Clinical trial results:
A randomized, open label study comparing safety and efficacy parameters for a high and a low dose of ambrisentan (adjusted for body weight) for the treatment of pulmonary arterial hypertension in paediatric patients aged 8 years up to 18 years

Summary

EudraCT number	2010-019547-19
Trial protocol	GR NL HU DE ES FR IT Outside EU/EEA
Global end of trial date	12 November 2013

Results information

Result version number	v2 (current)
This version publication date	12 October 2019
First version publication date	24 August 2019
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	AMB112529

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, TW8 9GS
Public contact	GSK Response Center, GlaxoSmithKline, 1 8664357343, GSKClinicalSupportHD@gsk.com
Scientific contact	GSK Response Center, GlaxoSmithKline, 1 8664357343, GSKClinicalSupportHD@gsk.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000434-PIP01-08
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	12 November 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	12 November 2013
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety, tolerability, pharmacokinetics and efficacy of ambrisentan in the paediatric PAH population

Protection of trial subjects:

The independent data monitoring committee (IDMC) were involved in this study to ensure objectives such as medical and/or statistical review of safety and/or efficacy concerns in order to protect the ethical and safety interests of participants and to protect scientific validity of the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 January 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Safety
Long term follow-up duration	10 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 6
Country: Number of subjects enrolled	France: 3
Country: Number of subjects enrolled	Germany: 3
Country: Number of subjects enrolled	Hungary: 5
Country: Number of subjects enrolled	Italy: 2
Country: Number of subjects enrolled	Japan: 5
Country: Number of subjects enrolled	Russian Federation: 8
Country: Number of subjects enrolled	Spain: 2
Country: Number of subjects enrolled	United States: 7
Worldwide total number of subjects	41
EEA total number of subjects	15

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	14
Adolescents (12-17 years)	27
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study investigated the safety and efficacy of a high and low dose ambrisentan (adjusted as per participants body weight) administered orally in participants aged 8 to 18 years with pulmonary arterial hypertension (PAH).

Pre-assignment

Screening details:

A total of 41 participants were enrolled and randomized.

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	Low dose ambrisentan

Arm description:

Participants received ambrisentan low dose tablet either 2.5 milligram (mg) or 5 mg orally once daily for 24 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:

Participants received ambrisentan low dose tablet either 2.5 mg or 5 mg orally once daily for 24 weeks.

Arm title	High dose ambrisentan

Arm description:

Participants received ambrisentan high dose tablet either 5 mg, 7.5 mg or 10 mg orally once daily for 24 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:

Participants received ambrisentan high dose tablet either 5 mg, 7.5 mg or 10 mg orally once daily for 24 weeks.

Number of subjects in period 1	Low dose ambrisentan	High dose ambrisentan
Started	21	20
Completed	19	18
Not completed	2	2
Physician decision	1	-
Adverse event, non-fatal	1	1
Lost to follow-up	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Low dose ambrisentan
Reporting group description:	
Participants received ambrisentan low dose tablet either 2.5 milligram (mg) or 5 mg orally once daily for 24 weeks.	
Reporting group title	High dose ambrisentan
Reporting group description:	
Participants received ambrisentan high dose tablet either 5 mg, 7.5 mg or 10 mg orally once daily for 24 weeks.	

Reporting group values	Low dose ambrisentan	High dose ambrisentan	Total
Number of subjects	21	20	41
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	7	7	14
Adolescents (12-17 years)	14	13	27
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	11.8	12.3	
standard deviation	± 2.70	± 2.85	-
Sex: Female, Male Units: Subjects			
Female	12	15	27
Male	9	5	14
Race/Ethnicity, Customized Units: Subjects			
African American/African Heritage	2	0	2
American Indian or Alaskan Native	1	0	1
Asian - Central/South Asian Heritage	1	0	1
Asian - East Asian Heritage	1	0	1
Asian - Japanese Heritage	5	0	5
Asian - South East Asian Heritage	0	1	1
White - White/Caucasian/European Heritage	11	19	30

End points

End points reporting groups

Reporting group title	Low dose ambrisentan
Reporting group description:	
Participants received ambrisentan low dose tablet either 2.5 milligram (mg) or 5 mg orally once daily for 24 weeks.	
Reporting group title	High dose ambrisentan
Reporting group description:	
Participants received ambrisentan high dose tablet either 5 mg, 7.5 mg or 10 mg orally once daily for 24 weeks.	

Primary: Number of participants with treatment-emergent adverse events (AEs) and serious treatment-emergent adverse events (SAEs)

End point title	Number of participants with treatment-emergent adverse events (AEs) and serious treatment-emergent adverse events (SAEs)[1]

End point description:

AEs defined as any untoward medical occurrence in a patient or clinical investigation participant, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. SAEs 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 or incapacity, or is a congenital anomaly or birth defect, medical events that may not immediately life threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention as per medical or scientific judgement and events of drug-induced liver injury with hyperbilirubinaemia. Safety population comprised of all randomized participants who received at least 1 dose of study drug.

End point type	Primary

End point timeframe:

Up to 24 Weeks

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: No statistical analyses have been performed for this outcome measure.

End point values	Low dose ambrisentan	High dose ambrisentan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21[2]	20[3]		
Units: Participants				
Any AEs	16	16		
Any SAEs	6	2		

Notes:

[2] - Safety Population

[3] - Safety Population

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants with post Baseline Potential Clinical importance (PCI) value for clinical chemistry parameters: alanine amino transferase (ALT), aspartate aminotransferase (AST), gamma glutamyl transferase (GGT), total

bilirubin and creatinine

End point title	Number of participants with post Baseline Potential Clinical importance (PCI) value for clinical chemistry parameters: alanine amino transferase (ALT), aspartate aminotransferase (AST), gamma glutamyl transferase (GGT), total bilirubin and creatinine[4]

End point description:

Blood samples were collected from participants for analysis of following clinical chemistry parameters: ALT, AST, GGT, total bilirubin and creatinine. PCI ranges were <3 times the upper limit of normal (ULN), <34.2 Micromoles per liter (UMOL/L) for total bilirubin and <176.8 (UMOL/L) for creatinine. Only those parameters having any time post-Baseline PCI values were presented. Day 1 was considered as Baseline.

End point type	Primary

End point timeframe:

Up to 24 Weeks

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: No statistical analyses have been performed for this outcome measure.

End point values	Low dose ambrisentan	High dose ambrisentan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21[5]	20[6]		
Units: Participants				
ALT	0	0		
AST	0	0		
GGT	0	0		
Total bilirubin	1	0		
Creatinine	0	0		

Notes:

[5] - Safety Population

[6] - Safety Population

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants with post Baseline PCI value for hematology parameter: hemoglobin

End point title	Number of participants with post Baseline PCI value for hematology parameter: hemoglobin[7]

End point description:

Blood samples were collected from participants for analysis of following hematology parameters: hemoglobin. PCI ranges were Males: 98 to180 grams per liter (G/L), Females: 91 to 161 (G/L) for hemoglobin. Only those parameters having any time post-Baseline PCI values were presented. Day 1 was considered as Baseline.

End point type	Primary

End point timeframe:

Up to 24 Weeks

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: No statistical analyses have been performed for this outcome measure.

End point values	Low dose ambrisentan	High dose ambrisentan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21[8]	20[9]		
Units: Participants				
Reference high range	0	2		
Reference low range	1	0		

Notes:

[8] - Safety Population

[9] - Safety Population

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants with post Baseline PCI value for hematology parameter: hematocrit

End point title	Number of participants with post Baseline PCI value for hematology parameter: hematocrit[10]

End point description:

Blood samples were collected from participants for analysis of following hematology parameter: hematocrit. PCI ranges were males: <0.32 to >0.54, females: <0.29 to >0.506 proportion of red blood cells in blood for hematocrit. Only those parameters having any time post-Baseline PCI values were presented. Day 1 was considered as Baseline.

End point type	Primary

End point timeframe:

Up to 24 Weeks

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: No statistical analyses have been performed for this outcome measure.

End point values	Low dose ambrisentan	High dose ambrisentan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21[11]	20[12]		
Units: Participants				
Reference high range	0	2		
Reference low range	1	2		

Notes:

[11] - Safety Population

[12] - Safety Population

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants with post Baseline PCI value for hematology parameter: platelet count

End point title	Number of participants with post Baseline PCI value for hematology parameter: platelet count[13]

End point description:

Blood samples were collected from participants for analysis of following hematology parameter: platelet count. PCI ranges were 100 to 400 for Giga cells per liter platelet count. Only those parameters having any time post-Baseline PCI values were presented. Day 1 was considered as Baseline.

End point type	Primary

End point timeframe:

Up to 24 Weeks

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: No statistical analyses have been performed for this outcome measure.

End point values	Low dose ambrisentan	High dose ambrisentan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21[14]	20[15]		
Units: Participants				
Reference high range	0	0		
Reference low range	0	1		

Notes:

[14] - Safety Population

[15] - Safety Population

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants with abnormal value for physical examination parameter: liver size

End point title	Number of participants with abnormal value for physical examination parameter: liver size[16]

End point description:

Physical examination included measurement of liver size. Any abnormal enlargement or reduction in the size of the liver is reported.

End point type	Primary

End point timeframe:

Week 12 and 24

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: No statistical analyses have been performed for this outcome measure.

End point values	Low dose ambrisentan	High dose ambrisentan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21[17]	20[18]		
Units: Participants				
Week 12, Abnormal: Improved, n=20, 19	1	1		
Week 12, Abnormal: Worsened, n=20, 19	1	1		
Week 12, Abnormal: Unchanged, n=20, 19	1	0		
Week 24, Abnormal: Improved, n=19, 18	2	1		
Week 24, Abnormal: Worsened, n=19, 18	0	0		
Week 24, Abnormal: Unchanged, n=19, 18	0	0		

Notes:

[17] - Safety population. Participants with available data at the specified time points were analyzed.

[18] - Safety population. Participants with available data at the specified time points were analyzed.

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants with abnormal value for physical examination parameter: jugular venous pressure

End point title	Number of participants with abnormal value for physical examination parameter: jugular venous pressure[19]

End point description:

Physical examination of participants jugular venous pressure is measured.

End point type	Primary

End point timeframe:

Week 12 and 24

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: No statistical analyses have been performed for this outcome measure.

End point values	Low dose ambrisentan	High dose ambrisentan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21[20]	20[21]		
Units: Participants				
Week 12, Abnormal: Improved, n=20, 19	0	1		
Week 12, Abnormal: Worsened, n=20, 19	0	1		
Week 12, Abnormal: Unchanged, n=20, 19	0	3		
Week 24, Abnormal: Improved, n=19, 18	0	1		
Week 24, Abnormal: Worsened, n=19, 18	1	0		
Week 24, Abnormal: Unchanged, n=19, 18	0	4		

Notes:

[20] - Safety population. Participants with available data at the specified time points were analyzed.

[21] - Safety population. Participants with available data at the specified time points were analyzed.

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants with abnormal value for physical examination parameter: peripheral edema

End point title	Number of participants with abnormal value for physical examination parameter: peripheral edema[22]

End point description:

Physical examination of paricipants peripheral edema is measured. Day 1 was considered as Baseline.

End point type	Primary

End point timeframe:

Week 12 and 24

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: No statistical analyses have been performed for this outcome measure.

End point values	Low dose ambrisentan	High dose ambrisentan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21[23]	20[24]		
Units: Participants				
Week 12, Abnormal: Improved, n=20, 19	0	0		
Week 12, Abnormal: Worsened, n=20, 19	1	1		
Week 12, Abnormal: Unchanged, n=20, 19	0	1		
Week 24, Abnormal: Improved, n=19, 18	1	0		
Week 24, Abnormal: Worsened, n=19, 18	1	0		
Week 24, Abnormal: Unchanged, n=19, 18	0	0		

Notes:

[23] - Safety population. Participants with available data at the specified time points were analyzed.

[24] - Safety population. Participants with available data at the specified time points were analyzed.

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants with abnormal value for physical examination parameter: ascites

End point title	Number of participants with abnormal value for physical examination parameter: ascites[25]

End point description:

Physcial examination of paricipants ascites was measured. Day 1 was considered as Baseline.

End point type	Primary

End point timeframe:

Week 12 and 24

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: No statistical analyses have been performed for this outcome measure.

End point values	Low dose ambrisentan	High dose ambrisentan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21[26]	20[27]		
Units: Participants				
Week 12, Abnormal: Improved, n=20, 19	0	0		
Week 12, Abnormal: Worsened, n=20, 19	0	0		

Week 12, Abnormal: Unchanged, n=20, 19	0	0		
Week 24, Abnormal: Improved, n=19, 18	0	0		
Week 24, Abnormal: Worsened, n=19, 18	0	0		
Week 24, Abnormal: Unchanged, n=19, 18	0	0		

Notes:

[26] - Safety population. Participants with available data at the specified time points were analyzed.

[27] - Safety population. Participants with available data at the specified time points were analyzed.

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of physical examination parameter: saturated oxygen level

End point title	Percentage of physical examination parameter: saturated oxygen level[28]

End point description:

Physical examination of participants saturated oxygen level was measured. Day 1 was considered as Baseline.

End point type	Primary

End point timeframe:

Week 12 and 24

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: No statistical analyses have been performed for this outcome measure.

End point values	Low dose ambrisentan	High dose ambrisentan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21[29]	20[30]		
Units: Percentage of oxygen saturation				
arithmetic mean (standard deviation)				
Week 12, n=20, 18	96.9 (± 2.59)	96.9 (± 6.93)		
Week 24, n=19, 18	97.3 (± 1.85)	97.4 (± 1.92)		

Notes:

[29] - Safety population. Participants with available data at the specified time points were analyzed.

[30] - Safety population. Participants with available data at the specified time points were analyzed.

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants with post Baseline PCI value for vital signs parameter: systolic blood pressure (SBP) and diastolic blood pressure (DBP)

End point title	Number of participants with post Baseline PCI value for vital signs parameter: systolic blood pressure (SBP) and diastolic blood pressure (DBP)[31]

End point description:

SBP and DBP were measured in semi-supine position after 5 minutes rest for the participants at indicated time points. PCI ranges were <80 to >160 millimeters of mercury (mmHg) for SDP and <40 to >110 mmHg for DBP. Only those parameters having any time post-Baseline PCI values were presented. Day 1 was considered as Baseline.

End point type	Primary

End point timeframe:

Up to 24 Weeks

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: No statistical analyses have been performed for this outcome measure.

End point values	Low dose ambrisentan	High dose ambrisentan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21[32]	20[33]		
Units: Participants				
SBP, Reference range high	0	0		
SBP, Reference range low	1	2		
DBP, Reference range high	0	0		
DBP, Reference range low	0	0		

Notes:

[32] - Safety population

[33] - Safety population

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants with post Baseline PCI value for vital signs parameter: heart rate

End point title	Number of participants with post Baseline PCI value for vital signs parameter: heart rate[34]

End point description:

Heart rate was measured in semi-supine position after 5 minutes rest for the participants at indicated time points. PCI ranges were <50 to >120 beats per minute (beats/min). Only those parameters having any time post-Baseline PCI values were presented. Day 1 was considered as Baseline.

End point type	Primary

End point timeframe:

Up to 24 Weeks

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: No statistical analyses have been performed for this outcome measure.

End point values	Low dose ambrisentan	High dose ambrisentan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21[35]	20[36]		
Units: Participants				
Reference range high	2	2		
Reference range low	1	0		

Notes:

[35] - Safety population

[36] - Safety population

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants with post Baseline PCI value for vital signs parameter: weight

End point title	Number of participants with post Baseline PCI value for vital signs parameter: weight[37]

End point description:

Weight of the participants was measured. PCI ranges were <20 kilograms (kg) for weight. Only those parameters having any time post-Baseline PCI values were presented. Day 1 was considered as Baseline.

End point type	Primary

End point timeframe:

Up to 24 Weeks

Notes:

[37] - 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: No statistical analyses have been performed for this outcome measure.

End point values	Low dose ambrisentan	High dose ambrisentan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21[38]	20[39]		
Units: Participants				
Reference range high	0	0		
Reference range low	0	0		

Notes:

[38] - Safety population

[39] - Safety population

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline of pubertal development: Men- testicular volume (TV) at Weeks 12 and 24

End point title	Change from Baseline of pubertal development: Men- testicular volume (TV) at Weeks 12 and 24[40]

End point description:

Testicular volume was assessed by Prader's orchiodometer and the assessment was performed by a pediatric endocrinologist using the Tanner's criteria. Only those parameters having status - overall were presented. Day 1 was considered as Baseline. Change from Baseline was calculated by subtracting Baseline value from the specified time point value. Male participants with available data at the specified time points were analyzed.

End point type	Primary

End point timeframe:

Baseline, Week 12 and 24

Notes:

[40] - 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: No statistical analyses have been performed for this outcome measure.

End point values	Low dose ambrisentan	High dose ambrisentan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9[41]	5[42]		
Units: Milliliter				
arithmetic mean (standard deviation)				
Week 12, Right TV, n=7, 4	0.4 (± 1.27)	0.3 (± 0.50)		
Week 12, Left TV, n=8, 5	0.0 (± 0.53)	0.2 (± 0.45)		
Week 24, Right TV, n=6, 4	0.5 (± 1.38)	0.1 (± 0.25)		
Week 24, Left TV, n=7, 5	1.4 (± 2.76)	0.5 (± 1.50)		

Notes:

[41] - Safety population.

[42] - Safety population.

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in plasma endocrine parameter - Female : Follicle stimulating hormone (FSH) and Luteinizing hormone (LH) at Weeks 12 and 24

End point title	Change from Baseline in plasma endocrine parameter - Female : Follicle stimulating hormone (FSH) and Luteinizing hormone (LH) at Weeks 12 and 24[43]

End point description:

FSH and LH level of participants were measured. Only those parameters having status - overall were presented. Day 1 was considered as Baseline. Change from Baseline was calculated by subtracting Baseline value from the specified time point value. Female participants with available data at the specified time points were analyzed.

End point type	Primary

End point timeframe:

Baseline, Week 12 and 24

Notes:

[43] - 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: No statistical analyses have been performed for this outcome measure.

End point values	Low dose ambrisentan	High dose ambrisentan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12[44]	15[45]		
Units: International unit per Liter				
arithmetic mean (standard deviation)				
Week 12, FSH, n=11, 13	0.586 (± 1.412)	-0.023 (± 2.104)		
Week 24, FSH, n=10, 12	0.010 (± 1.390)	1.542 (± 2.518)		
Week 12, LH, n=11, 13	0.39 (± 3.117)	-0.28 (± 6.881)		
Week 24, LH, n=11, 13	-0.56 (± 1.192)	1.15 (± 6.806)		

Notes:

[44] - Safety population.

[45] - Safety population.

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in plasma endocrine parameter - Female : Inhibin B at Weeks 12 and 24

End point title	Change from Baseline in plasma endocrine parameter - Female : Inhibin B at Weeks 12 and 24[46]

End point description:

Inhibin B level of participants were measured. Only those parameters having status - overall were presented. Day 1 was considered as Baseline. Change from Baseline was calculated by subtracting Baseline value from the specified time point value. Female participants with available data at the specified time points were analyzed.

End point type	Primary

End point timeframe:

Baseline, Week 12 and 24

Notes:

[46] - 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: No statistical analyses have been performed for this outcome measure.

End point values	Low dose ambrisentan	High dose ambrisentan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12[47]	15[48]		
Units: Nanogram per liter				
arithmetic mean (standard deviation)				
Week 12, Right TV, n=9, 7	4.9 (± 10.03)	1.7 (± 33.70)		
Week 24, Left TV, n=9, 7	-5.2 (± 36.44)	16.0 (± 37.96)		

Notes:

[47] - Safety population.

[48] - Safety population.

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in plasma endocrine parameter - Female : Sex hormone binding globulin at Weeks 12 and 24

End point title	Change from Baseline in plasma endocrine parameter - Female : Sex hormone binding globulin at Weeks 12 and 24[49]

End point description:

Sex hormone binding globulin level of participants were measured. Only those parameters having status - overall were presented. Day 1 was considered as Baseline. Change from Baseline was calculated by subtracting Baseline value from the specified time point value. Female participants with available data at the specified time points were analyzed.

End point type	Primary

End point timeframe:

Baseline, Week 12 and 24

Notes:

[49] - 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: No statistical analyses have been performed for this outcome measure.

End point values	Low dose ambrisentan	High dose ambrisentan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12[50]	15[51]		
Units: Milliliter				
arithmetic mean (standard deviation)				
Week 12, Right TV, n=10, 9	1.3 (± 9.55)	7.4 (± 18.91)		
Week 24, Left TV, n=10, 8	-9.2 (± 13.62)	3.1 (± 14.21)		

Notes:

[50] - Safety population.

[51] - Safety population.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the 6 minutes walking distance (6MWD) test

End point title	Change from Baseline in the 6 minutes walking distance (6MWD) test

End point description:

Participant's 6MWD data has been presented into three categories as overall, with oxygen use and without oxygen use. Day 1 was considered as Baseline. Change from Baseline was calculated by subtracting Baseline value from the specified time point value. 99999 indicates that standard deviation could not be calculated for single participant. Intent-to-Treat (ITT) population consist of all randomized participants who received at least one dose of study drug.

End point type	Secondary

End point timeframe:

Baseline, Weeks 4, 8, 12, 16, 20 and 24

End point values	Low dose ambrisentan	High dose ambrisentan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21[52]	20[53]		
Units: Meters				
arithmetic mean (standard deviation)				
Week 4, Overall, n=21, 18	33.10 (± 66.979)	24.96 (± 71.254)		
Week 4, With oxygen use, n=2, 1	-16.00 (± 11.314)	85.20 (± 99999)		
Week 4, Without oxygen use, n=19, 17	38.27 (± 68.421)	21.41 (± 71.793)		
Week 8, Overall, n=20, 18	23.84 (± 65.154)	37.70 (± 74.339)		
Week 8, With oxygen use, n=2, 1	-16.00 (± 22.627)	81.10 (± 99999)		
Week 8, Without oxygen use, n=18, 17	28.26 (± 67.133)	35.15 (± 75.809)		
Week 12, Overall, n=19, 18	29.51 (± 79.657)	40.29 (± 69.137)		
Week 12, With oxygen use, n=2, 1	-1.00 (± 65.054)	75.40 (± 99999)		
Week 12, Without oxygen use, n=17, 17	33.09 (± 82.121)	38.22 (± 70.690)		

Week 16, Overall, n=19, 18	22.31 (± 88.832)	36.43 (± 78.220)		
Week 16, With oxygen use, n=2, 1	-21.00 (± 57.983)	65.40 (± 99999)		
Week 16, Without oxygen use, n=17, 17	27.41 (± 91.681)	34.73 (± 80.282)		
Week 20, Overall, n=19, 18	48.49 (± 90.645)	31.19 (± 71.209)		
Week 20, With oxygen use, n=3, 1	-0.33 (± 43.753)	73.20 (± 99999)		
Week 20, Without oxygen use, n=16, 17	57.64 (± 95.070)	28.72 (± 72.600)		
Week 24, Overall, n=18, 18	55.14 (± 102.182)	26.25 (± 62.011)		
Week 24, With oxygen use, n=3, 1	43.00 (± 53.395)	65.90 (± 99999)		
Week 24, Without oxygen use, n=15, 17	57.57 (± 110.605)	23.92 (± 63.100)		

Notes:

[52] - Intent-to-treat population. Participants with available data at specified time points were analyzed.

[53] - Intent-to-treat population. Participants with available data at specified time points were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to the first clinical worsening of pulmonary arterial hypertension (PAH)

End point title	Time to the first clinical worsening of pulmonary arterial hypertension (PAH)

End point description:

Time to clinical worsening of PAH is defined as the time from randomization to the first occurrence of death or placed for lung transplant, hospitalization due to PAH deterioration, addition or increased dose of other targeted PAH therapeutic agents like prostanoids and PDE-5 inhibitors) and/or atrial septostomy, other PAH related deterioration identified by increase in WHO functional class, deterioration in exercise testing and clinical signs or symptoms of right sided heart failure.

End point type	Secondary

End point timeframe:

Up to Week 24

End point values	Low dose ambrisentan	High dose ambrisentan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3[54]	3[55]		
Units: Days				
arithmetic mean (standard deviation)	77.3 (± 62.56)	71.7 (± 29.26)		

Notes:

[54] - Intent-to-treat population. Participants with available data at specified time points were analyzed.

[55] - Intent-to-treat population. Participants with available data at specified time points were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Subject Global Assessment to Week 24 using the SF-10 health survey for children

End point title	Change from Baseline in Subject Global Assessment to Week 24 using the SF-10 health survey for children

End point description:

Short-form 10 (SF-10) Health Survey for Children is a 10-item parent-completed health assessment that measures physical and psychosocial functioning for children ages five and over. Each item has either 4, 5 or 6 response choices with associated point systems. Two summary scores were calculated: a Physical Summary Score (PHS) and a Psychosocial Summary Score (PSS) with a range of 5 to 30 points for each 5-item score. This aggregated point score was then standardized and transformed to a norm-based scoring metric in accordance with the developer's algorithms using associated mean and standard deviation derived from 2006 sample data. This generated the final standardized norm-based scores for PHS (range -10.90 to 57.21) and for PSS (range 8.81 to 62.28), respectively. A higher value on each summary score indicates better functioning. Day 1 was considered as Baseline. Change from Baseline was calculated by subtracting Baseline value from the specified time point value.

End point type	Secondary

End point timeframe:

Baseline and Week 24

End point values	Low dose ambrisentan	High dose ambrisentan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21[56]	20[57]		
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Physical health summary, n=16, 15	0.194 (± 11.7733)	2.811 (± 13.1172)		
Psychosocial summary, n=16, 15	0.725 (± 8.6431)	0.412 (± 10.1331)		

Notes:

[56] - Intent-to-treat population. Participants with available data at specified time points were analyzed.

[57] - Intent-to-treat population. Participants with available data at specified time points were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in world health organization (WHO) functional class to Week 24

End point title	Change from baseline in world health organization (WHO) functional class to Week 24

End point description:

PAH was classified by WHO functional class (FC) at specific time points. There were four WHO FC grades based on severity of PAH symptoms (Class I=none, Class IV=most severe). Grades were then mapped to numeric scale, for which scores ranged from 1 to 4 (Class I=1 and Class IV=4). Score at Day 1 was considered as Baseline. Change from Baseline was calculated by subtracting Baseline value from the specified time point value.

End point type	Secondary

End point timeframe:

Baseline, Week 4, 8, 12, 16, 20 and 24

End point values	Low dose ambrisentan	High dose ambrisentan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21[58]	20[59]		
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Week 4, n=21, 19	-0.1 (± 0.36)	-0.1 (± 0.23)		
Week 8, n=20, 19	-0.1 (± 0.45)	-0.1 (± 0.40)		
Week 12, n=20, 19	-0.1 (± 0.45)	0.0 (± 0.58)		
Week 16, n=20, 18	-0.2 (± 0.49)	-0.2 (± 0.38)		
Week 20, n=19, 18	-0.2 (± 0.50)	-0.2 (± 0.38)		
Week 24, n=19, 18	-0.3 (± 0.56)	-0.2 (± 0.43)		

Notes:

[58] - Intent-to-treat population. Participants with available data at specified time points were analyzed.

[59] - Intent-to-treat population. Participants with available data at specified time points were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Ratio to Baseline in plasma N-terminal pro-B type natriuretic peptide (NT-Pro BNP) concentration at Week 24

End point title	Ratio to Baseline in plasma N-terminal pro-B type natriuretic peptide (NT-Pro BNP) concentration at Week 24

End point description:

NT-Pro BNP plasma concentrations were determined at specific time points. Geometric mean and SD logs has been presented. Day 1 was considered as Baseline. Ratio to Baseline is expressed as percentage change from Baseline. Change from Baseline was calculated by subtracting Baseline value from the specified time point value.

End point type	Secondary

End point timeframe:

Baseline, Week 12 and 24

End point values	Low dose ambrisentan	High dose ambrisentan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21[60]	20[61]		
Units: Percentage Change				
geometric mean (standard deviation)				
Week 12, n=19, 17	-15.93 (± 0.895)	-12.43 (± 0.862)		
Week 24, n=18, 17	-30.91 (± 0.851)	-28.25 (± 1.179)		

Notes:

[60] - Intent-to-treat population. Participants with available data at specified time points were analyzed.

[61] - Intent-to-treat population. Participants with available data at specified time points were analyzed.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

On-treatment serious adverse events (SAEs) and non serious AEs were collected from the start of study treatment up to 24 weeks

Adverse event reporting additional description:

Safety Population was used. Safety Population comprised of all randomized participants who received at least one dose of a study drug

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	High dose ambrisentan

Reporting group description:

Participants received ambrisentan high dose tablet either 5 mg, 7.5 mg or 10 mg orally once daily for 24 weeks.

Reporting group title	Low dose ambrisentan

Reporting group description:

Participants received ambrisentan low dose tablet either 2.5 mg or 5 mg orally once daily for 24 weeks.

Serious adverse events	High dose ambrisentan	Low dose ambrisentan	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 20 (10.00%)	6 / 21 (28.57%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events			
Cardiac disorders			
Cardiac failure acute			
subjects affected / exposed	1 / 20 (5.00%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Right ventricular failure			
subjects affected / exposed	1 / 20 (5.00%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Syncope			

subjects affected / exposed	0 / 20 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	0 / 20 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary hypertension			
subjects affected / exposed	0 / 20 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Device related infection			
subjects affected / exposed	1 / 20 (5.00%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 20 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Product issues			
Device breakage			
subjects affected / exposed	0 / 20 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	High dose ambrisentan	Low dose ambrisentan	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 20 (80.00%)	16 / 21 (76.19%)	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Face oedema			
subjects affected / exposed	2 / 20 (10.00%)	1 / 21 (4.76%)	
occurrences (all)	2	1	
Fatigue			
subjects affected / exposed	1 / 20 (5.00%)	1 / 21 (4.76%)	
occurrences (all)	1	1	
Pyrexia			
subjects affected / exposed	1 / 20 (5.00%)	2 / 21 (9.52%)	
occurrences (all)	2	2	
Oedema peripheral			
subjects affected / exposed	1 / 20 (5.00%)	2 / 21 (9.52%)	
occurrences (all)	1	2	
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	1 / 20 (5.00%)	1 / 21 (4.76%)	
occurrences (all)	1	1	
Nasal congestion			
subjects affected / exposed	2 / 20 (10.00%)	2 / 21 (9.52%)	
occurrences (all)	3	2	
Oropharyngeal pain			
subjects affected / exposed	1 / 20 (5.00%)	1 / 21 (4.76%)	
occurrences (all)	1	2	
Investigations			
International normalised ratio increased			
subjects affected / exposed	1 / 20 (5.00%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			

Joint injury			
subjects affected / exposed	1 / 20 (5.00%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Limb injury			
subjects affected / exposed	1 / 20 (5.00%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Toxicity to various agents			
subjects affected / exposed	1 / 20 (5.00%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Cyanosis			
subjects affected / exposed	1 / 20 (5.00%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Palpitations			
subjects affected / exposed	1 / 20 (5.00%)	1 / 21 (4.76%)	
occurrences (all)	1	1	
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 20 (5.00%)	1 / 21 (4.76%)	
occurrences (all)	1	1	
Headache			
subjects affected / exposed	6 / 20 (30.00%)	4 / 21 (19.05%)	
occurrences (all)	9	5	
Blood and lymphatic system disorders			
Heparin-induced thrombocytopenia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Lymphopenia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Neutropenia			
subjects affected / exposed	1 / 20 (5.00%)	1 / 21 (4.76%)	
occurrences (all)	1	1	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 20 (5.00%)	4 / 21 (19.05%)	
occurrences (all)	2	4	

Abdominal pain upper			
subjects affected / exposed	2 / 20 (10.00%)	3 / 21 (14.29%)	
occurrences (all)	4	3	
Diarrhoea			
subjects affected / exposed	0 / 20 (0.00%)	2 / 21 (9.52%)	
occurrences (all)	0	3	
Dry mouth			
subjects affected / exposed	1 / 20 (5.00%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Gastritis			
subjects affected / exposed	1 / 20 (5.00%)	1 / 21 (4.76%)	
occurrences (all)	1	1	
Nausea			
subjects affected / exposed	3 / 20 (15.00%)	4 / 21 (19.05%)	
occurrences (all)	3	5	
Vomiting			
subjects affected / exposed	0 / 20 (0.00%)	2 / 21 (9.52%)	
occurrences (all)	0	2	
Hepatobiliary disorders			
Hepatomegaly			
subjects affected / exposed	1 / 20 (5.00%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Dermatitis atopic			
subjects affected / exposed	1 / 20 (5.00%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Dermatitis contact			
subjects affected / exposed	1 / 20 (5.00%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Erythema			
subjects affected / exposed	2 / 20 (10.00%)	1 / 21 (4.76%)	
occurrences (all)	2	1	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 20 (10.00%)	1 / 21 (4.76%)	
occurrences (all)	2	1	

Myalgia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Neck pain			
subjects affected / exposed	1 / 20 (5.00%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Pain in extremity			
subjects affected / exposed	1 / 20 (5.00%)	2 / 21 (9.52%)	
occurrences (all)	1	3	
Infections and infestations			
Ear infection			
subjects affected / exposed	1 / 20 (5.00%)	1 / 21 (4.76%)	
occurrences (all)	1	2	
Gastroenteritis			
subjects affected / exposed	1 / 20 (5.00%)	2 / 21 (9.52%)	
occurrences (all)	1	3	
Gastroenteritis viral			
subjects affected / exposed	1 / 20 (5.00%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Laryngitis			
subjects affected / exposed	2 / 20 (10.00%)	0 / 21 (0.00%)	
occurrences (all)	2	0	
Nasopharyngitis			
subjects affected / exposed	2 / 20 (10.00%)	3 / 21 (14.29%)	
occurrences (all)	2	4	
Pharyngitis			
subjects affected / exposed	1 / 20 (5.00%)	2 / 21 (9.52%)	
occurrences (all)	1	3	
Pneumonia			
subjects affected / exposed	0 / 20 (0.00%)	2 / 21 (9.52%)	
occurrences (all)	0	3	
Respiratory tract infection			
subjects affected / exposed	1 / 20 (5.00%)	1 / 21 (4.76%)	
occurrences (all)	1	1	
Upper respiratory tract infection			

subjects affected / exposed	1 / 20 (5.00%)	3 / 21 (14.29%)	
occurrences (all)	1	4	
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 20 (5.00%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 21 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 June 2010	Amendment No. 1 • Clarify the inclusion criteria that existing drug treatment for pulmonary arterial hypertension (PAH) would continue unchanged throughout the study. • Clarify that two forms of contraception is required only for female participants of child bearing potential who are sexually active. • Expand the eligibility for the continuation study to all participants who participate in this study and in whom continued treatment with ambrisentan is desired. • Specify that participants will be given a diary card to collect information about dosing and days missed from school. • Remove references to "brain natriuretic peptide" and clarify that it is N-terminal pro-B-type Natriuretic Peptide that is being assessed. • Add more specific references for the Tanner development criteria. • Change the wording of the questions regarding days missed from school to make it clear that the total number of days missed includes the days missed because of PAH and that the days missed because of PAH are due to symptoms of PAH and do not include clinic visits. • Remove the requirement for an unblinded person to enter compliance data into InForm. • Allow the investigator to be unblinded to treatment for an individual patient once that participant has completed the study.
26 October 2010	Amendment No. 2 • To clarify that it is hepatitis B surface antigen, and not hepatitis B surface antibody, that is being assessed as part of the exclusion criteria. • Add the United States (US) Investigational New Drug (IND) number to the Sponsor Information Page and clarify that the medical monitor and Serious Adverse Events contact are the same person.
02 February 2011	Amendment No. 3 • Add oestrogen to the laboratory tests being performed on female participants at all times that pubertal development assessments are performed. • Remove testosterone from the laboratory tests being performed on female participants at all times that the pubertal development assessments are performed. • Change the storage requirements for the study medication to store below 30°C.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
11 July 2013	Global Enrolment Hold due to preclinical findings.	-

Notes:

Limitations and caveats

None reported