Clinical trial results:
An open-label extension study of the long-term safety, tolerability and efficacy of ambrisentan in subjects with inoperable chronic thromboembolic pulmonary hypertension (CTEPH)

Summary

EudraCT number	2012-001642-17
Trial protocol	ES AT DE GB CZ NL IT
Global end of trial date	18 November 2015

Results information

Result version number	v2 (current)
This version publication date	03 August 2017
First version publication date	30 July 2016
Version creation reason	• Correction of full data set Changes required.

Trial information

Trial identification

Sponsor protocol code	AMB116457

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	GlaxoSmithKline
Sponsor organisation address	980 Great West Road, Brentford, Middlesex, United Kingdom,
Public contact	GSK Response Center, GlaxoSmithKline, 1-866 4357343,
Scientific contact	GSK Response Center, GlaxoSmithKline, 1-866 4357343,

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	07 April 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 November 2015
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective is the long-term safety and tolerability of ambrisentan in the CTEPH population (see Safety).
- Safety assessments:
- Adverse Events;
- Serious Adverse Events;
- Clinical laboratory parameters (including liver safety and haematological parameters);
- Physical examination (including jugular venous pressure, liver size, peripheral oedema, ascites and signs of deep vein thrombosis);
- Vital Signs (including body mass index at the entry visit only);
The time to change in dose of ambrisentan or other targeted PAH therapeutic agents (prostanoids, PDE-5 inhibitors) due to tolerability issues (e.g. adverse events).

Protection of trial subjects:

The Independent Data Monitoring Committee (IDMC) recommended that the Sponsor stop the study at any time if they consider that the potential risks outweigh the potential benefits (based on review of safety [adverse experiences] data every three months).
A subject may also be discontinued from Investigational Product, or from the study, for the following reasons:
• Liver chemistry values exceeding the threshold criteria (as outlined in the protocol);
• Adverse event which in the opinion of the investigator requires withdrawal;
• Pregnancy;
• Consent withdrawn;
• Lost to follow-up;
• Protocol violation;
• Termination of study by sponsor;
• Investigator’s discretion (document reason in eCRF).
Subjects discontinuing investigation product are encouraged to stay in the study at their and the investigators discretion.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 January 2014
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	Japan: 3
Country: Number of subjects enrolled	China: 3
Country: Number of subjects enrolled	Mexico: 2
Country: Number of subjects enrolled	Russian Federation: 1
Country: Number of subjects enrolled	Netherlands: 1

Country: Number of subjects enrolled	Spain: 4
Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	Czech Republic: 1
Country: Number of subjects enrolled	Germany: 3
Worldwide total number of subjects	19
EEA total number of subjects	10

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)	12
From 65 to 84 years	7
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This was an open label, long-term extension study to the double-blind, placebo-controlled study AMB115811 (NCT01884675). Only those participants (par.) in study AMB115811 were eligible for enrollment in this study. The planned duration was a minimum of 18 months, but the study was terminated due to futility of enrollment in study AMB115811.

Pre-assignment

Screening details:

Out of the 33 participants randomized (16 participants in the Placebo arm and 17 in the Ambrisentan arm) in study AMB115811, a total of 19 participants were enrolled in this extension study.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Previous Placebo

Arm description:

Participants received placebo tablet once daily (OD) for 16 weeks in study AMB115811. Upon enrollment in the extension study AMB116457, participants received ambrisentan 5 milligrams (mg) tablet OD. The dose could be up-titrated to ambrisentan 10 mg OD or adjusted back to ambrisentan 5 mg OD.

Arm type	Experimental
Investigational medicinal product name	5 mg or 10 mg of Ambrisentan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

5 mg or 10 mg tablet of Ambrisentan administered orally once daily

Arm title	Previous Ambrisentan

Arm description:

Participants received ambrisentan 5 mg tablet OD for 16 weeks in study AMB115811. Upon enrollment in the extension study AMB116457, participants continued to receive ambrisentan 5 mg OD. The dose could be up-titrated to ambrisentan 10 mg OD or adjusted back to ambrisentan 5 mg OD.

Arm type	Experimental
Investigational medicinal product name	5 mg or 10 mg of Ambrisentan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

5 mg or 10 mg tablet of Ambrisentan administered orally once daily

Number of subjects in period 1	Previous Placebo	Previous Ambrisentan
Started	9	10
Completed	0	0
Not completed	9	10
Adverse event, non-fatal	1	-
Study Closed/terminated	7	10
Death	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Previous Placebo
Reporting group description:	
Participants received placebo tablet once daily (OD) for 16 weeks in study AMB115811. Upon enrollment in the extension study AMB116457, participants received ambrisentan 5 milligrams (mg) tablet OD. The dose could be up-titrated to ambrisentan 10 mg OD or adjusted back to ambrisentan 5 mg OD.	
Reporting group title	Previous Ambrisentan
Reporting group description:	
Participants received ambrisentan 5 mg tablet OD for 16 weeks in study AMB115811. Upon enrollment in the extension study AMB116457, participants continued to receive ambrisentan 5 mg OD. The dose could be up-titrated to ambrisentan 10 mg OD or adjusted back to ambrisentan 5 mg OD.	

Reporting group values	Previous Placebo	Previous Ambrisentan	Total
Number of subjects	9	10	19
Age categorical Units: Subjects			
Age continuous			
Participant characteristics at the start of the extension study.			
Units: years			
median	63	61	
inter-quartile range (Q1-Q3)	58 to 69	47 to 66	-
Gender categorical Units: Subjects			
Female	6	4	10
Male	3	6	9
Race Units: Subjects			
Asian - East Asian Heritage	2	1	3
Asian - Japanese Heritage	2	1	3
White - White/Caucasian/European Heritage	5	8	13

End points

End points reporting groups

Reporting group title	Previous Placebo

Reporting group description:

Participants received placebo tablet once daily (OD) for 16 weeks in study AMB115811. Upon enrollment in the extension study AMB116457, participants received ambrisentan 5 milligrams (mg) tablet OD. The dose could be up-titrated to ambrisentan 10 mg OD or adjusted back to ambrisentan 5 mg OD.

Reporting group title	Previous Ambrisentan

Reporting group description:

Participants received ambrisentan 5 mg tablet OD for 16 weeks in study AMB115811. Upon enrollment in the extension study AMB116457, participants continued to receive ambrisentan 5 mg OD. The dose could be up-titrated to ambrisentan 10 mg OD or adjusted back to ambrisentan 5 mg OD.

Subject analysis set title	Previous Placebo
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received placebo tablet once daily (OD) for 16 weeks in study AMB115811. Upon enrollment in the extension study AMB116457, participants received ambrisentan 5 milligrams (mg) tablet OD. The dose could be up-titrated to ambrisentan 10 mg OD or adjusted back to ambrisentan 5 mg OD.

Subject analysis set title	Previous Ambrisentan
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received ambrisentan 5 mg tablet OD for 16 weeks in study AMB115811. Upon enrollment in the extension study AMB116457, participants continued to receive ambrisentan 5 mg OD. The dose could be up-titrated to ambrisentan 10 mg OD or adjusted back to ambrisentan 5 mg OD.

Primary: Number of participants with any adverse event (AE) or serious adverse event (SAE)

End point title	Number of participants with any adverse event (AE) or serious adverse event (SAE)[1]

End point description:

An AE is any untoward medical occurrence in a clinical investigation participant, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Serious Adverse Event (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, is a congenital anomaly/birth defect. Refer to the general AE/SAE module for a list of AEs and SAEs. Participant's final visit in Study AMB115811 was used as the entry visit of this open-label extension study. Safety (Extension) Population: all participants who enrolled and took at least one dose of study treatment during the extension study.

End point type	Primary

End point timeframe:

From Entry Visit of the extension study up to approximately 16 months

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: There are no statistical data to report.

End point values	Previous Placebo	Previous Ambrisentan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9[2]	10[3]		
Units: Participants				
Any AE	8	6		
Any SAE	3	0		

Notes:

[2] - Safety (Extension) Population

[3] - Safety (Extension) Population

Statistical analyses

No statistical analyses for this end point

Primary: Change from study AMB115811 Baseline in basophils, eosinophils, lymphocytes, monocytes, total neutrophils (Absolute Neutrophil Count [ANC]), platelet count, and white blood cell (WBC) count at the indicated time points

End point title	Change from study AMB115811 Baseline in basophils, eosinophils, lymphocytes, monocytes, total neutrophils (Absolute Neutrophil Count [ANC]), platelet count, and white blood cell (WBC) count at the indicated time points[4]

End point description:

Hematology parameters were assessed at Entry visit of the extension study, Month 1, Month 3, Month 6, Month 9, Month 12, Month 15, and end of study. Change from study AMB115811 Baseline in basophils, eosinophils, lymphocytes, monocytes, total neutrophils (ANC), platelet count, and WBC count are summarized. AMB115811 Baseline is the last value recorded on or prior to start of study treatment in that study. Change from AMB115811 Baseline was calculated as the value at the indicated visit minus the Baseline value. Participant's final visit in Study AMB115811 was used as the entry visit of this open-label extension study. Only those participants available at the specified time points were analyzed (represented by n=X, X in the category titles). Instances where 99999 has been mentioned indicate that data was not available or participants were not analyzed.

End point type	Primary

End point timeframe:

Baseline from study AMB115811; Entry visit of the extension study; Months 1, 3, 6, 9, 12, 15; and End of Study (assessed up to approximately 16 months)

Notes:

[4] - 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: There are no statistical data to report.

End point values	Previous Placebo	Previous Ambrisentan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9[5]	10[6]		
Units: Giga per Liter (GI/L)				
median (inter-quartile range (Q1-Q3))				
Basophils, Entry visit, n=9, 10	-0.01 (-0.02 to 0)	0 (-0.01 to 0.01)		
Basophils, Month 1, n=7, 10	-0.01 (-0.01 to 0)	0 (-0.02 to 0)		
Basophils, Month 3, n=7, 8	-0.01 (-0.02 to 0.01)	0 (-0.01 to 0.02)		
Basophils, Month 6, n=5, 6	0 (-0.02 to 0)	0 (-0.01 to 0.03)		
Basophils, Month 9, n=2, 5	-0.025 (-0.04 to -0.01)	-0.01 (-0.02 to -0.01)		
Basophils, Month 12, n=1, 3	-0.02 (-0.02 to -0.02)	0 (-0.02 to 0.01)		
Basophils, Month 15, n=0, 1	99999 (99999 to 99999)	-0.01 (-0.01 to -0.01)		
Basophils, End of study, n=8, 9	-0.005 (-0.025 to 0.015)	0 (0 to 0)		

Eosinophils, Entry visit , n=9, 10	-0.01 (-0.09 to 0.04)	0.005 (-0.09 to 0.03)		
Eosinophils, Month 1, n=7, 10	-0.02 (-0.03 to 0.01)	-0.025 (-0.06 to 0.03)		
Eosinophils, Month 3, n=7, 8	-0.03 (-0.05 to 0.02)	-0.005 (-0.055 to 0.075)		
Eosinophils, Month 6, n=5, 6	0.02 (-0.03 to 0.11)	-0.035 (-0.07 to 0)		
Eosinophils, Month 9, n=2, 5	0.155 (-0.04 to 0.35)	-0.02 (-0.02 to 0.15)		
Eosinophils, Month 12, n=1, 3	-0.12 (-0.12 to -0.12)	0.15 (-0.06 to 0.27)		
Eosinophils, Month 15, n=0, 1	99999 (99999 to 99999)	0.19 (0.19 to 0.19)		
Eosinophils, End of study, n=8, 9	-0.02 (-0.055 to 0.035)	0.01 (-0.03 to 0.03)		
Lymphocytes, Entry visit , n=9, 10	-0.05 (-0.16 to 0.19)	-0.09 (-0.47 to 0)		
Lymphocytes, Month 1, n=7, 10	-0.19 (-0.46 to 0.14)	-0.225 (-0.27 to 0.08)		
Lymphocytes, Month 3, n=7, 8	-0.04 (-0.18 to 0.24)	-0.215 (-0.795 to 0.185)		
Lymphocytes, Month 6, n=5, 6	-0.25 (-0.34 to -0.17)	-0.11 (-1.03 to -0.01)		
Lymphocytes, Month 9, n=2, 5	-0.075 (-0.38 to 0.23)	-0.36 (-0.49 to -0.09)		
Lymphocytes, Month 12, n=1, 3	-0.09 (-0.09 to -0.09)	-0.26 (-0.28 to 0.48)		
Lymphocytes, Month 15, n=0, 1	99999 (99999 to 99999)	-0.73 (-0.73 to -0.73)		
Lymphocytes, End of study, n=8, 9	-0.09 (-0.28 to 0.005)	-0.23 (-0.39 to 0.08)		
Monocytes, Entry visit, n=9, 10	-0.06 (-0.09 to 0.05)	-0.055 (-0.15 to 0.01)		
Monocytes, Month 1, n=7, 10	0 (-0.05 to 0.06)	0 (-0.17 to 0.13)		
Monocytes, Month 3, n=7, 8	0.01 (-0.08 to 0.22)	-0.035 (-0.175 to 0.025)		
Monocytes, Month 6, n=5, 6	0.08 (0.03 to 0.1)	-0.035 (-0.2 to 0.05)		
Monocytes, Month 9, n=2, 5	0.075 (-0.13 to 0.28)	0.06 (-0.1 to 0.2)		
Monocytes, Month 12, n=1, 3	0.01 (0.01 to 0.01)	-0.1 (-0.14 to 0.06)		
Monocytes, Month 15, n=0, 1	99999 (99999 to 99999)	0.13 (0.13 to 0.13)		
Monocytes, End of study, n=8, 9	-0.005 (-0.11 to 0.105)	0.03 (-0.09 to 0.1)		
Total Neutrophils, Entry visit , n=9, 10	-0.39 (-0.55 to 0.84)	-0.595 (-1.06 to 0.83)		
Total Neutrophils, Month 1, n=7, 10	0.22 (-1.45 to 0.53)	-0.55 (-1 to 0.32)		
Total Neutrophils, Month 3, n=7, 8	0.19 (-0.12 to 0.45)	-0.675 (-0.965 to -0.085)		
Total Neutrophils, Month 6, n=5, 6	0.15 (0.04 to 0.29)	-0.285 (-0.45 to -0.25)		
Total Neutrophils, Month 9, n=2, 5	-1.135 (-1.72 to -0.55)	-0.59 (-0.81 to 0.61)		
Total Neutrophils, Month 12, n=1, 3	1.73 (1.73 to 1.73)	-0.29 (-0.78 to -0.23)		
Total Neutrophils, Month 15, n=0, 1	99999 (99999 to 99999)	-0.94 (-0.94 to -0.94)		

Total Neutrophils, End of study, n=8, 9	-0.025 (-0.435 to 0.52)	-0.74 (-1.39 to -0.25)		
Platelet count, Entry visit , n=9, 9	-7 (-10 to 5)	-7 (-40 to 19)		
Platelet count, Month 1, n=7, 10	-16 (-31 to 5)	-1.5 (-29 to 26)		
Platelet count, Month 3, n=7, 8	-9 (-34 to 7)	17 (-8 to 28)		
Platelet count, Month 6, n=5, 6	-17 (-18 to -8)	-2 (-27 to 7)		
Platelet count, Month 9, n=2, 5	-11 (-20 to -2)	-6 (-21 to 8)		
Platelet count, Month 12, n=1, 3	-78 (-78 to -78)	-9 (-34 to 11)		
Platelet count, Month 15, n=0, 1	99999 (99999 to 99999)	-49 (-49 to -49)		
Platelet count, End of study, n=8, 9	-5 (-53 to 9.5)	12 (-4 to 14)		
WBC count, Entry visit, n=9, 10	-0.2 (-1.4 to 0.9)	-0.65 (-1.6 to 0.6)		
WBC count, Month 1, n=7, 10	-0.1 (-1.5 to 0.5)	-0.5 (-1.1 to -0.2)		
WBC count, Month 3, n=7, 8	0.2 (-0.4 to 0.8)	-1.1 (-1.65 to -0.15)		
WBC count, Month 6, n=5, 6	0.1 (0 to 0.2)	-0.55 (-1.5 to -0.3)		
WBC count, Month 9, n=2, 5	-1 (-1.1 to -0.9)	-0.6 (-1.1 to 0.3)		
WBC count, Month 12, n=1, 3	1.5 (1.5 to 1.5)	-0.7 (-0.8 to 0.3)		
WBC count, Month 15, n=0, 1	99999 (99999 to 99999)	-1.4 (-1.4 to -1.4)		
WBC count, End of study, n=8, 9	-0.25 (-0.6 to 0.6)	-1 (-1.4 to -0.5)		

Notes:

[5] - Safety (Extension) Population

[6] - Safety (Extension) Population

Statistical analyses

No statistical analyses for this end point

Primary: Change from study AMB115811 Baseline in hemoglobin and mean corpuscle hemoglobin concentration (MCHC) at the indicated time points

End point title	Change from study AMB115811 Baseline in hemoglobin and mean corpuscle hemoglobin concentration (MCHC) at the indicated time points[7]

End point description:

Hematology parameters were assessed at Entry visit of the extension study, Month 1, Month 3, Month 6, Month 9, Month 12, Month 15, and end of study. Change from study AMB115811 Baseline in hemoglobin and MCHC is summarized. AMB115811 Baseline is the last value recorded on or prior to start of study treatment in that study. Change from AMB115811 Baseline was calculated as the value at the indicated visit minus the Baseline value. Participant's final visit in Study AMB115811 was used as the entry visit of this open-label extension study. Only those participants available at the specified time points were analyzed (represented by n=X, X in the category titles). Instances where 99999 has been mentioned indicate that data was not available or participants were not analyzed.

End point type	Primary

End point timeframe:

Baseline from study AMB115811; Entry visit of the extension study; Months 1, 3, 6, 9, 12, 15; and End of Study (assessed up to approximately 16 months)

Notes:

[7] - 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: There are no statistical data to report.

End point values	Previous Placebo	Previous Ambrisentan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9[8]	10[9]		
Units: Grams per Liter (g/L)				
median (inter-quartile range (Q1-Q3))				
Hemoglobin, Entry visit, n=9, 10	-5 (-10 to 2)	-5.5 (-9 to -3)		
Hemoglobin, Month 1, n=7, 10	-3 (-7 to 1)	-6.5 (-9 to -4)		
Hemoglobin, Month 3, n=7, 8	-7 (-25 to 8)	-10.5 (-14.5 to -1)		
Hemoglobin, Month 6, n=5, 6	-10 (-18 to 0)	-6.5 (-12 to -3)		
Hemoglobin, Month 9, n=2, 5	-25 (-31 to -19)	-6 (-6 to -4)		
Hemoglobin, Month 12, n=1, 3	21 (21 to 21)	-6 (-9 to -2)		
Hemoglobin, Month 15, n=0, 1	99999 (99999 to 99999)	-11 (-11 to -11)		
Hemoglobin, End of study, n=8, 9	-10 (-15.5 to -2)	-8 (-11 to -2)		
MCHC, Entry visit, n=9, 10	6 (-1 to 9)	4 (-4 to 9)		
MCHC, Month 1, n=7, 10	5 (-9 to 10)	1 (-4 to 6)		
MCHC, Month 3, n=7, 8	1 (-2 to 4)	4.5 (-2.5 to 6)		
MCHC, Month 6, n=5, 6	3 (1 to 5)	-1.5 (-2 to 0)		
MCHC, Month 9, n=2, 5	0.5 (-2 to 3)	-1 (-8 to 0)		
MCHC, Month 12, n=1, 3	6 (6 to 6)	-4 (-9 to 5)		
MCHC, Month 15, n=0, 1	99999 (99999 to 99999)	1 (1 to 1)		
MCHC, End of study, n=8, 9	-2 (-6 to 2.5)	-6 (-9 to -1)		

Notes:

[8] - Safety (Extension) Population

[9] - Safety (Extension) Population

Statistical analyses

No statistical analyses for this end point

Primary: Change from study AMB115811 Baseline in hematocrit at the indicated time points

End point title	Change from study AMB115811 Baseline in hematocrit at the indicated time points[10]

End point description:

Hematology parameters were assessed at Entry visit of the extension study, Month 1, Month 3, Month 6, Month 9, Month 12, Month 15, and end of study. Change from study AMB115811 Baseline in hematocrit is summarized. AMB115811 Baseline is the last value recorded on or prior to start of study treatment in that study. Change from AMB115811 Baseline was calculated as the value at the indicated visit minus the Baseline value. Participant's final visit in study AMB115811 was used as the entry visit of this open-label extension study. Only those participants available at the specified time points were analyzed (represented by n=X, X in the category titles). Instances where 99999 has been mentioned indicate that data was not available or participants were not analyzed.

End point type	Primary

End point timeframe:

Baseline from study AMB115811; Entry visit of the extension study; Months 1, 3, 6, 9, 12, 15; and End of Study (assessed up to approximately 16 months)

Notes:

[10] - 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: There are no statistical data to report.

End point values	Previous Placebo	Previous Ambrisentan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9[11]	10[12]		
Units: Proportion of 1				
median (inter-quartile range (Q1-Q3))				
Hematocrit, Entry visit, n=9, 10	-0.007 (-0.031 to 0.004)	-0.018 (-0.043 to -0.005)		
Hematocrit, Month 1, n=7, 10	-0.018 (-0.028 to 0.011)	-0.024 (-0.035 to -0.005)		
Hematocrit, Month 3, n=7, 8	-0.027 (-0.084 to 0.023)	-0.034 (-0.052 to -0.006)		
Hematocrit, Month 6, n=5, 6	-0.033 (-0.057 to 0.005)	-0.019 (-0.03 to -0.012)		
Hematocrit, Month 9, n=2, 5	-0.083 (-0.107 to -0.058)	-0.016 (-0.021 to -0.011)		
Hematocrit, Month 12, n=1, 3	0.058 (0.058 to 0.058)	-0.009 (-0.036 to 0.001)		
Hematocrit, Month 15, n=0, 1	99999 (99999 to 99999)	-0.034 (-0.034 to -0.034)		
Hematocrit, End of study, n=8, 9	-0.033 (-0.049 to 0.004)	-0.015 (-0.024 to -0.001)		

Notes:

[11] - Safety (Extension) Population

[12] - Safety (Extension) Population

Statistical analyses

No statistical analyses for this end point

Primary: Change from study AMB115811 Baseline in mean corpuscle volume at the indicated time points

End point title	Change from study AMB115811 Baseline in mean corpuscle volume at the indicated time points[13]

End point description:

Hematology parameters were assessed at Entry visit of the extension study, Month 1, Month 3, Month 6, Month 9, Month 12, Month 15, and end of study. Change from study AMB115811 Baseline in mean corpuscle volume is summarized. AMB115811 Baseline is the last value recorded on or prior to start of study treatment in that study. Change from AMB115811 Baseline was calculated as the value at the indicated visit minus the Baseline value. Participant's final visit in study AMB115811 was used as the entry visit of this open-label extension study. Only those participants available at the specified time points were analyzed (represented by n=X, X in the category titles). Instances where 99999 has been mentioned indicate that data was not available or participants were not analyzed.

End point type	Primary

End point timeframe:

Baseline from study AMB115811; Entry visit of the extension study; Months 1, 3, 6, 9, 12, 15; and End of Study (assessed up to approximately 16 months)

Notes:

[13] - 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: There are no statistical data to report.

End point values	Previous Placebo	Previous Ambrisentan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9[14]	10[15]		
Units: Femtoliter (fL)				
median (inter-quartile range (Q1-Q3))				
Mean corpuscle volume, Entry visit, n=9, 10	-2 (-4 to -1)	-0.5 (-2 to 0)		
Mean corpuscle volume, Month 1, n=7, 10	-2 (-4 to 1)	-0.5 (-3 to 1)		
Mean corpuscle volume, Month 3, n=7, 8	-2 (-6 to 1)	-1 (-4 to -0.5)		
Mean corpuscle volume, Month 6, n=5, 6	-3 (-3 to 0)	-0.5 (-2 to 0)		
Mean corpuscle volume, Month 9, n=2, 5	-7 (-11 to -3)	0 (0 to 1)		
Mean corpuscle volume, Month 12, n=1, 3	-2 (-2 to -2)	2 (-1 to 2)		
Mean corpuscle volume, Month 15, n=0, 1	99999 (99999 to 99999)	1 (1 to 1)		
Mean corpuscle volume, End of study, n=8, 9	-2.5 (-3.5 to 0.5)	0 (0 to 2)		

Notes:

[14] - Safety (Extension) Population

[15] - Safety (Extension) Population

Statistical analyses

No statistical analyses for this end point

Primary: Change from study AMB115811 Baseline in red blood cell count and reticulocytes at the indicated time points

End point title	Change from study AMB115811 Baseline in red blood cell count and reticulocytes at the indicated time points[16]

End point description:

Hematology parameters were assessed at Entry visit of the extension study, Month 1, Month 3, Month 6, Month 9, Month 12, Month 15, and end of study. Change from study AMB115811 Baseline in red blood cell count and reticulocytes is summarized. AMB115811 Baseline is the last value recorded on or prior to start of study treatment in that study. Change from AMB115811 Baseline was calculated as the value at the indicated visit minus the Baseline value. Participant's final visit in study AMB115811 was used as the entry visit of this open-label extension study. Only those participants available at the specified time points were analyzed (represented by n=X, X in the category titles). Instances where 99999 has been mentioned indicate that data was not available or par. were not analyzed.

End point type	Primary

End point timeframe:

Baseline from study AMB115811; Entry visit of the extension study; Months 1, 3, 6, 9, 12, 15; and End of Study (assessed up to approximately 16 months)

Notes:

[16] - 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: There are no statistical data to report.

End point values	Previous Placebo	Previous Ambrisentan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9[17]	10[18]		
Units: Tera per Liter (TI/L)				
median (inter-quartile range (Q1-Q3))				
Red blood cell count, Entry visit , n=9, 10	-0.2 (-0.3 to 0.2)	-0.15 (-0.4 to -0.1)		
Red blood cell count, Month 1, n=7, 10	0 (-0.5 to 0.2)	-0.25 (-0.3 to -0.1)		
Red blood cell count, Month 3, n=7, 8	0 (-0.7 to 0.4)	-0.25 (-0.45 to -0.05)		
Red blood cell count, Month 6, n=5, 6	-0.3 (-0.7 to 0.1)	-0.15 (-0.3 to 0)		
Red blood cell count, Month 9, n=2, 5	-0.55 (-0.6 to -0.5)	-0.2 (-0.2 to -0.1)		
Red blood cell count, Month 12, n=1, 3	0.7 (0.7 to 0.7)	-0.2 (-0.3 to -0.1)		
Red blood cell count, Month 15, n=0, 1	99999 (99999 to 99999)	-0.4 (-0.4 to -0.4)		
Red blood cell count, End of study, n=8, 9	-0.15 (-0.4 to 0)	-0.2 (-0.4 to 0.1)		
Reticulocytes, Entry visit, n=9, 10	0.001 (-0.004 to 0.012)	0 (-0.026 to 0.004)		
Reticulocytes, Month 1, n=7, 10	-0.007 (-0.016 to 0.024)	-0.001 (-0.02 to 0.011)		
Reticulocytes, Month 3, n=7, 8	0.001 (-0.016 to 0.011)	-0.001 (-0.022 to 0.011)		
Reticulocytes, Month 6, n=5, 6	0.005 (-0.023 to 0.018)	-0.019 (-0.032 to -0.005)		
Reticulocytes, Month 9, n=2, 5	-0.013 (-0.019 to -0.006)	0.005 (-0.04 to 0.014)		
Reticulocytes, Month 12, n=1, 3	-0.032 (-0.032 to -0.032)	0.017 (-0.003 to 0.027)		
Reticulocytes, Month 15, n=0, 1	99999 (99999 to 99999)	-0.011 (-0.011 to -0.011)		
Reticulocytes, End of study, n=8, 9	-0.007 (-0.022 to 0.018)	-0.002 (-0.049 to 0.001)		

Notes:

[17] - Safety (Extension) Population

[18] - Safety (Extension) Population

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants with clinical chemistry parameters of potential clinical concern at any time post entry visit

End point title	Number of participants with clinical chemistry parameters of potential clinical concern at any time post entry visit[19]

End point description:

Blood samples were collected post Entry visit of the extension study and up to end of study for evaluation of the clinical chemistry parameters of alanine amino transferase (ALT), aspartate amino transferase (AST), gamma glutamyl transferase (GGT), and total bilirubin. The clinical chemistry parameters of potential clinical concern high were defined as follows: ALT, AST, GGT >=3 times upper limit of normal (ULN); total bilirubin >=2 times ULN. Participants with both normal and high values were counted once under their worst case (high). Participant's final visit in study AMB115811 was used as the entry visit of this open-label extension study.

End point type	Primary

End point timeframe:

Post entry visit of the extension study and up to End of Study (assessed up to approximately 16 months)

Notes:

[19] - 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: There are no statistical data to report.

End point values	Previous Placebo	Previous Ambrisentan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9[20]	10[21]		
Units: Participants				
ALT, >clinical concern high	0	0		
AST, >clinical concern high	0	0		
GGT, >clinical concern high	1	0		
Total bilirubin, >clinical concern high	0	0		

Notes:

[20] - Safety (Extension) Population

[21] - Safety (Extension) Population

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants with creatinine values of potential clinical concern at any time post entry visit

End point title	Number of participants with creatinine values of potential clinical concern at any time post entry visit[22]

End point description:

Blood samples were collected at Entry visit of the extension study, Month 1, Month 3, Month 6, Month 9, Month 12, Month 15, and end of study plus any unscheduled lab tests for creatinine. A creatinine value of potential clinical concern high was defined as >=176.8 micromoles per Liter. Participants with both normal and high values were counted once under their worst case (high). Participant's final visit in study AMB115811 was used as the entry visit of this open-label extension study.

End point type	Primary

End point timeframe:

Entry visit of the extension study; Months 1, 3, 6, 9, 12, 15; and End of Study plus any unscheduled lab tests (assessed up to approximately 16 months)

Notes:

[22] - 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: There are no statistical data to report.

End point values	Previous Placebo	Previous Ambrisentan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9[23]	10[24]		
Units: Participants				
Creatinine, >clinical concern high	1	0		

Notes:

[23] - Safety (Extension) Population

[24] - Safety (Extension) Population

Statistical analyses

No statistical analyses for this end point

Primary: Change from study AMB115811 Baseline in systolic blood pressure (SBP) and diastolic blood pressure (DBP) assessed at the indicated time points

End point title	Change from study AMB115811 Baseline in systolic blood pressure (SBP) and diastolic blood pressure (DBP) assessed at the indicated time points[25]

End point description:

Vital signs including SBP and DBP were assessed at Entry visit of the extension study, Month 1, Month 3, Month 6, Month 9, Month 12, Month 15, and end of study. Change from study AMB115811 Baseline in SBP and DBP is summarized. AMB115811 Baseline is the last value recorded on or prior to start of study treatment in that study. Change from AMB115811 Baseline was calculated as the value at the indicated visit minus the Baseline value. Participant's final visit in study AMB115811 was used as the entry visit of this open-label extension study. Only those participants available at the specified time points were analyzed (represented by n=X, X in the category titles). Instances where 99999 has been mentioned indicate that data was not available or par. were not analyzed.

End point type	Primary

End point timeframe:

Baseline from study AMB115811; Entry visit of the extension study; Months 1, 3, 6, 9, 12, 15; and End of Study (assessed up to approximately 16 months)

Notes:

[25] - 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: There are no statistical data to report.

End point values	Previous Placebo	Previous Ambrisentan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9[26]	10[27]		
Units: millimeter of mercury (mmHg)				
median (inter-quartile range (Q1-Q3))				
Systolic blood pressure, Entry visit, n=9, 10	-6 (-11 to 3)	-3 (-8 to 11)		
Systolic blood pressure, Month 1, n=8, 10	-0.5 (-21 to 4.5)	-5.5 (-7 to 3)		
Systolic blood pressure, Month 3, n=8, 8	-4 (-13.5 to 14.5)	-4 (-8 to 0)		
Systolic blood pressure, Month 6, n=5, 6	-10 (-30 to -9)	-5 (-14 to 0)		
Systolic blood pressure, Month 9, n=3, 5	-1 (-14 to 14)	-2 (-6 to 4)		
Systolic blood pressure, Month 12, n=1, 4	15 (15 to 15)	-8.5 (-15.5 to 6.5)		
Systolic blood pressure, Month 15, n=0, 1	99999 (99999 to 99999)	-2 (-2 to -2)		
Systolic blood pressure, End of study, n=8, 10	2.5 (-14 to 12.5)	1 (-5 to 5)		
Diastolic blood pressure, Entry visit, n=9, 10	-5 (-11 to 5)	-9 (-12 to 4)		
Diastolic blood pressure, Month 1, n=8, 10	-9 (-17.5 to -3)	-7 (-10 to 4)		
Diastolic blood pressure, Month 3, n=8, 8	-1 (-10.5 to 10)	-11 (-15.5 to -4)		
Diastolic blood pressure, Month 6, n=5, 6	-13 (-18 to -10)	-11 (-12 to -7)		
Diastolic blood pressure, Month 9, n=3, 5	-5 (-7 to -4)	-7 (-12 to -5)		
Diastolic blood pressure, Month 12, n=1, 4	0 (0 to 0)	-9 (-16 to -5.5)		

Diastolic blood pressure, Month 15, n=0, 1	99999 (99999 to 99999)	-4 (-4 to -4)		
Diastolic blood pressure, End of study, n=8, 10	-4 (-12 to 12)	-9.5 (-18 to -2)		

Notes:

[26] - Safety (Extension) Population

[27] - Safety (Extension) Population

Statistical analyses

No statistical analyses for this end point

Primary: Change from study AMB115811 Baseline in heart rate at the indicated time points

End point title	Change from study AMB115811 Baseline in heart rate at the indicated time points[28]

End point description:

Vital signs including heart rate were assessed at Entry visit of the extension study, Month 1, Month 3, Month 6, Month 9, Month 12, Month 15, and end of study. Change from study AMB115811 Baseline in heart rate is summarized. AMB115811 Baseline is the last value recorded on or prior to start of study treatment in that study. Change from AMB115811 Baseline was calculated as the value at the indicated visit minus the Baseline value. Participant's final visit in study AMB115811 was used as the entry visit of this open-label extension study. Only those participants available at the specified time points were analyzed (represented by n=X, X in the category titles). Instances where 99999 has been mentioned indicate that data was not available or par. were not analyzed.

End point type	Primary

End point timeframe:

Baseline from study AMB115811; Entry visit of the extension study; Months 1, 3, 6, 9, 12, 15; and End of Study (assessed up to approximately 16 months)

Notes:

[28] - 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: There are no statistical data to report.

End point values	Previous Placebo	Previous Ambrisentan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9[29]	10[30]		
Units: beats per minute				
median (inter-quartile range (Q1-Q3))				
Heart rate, Entry visit, n=9, 10	-2 (-17 to 5)	-7 (-17 to 1)		
Heart rate, Month 1, n=8, 10	-12 (-19.5 to 4)	-2 (-7 to 3)		
Heart rate, Month 3, n=8, 8	-8.5 (-19 to 1.5)	-1 (-11 to 4.5)		
Heart rate, Month 6, n=5, 6	-19 (-24 to -14)	-3.5 (-6 to -1)		
Heart rate, Month 9, n=3, 5	-12 (-12 to -11)	-6 (-7 to -2)		
Heart rate, Month 12, n=1, 4	-12 (-12 to -12)	-12.5 (-16.5 to -4.5)		
Heart rate, Month 15, n=0, 1	99999 (99999 to 99999)	-11 (-11 to -11)		
Heart rate, End of study, n=8, 10	-10.5 (-15 to 1)	0.5 (-5 to 4)		

Notes:

[29] - Safety (Extension) Population

[30] - Safety (Extension) Population

Statistical analyses

No statistical analyses for this end point

Primary: Change from study AMB115811 Baseline in weight at the indicated time points

End point title	Change from study AMB115811 Baseline in weight at the indicated time points[31]

End point description:

Weight was measured at Entry visit of the extension study, Month 1, Month 3, Month 6, Month 9, Month 12, Month 15, and at end of study. Change from study AMB115811 Baseline in weight is summarized. AMB115811 Baseline is the last value recorded on or prior to start of study treatment in that study. Change from AMB115811 Baseline was calculated as the value at the indicated visit minus the Baseline value. Participant's final visit in study AMB115811 was used as the entry visit of this open-label extension study. Only those participants available at the specified time points were analyzed (represented by n=X, X in the category titles). Instances where 99999 has been mentioned indicate that data was not available or par. were not analyzed.

End point type	Primary

End point timeframe:

Baseline from study AMB115811; Entry visit of the extension study; Months 1, 3, 6, 9, 12, 15; and End of Study (assessed up to approximately 16 months)

Notes:

[31] - 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: There are no statistical data to report.

End point values	Previous Placebo	Previous Ambrisentan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9[32]	10[33]		
Units: kilogram (kg)				
median (inter-quartile range (Q1-Q3))				
Weight, Entry visit, n=9, 10	-1 (-1.5 to 1.4)	-1 (-2.8 to 0.5)		
Weight, Month 1, n=8, 10	0 (-1.5 to 0.6)	-0.5 (-2.2 to 0.5)		
Weight, Month 3, n=8, 8	-0.5 (-2 to 0.55)	-2 (-4.45 to 0.5)		
Weight, Month 6, n=5, 6	0 (-10 to 1.1)	-3.1 (-5 to -0.5)		
Weight, Month 9, n=3, 5	0 (-19.7 to 1.6)	-3.5 (-5.5 to 1)		
Weight, Month 12, n=1, 4	0 (0 to 0)	-1.15 (-3.25 to 1)		
Weight, Month 15, n=0, 1	99999 (99999 to 99999)	-2.5 (-2.5 to -2.5)		
Weight, End of study, n=8, 10	0 (-1 to 0.85)	-0.05 (-2 to 1.8)		

Notes:

[32] - Safety (Extension) Population

[33] - Safety (Extension) Population

Statistical analyses

No statistical analyses for this end point

Primary: Time to first change in dose of open-label ambrisentan due to tolerability issues in any participant

End point title	Time to first change in dose of open-label ambrisentan due to tolerability issues in any participant[34]

End point description:

The time to change in dose of ambrisentan or other targeted PAH (pulmonary arterial hypertension) therapeutic agents (prostanoids, PDE-5 inhibitors) due to tolerability issues (e.g. adverse events). Dosing data were collected, but after the study was terminated, not all endpoints listed in the protocol were analyzed, including time to first change in dose of open-label ambrisentan. This decision was documented in the reporting and analysis plan prior to database lock.

End point type	Primary

End point timeframe:

From the Entry visit of the extension study up to approximately 16 months

Notes:

[34] - 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: There are no statistical data to report.

End point values	Previous Placebo	Previous Ambrisentan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[35]	0[36]		
Units: Days				
number (not applicable)				

Notes:

[35] - This data was not analyzed.

[36] - This data was not analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from study AMB115811 Baseline in the 6 minutes walking distance (6MWD) at the indicated time points

End point title	Change from study AMB115811 Baseline in the 6 minutes walking distance (6MWD) at the indicated time points

End point description:

The 6-minute walk test was conducted according to the American Thoracic Society guidelines in accordance with local standard operating procedures. 6MWD was measured by a 6-minute walk test. This test measures the distance that a par. can walk in a period of 6 minutes. AMB115811 Baseline was the Week 0 value in that study. Change from study AMB115811 Baseline was calculated as the value at the indicated visit minus the Baseline value. Par.'s final visit in study AMB115811 was used as the entry visit of this extension study. For the Extension study, the visit schedule (Months 1, 3, 6, 9, 12 and 15) was mapped to the visit schedule (Months 5, 7, 10, 13, 16 and 19) for continuity with study AMB115811. Only those participants available at the specified time points were analyzed (represented by n=X, X in the category titles). Intent-to-treat (ITT) Population: all par. who were randomized and took at least one dose of study medication in the double-blind phase (placebo or ambrisentan).

End point type	Secondary

End point timeframe:

During Study AMB115811: Months 0 (Baseline), 1, 2, 3, 4, Early Withdrawal (EW); During Extension Study: Months 1, 3, 6, 9, 12, 15 and at End of Study (assessed up to approximately 20 months)

End point values	Previous Placebo	Previous Ambrisentan		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	16[37]	17[38]		
Units: Meters				
median (inter-quartile range (Q1-Q3))				
(AMB115811) Month 1, n=15, 17	5 (-1.5 to 16.5)	14 (1 to 42.5)		
Month 2, n=14, 16	7.5 (-14.5 to 22.5)	26.25 (3.25 to 61.25)		
Month 3, n=13, 15	5.5 (-23 to 39.5)	20.5 (4 to 68)		
Month 4, n=13, 15	-10 (-32.5 to 20)	25 (12 to 49)		
EW (AMB115811) visit, n=3, 2	7.5 (-46.5 to 43.5)	41.25 (0 to 82.5)		
(Extension study) Month 5, n=7, 9	0 (-15.5 to 40)	51.5 (19 to 80.5)		
Month 7, n=7, 8	-8 (-22.5 to 55)	57.5 (23.5 to 88.75)		
Month 10, n=5, 6	55 (-10.5 to 65)	52.25 (21 to 100)		
Month 13, n=2, 4	8.5 (-5.5 to 22.5)	33.25 (19 to 46.25)		
Month 16, n=1, 4	65 (65 to 65)	47.25 (23.5 to 61.25)		
Month 19, n=0, 1	99999 (99999 to 99999)	69 (69 to 69)		
End of study, n=7, 8	30 (4.5 to 43)	29.5 (4 to 80.25)		

Notes:

[37] - ITT Population

[38] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from study AMB115811 Baseline (BL) in World Health Organization (WHO) functional class (FC) at the indicated time points

End point title	Change from study AMB115811 Baseline (BL) in World Health Organization (WHO) functional class (FC) at the indicated time points

End point description:

WHO FC indicates severity of pulmonary arterial hypertension (PAH) and is an adaptation of the New York Heart Association classification, assessed by the investigator. There are 4 grades for WHO FC based on severity of symptoms (Class I = none, Class IV = most severe). Grades mapped to numeric scale 1-4 (i.e. Class IV = 4). WHO FC system links symptoms with activity limitations, allowing clinicians to predict disease progression and prognosis. AMB115811 BL is the last value recorded on or prior to start of study treatment in that study. Change from AMB115811 BL was calculated as the value at the indicated visit minus the BL value (positive change = worsening). Par.'s final visit in AMB115811 was used as entry visit of this ext study. For Ext study, the visit schedule (M1,3,6,9,12 and 15) was mapped to the visit schedule (M5,7,10,13,16 and 19) for continuity with study AMB115811. Only par. available at the specified TP were analyzed (represented by n=X,X in the category title).

End point type	Secondary

End point timeframe:

During Study AMB115811: Months 0 (Baseline), 1, 2, 3, 4, Early Withdrawal; During Extension Study: Months 1, 3, 6, 9, 12, 15 and at End of Study (assessed up to approximately 20 months)

End point values	Previous Placebo	Previous Ambrisentan		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	16[39]	17[40]		
Units: Scores on a scale				
median (inter-quartile range (Q1-Q3))				
(AMB115811) Month 1, n=15, 17	0 (0 to 0)	0 (0 to 0)		
Month 2, n=14, 16	0 (0 to 0)	0 (0 to 0)		
Month 3, n=13, 15	0 (0 to 0)	0 (-1 to 0)		
Month 4, n=13, 15	0 (0 to 0)	0 (-1 to 0)		
EW (AMB115811) visit, n=3, 2	0 (-1 to 0)	0 (0 to 0)		
(Extension study) Month 5, n=8, 10	0 (0 to 0)	0 (-1 to 0)		
Month 7, n=8, 8	0 (0 to 0.5)	0 (-1 to 0)		
Month 10, n=5, 6	0 (0 to 0)	-0.5 (-1 to 0)		
Month 13, n=3, 5	0 (0 to 0)	0 (0 to 0)		
Month 16, n=1, 4	0 (0 to 0)	0 (-0.5 to 0)		
Month 19, n=0, 1	99999 (99999 to 99999)	0 (0 to 0)		
End of study, n=8, 10	0 (-0.5 to 0)	0 (-1 to 0)		

Notes:

[39] - ITT Population

[40] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from study AMB115811 Baseline in Borg CR10 Scale (BCR10S) immediately following exercise at the indicated time points

End point title	Change from study AMB115811 Baseline in Borg CR10 Scale (BCR10S) immediately following exercise at the indicated time points

End point description:

BCR10S score was collected immediately following completion of the 6-minute walk test. Scores range from 0 to 10 (0=nothing at all, 10=extremely strong). If par.'s perception or feeling was stronger than "10", that is “extremely strong”, “Maximal” – a larger number could be used, for example 12 or still higher, that is “Absolute maximum”). AMB115811 BL data was calculated as average of 2 BCR10S values obtained following the 2 6MWD tests used in determining the BL 6MWD in that study. If only 1 measurement was available, it was used. Change from AMB115811 BL was calculated as the value at the indicated visit minus the BL value. Par.'s final visit in AMB115811 was used as the entry visit of extension study. For the Extension study, the visit schedule (Months 1, 3, 6, 9, 12 and 15) mapped to the visit schedule (Months 5, 7, 10, 13, 16 and 19) for continuity with AMB115811. Only those par. available at the specified time points were analyzed (represented by n=X,X in the category titles).

End point type	Secondary

End point timeframe:

During Study AMB115811: Months 0 (Baseline), 1, 2, 3, 4, Early Withdrawal; During Extension Study: Months 1, 3, 6, 9, 12, 15 and at End of Study (assessed up to approximately 20 months)

End point values	Previous Placebo	Previous Ambrisentan		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	16[41]	17[42]		
Units: Scores on a scale				
median (inter-quartile range (Q1-Q3))				
(AMB115811) Month 1, n=15, 17	0 (-1 to 0.75)	-0.4 (-0.5 to 0)		
Month 2, n=14, 16	0.25 (-0.5 to 1)	-0.2 (-1.13 to 1)		
Month 3, n=13, 15	0 (-0.5 to 2.25)	-0.4 (-1 to 1)		
Month 4, n=13, 15	1 (-0.5 to 2.5)	-0.5 (-1.5 to 1)		
EW (AMB115811) visit, n=3, 2	2 (-1.5 to 4)	-0.25 (-0.5 to 0)		
(Extension study) Month 5, n=7, 9	0 (-0.5 to 1.5)	1.5 (-0.5 to 2)		
Month 7, n=7, 8	0.5 (-0.5 to 2.5)	0 (-1.38 to 1.75)		
Month 10, n=5, 6	0.5 (0.5 to 1.5)	0.5 (-1.5 to 1)		
Month 13, n=2, 4	0.5 (0.5 to 0.5)	1 (-0.75 to 2.75)		
Month 16, n=1, 4	0.5 (0.5 to 0.5)	0.5 (-0.75 to 1.75)		
Month 19, n=0, 1	99999 (99999 to 99999)	1 (1 to 1)		
End of study, n=7, 8	1.25 (0 to 1.5)	0.88 (-0.25 to 1.5)		

Notes:

[41] - ITT Population

[42] - ITT Population

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:

Time to clinical worsening of CTEPH was defined as the time from randomization in Study AMB115811 to the first occurrence of any of the following events: death (all cause), lung transplantation, hospitalization for CTEPH deterioration, atrial septostomy, addition of parenteral prostanoids, appearance of two or more CTEPH worsening events. Worsening events included: >=20% of decrease in 6MWD; >=1 increase of WHO Functional Classes; worsening right ventricular failure; rapidly progressing cardiogenic, hepatic, or renal failure; refractory systolic hypotension (SBP <85 mmHg).

End point type	Secondary

End point timeframe:

From randomization up to End of Study for the extension study (assessed up to approximately 20 months)

End point values	Previous Placebo	Previous Ambrisentan		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	16[43]	17[44]		
Units: Participants				
number (not applicable)	2	0		

Notes:

[43] - ITT Population

[44] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from study AMB115811 Baseline in Quality of Life as measured by Short Form 36 Health Survey (SF-36)

End point title	Change from study AMB115811 Baseline in Quality of Life as measured by Short Form 36 Health Survey (SF-36)

End point description:

The SF-36 version 2 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). Baseline of study AMB115811 was to be used. Change from study AMB115811 Baseline was to be calculated as the value at the indicated visit minus the Baseline value. 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.

End point type	Secondary

End point timeframe:

Baseline from study AMB115811 up to End of Study for the extension study (assessed up to approximately 20 months from Baseline)

End point values	Previous Placebo	Previous Ambrisentan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[45]	0[46]		
Units: Scores on a scale				
median (inter-quartile range (Q1-Q3))	(to)	(to)		

Notes:

[45] - Health outcomes data collected in this study were excluded from analysis.

[46] - Health outcomes data collected in this study were excluded from analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change from study AMB115811 Baseline in plasma N-terminal pro-B-type natriuretic peptide (NT-proBNP)

End point title	Percent change from study AMB115811 Baseline in plasma N-terminal pro-B-type natriuretic peptide (NT-proBNP)

End point description:

The ratio to Baseline in NT-proBNP was calculated as the ratio of the value at the specified time-point to the AMB115811 Baseline value and was expressed as a percent change from AMB115811 Baseline. This

was done by taking the mean change on the log scale, exponentiating, subtracting 1 and multiplying by 100. Standard deviation (SD) of the logged values (log[SD]) have been presented. AMB115811 Baseline is the last value recorded on or prior to start of study treatment in that study. Participant's final visit in study AMB115811 was used as the entry visit of this open-label extension study. For the Extension study, the visit schedule (Months 1, 3, 6, 9, 12 and 15) was mapped to the visit schedule (Months 5, 7, 10, 13, 16 and 19) for continuity with study AMB115811. Only those participants available at the specified time points were analyzed (represented by n=X, X in the category titles).

End point type	Secondary

End point timeframe:

During Study AMB115811: Months 0 (Baseline), 1, 2, 3, 4, Early Withdrawal; During Extension Study: Months 1, 3, 6, 9, 12, 15 and at End of Study (assessed up to approximately 20 months from Baseline)

End point values	Previous Placebo	Previous Ambrisentan		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	16[47]	17[48]		
Units: Percent change				
geometric mean (standard deviation)				
(AMB115811) Month 1, n=13, 15	43.6 (± 0.41)	-15.8 (± 0.36)		
Month 2, n=13, 15	12.4 (± 0.49)	-23.3 (± 0.59)		
Month 3, n=12, 14	12.4 (± 0.59)	-21.9 (± 0.61)		
Month 4, n=12, 14	14.1 (± 0.55)	-29.4 (± 0.5)		
EW (AMB115811) visit, n=3, 2	35.7 (± 0.69)	-14.9 (± 0.31)		
(Extension study) Month 5, n=8, 10	-34.7 (± 1.22)	-24.5 (± 0.69)		
Month 7, n=8, 8	3.3 (± 0.64)	-32.5 (± 0.73)		
Month 10, n=5, 6	-36.5 (± 0.86)	-20.1 (± 0.78)		
Month 13, n=3, 5	-8.6 (± 0.6)	7.7 (± 0.79)		
Month 16, n=1, 4	-62.4 (± 99999)	-2.8 (± 1.15)		
Month 19, n=0, 1	99999 (± 99999)	43.1 (± 99999)		
End of study, n=8, 9	-13.2 (± 0.72)	-41.7 (± 0.86)		

Notes:

[47] - ITT Population

[48] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Start of Ambrisentan Treatment in 6 minutes walking distance at the indicated time points

End point title	Change from Start of Ambrisentan Treatment in 6 minutes walking distance at the indicated time points

End point description:

The 6 minute walk distance data in a previous outcome measure were also analyzed as change from start of ambrisentan treatment. As participants started to receive ambrisentan treatment in two studies, two different time points for start of ambrisentan treatment were used for this analysis. For participants who received ambrisentan treatment in Study AMB115811, the Baseline for that study was used. For participants who received placebo in Study AMB115811, entry visit of the Extension study was defined as Baseline. Change from start of ambrisentan was calculated as the value at the indicated visit minus the start of ambrisentan value. Only those participants available at the specified time points were analyzed (represented by n=X, X in the category title). Instances where 99999 has been mentioned indicate that data was not available or par. were not analyzed.

End point type	Secondary

End point timeframe:

Previous Placebo: Months 0 (Entry visit of the extension), 1, 3, 6, 9, 12; Previous Ambrisentan: Month 0 (Baseline of study AMB115811), 1, 2, 3, 4, Early Withdrawal (EW) (AMB115811), 5, 7, 10, 13, 16, 19; and at End of Study

End point values	Previous Placebo	Previous Ambrisentan		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9[49]	17[50]		
Units: Meters				
median (inter-quartile range (Q1-Q3))				
Month 1, n=7, 17	20 (15 to 30)	14 (1 to 42.5)		
Month 2, n=0, 16	99999 (99999 to 99999)	26.25 (3.25 to 61.25)		
Month 3, n=7, 15	20 (15 to 35)	20.5 (4 to 68)		
Month 4, n= 0, 15	99999 (99999 to 99999)	25 (12 to 49)		
EW (AMB115811), n=0, 2	99999 (99999 to 99999)	41.25 (0 to 82.5)		
Month 5, n=0, 9	99999 (99999 to 99999)	51.5 (19 to 80.5)		
Month 6, n=5, 0	45 (27 to 60)	99999 (99999 to 99999)		
Month 7, n=0, 8	99999 (99999 to 99999)	57.5 (23.5 to 88.75)		
Month 9, n=2, 0	32.5 (5 to 60)	99999 (99999 to 99999)		
Month 10, n=0, 6	99999 (99999 to 99999)	52.25 (21 to 100)		
Month 12, n=1, 0	45 (45 to 45)	99999 (99999 to 99999)		
Month 13, n=0, 4	99999 (99999 to 99999)	33.25 (19 to 46.25)		
Month 16, n=0, 4	99999 (99999 to 99999)	47.25 (23.5 to 61.25)		
Month 19, n=0, 1	99999 (99999 to 99999)	69 (69 to 69)		
End of study, n=7, 8	37 (0 to 60)	29.5 (4 to 80.25)		

Notes:

[49] - ITT Population. Placebo arm: includes par. who received ambrisentan treatment during extension study

[50] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Start of Ambrisentan Treatment in World Health Organization (WHO) functional class (FC) at the indicated time points

End point title	Change from Start of Ambrisentan Treatment in World Health Organization (WHO) functional class (FC) at the indicated time points

End point description:

The WHO functional class data in a previous outcome measure were also analyzed as change from start of ambrisentan treatment. As participants started to receive ambrisentan treatment in two studies, two

different time points for start of ambrisentan treatment were used for this analysis. For participants who received ambrisentan treatment in Study AMB115811, the Baseline for that study was used. For participants who received placebo in Study AMB115811, entry visit of the Extension study was defined as Baseline. Change from start of ambrisentan was calculated as the value at the indicated visit minus the start of ambrisentan value. Only those participants available at the specified time points were analyzed (represented by n=X, X in the category title). Instances where 99999 has been mentioned indicate that data was not available or par. were not analyzed.

End point type	Secondary

End point timeframe:

Previous Placebo: Months 0 (Entry visit of the extension), 1, 3, 6, 9, 12; Previous Ambrisentan: Month 0 (Baseline of study AMB115811), 1, 2, 3, 4, Early Withdrawal (EW) (AMB115811), 5, 7, 10, 13, 16, 19; and at End of Study

End point values	Previous Placebo	Previous Ambrisentan		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9[51]	17[52]		
Units: Scores on a scale				
median (inter-quartile range (Q1-Q3))				
Month 1, n=8, 17	0 (0 to 0)	0 (0 to 0)		
Month 2, n=0, 16	99999 (99999 to 99999)	0 (0 to 0)		
Month 3, n=8, 15	0 (0 to 0)	0 (-1 to 0)		
Month 4, n= 0, 15	99999 (99999 to 99999)	0 (-1 to 0)		
EW (AMB115811), n=0, 2	99999 (99999 to 99999)	0 (0 to 0)		
Month 5, n=0, 10	99999 (99999 to 99999)	0 (-1 to 0)		
Month 6, n=5, 0	0 (0 to 0)	99999 (99999 to 99999)		
Month 7, n=0, 8	99999 (99999 to 99999)	0 (-1 to 0)		
Month 9, n=3, 0	0 (0 to 0)	99999 (99999 to 99999)		
Month 10, n=0, 6	99999 (99999 to 99999)	-0.5 (-1 to 0)		
Month 12, n=1, 0	0 (0 to 0)	99999 (99999 to 99999)		
Month 13, n=0, 5	99999 (99999 to 99999)	0 (0 to 0)		
Month 16, n=0, 4	99999 (99999 to 99999)	0 (-0.5 to 0)		
Month 19, n=0, 1	99999 (99999 to 99999)	0 (0 to 0)		
End of study, n=8, 10	0 (0 to 0)	0 (-1 to 0)		

Notes:

[51] - ITT Population. Placebo arm: includes par. who received ambrisentan treatment during extension study

[52] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Start of Ambrisentan Treatment in Borg CR10 Scale

(BCR10S) immediately following exercise at the indicated time points

End point title	Change from Start of Ambrisentan Treatment in Borg CR10 Scale (BCR10S) immediately following exercise at the indicated time points

End point description:

The BCR10S data in a previous outcome measure were also analyzed as change from start of ambrisentan treatment. BCR10S score, a rating of perceived exertion, ranges from 0 to 10 (0=nothing at all, 10 extremely strong). If par.'s perception or feeling was stronger than "10", a larger number could be used. As participants started to receive ambrisentan treatment in two studies, two different time points for start of ambrisentan treatment were used for this analysis. For participants who received ambrisentan treatment in Study AMB115811, the Baseline for that study was used. For participants who received placebo in Study AMB115811, entry visit of the Extension study was defined as Baseline. Change from start of ambrisentan was calculated as the value at the indicated visit minus the start of ambrisentan value. Only those participants available at the specified time points were analyzed (represented by n=X, X in the category title).

End point type	Secondary

End point timeframe:

Previous Placebo: Months 0 (Entry visit of the extension), 1, 3, 6, 9, 12; Previous Ambrisentan: Month 0 (Baseline of study AMB115811), 1, 2, 3, 4, Early Withdrawal (EW) (AMB115811), 5, 7, 10, 13, 16, 19; and at End of Study

End point values	Previous Placebo	Previous Ambrisentan		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9[53]	17[54]		
Units: Scores on a scale				
median (inter-quartile range (Q1-Q3))				
Month 1, n=7, 17	0 (-1 to 1)	-0.4 (-0.5 to 0)		
Month 2, n=0, 16	99999 (99999 to 99999)	-0.2 (-1.13 to 1)		
Month 3, n=7, 15	0 (0 to 1)	-0.4 (-1 to 1)		
Month 4, n= 0, 15	99999 (99999 to 99999)	-0.5 (-1.5 to 1)		
EW (AMB115811), n=0, 2	99999 (99999 to 99999)	-0.25 (-0.5 to 0)		
Month 5, n=0, 9	99999 (99999 to 99999)	1.5 (-0.5 to 2)		
Month 6, n=5, 0	1 (1 to 2)	99999 (99999 to 99999)		
Month 7, n=0 , 8	99999 (99999 to 99999)	0 (-1.38 to 1.75)		
Month 9, n=2, 0	0.5 (-1 to 2)	99999 (99999 to 99999)		
Month 10, n=0, 6	99999 (99999 to 99999)	0.5 (-1.5 to 1)		
Month 12, n=1,0	1 (1 to 1)	99999 (99999 to 99999)		
Month 13, n=0, 4	99999 (99999 to 99999)	1 (-0.75 to 2.75)		
Month 16, n=0, 4	99999 (99999 to 99999)	0.5 (-0.75 to 1.75)		
Month 19, n=0, 1	99999 (99999 to 99999)	1 (1 to 1)		
End of study, n=7, 8	0 (-1 to 1)	0.88 (-0.25 to 1.5)		

Notes:

[53] - ITT Population. Placebo arm: includes par. who received ambrisentan treatment during extension study
[54] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change from Start of Ambrisentan Treatment in plasma N-terminal pro-B-type natriuretic peptide (NT-proBNP)

End point title	Percent change from Start of Ambrisentan Treatment in plasma N-terminal pro-B-type natriuretic peptide (NT-proBNP)

End point description:

The NT-proBNP data in a previous outcome measure were also analyzed as change from start of ambrisentan treatment. The ratio to start of ambrisentan in NT-proBNP was calculated as the ratio of the value at the specified time-point to the start of ambrisentan value and was expressed as a percent change from start of ambrisentan. This was done by taking the mean change on the log scale, exponentiating, subtracting 1 and multiplying by 100. Standard deviation (SD) of the logged values (log[SD]) have been presented. As par. started to receive ambrisentan treatment in 2 studies, 2 different time points for start of ambrisentan treatment were used for this analysis. For par. who received ambrisentan treatment in study AMB115811, the Baseline for that study was used. For par. who received placebo in Study AMB115811, entry visit of the Extension study was defined as Baseline. Only those par. available at the specified time points were analyzed (represented by n=X, X in the category title).

End point type	Secondary

End point timeframe:

Previous Placebo: Months 0 (Entry visit of the extension), 1, 3, 6, 9, 12; Previous Ambrisentan: Month 0 (Baseline of study AMB115811), 1, 2, 3, 4, Early Withdrawal (EW) (AMB115811), 5, 7, 10, 13, 16, 19; and at End of Study

End point values	Previous Placebo	Previous Ambrisentan		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9[55]	17[56]		
Units: Percent change				
geometric mean (standard deviation)				
Month 1, n=8, 15	-49.5 (± 1.4)	-15.8 (± 0.36)		
Month 2, n=0, 15	99999 (± 99999)	-23.3 (± 0.59)		
Month 3, n=8, 14	-20.1 (± 0.86)	-21.9 (± 0.61)		
Month 4, n= 0, 14	99999 (± 99999)	-29.4 (± 0.5)		
EW (AMB115811), n=0, 2	99999 (± 99999)	-14.9 (± 0.31)		
Month 5, n=1, 10	99999 (± 99999)	-24.5 (± 0.69)		
Month 6, n=5, 0	-53.5 (± 1.22)	99999 (± 99999)		
Month 7, n=0, 8	99999 (± 99999)	-32.5 (± 0.73)		
Month 9, n=3, 1	-11.2 (± 0.71)	99999 (± 99999)		

Month 10, n=0, 6	99999 (± 99999)	-20.1 (± 0.78)		
Month 12, n=1, 0	-67.9 (± 99999)	99999 (± 99999)		
Month 13, n=0, 5	99999 (± 99999)	7.7 (± 0.79)		
Month 16, n=0, 4	99999 (± 99999)	-2.8 (± 1.15)		
Month 19, n=0, 1	99999 (± 99999)	43.1 (± 99999)		
End of study, n=8, 9	-30.5 (± 0.85)	-41.7 (± 0.86)		

Notes:

[55] - ITT Population. Placebo arm: includes par. who received ambrisentan treatment during extension study

[56] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Time to first change in dose of open-label ambrisentan due to deterioration of clinical conditions in any participant

End point title	Time to first change in dose of open-label ambrisentan due to deterioration of clinical conditions in any participant

End point description:

The time to change in dose of ambrisentan or other targeted PAH therapeutic agents (prostanoids, PDE-5 inhibitors) due to deterioration of clinical condition. Dosing data were collected, but after the study was terminated, not all endpoints listed in the protocol were analyzed, including time to first change in dose of open-label ambrisentan. This decision was documented in the reporting and analysis plan prior to database lock.

End point type	Secondary

End point timeframe:

From Entry visit of the extension study up to End of Study (assessed up to approximately 16 months)

End point values	Previous Placebo	Previous Ambrisentan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[57]	0[58]		
Units: Days				
number (not applicable)				

Notes:

[57] - Data were not analyzed

[58] - Data were not analyzed

Statistical analyses

No statistical analyses for this end point

Secondary: Time to first addition of another targeted PAH therapeutic agent due to deterioration of clinical condition or lack of beneficial effect with previous therapy in any participant

End point title	Time to first addition of another targeted PAH therapeutic agent due to deterioration of clinical condition or lack of beneficial effect with previous therapy in any participant

End point description:

The time to addition of another targeted PAH therapeutic agents (prostanoids, PDE-5 inhibitors) due to the following reasons: Deterioration of clinical condition; Lack of beneficial effect with previous therapy (not reaching set treatment goals). PAH therapies were collected, but after the study was terminated, not all endpoints listed in the protocol were analyzed, including time to first addition of another targeted PAH therapeutic agent. This decision was documented in the reporting and analysis plan prior to database lock.

End point type	Secondary

End point timeframe:

From Entry visit of the extension study up to End of Study (assessed up to approximately 16 months)

End point values	Previous Placebo	Previous Ambrisentan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[59]	0[60]		
Units: Days				
number (not applicable)				

Notes:

[59] - Data were not analyzed

[60] - Data were not analyzed

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment-emergent adverse events (TEAEs) will include AEs up to 30 days after their last dose, assessed up to approximately 16 months.

Adverse event reporting additional description:

TEAEs are reported for the Safety (Extension) Population. TEAEs are: a) new events that started during the extension study. For par. withdrawn from the study, TEAEs included AEs up to 30 days after last dose b) ongoing AEs that started before the extension study but were either not reported in study AMB115811 or worsened during the extension study.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Previous Placebo

Reporting group description:

Participants received placebo tablet once daily (OD) for 16 weeks in study AMB115811. Upon enrollment in the extension study AMB116457, participants received ambrisentan 5 milligrams (mg) tablet OD. The dose could be up-titrated to ambrisentan 10 mg OD or adjusted back to ambrisentan 5 mg OD.

Reporting group title	Previous Ambrisentan

Reporting group description:

Participants received ambrisentan 5 mg tablet OD for 16 weeks in study AMB115811. Upon enrollment in the extension study AMB116457, participants continued to receive ambrisentan 5 mg OD. The dose could be up-titrated to ambrisentan 10 mg OD or adjusted back to ambrisentan 5 mg OD.

Serious adverse events	Previous Placebo	Previous Ambrisentan	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 9 (33.33%)	0 / 10 (0.00%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events			
Investigations			
Electrocardiogram repolarisation abnormality			
subjects affected / exposed	1 / 9 (11.11%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oxygen saturation decreased			
subjects affected / exposed	1 / 9 (11.11%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			

Aortic stenosis			
subjects affected / exposed	1 / 9 (11.11%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 9 (11.11%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradyarrhythmia			
subjects affected / exposed	1 / 9 (11.11%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	2 / 9 (22.22%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Right ventricular failure			
subjects affected / exposed	1 / 9 (11.11%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	1 / 9 (11.11%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Implant site extravasation			
subjects affected / exposed	1 / 9 (11.11%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	1 / 9 (11.11%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	1 / 9 (11.11%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	1 / 9 (11.11%)	0 / 10 (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	Previous Placebo	Previous Ambrisentan	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 9 (88.89%)	6 / 10 (60.00%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 9 (11.11%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 9 (11.11%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Blood creatinine increased			
subjects affected / exposed	1 / 9 (11.11%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Blood potassium decreased			
subjects affected / exposed	1 / 9 (11.11%)	0 / 10 (0.00%)	
occurrences (all)	2	0	
Injury, poisoning and procedural complications			
Foot fracture			
subjects affected / exposed	1 / 9 (11.11%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			

Cyanosis			
subjects affected / exposed	1 / 9 (11.11%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Tachycardia			
subjects affected / exposed	1 / 9 (11.11%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 9 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Headache			
subjects affected / exposed	1 / 9 (11.11%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
Migraine			
subjects affected / exposed	0 / 9 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 9 (11.11%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 9 (11.11%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Fatigue			
subjects affected / exposed	1 / 9 (11.11%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Hyperthermia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Influenza like illness			
subjects affected / exposed	0 / 9 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Non-cardiac chest pain			
subjects affected / exposed	1 / 9 (11.11%)	0 / 10 (0.00%)	
occurrences (all)	1	0	

Oedema			
subjects affected / exposed	1 / 9 (11.11%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Oedema peripheral			
subjects affected / exposed	3 / 9 (33.33%)	0 / 10 (0.00%)	
occurrences (all)	3	0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 9 (22.22%)	1 / 10 (10.00%)	
occurrences (all)	2	1	
Hiatus hernia			
subjects affected / exposed	1 / 9 (11.11%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Vomiting			
subjects affected / exposed	1 / 9 (11.11%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 9 (11.11%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Dyspnoea			
subjects affected / exposed	1 / 9 (11.11%)	0 / 10 (0.00%)	
occurrences (all)	2	0	
Epistaxis			
subjects affected / exposed	1 / 9 (11.11%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
Haemoptysis			
subjects affected / exposed	1 / 9 (11.11%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Productive cough			
subjects affected / exposed	1 / 9 (11.11%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	1 / 9 (11.11%)	0 / 10 (0.00%)	
occurrences (all)	1	0	

Renal impairment			
subjects affected / exposed	1 / 9 (11.11%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 9 (11.11%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Back pain			
subjects affected / exposed	0 / 9 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Tendonitis			
subjects affected / exposed	1 / 9 (11.11%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Bacteriuria			
subjects affected / exposed	1 / 9 (11.11%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Bronchitis bacterial			
subjects affected / exposed	1 / 9 (11.11%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Erysipelas			
subjects affected / exposed	0 / 9 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	5	
Nasopharyngitis			
subjects affected / exposed	1 / 9 (11.11%)	2 / 10 (20.00%)	
occurrences (all)	1	3	
Respiratory tract infection			
subjects affected / exposed	1 / 9 (11.11%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Tonsillitis			
subjects affected / exposed	1 / 9 (11.11%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Tracheitis			
subjects affected / exposed	1 / 9 (11.11%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			

Iron deficiency subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 10 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 March 2013	Update to maximum study sample size following changes to the Double-Blind study (AMB115811) Correction to the IP storage conditions to change from 15-30ºC to up to 30 ºC. Revision of pregnancy follow-up information to include partners of male subjects in the study and to be consistent with the AMB115811 study Correct to the description of several efficacy assessments and timepoints to remove the requirement to perform efficacy tests 30 days after discontinuation of IP (safety only is required for this follow-up)
03 July 2013	Clarification on the study design: subject's study participation duration Clarifications on inclusion criteria: -in case of prematurely withdrawal from study AMB115811 for whatever reason, the investigator to decide whether or not the subject received the IP. -addition of some general inclusion criteria on reliable methods of contraception, non participation to another study and signature of the approved consent form. Clarification on the treatment given after the end of the study Change in the visit window of month 1 and monthly visits (+/- 7 days) Vital signs, clarification on blood pressure measurements Clarification on the study medication storage temperatures

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported