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	v2
This version publication date	17 November 2016
First version publication date	01 April 2016
Version creation reason	• Correction of full data set Changes required per updates to the ctgov version.

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	59.8	61.2	
standard deviation	± 8.99	± 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:

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.

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 per square				
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

	natriuretic peptide (NT-proBNP)

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*[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. Due to the small participant numbers in this study, the SF-36 data were not analysed. 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 >=3xupper limit of normal (ULN) respectively. AST: lower concern value and high concern value was considered as none or >=3xULN respectively. Creatinine: lower concern value and high concern value was considered as none and >=176.8 micromoles per liter(umol/L) respectively. GGT: lower concern value and high concern value was considered as none and >=3xULN respectively. For TB: lower concern value was none and high concern value was >=2xULN. 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. Due to the small participant numbers in this study, testicular function data were not analysed. 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	0 / 16 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Vascular disorders			
Peripheral venous disease			
subjects affected / exposed	0 / 16 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Hypertension			
subjects affected / exposed	0 / 16 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	2 / 16 (12.50%)	3 / 17 (17.65%)	
occurrences (all)	2	4	
Non-cardiac chest pain			
subjects affected / exposed	0 / 16 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Feeling abnormal			
subjects affected / exposed	0 / 16 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Chest discomfort			
subjects affected / exposed	1 / 16 (6.25%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Reproductive system and breast disorders			
Nipple pain			
subjects affected / exposed	0 / 16 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	1 / 16 (6.25%)	1 / 17 (5.88%)	
occurrences (all)	1	1	
Haemoptysis			
subjects affected / exposed	3 / 16 (18.75%)	0 / 17 (0.00%)	
occurrences (all)	3	0	
Productive cough			

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

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

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: