|
| Reporting group title | Placebo |
| Reporting group description: | |
| Participants received a matching placebo tablet once daily for a period of 16 weeks. | |
| Reporting group title | Ambrisentan 5mg |
| Reporting group description: | |
| Participants received an ambrisentan 5milligram (mg) tablet, once daily for a period of 16 weeks. | |

Primary: Change from Baseline in Six Minutes Walking Distance (6MWD) at Week 16

| | |
|--|---|
| End point title | Change from Baseline in Six Minutes Walking Distance (6MWD) at Week 16 ^[1] |
| End point description: | |
| <p>The 6-minute walk test(6MWT) was conducted according to the American Thoracic Society guidelines in accordance with local standard operating procedures. 6MWD was measured by a 6MWT. This test measures the distance that a participant can walk in a period of 6 minutes. Change from BL was calculated at Weeks 4, 8, 12 and 16 as the value at the specified visit minus the BL value. Data at BL was based on average of two consecutive test results during Screening/BL period that differ by <10%. If only one measurement was available, that measurement was used. In any cases where the protocol-defined criteria for BL 6MWD was not met, the BL value was based on the last two consecutive measurements for a participant. Intent-to-Treat (ITT) Population: comprised of all randomized participants who received at least 1 dose of study drug. Only participants with available data at BL and the specified timepoint (represented as n=X, X for placebo and ambrisentan respectively) were summarized.</p> | |
| End point type | Primary |
| End point timeframe: | |
| Baseline (BL) (Week 0); Weeks 4, 8, 12 and 16/Early Withdrawal | |

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: As this study was terminated for futility of enrollment, the achieved sample size was approximately 1/5th of the intended sample size. As a result, the approach to characterizing the data was descriptive in nature with no formal hypotheses tested.

| End point values | Placebo | Ambrisentan 5mg | | |
|---------------------------------------|---------------------|-----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 16 | 17 | | |
| Units: Meters | | | | |
| median (inter-quartile range (Q1-Q3)) | | | | |
| Week 4, n=15, 17 | 5 (-1.5 to 16.5) | 14 (1 to 42.5) | | |
| Week 8, n=14, 16 | 7.5 (-14.5 to 22.5) | 26.25 (3.25 to 61.25) | | |
| Week 12, n=13, 15 | 5.5 (-23 to 39.5) | 20.5 (4 to 68) | | |
| Week 16, n=13, 15 | -10 (-32.5 to 20) | 25 (12 to 49) | | |
| Early Withdrawal, n=3, 2 | 7.5 (-46.5 to 43.5) | 41.25 (0 to 82.5) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in pulmonary vascular resistance (PVR) at Week 16

| | |
|-----------------|--|
| End point title | Change from Baseline in pulmonary vascular resistance (PVR) at Week 16 |
|-----------------|--|

End point description:

PVR is a measure of cardiopulmonary haemodynamics. Change from Baseline was calculated as value at specified visit minus Baseline value. Baseline is the last value recorded on or prior to start of study treatment. ITT Population. Only those participants with available data at Baseline and the specified time point were analyzed.

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

End point timeframe:

Baseline (Week 0) and Week 16

| End point values | Placebo | Ambrisentan 5mg | | |
|---------------------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 11 | 13 | | |
| Units: Dynes*second/centimeter^5 | | | | |
| median (inter-quartile range (Q1-Q3)) | -103 (-122 to -88) | -130 (-502 to -78) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in WHO Functional Class (FC) at Weeks 4, 8, 12 and 16/Early Withdrawal

| | |
|-----------------|---|
| End point title | Change from Baseline in WHO Functional Class (FC) at Weeks 4, 8, 12 and 16/Early Withdrawal |
|-----------------|---|

End point description:

The WHO FC indicates the severity of PAH and is an adaptation of the New York Heart Association classification as assessed by the investigator. There are four grades for WHO FC based on severity of symptoms (Class I = none, Class IV = most severe). This functional classification system links symptoms with activity limitations, and allows clinicians to predict disease progression and prognosis, and the need for specific treatment regimens irrespective of the underlying etiology of PAH. BL is the last value recorded on or prior to start of study treatment. Change from BL was calculated as the value at specified visit minus the BL value. For analysis purposes, the WHO FC Class categories of I-IV were mapped to a numeric scale of 1-4. Intent-to-Treat (ITT) Population: comprised of all randomized participants who received at least 1 dose of study drug. Only participants with available data at BL and the specified timepoint (represented as n=X,X in the category titles) were summarized.

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

End point timeframe:

Baseline (BL) (Week 0); Weeks 4, 8, 12 and 16/Early Withdrawal

| End point values | Placebo | Ambrisentan 5mg | | |
|---------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 16 | 17 | | |
| Units: Scores on a scale | | | | |
| median (inter-quartile range (Q1-Q3)) | | | | |
| Week 4, n=15, 17 | 0 (0 to 0) | 0 (0 to 0) | | |
| Week 8, n=14, 16 | 0 (0 to 0) | 0 (0 to 0) | | |
| Week 12, n=13, 15 | 0 (0 to 0) | 0 (-1 to 0) | | |
| Week 16, n=13, 15 | 0 (0 to 0) | 0 (-1 to 0) | | |
| Early Withdrawal, n=3, 2 | 0 (-1 to 0) | 0 (0 to 0) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Borg CR10 Scale (BCR10S) immediately following exercise at Weeks 4, 8, 12 and 16/Early Withdrawal

| | |
|-----------------|---|
| End point title | Change from Baseline in Borg CR10 Scale (BCR10S) immediately following exercise at Weeks 4, 8, 12 and 16/Early Withdrawal |
|-----------------|---|

End point description:

The BCR10S score was collected immediately following completion of the 6-minute walk test. Baseline data was calculated as the average of the two BCR10S values obtained following the two 6MWD tests used in determining the Baseline 6MWD. If only one measurement was available, that measurement has been used. BCR10S scores ranges from 0 to 10 (0=nothing at all, 10=extremely strong). If participant's perception or feeling was stronger than "10", i.e "extremely strong", "Maximal" – a larger number could be used, e.g. 12 or still higher i.e "Absolute maximum"). Change from Baseline was calculated as the value at specified visit minus the Baseline value. Intent-to-Treat (ITT) Population: comprised of all randomized participants who received at least 1 dose of study drug. Only those participants with available data at Baseline and the specified time point (represented as n=X, X for placebo and ambrisentan respectively) were summarized.

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

End point timeframe:

Baseline (Week 0); Weeks 4, 8, 12 and 16/Early Withdrawal

| End point values | Placebo | Ambrisentan 5mg | | |
|---------------------------------------|------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 16 | 17 | | |
| Units: Scores on a scale | | | | |
| median (inter-quartile range (Q1-Q3)) | | | | |
| Week 4, n=15, 17 | 0 (-1 to 0.75) | -0.4 (-0.5 to 0) | | |
| Week 8, n=14, 16 | 0.25 (-0.5 to 1) | -0.2 (-1.13 to 1) | | |
| Week 12, n=13, 15 | 0 (-0.5 to 2.25) | -0.4 (-1 to 1) | | |
| Week 16, n=13, 15 | 1 (-0.5 to 2.5) | -0.5 (-1.5 to 1) | | |
| Early Withdrawal, n=3, 2 | 2 (-1.5 to 4) | -0.25 (-0.5 to 0) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with clinical worsening of chronic thromboembolic pulmonary hypertension (CTEPH)

| | |
|-----------------|---|
| End point title | Number of participants with clinical worsening of chronic thromboembolic pulmonary hypertension (CTEPH) |
|-----------------|---|

End point description:

Clinical worsening of CTEPH is defined by the time from randomization to the first occurrence of death, lung transplantation, hospitalization for CTEPH, atrial septostomy, addition of parenteral prostanoids, or study withdrawal due to two or more early escape criteria included: a decrease from BL of at least 20% in the distance walked during the six-minute walk test; an increase of one or more WHO functional class; worsening right ventricular failure (e.g., as indicated by increased jugular venous pressure; new/worsening hepatomegaly, ascites, or peripheral edema; worsening echocardiographic parameters such as tricuspid annulus plane systolic excursion (TAPSE) and Tissue Doppler Imaging (TDI) (of the tricuspid annulus; rapidly progressing cardiogenic, hepatic, or renal failure; refractory systolic hypotension(systolic blood pressure less than 85 millimeter of mercury[mmHg])). ITT Population.

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

End point timeframe:

From randomization to Week 16/Follow up visit (21 weeks)

| End point values | Placebo | Ambrisentan 5mg | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 16 | 17 | | |
| Units: Participants | | | | |
| number (not applicable) | 0 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in mean right atrial pressure (mRAP) and mean pulmonary artery pressure (mPAP) at Week 16

| | |
|-----------------|--|
| End point title | Change from Baseline in mean right atrial pressure (mRAP) and mean pulmonary artery pressure (mPAP) at Week 16 |
|-----------------|--|

End point description:

mPAP and mRAP are measures of cardiopulmonary hemodynamics. Baseline is the last value recorded on or prior to start of study treatment. Change from Baseline was calculated as the value at specified visit minus the Baseline value. Intent-to-Treat (ITT) Population: comprised of all randomized participants who received at least 1 dose of study drug. Only those participants with available data at Baseline and the specified time point (represented as n=X, X for placebo and ambrisentan respectively) were summarized.

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

End point timeframe:

Baseline (Week 0) and Week 16

| End point values | Placebo | Ambrisentan 5mg | | |
|---------------------------------------|-----------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 16 | 17 | | |
| Units: Millimeter of mercury (mmHg) | | | | |
| median (inter-quartile range (Q1-Q3)) | | | | |
| mRAP, Week 16, n=11, 13 | -2 (-5 to 4) | -1 (-4 to 3) | | |
| mPAP, Week 16, n=11, 12 | -6 (-10 to -1) | -3 (-11.6 to 2) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in cardiac index at Week 16

| | |
|---|--|
| End point title | Change from Baseline in cardiac index at Week 16 |
| End point description: Cardiac index is measure of cardiopulmonary hemodynamics. Baseline is the last value recorded on or prior to start of study treatment. Change from Baseline was calculated as the value at specified visit minus the Baseline value. Intent-to-Treat (ITT) Population: comprised of all randomized participants who received at least 1 dose of study drug. Only those participants with available data at Baseline and the specified time point were summarized. | |
| End point type | Secondary |
| End point timeframe: Baseline (Week 0) and Week 16 | |

| End point values | Placebo | Ambrisentan 5mg | | |
|---|---------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 11 | 12 | | |
| Units: Litre per minute per meter squared | | | | |
| median (inter-quartile range (Q1-Q3)) | 0.1 (-0.04 to 0.37) | 0.44 (0.03 to 1.015) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change from Baseline in plasma N-terminal pro-B-type natriuretic peptide (NT-proBNP)

| | |
|-----------------|--|
| End point title | Percent change from Baseline in plasma N-terminal pro-B-type |
|-----------------|--|

End point description:

The ratio to baseline [BL] in NT-proBNP was calculated as the ratio of the value at the specified time-point to the BL value and was expressed as a percent change from BL. For each treatment group, the mean change from BL at the specified time-point was determined on the log scale. This mean was then back transformed to give a geometric mean (GM) of the ratio of the value at the specified time-point to BL on the original scale. The GM was expressed as a percentage ($100 \times [GM - 1]$). Standard Deviation (SD) is the SD of the mean change from baseline values on the log scale. Intent-to-Treat (ITT) Population: comprised of all randomized participants who received at least 1 dose of study drug. Only those participants with available data at Baseline and the specified time point (represented as n=X, X for placebo and ambrisentan respectively) were summarized.

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

End point timeframe:

| |
|---|
| Baseline (Week 0); Weeks 4, 8, 12 and 16/Early Withdrawal |
|---|

| End point values | Placebo | Ambrisentan 5mg | | |
|-------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 16 | 17 | | |
| Units: Percent change | | | | |
| geometric mean (standard deviation) | | | | |
| Week 4, n=13, 15 | 43.6 (± 0.41) | -15.8 (± 0.36) | | |
| Week 8, n=13, 15 | 12.4 (± 0.49) | -23.3 (± 0.59) | | |
| Week 12, n=12, 14 | 12.4 (± 0.59) | -21.9 (± 0.61) | | |
| Week 16, n=12, 14 | 14.1 (± 0.55) | -29.4 (± 0.5) | | |
| Early withdrawal, n=3, 2 | 35.7 (± 0.69) | -14.9 (± 0.31) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Quality of Life as measured by Short form 36 Health Survey (SF-36)

| | |
|-----------------|--|
| End point title | Change from Baseline in Quality of Life as measured by Short form 36 Health Survey (SF-36) |
|-----------------|--|

End point description:

The SF-36 v2 is a self-administered, health-related quality of life (QoL) metric. It is a 36-item questionnaire designed to measure 8 domains of functional health status and well-being: physical functioning, role-physical, bodily pain, general health perceptions, vitality, social functioning, role-emotional, and mental health as well as 2 summary measures (Physical Health and Mental Health). Each domain is scored from 0 (poorer health) to 100 (better health). Change from Baseline was calculated as the post-Baseline score minus the Baseline score. The SF-36 data were collected, but after the study was terminated, not all endpoints listed in the protocol were analyzed, including the SF-36. This decision was documented in the reporting and analysis plan prior to database lock. ITT Population.

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

End point timeframe:

| |
|---|
| Baseline and up to Week 16/Early Withdrawal |
|---|

| End point values | Placebo | Ambrisentan 5mg | | |
|-----------------------------|------------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[2] | 0 ^[3] | | |
| Units: Scores on a scale | | | | |
| number (not applicable) | | | | |

Notes:

[2] - This endpoint was not summarized therefore there is no data to present.

[3] - This endpoint was not summarized therefore there is no data to present.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with any adverse events (AEs) and serious adverse events (SAEs)

| | |
|-----------------|--|
| End point title | Number of participants with any adverse events (AEs) and serious adverse events (SAEs) |
|-----------------|--|

End point description:

AE is defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e., lack of efficacy), abuse or misuse. A SAE is defined as any untoward medical occurrence that, at any dose results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in disability/incapacity or is a congenital anomaly/birth defect or important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. ITT Population

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

End point timeframe:

From the start of study treatment and until follow up (Week 16/Follow up)

| End point values | Placebo | Ambrisentan 5mg | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 16 | 17 | | |
| Units: Participants | | | | |
| number (not applicable) | | | | |
| Any AE | 15 | 11 | | |
| Any SAE | 1 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in haemoglobin levels at Weeks 4, 8, 12, and

16/Early Withdrawal

| | |
|-----------------|---|
| End point title | Change from Baseline in haemoglobin levels at Weeks 4, 8, 12, and 16/Early Withdrawal |
|-----------------|---|

End point description:

Haemoglobin levels were assessed at Screening, Baseline, Weeks 4, 8, 12, and 16/Early Withdrawal. Baseline is the last value recorded on or prior to start of study treatment. Change from Baseline was calculated as the post-Baseline value minus the Baseline value. Intent-to-Treat (ITT) Population: comprised of all randomized participants who received at least 1 dose of study drug. Only those participants with available data at Baseline and the specified time point (represented as n=X, X for placebo and ambrisentan respectively) were summarized.

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

End point timeframe:

Baseline (Week 0); Weeks 4, 8, 12, and 16/Early Withdrawal

| End point values | Placebo | Ambrisentan 5mg | | |
|---------------------------------------|-----------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 16 | 17 | | |
| Units: Grams per liter | | | | |
| median (inter-quartile range (Q1-Q3)) | | | | |
| Week 4, n=15, 15 | -2 (-5 to 6) | -5 (-10 to 2) | | |
| Week 8, n=13, 16 | 0 (-8 to 3) | -7.5 (-10.5 to 1.5) | | |
| Week 12, n=13, 14 | 2 (-6 to 8) | -5 (-9 to -1) | | |
| Week 16, n=13, 15 | -3 (-10 to 2) | -6 (-9 to -3) | | |
| Early withdrawal, n=3, 2 | -2 (-2 to 26) | -14.5 (-16 to -13) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in haematocrit levels at Weeks 4, 8, 12, and 16/Early Withdrawal

| | |
|-----------------|---|
| End point title | Change from Baseline in haematocrit levels at Weeks 4, 8, 12, and 16/Early Withdrawal |
|-----------------|---|

End point description:

Haematocrit levels were assessed at Screening, Baseline, Weeks 4, 8, 12, and 16/Early Withdrawal. Baseline is the last value recorded on or prior to start of study treatment. Change from Baseline was calculated as the post-Baseline value minus the Baseline value. Intent-to-Treat (ITT) Population: comprised of all randomized participants who received at least 1 dose of study drug. Only those participants with available data at Baseline and the specified time point (represented as n=X, X for placebo and ambrisentan respectively) were summarized.

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

End point timeframe:

Baseline (Week 0); Weeks 4, 8, 12, and 16/Early Withdrawal

| End point values | Placebo | Ambrisentan 5mg | | |
|---------------------------------------|--------------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 16 | 17 | | |
| Units: Proportion of 1 | | | | |
| median (inter-quartile range (Q1-Q3)) | | | | |
| Week 4, n=15, 15 | 0 (-0.016 to 0.015) | -0.015 (-0.033 to 0.012) | | |
| Week 8, n=13, 16 | -0.003 (-0.026 to 0.014) | -0.021 (-0.035 to 0.003) | | |
| Week 12, n=13, 14 | 0.007 (-0.017 to 0.022) | -0.023 (-0.029 to -0.004) | | |
| Week 16, n=13, 15 | -0.007 (-0.031 to 0.004) | -0.019 (-0.033 to -0.003) | | |
| Early withdrawal, n=3, 2 | -0.008 (-0.01 to 0.083) | -0.03 (-0.032 to -0.028) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with significant liver events at Weeks 4, 8, 12, and 16/Early Withdrawal

| | |
|-----------------|---|
| End point title | Number of participants with significant liver events at Weeks 4, 8, 12, and 16/Early Withdrawal |
|-----------------|---|

End point description:

A significant liver chemistry result is defined as any result which met the stopping criteria defined in the study protocol. Liver events were assessed at Screening, Baseline, Weeks 4, 8, 12, and 16/Early Withdrawal. Number of participants who reported a significant liver chemistry result are presented. ITT population.

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

End point timeframe:

Weeks 4, 8, 12, and 16/Early Withdrawal

| End point values | Placebo | Ambrisentan 5mg | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 16 | 17 | | |
| Units: Participants | | | | |
| number (not applicable) | 0 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in supine systolic blood pressure (SBP) and diastolic blood pressure (DBP) assessed at Weeks 4, 8, 12, and 16/Early Withdrawal

| | |
|-----------------|--|
| End point title | Change from Baseline in supine systolic blood pressure (SBP) |
|-----------------|--|

and diastolic blood pressure (DBP) assessed at Weeks 4, 8, 12, and 16/Early Withdrawal

End point description:

Vital sign measurements including supine systolic and diastolic blood pressure at Weeks 4, 8, 12, and 16/Early Withdrawal weeks. Supine blood pressure measurement was taken in a supine position having rested in this position for at least 10 minutes before each reading. Baseline is the last value recorded on or prior to start of study treatment. Change from Baseline was calculated as the post-Baseline value minus the Baseline value. Intent-to-Treat (ITT) Population: comprised of all randomized participants who received at least 1 dose of study drug. Only those participants with available data at Baseline and the specified time point (represented as n=X, X for placebo and ambrisentan respectively) were summarized.

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

End point timeframe:

Baseline (Week 0); Weeks 4, 8, 12, and 16/Early Withdrawal

| End point values | Placebo | Ambrisentan 5mg | | |
|---------------------------------------|-----------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 16 | 17 | | |
| Units: millimeter of mercury (mmHg) | | | | |
| median (inter-quartile range (Q1-Q3)) | | | | |
| DBP, Week 4, n=15, 17 | 0 (-5 to 9) | -1 (-12 to 1) | | |
| DBP, Week 8, n=14, 16 | 1.5 (-7 to 13) | -9 (-16 to -5.5) | | |
| DBP, Week 12, n=13, 15 | 1 (0 to 7) | -8 (-14 to 5) | | |
| DBP, Week 16, n=13, 15 | -2 (-10 to 8) | -10 (-16 to 3) | | |
| DBP, Early Withdrawal, n=3, 2 | 16 (8 to 26) | -17 (-19 to -15) | | |
| SBP, Week 4, n=15, 17 | 0 (-10 to 4) | -4 (-9 to 19) | | |
| SBP, Week 8, n=14, 16 | 5.5 (-8 to 14) | -10 (-18.5 to -2.5) | | |
| SBP, Week 12, n=13, 15 | -2 (-12 to 11) | -5 (-10 to 0) | | |
| SBP, Week 16, n=13, 15 | -4 (-11 to 15) | -6 (-8 to 10) | | |
| SBP, Early Withdrawal, n=3, 2 | 15 (10 to 18) | -8 (-16 to 0) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in heart rate assessed at Weeks 4, 8, 12, and 16/Early Withdrawal

| | |
|-----------------|--|
| End point title | Change from Baseline in heart rate assessed at Weeks 4, 8, 12, and 16/Early Withdrawal |
|-----------------|--|

End point description:

Vital sign measurements including heart rate at Weeks 4, 8, 12, and 16/Early Withdrawal weeks. Baseline is the last value recorded on or prior to start of study treatment. Change from Baseline was calculated as the post-Baseline value minus the Baseline value. Intent-to-Treat (ITT) Population: comprised of all randomized participants who received at least 1 dose of study drug. Only those participants with available data at Baseline and the specified time point (represented as n=X, X for placebo and ambrisentan respectively) were summarized.

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

End point timeframe:

Baseline (Week 0); Weeks 4, 8, 12, and 16/Early Withdrawal

| End point values | Placebo | Ambrisentan 5mg | | |
|---------------------------------------|-----------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 16 | 17 | | |
| Units: beats per minute | | | | |
| median (inter-quartile range (Q1-Q3)) | | | | |
| Week 4, n=15, 17 | 0 (-14 to 3) | 4 (-3 to 10) | | |
| Week 8, n=14, 16 | -8 (-17 to 3) | 1 (-12.5 to 8.5) | | |
| Week 12, n=13, 15 | -2 (-15 to 3) | 0 (-6 to 5) | | |
| Week 16, n=13, 15 | 0 (-17 to 8) | -1 (-14 to 2) | | |
| Early withdrawal, n=3, 2 | -6 (-24 to -3) | -18 (-32 to -4) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants (par) with clinical chemistry parameters of potential clinical concern any time post Baseline

| | |
|-----------------|--|
| End point title | Number of participants (par) with clinical chemistry parameters of potential clinical concern any time post Baseline |
|-----------------|--|

End point description:

Clinical chemistry parameters including alanine amino transferase(ALT), aspartate amino transferase(AST), creatinine, gamma glutamyl transferase(GGT) and total bilirubin(TB) assessed any time post BL. ALT: lower concern value and high concern value was considered as none and $\geq 3 \times$ upper limit of normal (ULN) respectively. AST: lower concern value and high concern value was considered as none or $\geq 3 \times$ ULN respectively. Creatinine: lower concern value and high concern value was considered as none and ≥ 176.8 micromoles per liter($\mu\text{mol/L}$) respectively. GGT: lower concern value and high concern value was considered as none and $\geq 3 \times$ ULN respectively. For TB: lower concern value was none and high concern value was $\geq 2 \times$ ULN. Par with both normal and low values were counted once under their worst case (Low). Par with both normal and high values were counted once under their worst case (High). Par with both high and low values are counted under both categories. ITT Population.

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

End point timeframe:

Baseline (BL) (Week 0), Weeks 4, 8, 12 and 16/early withdrawal,

| End point values | Placebo | Ambrisentan 5mg | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 16 | 17 | | |
| Units: Participants | | | | |
| number (not applicable) | | | | |
| ALT, >clinical concern high | 0 | 0 | | |
| ALT, <clinical concern low | 0 | 0 | | |

| | | | | |
|------------------------------------|---|---|--|--|
| AST, >clinical concern high | 0 | 0 | | |
| AST, <clinical concern low | 0 | 0 | | |
| Creatinine, >clinical concern high | 0 | 0 | | |
| Creatinine, <clinical concern low | 0 | 0 | | |
| GGT, >clinical concern high | 1 | 1 | | |
| GGT, <clinical concern low | 0 | 0 | | |
| TB, >clinical concern high | 0 | 0 | | |
| TB, <clinical concern low | 0 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants (par) with hematology parameters of potential clinical concern any time post Baseline

| | |
|-----------------|--|
| End point title | Number of participants (par) with hematology parameters of potential clinical concern any time post Baseline |
|-----------------|--|

End point description:

Hematology parameters including hemoglobin(Hb), international normalized ratio(INR), and platelet count assessed any time post BL. BL is the last value recorded on or prior to start of study treatment. For Hb: lower concern value and high concern value was considered as <100 gram per liter (G/L) and none respectively. For INR: lower concern value and high concern value was considered as none or >5 prothrombin time respectively. For platelet count: lower concern value and high concern value was considered as <50 giga cells per liter (GI/L) and >500 GI/L respectively. Par with both normal and low values were counted once under their worst case(Low). Par with both normal and high values were counted once under their worst case(High). Par with both high and low values are counted under both categories. ITT Population: all randomized par who received at least 1 dose of study drug. Only par with available data at BL and the specified timepoint(n=X,X in the category titles) were summarized.

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

End point timeframe:

Baseline (BL) (Week 0), Weeks 4, 8, 12 and 16/early withdrawal

| End point values | Placebo | Ambrisentan 5mg | | |
|--|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 16 | 17 | | |
| Units: Participants | | | | |
| number (not applicable) | | | | |
| Hemoglobin, >clinical concern high, n=16, 17 | 0 | 0 | | |
| Hemoglobin, <clinical concern low, n=16, 17 | 0 | 0 | | |
| INR, >clinical concern high, n=2, 0 | 0 | 0 | | |
| INR, <clinical concern low, n=2, 0 | 0 | 0 | | |
| Platelet count, >clinical concern high, n=16, 17 | 0 | 0 | | |
| Platelet count, <clinical concern low, n=16, 17 | 0 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with testicular function (males only) of potential clinical concern any time post Baseline

| | |
|-----------------|---|
| End point title | Number of participants with testicular function (males only) of potential clinical concern any time post Baseline |
|-----------------|---|

End point description:

For male participants testicular function (total testosterone, sex hormone binding globulin [SHBG]-calculated free testosterone), follicle stimulating hormone (FSH), luteinizing hormone (LH), and inhibin B were assessed at Weeks 4 and 16/early withdrawal. The testicular function data were collected, but after the study was terminated, not all endpoints listed in the protocol were analyzed, including Testicular Function. This decision was documented in the reporting and analysis plan prior to database lock. ITT Population.

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

End point timeframe:

Baseline, Weeks 4 and 16/early withdrawal

| End point values | Placebo | Ambrisentan 5mg | | |
|-----------------------------|------------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[4] | 0 ^[5] | | |
| Units: Participants | | | | |
| number (not applicable) | | | | |

Notes:

[4] - This endpoint was not summarized therefore there are no data to present.

[5] - This endpoint was not summarized therefore there are no data to present.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Serious and non-serious treatment emergent adverse events (AEs) were collected from the start of study treatment and until the follow up contact (Week 21)

Adverse event reporting additional description:

AEs and serious AEs (SAEs) were collected from the members of ITT population which comprised of all randomized participants who received at least 1 dose of study drug. Treatment-emergent AEs (TEAEs) were defined as post-first dose AEs. Includes AEs up to 30 days after stopping study treatment.

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

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 17.0 |

Reporting groups

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

Reporting group description:

Participants received a matching placebo tablet once daily for a period of 16 weeks.

| | |
|-----------------------|-----------------|
| Reporting group title | Ambrisentan 5mg |
|-----------------------|-----------------|

Reporting group description:

Participants received an ambrisentan 5milligram (mg) tablet, once daily for a period of 16 weeks.

| Serious adverse events | Placebo | Ambrisentan 5mg | |
|---|----------------|-----------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 17 (0.00%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthma | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 17 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Placebo | Ambrisentan 5mg | |
|---|------------------|------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 15 / 16 (93.75%) | 11 / 17 (64.71%) | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |

| | | | |
|--|----------------------|----------------------|--|
| Fibroma subjects affected / exposed occurrences (all) | 0 / 16 (0.00%) 0 | 1 / 17 (5.88%) 1 | |
| Vascular disorders Peripheral venous disease subjects affected / exposed occurrences (all) | 0 / 16 (0.00%) 0 | 1 / 17 (5.88%) 1 | |
| Hypertension subjects affected / exposed occurrences (all) | 0 / 16 (0.00%) 0 | 1 / 17 (5.88%) 1 | |
| General disorders and administration site conditions Oedema peripheral subjects affected / exposed occurrences (all) | 2 / 16 (12.50%) 2 | 3 / 17 (17.65%) 4 | |
| Non-cardiac chest pain subjects affected / exposed occurrences (all) | 0 / 16 (0.00%) 0 | 1 / 17 (5.88%) 1 | |
| Feeling abnormal subjects affected / exposed occurrences (all) | 0 / 16 (0.00%) 0 | 1 / 17 (5.88%) 1 | |
| Chest discomfort subjects affected / exposed occurrences (all) | 1 / 16 (6.25%) 1 | 0 / 17 (0.00%) 0 | |
| Reproductive system and breast disorders Nipple pain subjects affected / exposed occurrences (all) | 0 / 16 (0.00%) 0 | 1 / 17 (5.88%) 1 | |
| Respiratory, thoracic and mediastinal disorders Epistaxis subjects affected / exposed occurrences (all) | 1 / 16 (6.25%) 1 | 1 / 17 (5.88%) 1 | |
| Haemoptysis subjects affected / exposed occurrences (all) | 3 / 16 (18.75%) 3 | 0 / 17 (0.00%) 0 | |
| Productive cough | | | |

| | | | |
|--|--|--|--|
| <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Pleurisy</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>1 / 16 (6.25%)</p> <p>1</p> <p>1 / 16 (6.25%)</p> <p>1</p> | <p>0 / 17 (0.00%)</p> <p>0</p> <p>0 / 17 (0.00%)</p> <p>0</p> | |
| <p>Investigations</p> <p>Weight increased</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>1 / 16 (6.25%)</p> <p>1</p> | <p>0 / 17 (0.00%)</p> <p>0</p> | |
| <p>Injury, poisoning and procedural complications</p> <p>Thermal burn</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Joint dislocation</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>1 / 16 (6.25%)</p> <p>1</p> <p>1 / 16 (6.25%)</p> <p>1</p> | <p>0 / 17 (0.00%)</p> <p>0</p> <p>0 / 17 (0.00%)</p> <p>0</p> | |
| <p>Cardiac disorders</p> <p>Tachycardia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Atrial fibrillation</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>0 / 16 (0.00%)</p> <p>0</p> <p>1 / 16 (6.25%)</p> <p>1</p> | <p>1 / 17 (5.88%)</p> <p>1</p> <p>0 / 17 (0.00%)</p> <p>0</p> | |
| <p>Nervous system disorders</p> <p>Dizziness</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Headache</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Hypoaesthesia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Movement disorder</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>1 / 16 (6.25%)</p> <p>1</p> <p>3 / 16 (18.75%)</p> <p>3</p> <p>1 / 16 (6.25%)</p> <p>1</p> <p>1 / 16 (6.25%)</p> <p>1</p> | <p>1 / 17 (5.88%)</p> <p>1</p> <p>2 / 17 (11.76%)</p> <p>2</p> <p>0 / 17 (0.00%)</p> <p>0</p> <p>0 / 17 (0.00%)</p> <p>0</p> | |

| | | | |
|--|---|---|--|
| Blood and lymphatic system disorders Lymphadenopathy subjects affected / exposed occurrences (all) | 0 / 16 (0.00%) 0 | 1 / 17 (5.88%) 1 | |
| Eye disorders Eyelid oedema subjects affected / exposed occurrences (all) | 1 / 16 (6.25%) 1 | 1 / 17 (5.88%) 1 | |
| Gastrointestinal disorders Abdominal pain upper subjects affected / exposed occurrences (all) Dyspepsia subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) Cheilitis subjects affected / exposed occurrences (all) Hypoaesthesia oral subjects affected / exposed occurrences (all) | 0 / 16 (0.00%) 0 1 / 16 (6.25%) 1 1 / 16 (6.25%) 1 1 / 16 (6.25%) 1 1 / 16 (6.25%) 1 | 1 / 17 (5.88%) 1 0 / 17 (0.00%) 0 1 / 17 (5.88%) 1 0 / 17 (0.00%) 0 0 / 17 (0.00%) 0 | |
| Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all) | 1 / 16 (6.25%) 1 | 0 / 17 (0.00%) 0 | |
| Musculoskeletal and connective tissue disorders Neck pain subjects affected / exposed occurrences (all) | 2 / 16 (12.50%) 2 | 0 / 17 (0.00%) 0 | |
| Infections and infestations Erysipelas subjects affected / exposed occurrences (all) Nasopharyngitis | 0 / 16 (0.00%) 0 | 1 / 17 (5.88%) 1 | |

| | | | |
|---|-----------------|----------------|--|
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 17 (5.88%) | |
| occurrences (all) | 0 | 1 | |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 17 (5.88%) | |
| occurrences (all) | 0 | 1 | |
| Onychomycosis | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 17 (5.88%) | |
| occurrences (all) | 0 | 1 | |
| Bronchitis | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 17 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Influenza | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 17 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 2 / 16 (12.50%) | 0 / 17 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Metabolism and nutrition disorders | | | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 17 (0.00%) | |
| occurrences (all) | 1 | 0 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 04 April 2013 | Revision to anticipated treatment effect size and therefore study sample size. Clarification that exclusion criteria for renal impairment is based on the estimated Creatinine Clearance method. Clarification of subjects who should be sent to the operability adjudication committee. Clarification that on withdrawal from the study and entry into the open-label extension, the prior blind will be maintained (except in medical emergency) and Investigators should consider carefully treatment of the subject. Revision to reporting timelines and withdrawal of IP in event of pregnancy. Deletion of contradictory text in Section 6.3.5.1: Definition of an AE |
| 16 July 2013 | Clarification on the study design: subject's study participation in the open label extension. Clarification on the treatment after the end of the study |
| 18 July 2013 | Clarification on the amendment 03 about the date of study end |
| 16 August 2013 | Addition of an exclusion criterion excluding subjects who have previously undergone a balloon pulmonary angioplasty |
| 02 January 2014 | Clarification on the population included in the open label extension study |
| 23 April 2014 | Addition of information on the registration of riociguat in CTEPH Revision of the timelines for CTEPH diagnosis and RHC to be done prior to screening Increase of the upper limit of inclusion age from 75 to 80 years Addition of balloon pulmonary angioplasty as an exclusion criteria Description of country specific amendments (China, Russia, and United Kingdom) |
| 11 July 2014 | To clarify that riociguat is a prohibited medication in the study |
| 11 August 2014 | To integrate the previous amendment No.05 (specific to Italy) and new global amendment No.07 in the same protocol |
| 16 February 2015 | To provide clarity following GSK decision to stop the study early. |

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.

This study was terminated early therefore all analyses were not necessarily run as planned.

Notes: