

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	v1	
This version publication date	24 August 2019	
First version publication date	24 August 2019	

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	
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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		

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	Safety, Efficacy	
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	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
Country: Number of subjects enrolled	Argentina: 6
Worldwide total number of subjects	41
EEA total number of subjects	15

Notes:

Subi	ects	enro	lled	ner	age	group
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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.

2 i 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
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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	

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

Number of participants with post Baseline PCI value for hematology parameter: hemoglobin ^[7]
 nematology parameter. Hemoglobin-

End point description:

Blood samples were collected from participants for analysis of following hematology parameters: hemoglobin. PCI ranges were Males: 98 to 180 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.

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	

[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	Drimary
Liid poilit type	[PI III di y

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.

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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.

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	

- [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 jug	ular 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	

[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 part parameter: ascites	icipants with abnormal value for physical examination
End point title	Number of participants with abnormal value for physical examination parameter: ascites ^[25]
End point description:	·
Physcial examination of paricip	ants 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.

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	

- [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			
Percentage of physical examination parameter: saturated oxygen level ^[28]			
End point description:	•		
Physical examination of participar Baseline.	nts saturated oxygen level was measured. Day 1 was considered as		
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)

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

[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

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	
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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
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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.

End naint tuna	Duine a m /
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.

End point values	Low dose ambrisentan	High dose ambrisentan	
Subject group type	Reporting group	Reporting group	
Number of subjects analysed	21 ^[41]	20 ^[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)	

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

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.

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	21 ^[44]	20 ^[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. Participants with available data at the specified time points were analyzed.
- [45] Safety population. Participants with available data at the specified time points were analyzed.

Statistical analyses

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.

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	21 ^[47]	20 ^[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. Participants with available data at the specified time points were analyzed.
- [48] Safety population. Participants with available data at the specified time points were analyzed.

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.

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.

End point values	Low dose ambrisentan	High dose ambrisentan	
Subject group type	Reporting group	Reporting group	
Number of subjects analysed	21 ^[50]	20 ^[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)	

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

Statistical analyses

No statistical analyses for this end point

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)	

- [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 (Items 1, 2a, 2b, 3, and 5) and psychosocial (Items 4, 6, 7, 8, and 9) functioning for children ages five and over. Each item has either 4, 5 or 6 response choices with associated point systems. An aggregated point score was generated across the 5 items within each summary score (range of 5 to 30 points for each 5-item score). This aggregated point score was then standardised and transformed to a norm-based scoring metric in accordance with the developer's guidelines. 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)	

- [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.

EU-CTR publication date: 24 August 2019

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
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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
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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	

Non-serious adverse events	High dose ambrisentan	Low dose ambrisentan	
Total subjects affected by non-serious	difficilitati	umbriserreari	
adverse events subjects affected / exposed	16 / 20 (80.00%)	16 / 21 (76.19%)	
General disorders and administration	10 / 20 (00:00 /0)	10 / 21 (70.1370)	
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 / 5 000/)	1 / 21 / 4 760/)	
	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	
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Limb injury			
subjects affected / exposed	1 / 20 (5.00%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Toxicity to various agents subjects affected / exposed		0 (01 (0 000)	
	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)			
occurrences (un)	1	1	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 20 (5.00%)	4 / 21 (19.05%)	
occurrences (all)	2	4	

Abdominal pain upper	ı		
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 / 5 000/)	0 / 31 /0 000/)	
	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 / 20 (10.0070)	1 / 21 (4./070)	
	2	1	

Myalgia subjects affected / exposed	1 / 20 /5 000/)	0 / 21 /0 000/)	
occurrences (all)	1 / 20 (5.00%)	0 / 21 (0.00%) 0	
Pain in extremity			
subjects affected / exposed	1 / 20 (5.00%)	2 / 21 (9.52%)	
occurrences (all)	1	3	
Neck pain			
subjects affected / exposed	1 / 20 (5.00%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Infections and infestations	1		
Ear infection			
subjects affected / exposed	1 / 20 (5.00%)	1 / 21 (4.76%)	
occurrences (all)	1	2	
Gastroenteritis viral			
subjects affected / exposed	1 / 20 (5.00%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Gastroenteritis			
subjects affected / exposed	1 / 20 (5.00%)	2 / 21 (9.52%)	
occurrences (all)	1	3	
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	
Pneumonia			
subjects affected / exposed	0 / 20 (0.00%)	2 / 21 (9.52%)	
occurrences (all)	0	3	
Pharyngitis			
subjects affected / exposed	1 / 20 (5.00%)	2 / 21 (9.52%)	
occurrences (all)	1	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 occurrences (all)	1 / 20 (5.00%) 1	3 / 21 (14.29%) 4	
Viral upper respiratory tract infection subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1	0 / 21 (0.00%) 0	
Metabolism and nutrition disorders Hypokalaemia subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1	0 / 21 (0.00%) 0	

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