Clinical trial results:
An open-label, long term extension study for treatment of pulmonary arterial hypertension in paediatric patients aged 8 years up to 18 years who have participated in AMB112529 and in whom continued treatment with ambrisentan is desired

Summary

EudraCT number	2010-021572-29
Trial protocol	GR DE NL ES HU IT FR
Global end of trial date	09 June 2022

Results information

Result version number	v1 (current)
This version publication date	21 December 2022
First version publication date	21 December 2022

Trial information

Trial identification

Sponsor protocol code	114588

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?	No
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 August 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 June 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is the safety and tolerability of ambrisentan in the paediatric PAH population

Protection of trial subjects:

Not Applicable

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 June 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 5
Country: Number of subjects enrolled	France: 3
Country: Number of subjects enrolled	Germany: 2
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: 7
Country: Number of subjects enrolled	Spain: 2
Country: Number of subjects enrolled	United States: 7
Worldwide total number of subjects	38
EEA total number of subjects	14

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	14

Adolescents (12-17 years)	24
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This was an open label, long term extension of study AMB112529 (NCT01342952) which evaluated safety and tolerability of ambrisentan in the pediatric (aged 8 years up to 18 years) Pulmonary Arterial Hypertension (PAH) population.

Pre-assignment

Screening details:

A total of 38 participants were enrolled in this study.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Ambrisentan 2.5 mg (ITT)

Arm description:

Participants received 2.5 milligrams (mg) dose of ambrisentan orally in tablet/s form once daily. The Intent-to-Treat (ITT) Population consisted of all participants who received at least 1 dose of study drug. Participants were considered as belonging to ITT treatment group at the start of study AMB114588.

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:

Ambrisentan was administered as oral tablet

Arm title	Ambrisentan 5 mg (ITT)

Arm description:

Participants received 5 mg dose of ambrisenten orally in tablet/s form once daily. The ITT Population consisted of all participants who received at least 1 dose of study drug. Participants were considered as belonging to ITT treatment group at the start of study AMB114588.

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:

Ambrisentan was administered as oral tablet

Arm title	Ambrisentan 7.5 mg (ITT)

Arm description:

Participants received 7.5 mg dose of ambrisentan orally in tablet/s form once daily. The ITT Population consisted of all participants who received at least 1 dose of study drug. Participants were considered as belonging to ITT treatment group at the start of study AMB114588.

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:

Ambrisentan was administered as oral tablet

Arm title	Ambrisentan 10 mg (ITT)

Arm description:

Participants received 10 mg dose of ambrisentan orally in tablet/s form once daily. The ITT Population consisted of all participants who received at least 1 dose of study drug. Participants were considered as belonging to ITT treatment group at the start of study AMB114588.

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:

Ambrisentan was administered as oral tablet

Number of subjects in period 1	Ambrisentan 2.5 mg (ITT)	Ambrisentan 5 mg (ITT)	Ambrisentan 7.5 mg (ITT)
Started	9	19	5
Intent-to-Treat Population	9	19	5
Completed	5	8	3
Not completed	4	11	2
Adverse event, serious fatal	-	5	1
Consent withdrawn by subject	1	1	-
Physician decision	3	3	1
Lost to follow-up	-	2	-

Number of subjects in period 1	Ambrisentan 10 mg (ITT)
Started	5
Intent-to-Treat Population	5
Completed	5
Not completed	0
Adverse event, serious fatal	-
Consent withdrawn by subject	-
Physician decision	-
Lost to follow-up	-

Baseline characteristics

Reporting groups	
Reporting group title	Ambrisentan 2.5 mg (ITT)
Reporting group description:	
Participants received 2.5 milligrams (mg) dose of ambrisentan orally in tablet/s form once daily. The Intent-to-Treat (ITT) Population consisted of all participants who received at least 1 dose of study drug. Participants were considered as belonging to ITT treatment group at the start of study AMB114588.	
Reporting group title	Ambrisentan 5 mg (ITT)
Reporting group description:	
Participants received 5 mg dose of ambrisenten orally in tablet/s form once daily. The ITT Population consisted of all participants who received at least 1 dose of study drug. Participants were considered as belonging to ITT treatment group at the start of study AMB114588.	
Reporting group title	Ambrisentan 7.5 mg (ITT)
Reporting group description:	
Participants received 7.5 mg dose of ambrisentan orally in tablet/s form once daily. The ITT Population consisted of all participants who received at least 1 dose of study drug. Participants were considered as belonging to ITT treatment group at the start of study AMB114588.	
Reporting group title	Ambrisentan 10 mg (ITT)
Reporting group description:	
Participants received 10 mg dose of ambrisentan orally in tablet/s form once daily. The ITT Population consisted of all participants who received at least 1 dose of study drug. Participants were considered as belonging to ITT treatment group at the start of study AMB114588.	

Reporting group values	Ambrisentan 2.5 mg (ITT)	Ambrisentan 5 mg (ITT)	Ambrisentan 7.5 mg (ITT)
Number of subjects	9	19	5
Age categorical			
Baseline characteristics were presented for ITT Population, consisted of all participants who received at least 1 dose of study drug. Participants were considered as belonging to ITT population at the start of study AMB114588			
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)	6	7	1
Adolescents (12-17 years)	3	12	4
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous			
Baseline characteristics were presented for ITT Population, consisted of all participants who received at least 1 dose of study drug. Participants were considered as belonging to ITT population at the start of study AMB114588			
Units: years			
arithmetic mean	9.7	11.9	12.6
standard deviation	± 2.29	± 2.57	± 2.61
Sex: Female, Male			
Baseline characteristics were presented for ITT Population, consisted of all participants who received at least 1 dose of study drug. Participants were considered as belonging to ITT population at the start of study AMB114588			

Units: Participants			
Female	7	9	4
Male	2	10	1
Race/Ethnicity, Customized			
Baseline characteristics were presented for ITT Population, consisted of all participants who received at least 1 dose of study drug. Participants were considered as belonging to ITT population at the start of study AMB114588			
Units: Subjects			
African American/African Heritage	1	1	0
American Indian or Alaskan Native	1	0	0
Asian - Central/South Asian Heritage	0	1	0
Asian - East Asian Heritage	0	1	0
Asian - Japanese Heritage	3	2	0
Asian - South East Asian Heritage	0	0	1
White - White/Caucasian/European Heritage	4	14	4

Reporting group values	Ambrisentan 10 mg (ITT)	Total	
Number of subjects	5	38	
Age categorical			
Baseline characteristics were presented for ITT Population, consisted of all participants who received at least 1 dose of study drug. Participants were considered as belonging to ITT population at the start of study AMB114588			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	14	
Adolescents (12-17 years)	5	24	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Age Continuous			
Baseline characteristics were presented for ITT Population, consisted of all participants who received at least 1 dose of study drug. Participants were considered as belonging to ITT population at the start of study AMB114588			
Units: years			
arithmetic mean	15.2		
standard deviation	± 0.84	-	
Sex: Female, Male			
Baseline characteristics were presented for ITT Population, consisted of all participants who received at least 1 dose of study drug. Participants were considered as belonging to ITT population at the start of study AMB114588			
Units: Participants			
Female	5	25	
Male	0	13	
Race/Ethnicity, Customized			
Baseline characteristics were presented for ITT Population, consisted of all participants who received at least 1 dose of study drug. Participants were considered as belonging to ITT population at the start of study AMB114588			
Units: Subjects			

African American/African Heritage	0	2	
American Indian or Alaskan Native	0	1	
Asian - Central/South Asian Heritage	0	1	
Asian - East Asian Heritage	0	1	
Asian - Japanese Heritage	0	5	
Asian - South East Asian Heritage	0	1	
White - White/Caucasian/European Heritage	5	27	

Subject analysis sets

Subject analysis set title	Ambrisentan 2.5 mg (Safety)
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants received ambrisentan 2.5 mg tablet/s orally once daily. The Safety Population consisted of all participants who received at least 1 dose of study drug. Participants were considered as belonging to the treatment group according to the highest dose received in the extension study (AMB114588).

Subject analysis set title	Ambrisentan 5 mg (Safety)
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants received ambrisentan 5 mg tablet/s orally once daily. The Safety Population consisted of all participants who received at least 1 dose of study drug. Participants were considered as belonging to the treatment group according to the highest dose received in the extension study (AMB114588).

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Subject analysis set title	Ambrisentan 5 mg (Safety)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

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Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received ambrisentan 10 mg tablet/s orally once daily. The Safety Population consisted of all participants who received at least 1 dose of study drug. Participants were considered as belonging to the treatment group according to the highest dose received in the extension study (AMB114588).

Reporting group values	Ambrisentan 2.5 mg (Safety)	Ambrisentan 5 mg (Safety)	Ambrisentan 7.5 mg (Safety)
Number of subjects	4	16	6
Age categorical			
Baseline characteristics were presented for ITT Population, consisted of all participants who received at least 1 dose of study drug. Participants were considered as belonging to ITT population at the start of study AMB114588			
Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age Continuous			
Baseline characteristics were presented for ITT Population, consisted of all participants who received at least 1 dose of study drug. Participants were considered as belonging to ITT population at the start of study AMB114588			
Units: years arithmetic mean standard deviation	±	±	±
Sex: Female, Male			
Baseline characteristics were presented for ITT Population, consisted of all participants who received at least 1 dose of study drug. Participants were considered as belonging to ITT population at the start of study AMB114588			
Units: Participants			
Female Male			
Race/Ethnicity, Customized			
Baseline characteristics were presented for ITT Population, consisted of all participants who received at least 1 dose of study drug. Participants were considered as belonging to ITT population at the start of study AMB114588			
Units: Subjects			
African American/African Heritage American Indian or Alaskan Native Asian - Central/South Asian Heritage Asian - East Asian Heritage Asian - Japanese Heritage Asian - South East Asian Heritage White - White/Caucasian/European Heritage			

Reporting group values	Ambrisentan 10 mg (Safety)	Ambrisentan 5 mg (Safety)	Ambrisentan 7.5 mg (Safety)
Number of subjects	12	10	5

Age categorical			
Baseline characteristics were presented for ITT Population, consisted of all participants who received at least 1 dose of study drug. Participants were considered as belonging to ITT population at the start of study AMB114588			
Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age Continuous			
Baseline characteristics were presented for ITT Population, consisted of all participants who received at least 1 dose of study drug. Participants were considered as belonging to ITT population at the start of study AMB114588			
Units: years			
arithmetic mean			
standard deviation	±	±	±
Sex: Female, Male			
Baseline characteristics were presented for ITT Population, consisted of all participants who received at least 1 dose of study drug. Participants were considered as belonging to ITT population at the start of study AMB114588			
Units: Participants			
Female Male			
Race/Ethnicity, Customized			
Baseline characteristics were presented for ITT Population, consisted of all participants who received at least 1 dose of study drug. Participants were considered as belonging to ITT population at the start of study AMB114588			
Units: Subjects			
African American/African Heritage American Indian or Alaskan Native Asian - Central/South Asian Heritage Asian - East Asian Heritage Asian - Japanese Heritage Asian - South East Asian Heritage White - White/Caucasian/European Heritage			

Reporting group values	Ambrisentan 10 mg (Safety)	Ambrisentan 2.5 mg (Safety)	Ambrisentan 5 mg (Safety)
Number of subjects	9	3	9
Age categorical			
Baseline characteristics were presented for ITT Population, consisted of all participants who received at least 1 dose of study drug. Participants were considered as belonging to ITT population at the start of study AMB114588			
Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days)			

Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age Continuous			
Baseline characteristics were presented for ITT Population, consisted of all participants who received at least 1 dose of study drug. Participants were considered as belonging to ITT population at the start of study AMB114588			
Units: years arithmetic mean standard deviation	±	±	±
Sex: Female, Male			
Baseline characteristics were presented for ITT Population, consisted of all participants who received at least 1 dose of study drug. Participants were considered as belonging to ITT population at the start of study AMB114588			
Units: Participants			
Female Male			
Race/Ethnicity, Customized			
Baseline characteristics were presented for ITT Population, consisted of all participants who received at least 1 dose of study drug. Participants were considered as belonging to ITT population at the start of study AMB114588			
Units: Subjects			
African American/African Heritage American Indian or Alaskan Native Asian - Central/South Asian Heritage Asian - East Asian Heritage Asian - Japanese Heritage Asian - South East Asian Heritage White - White/Caucasian/European Heritage			

Reporting group values	Ambrisentan 10 mg (Safety)	Ambrisentan 5 mg (Safety)	Ambrisentan 7.5 mg (Safety)
Number of subjects	10	6	3
Age categorical			
Baseline characteristics were presented for ITT Population, consisted of all participants who received at least 1 dose of study drug. Participants were considered as belonging to ITT population at the start of study AMB114588			
Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			

Age Continuous			
Baseline characteristics were presented for ITT Population, consisted of all participants who received at least 1 dose of study drug. Participants were considered as belonging to ITT population at the start of study AMB114588			
Units: years arithmetic mean standard deviation	± ±	± ±	± ±
Sex: Female, Male			
Baseline characteristics were presented for ITT Population, consisted of all participants who received at least 1 dose of study drug. Participants were considered as belonging to ITT population at the start of study AMB114588			
Units: Participants			
Female Male			
Race/Ethnicity, Customized			
Baseline characteristics were presented for ITT Population, consisted of all participants who received at least 1 dose of study drug. Participants were considered as belonging to ITT population at the start of study AMB114588			
Units: Subjects			
African American/African Heritage American Indian or Alaskan Native Asian - Central/South Asian Heritage Asian - East Asian Heritage Asian - Japanese Heritage Asian - South East Asian Heritage White - White/Caucasian/European Heritage			

Reporting group values	Ambrisentan 10 mg (Safety)	Ambrisentan 2.5 mg (Safety)	Ambrisentan 5 mg (Safety)
Number of subjects	7	1	3
Age categorical			
Baseline characteristics were presented for ITT Population, consisted of all participants who received at least 1 dose of study drug. Participants were considered as belonging to ITT population at the start of study AMB114588			
Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age Continuous			
Baseline characteristics were presented for ITT Population, consisted of all participants who received at least 1 dose of study drug. Participants were considered as belonging to ITT population at the start of study AMB114588			
Units: years arithmetic mean standard deviation	± ±	± ±	± ±

Sex: Female, Male			
Baseline characteristics were presented for ITT Population, consisted of all participants who received at least 1 dose of study drug. Participants were considered as belonging to ITT population at the start of study AMB114588			
Units: Participants			
Female Male			
Race/Ethnicity, Customized			
Baseline characteristics were presented for ITT Population, consisted of all participants who received at least 1 dose of study drug. Participants were considered as belonging to ITT population at the start of study AMB114588			
Units: Subjects			
African American/African Heritage American Indian or Alaskan Native Asian - Central/South Asian Heritage Asian - East Asian Heritage Asian - Japanese Heritage Asian - South East Asian Heritage White - White/Caucasian/European Heritage			

Reporting group values	Ambrisentan 7.5 mg (Safety)	Ambrisentan 10 mg (Safety)	Ambrisentan 2.5 mg (Safety)
Number of subjects	1	3	2
Age categorical			
Baseline characteristics were presented for ITT Population, consisted of all participants who received at least 1 dose of study drug. Participants were considered as belonging to ITT population at the start of study AMB114588			
Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age Continuous			
Baseline characteristics were presented for ITT Population, consisted of all participants who received at least 1 dose of study drug. Participants were considered as belonging to ITT population at the start of study AMB114588			
Units: years			
arithmetic mean			0.0
standard deviation	±	±	± 11.31
Sex: Female, Male			
Baseline characteristics were presented for ITT Population, consisted of all participants who received at least 1 dose of study drug. Participants were considered as belonging to ITT population at the start of study AMB114588			
Units: Participants			
Female Male			

Race/Ethnicity, Customized			
Baseline characteristics were presented for ITT Population, consisted of all participants who received at least 1 dose of study drug. Participants were considered as belonging to ITT population at the start of study AMB114588			
Units: Subjects			
African American/African Heritage American Indian or Alaskan Native Asian - Central/South Asian Heritage Asian - East Asian Heritage Asian - Japanese Heritage Asian - South East Asian Heritage White - White/Caucasian/European Heritage			

Reporting group values	Ambrisentan 5 mg (Safety)	Ambrisentan 10 mg (Safety)	Ambrisentan 5 mg (Safety)
Number of subjects	5	4	2
Age categorical			
Baseline characteristics were presented for ITT Population, consisted of all participants who received at least 1 dose of study drug. Participants were considered as belonging to ITT population at the start of study AMB114588			
Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age Continuous			
Baseline characteristics were presented for ITT Population, consisted of all participants who received at least 1 dose of study drug. Participants were considered as belonging to ITT population at the start of study AMB114588			
Units: years			
arithmetic mean	14.0		
standard deviation	± 67.48	±	±
Sex: Female, Male			
Baseline characteristics were presented for ITT Population, consisted of all participants who received at least 1 dose of study drug. Participants were considered as belonging to ITT population at the start of study AMB114588			
Units: Participants			
Female Male			
Race/Ethnicity, Customized			
Baseline characteristics were presented for ITT Population, consisted of all participants who received at least 1 dose of study drug. Participants were considered as belonging to ITT population at the start of study AMB114588			
Units: Subjects			
African American/African Heritage American Indian or Alaskan Native Asian - Central/South Asian Heritage			

Asian - East Asian Heritage			
Asian - Japanese Heritage			
Asian - South East Asian Heritage			
White - White/Caucasian/European Heritage			

Reporting group values	Ambrisentan 10 mg (Safety)	Ambrisentan 7.5 mg (Safety)	Ambrisentan 10 mg (Safety)
Number of subjects	2	2	5
Age categorical			
Baseline characteristics were presented for ITT Population, consisted of all participants who received at least 1 dose of study drug. Participants were considered as belonging to ITT population at the start of study AMB114588			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age Continuous			
Baseline characteristics were presented for ITT Population, consisted of all participants who received at least 1 dose of study drug. Participants were considered as belonging to ITT population at the start of study AMB114588			
Units: years			
arithmetic mean			
standard deviation	±	±	±
Sex: Female, Male			
Baseline characteristics were presented for ITT Population, consisted of all participants who received at least 1 dose of study drug. Participants were considered as belonging to ITT population at the start of study AMB114588			
Units: Participants			
Female			
Male			
Race/Ethnicity, Customized			
Baseline characteristics were presented for ITT Population, consisted of all participants who received at least 1 dose of study drug. Participants were considered as belonging to ITT population at the start of study AMB114588			
Units: Subjects			
African American/African Heritage			
American Indian or Alaskan Native			
Asian - Central/South Asian Heritage			
Asian - East Asian Heritage			
Asian - Japanese Heritage			
Asian - South East Asian Heritage			
White - White/Caucasian/European Heritage			

Reporting group values	Ambrisentan 5 mg (Safety)	Ambrisentan 5 mg (Safety)	Ambrisentan 10 mg (Safety)
Number of subjects	4	1	1

Age categorical			
Baseline characteristics were presented for ITT Population, consisted of all participants who received at least 1 dose of study drug. Participants were considered as belonging to ITT population at the start of study AMB114588			
Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age Continuous			
Baseline characteristics were presented for ITT Population, consisted of all participants who received at least 1 dose of study drug. Participants were considered as belonging to ITT population at the start of study AMB114588			
Units: years			
arithmetic mean			
standard deviation	±	±	±
Sex: Female, Male			
Baseline characteristics were presented for ITT Population, consisted of all participants who received at least 1 dose of study drug. Participants were considered as belonging to ITT population at the start of study AMB114588			
Units: Participants			
Female Male			
Race/Ethnicity, Customized			
Baseline characteristics were presented for ITT Population, consisted of all participants who received at least 1 dose of study drug. Participants were considered as belonging to ITT population at the start of study AMB114588			
Units: Subjects			
African American/African Heritage American Indian or Alaskan Native Asian - Central/South Asian Heritage Asian - East Asian Heritage Asian - Japanese Heritage Asian - South East Asian Heritage White - White/Caucasian/European Heritage			

End points

End points reporting groups

Reporting group title	Ambrisentan 2.5 mg (ITT)
Reporting group description:	
Participants received 2.5 milligrams (mg) dose of ambrisentan orally in tablet/s form once daily. The Intent-to-Treat (ITT) Population consisted of all participants who received at least 1 dose of study drug. Participants were considered as belonging to ITT treatment group at the start of study AMB114588.	
Reporting group title	Ambrisentan 5 mg (ITT)
Reporting group description:	
Participants received 5 mg dose of ambrisenten orally in tablet/s form once daily. The ITT Population consisted of all participants who received at least 1 dose of study drug. Participants were considered as belonging to ITT treatment group at the start of study AMB114588.	
Reporting group title	Ambrisentan 7.5 mg (ITT)
Reporting group description:	
Participants received 7.5 mg dose of ambrisentan orally in tablet/s form once daily. The ITT Population consisted of all participants who received at least 1 dose of study drug. Participants were considered as belonging to ITT treatment group at the start of study AMB114588.	
Reporting group title	Ambrisentan 10 mg (ITT)
Reporting group description:	
Participants received 10 mg dose of ambrisentan orally in tablet/s form once daily. The ITT Population consisted of all participants who received at least 1 dose of study drug. Participants were considered as belonging to ITT treatment group at the start of study AMB114588.	
Subject analysis set title	Ambrisentan 2.5 mg (Safety)
Subject analysis set type	Safety analysis
Subject analysis set description:	
Participants received ambrisentan 2.5 mg tablet/s orally once daily. The Safety Population consisted of all participants who received at least 1 dose of study drug. Participants were considered as belonging to the treatment group according to the highest dose received in the extension study (AMB114588).	
Subject analysis set title	Ambrisentan 5 mg (Safety)
Subject analysis set type	Safety analysis
Subject analysis set description:	
Participants received ambrisentan 5 mg tablet/s orally once daily. The Safety Population consisted of all participants who received at least 1 dose of study drug. Participants were considered as belonging to the treatment group according to the highest dose received in the extension study (AMB114588).	
Subject analysis set title	Ambrisentan 7.5 mg (Safety)
Subject analysis set type	Safety analysis
Subject analysis set description:	
Participants received ambrisentan 7.5 mg tablet/s orally once daily. The Safety Population consisted of all participants who received at least 1 dose of study drug. Participants were considered as belonging to the treatment group according to the highest dose received in the extension study (AMB114588).	
Subject analysis set title	Ambrisentan 10 mg (Safety)
Subject analysis set type	Safety analysis
Subject analysis set description:	
Participants received ambrisentan 10 mg tablet/s orally once daily. The Safety Population consisted of all participants who received at least 1 dose of study drug. Participants were considered as belonging to the treatment group according to the highest dose received in the extension study (AMB114588).	
Subject analysis set title	Ambrisentan 5 mg (Safety)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants received ambrisentan 5 mg tablet/s orally once daily. The Safety Population consisted of all participants who received at least 1 dose of study drug. Participants were considered as belonging to the treatment group according to the highest dose received in the extension study (AMB114588).	
Subject analysis set title	Ambrisentan 7.5 mg (Safety)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received ambrisentan 7.5 mg tablet/s orally once daily. The Safety Population consisted of all participants who received at least 1 dose of study drug. Participants were considered as belonging to the treatment group according to the highest dose received in the extension study (AMB114588).

Subject analysis set title	Ambrisentan 10 mg (Safety)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received ambrisentan 10 mg tablet/s orally once daily. The Safety Population consisted of all participants who received at least 1 dose of study drug. Participants were considered as belonging to the treatment group according to the highest dose received in the extension study (AMB114588).

Subject analysis set title	Ambrisentan 2.5 mg (Safety)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received ambrisentan 2.5 mg tablet/s orally once daily. The Safety Population consisted of all participants who received at least 1 dose of study drug. Participants were considered as belonging to the treatment group according to the highest dose received in the extension study (AMB114588).

Subject analysis set title	Ambrisentan 5 mg (Safety)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received ambrisentan 5 mg tablet/s orally once daily. The Safety Population consisted of all participants who received at least 1 dose of study drug. Participants were considered as belonging to the treatment group according to the highest dose received in the extension study (AMB114588).

Subject analysis set title	Ambrisentan 10 mg (Safety)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received ambrisentan 10 mg tablet/s orally once daily. The Safety Population consisted of all participants who received at least 1 dose of study drug. Participants were considered as belonging to the treatment group according to the highest dose received in the extension study (AMB114588).

Subject analysis set title	Ambrisentan 5 mg (Safety)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received ambrisentan 5 mg tablet/s orally once daily. The Safety Population consisted of all participants who received at least 1 dose of study drug. Participants were considered as belonging to the treatment group according to the highest dose received in the extension study (AMB114588).

Subject analysis set title	Ambrisentan 7.5 mg (Safety)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received ambrisentan 7.5 mg tablet/s orally once daily. The Safety Population consisted of all participants who received at least 1 dose of study drug. Participants were considered as belonging to the treatment group according to the highest dose received in the extension study (AMB114588).

Subject analysis set title	Ambrisentan 10 mg (Safety)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received ambrisentan 10 mg tablet/s orally once daily. The Safety Population consisted of all participants who received at least 1 dose of study drug. Participants were considered as belonging to the treatment group according to the highest dose received in the extension study (AMB114588).

Subject analysis set title	Ambrisentan 2.5 mg (Safety)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received ambrisentan 2.5 mg tablet/s orally once daily. The Safety Population consisted of all participants who received at least 1 dose of study drug. Participants were considered as belonging to the treatment group according to the highest dose received in the extension study (AMB114588).

Subject analysis set title	Ambrisentan 5 mg (Safety)
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Subject analysis set description:

Participants received ambrisentan 5 mg tablet/s orally once daily. The Safety Population consisted of all participants who received at least 1 dose of study drug. Participants were considered as belonging to the treatment group according to the highest dose received in the extension study (AMB114588).

Subject analysis set title	Ambrisentan 7.5 mg (Safety)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received ambrisentan 7.5 mg tablet/s orally once daily. The Safety Population consisted of all participants who received at least 1 dose of study drug. Participants were considered as belonging to the treatment group according to the highest dose received in the extension study (AMB114588).

Subject analysis set title	Ambrisentan 10 mg (Safety)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received ambrisentan 10 mg tablet/s orally once daily. The Safety Population consisted of all participants who received at least 1 dose of study drug. Participants were considered as belonging to the treatment group according to the highest dose received in the extension study (AMB114588).

Subject analysis set title	Ambrisentan 2.5 mg (Safety)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received ambrisentan 2.5 mg tablet/s orally once daily. The Safety Population consisted of all participants who received at least 1 dose of study drug. Participants were considered as belonging to the treatment group according to the highest dose received in the extension study (AMB114588).

Subject analysis set title	Ambrisentan 5 mg (Safety)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received ambrisentan 5 mg tablet/s orally once daily. The Safety Population consisted of all participants who received at least 1 dose of study drug. Participants were considered as belonging to the treatment group according to the highest dose received in the extension study (AMB114588).

Subject analysis set title	Ambrisentan 10 mg (Safety)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received ambrisentan 10 mg tablet/s orally once daily. The Safety Population consisted of all participants who received at least 1 dose of study drug. Participants were considered as belonging to the treatment group according to the highest dose received in the extension study (AMB114588).

Subject analysis set title	Ambrisentan 5 mg (Safety)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received ambrisentan 5 mg tablet/s orally once daily. The Safety Population consisted of all participants who received at least 1 dose of study drug. Participants were considered as belonging to the treatment group according to the highest dose received in the extension study (AMB114588).

Subject analysis set title	Ambrisentan 10 mg (Safety)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received ambrisentan 10 mg tablet/s orally once daily. The Safety Population consisted of all participants who received at least 1 dose of study drug. Participants were considered as belonging to the treatment group according to the highest dose received in the extension study (AMB114588).

Subject analysis set title	Ambrisentan 7.5 mg (Safety)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received ambrisentan 7.5 mg tablet/s orally once daily. The Safety Population consisted of all participants who received at least 1 dose of study drug. Participants were considered as belonging to the treatment group according to the highest dose received in the extension study (AMB114588).

Subject analysis set title	Ambrisentan 10 mg (Safety)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received ambrisentan 10 mg tablet/s orally once daily. The Safety Population consisted of all participants who received at least 1 dose of study drug. Participants were considered as belonging to the treatment group according to the highest dose received in the extension study (AMB114588).

Subject analysis set title	Ambrisentan 5 mg (Safety)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received ambrisentan 5 mg tablet/s orally once daily. The Safety Population consisted of all participants who received at least 1 dose of study drug. Participants were considered as belonging to the treatment group according to the highest dose received in the extension study (AMB114588).

Subject analysis set title	Ambrisentan 5 mg (Safety)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received ambrisentan 5 mg tablet/s orally once daily. The Safety Population consisted of all participants who received at least 1 dose of study drug. Participants were considered as belonging to the treatment group according to the highest dose received in the extension study (AMB114588).

Subject analysis set title	Ambrisentan 10 mg (Safety)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received ambrisentan 10 mg tablet/s orally once daily. The Safety Population consisted of all participants who received at least 1 dose of study drug. Participants were considered as belonging to the treatment group according to the highest dose received in the extension study (AMB114588).

Primary: Number of Participants With Non-serious Treatment-emergent Adverse Events (Non-STEAEs) and Serious Treatment-emergent Adverse Events (STEAEs)

End point title	Number of Participants With Non-serious Treatment-emergent Adverse Events (Non-STEAEs) and Serious Treatment-emergent Adverse Events (STEAEs)[1]

End point description:

AE was defined as any untoward medical occurrence in participant/clinical investigation participant,temporally associated with use of medicinal product,whether/not considered related to medicinal product.SAE was defined as any untoward medical occurrence that,at any dose:results in death,is life threatening,requires hospitalization/prolongation of existing hospitalization,results in disability or incapacity, or is congenital anomaly or birth defect,important medical events that may not immediately life threatening or result in death or hospitalization but may jeopardize participant or may require medical or surgical intervention as per medical or scientific judgement or associated with drug-induced liver injury.TEAE is any event that was not present prior to initiation of study treatment/any event already present that worsens in either intensity/frequency following exposure to study treatment.Safety Population consisted of all participants who received at least 1 dose of study drug.

End point type	Primary

End point timeframe:

Up to 10 years and 11 months

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There are no statistical data to report

End point values	Ambrisentan 2.5 mg (Safety)	Ambrisentan 5 mg (Safety)	Ambrisentan 7.5 mg (Safety)	Ambrisentan 10 mg (Safety)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	4[2]	16[3]	6[4]	12[5]
Units: Participants				
Non-STEAEs	3	13	5	10
STEAEs	2	7	4	8

Notes:

[2] - Safety Population

[3] - Safety Population

[4] - Safety Population

[5] - Safety Population

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Liver function parameters: Alanine Amino Transferase (ALT), Aspartate Amino Transferase (AST), Gamma Glutamyl Transferase (GGT), Total Bilirubin

End point title	Change from Baseline in Liver function parameters: Alanine Amino Transferase (ALT), Aspartate Amino Transferase (AST), Gamma Glutamyl Transferase (GGT), Total Bilirubin[6]

End point description:

Blood samples were collected from participants for analysis of following clinical chemistry parameters: ALT, AST, GGT, total bilirubin. Baseline was the last value recorded prior to start of study treatment from AMB112529. Change from Baseline was calculated by subtracting the Baseline value from the end of study post-dose visit value. Only those participants with available data at the specified time points were analyzed.

End point type	Primary

End point timeframe:

Baseline (Day 1) and up to 10 years and 11 months

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There are no statistical data to report

End point values	Ambrisentan 2.5 mg (Safety)	Ambrisentan 5 mg (Safety)	Ambrisentan 7.5 mg (Safety)	Ambrisentan 10 mg (Safety)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	4[7]	10[8]	5[9]	9[10]
Units: Millimoles per liter				
arithmetic mean (standard deviation)				
ALT	-7.5 (± 12.56)	-1.0 (± 8.64)	0.8 (± 4.09)	4.0 (± 7.42)
AST	-11.8 (± 6.29)	-5.6 (± 7.23)	-1.0 (± 2.55)	-2.1 (± 8.13)
GGT	-0.5 (± 15.00)	-7.0 (± 10.45)	-0.8 (± 8.44)	-4.6 (± 28.30)
Total bilirubin	-5.3 (± 12.47)	-4.0 (± 3.30)	-2.8 (± 6.06)	3.1 (± 8.45)

Notes:

[7] - Safety Population

[8] - Safety Population

[9] - Safety Population

[10] - Safety Population

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Chemistry parameters: Calcium, Chloride, Carbon dioxide (CO2) content, Glucose, Potassium, Magnesium, Sodium, Phosphorus inorganic, Blood Urea Nitrogen (BUN)

End point title	Change from Baseline in Chemistry parameters: Calcium, Chloride, Carbon dioxide (CO2) content, Glucose, Potassium, Magnesium, Sodium, Phosphorus inorganic, Blood Urea Nitrogen (BUN)[11]

End point description:

Blood samples were collected from participants for analysis of following clinical chemistry parameters: Calcium, chloride, CO2 content, glucose, potassium, magnesium, sodium, phosphorus inorganic, and BUN. Baseline was the last value recorded prior to start of study treatment from AMB112529. Change from Baseline was calculated by subtracting the Baseline value from the end of study post-dose visit value. Only those participants with available data at the specified time points were analyzed.

End point type	Primary

End point timeframe:

Baseline (Day 1) and up to 10 years and 11 months

Notes:

[11] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There are no statistical data to report

End point values	Ambrisentan 5 mg (Safety)	Ambrisentan 7.5 mg (Safety)	Ambrisentan 10 mg (Safety)	Ambrisentan 2.5 mg (Safety)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	10[12]	5[13]	9[14]	3[15]
Units: Millimoles per liter				
arithmetic mean (standard deviation)				
Calcium	-0.054 (± 0.0779)	0.028 (± 0.0630)	-0.060 (± 0.1075)	-0.150 (± 0.1769)
Chloride	2.6 (± 1.65)	0.4 (± 3.44)	-0.6 (± 2.96)	1.7 (± 5.13)
CO2 content	2.2 (± 1.87)	0.2 (± 3.70)	0.0 (± 1.80)	-0.3 (± 2.89)
Glucose	-0.150 (± 1.1414)	0.120 (± 0.5541)	0.478 (± 0.9107)	0.167 (± 0.4163)
Potassium	-0.07 (± 0.337)	-0.02 (± 0.148)	-0.12 (± 0.327)	-0.30 (± 0.529)
Magnesium	-0.062 (± 0.0898)	0.028 (± 0.0683)	0.012 (± 0.0716)	-0.100 (± 0.0872)
Sodium	1.0 (± 1.63)	-0.2 (± 0.84)	0.7 (± 1.87)	2.7 (± 1.15)
Phosphorus inorganic	-0.159 (± 0.3055)	-0.212 (± 0.3440)	-0.108 (± 0.2408)	-0.340 (± 0.1311)
BUN	-0.51 (± 1.649)	-0.14 (± 1.274)	0.33 (± 1.507)	-0.10 (± 1.808)

Notes:

[12] - Safety Population

[13] - Safety Population

[14] - Safety Population

[15] - Safety Population

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Chemistry parameters: Alkaline Phosphatase (ALP), Creatine kinase (CK), Lactate Dehydrogenase (LDH)

End point title	Change from Baseline in Chemistry parameters: Alkaline Phosphatase (ALP), Creatine kinase (CK), Lactate Dehydrogenase (LDH)[16]

End point description:

Blood samples were collected from participants for analysis of following clinical chemistry parameters: ALP, CK, LDH. Baseline was the last value recorded prior to start of study treatment from AMB112529. Change from Baseline was calculated by subtracting the Baseline value from the end of study post-dose visit value. Only those participants with available data at the specified time points were analyzed.

End point type	Primary

End point timeframe:

Baseline (Day 1) and up to 10 years and 11 months

Notes:

[16] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There are no statistical data to report

End point values	Ambrisentan 5 mg (Safety)	Ambrisentan 7.5 mg (Safety)	Ambrisentan 10 mg (Safety)	Ambrisentan 2.5 mg (Safety)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	10[17]	5[18]	9[19]	3[20]
Units: International units per Liter				
arithmetic mean (standard deviation)				
ALP	-109.5 (± 71.51)	-148.8 (± 151.78)	-135.6 (± 97.33)	-77.7 (± 57.01)
CK	4.0 (± 100.83)	46.6 (± 89.55)	-9.7 (± 13.96)	-18.7 (± 23.07)
LDH	-48.9 (± 71.64)	-12.8 (± 22.58)	-28.3 (± 37.23)	-40.3 (± 45.54)

Notes:

[17] - Safety Population

[18] - Safety Population

[19] - Safety Population

[20] - Safety Population

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Chemistry parameters: Creatinine, Uric acid

End point title	Change from Baseline in Chemistry parameters: Creatinine, Uric acid[21]

End point description:

Blood samples were collected from participants for analysis of following clinical chemistry parameters: Creatinine, uric acid. Baseline was the last value recorded prior to start of study treatment from AMB112529. Change from Baseline was calculated by subtracting the Baseline value from the end of study post-dose visit value. Only those participants with available data at the specified time points were analyzed.

End point type	Primary

End point timeframe:

Baseline (Day 1) and up to 10 years and 11 months

Notes:

[21] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: There are no statistical data to report

End point values	Ambrisentan 5 mg (Safety)	Ambrisentan 7.5 mg (Safety)	Ambrisentan 10 mg (Safety)	Ambrisentan 2.5 mg (Safety)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	10[22]	5[23]	9[24]	3[25]
Units: Micromoles per liter				
arithmetic mean (standard deviation)				
Creatinine	8.16 (± 9.602)	10.26 (± 8.008)	19.31 (± 14.698)	6.27 (± 19.775)
Uric acid	-83.60 (± 90.103)	-45.40 (± 77.584)	21.22 (± 79.330)	-64.67 (± 119.169)

Notes:

[22] - Safety Population

[23] - Safety Population

[24] - Safety Population

[25] - Safety Population

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Chemistry parameters: Albumin, Total protein

End point title	Change from Baseline in Chemistry parameters: Albumin, Total protein[26]

End point description:

Blood samples were collected from participants for analysis of following clinical chemistry parameters: Albumin, total protein. Baseline was the last value recorded prior to start of study treatment from AMB112529. Change from Baseline was calculated by subtracting the Baseline value from the end of study post-dose visit value. Only those participants with available data at the specified time points were analyzed.

End point type	Primary

End point timeframe:

Baseline (Day 1) and up to 10 years and 11 months

Notes:

[26] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There are no statistical data to report

End point values	Ambrisentan 5 mg (Safety)	Ambrisentan 7.5 mg (Safety)	Ambrisentan 10 mg (Safety)	Ambrisentan 2.5 mg (Safety)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	10[27]	5[28]	9[29]	3[30]
Units: Grams per liter				
arithmetic mean (standard deviation)				
Albumin	-1.2 (± 3.16)	1.6 (± 1.14)	-2.0 (± 4.42)	-3.3 (± 4.04)
Total protein	-3.4 (± 4.93)	3.0 (± 5.24)	-3.0 (± 7.33)	-3.7 (± 4.51)

Notes:

[27] - Safety Population

[28] - Safety Population

[29] - Safety Population

[30] - Safety Population

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Hematology parameters: Hemoglobin and Mean Corpuscle Hemoglobin Concentration (MCHC)

End point title	Change from Baseline in Hematology parameters: Hemoglobin and Mean Corpuscle Hemoglobin Concentration (MCHC)[31]

End point description:

Blood samples were collected from participants for analysis of following hematology parameters: Hemoglobin and MCHC. Baseline was the last value recorded prior to start of study treatment from AMB112529. Change from Baseline was calculated by subtracting the Baseline value from the end of study post-dose visit value. Only those participants with available data at the specified time points were analyzed.

End point type	Primary

End point timeframe:

Baseline (Day 1) and up to 10 years and 11 months

Notes:

[31] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There are no statistical data to report

End point values	Ambrisentan 7.5 mg (Safety)	Ambrisentan 10 mg (Safety)	Ambrisentan 2.5 mg (Safety)	Ambrisentan 5 mg (Safety)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	5[32]	9[33]	3[34]	9[35]
Units: Grams per Liter				
arithmetic mean (standard deviation)				
Hemoglobin	0.8 (± 9.71)	1.3 (± 20.12)	-23.0 (± 38.63)	-4.7 (± 16.15)
MCHC	-6.0 (± 12.98)	-1.1 (± 11.72)	-9.3 (± 16.01)	-12.4 (± 17.31)

Notes:

[32] - Safety Population

[33] - Safety Population

[34] - Safety Population

[35] - Safety Population

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Hematology parameters: Hematocrit

End point title	Change from Baseline in Hematology parameters:

End point description:

Blood samples were collected from participants for analysis of following hematology parameters: Hematocrit. Baseline was the last value recorded prior to start of study treatment from AMB112529. Change from Baseline was calculated by subtracting the Baseline value from the end of study post-dose visit value. Only those participants with available data at the specified time points were analyzed.

End point type	Primary

End point timeframe:

Baseline (Day 1) and up to 10 years and 11 months

Notes:

[36] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There are no statistical data to report

End point values	Ambrisentan 7.5 mg (Safety)	Ambrisentan 10 mg (Safety)	Ambrisentan 2.5 mg (Safety)	Ambrisentan 5 mg (Safety)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	5[37]	9[38]	3[39]	9[40]
Units: Proportion of red blood cells in blood				
arithmetic mean (standard deviation)	0.0100 (± 0.02884)	0.0040 (± 0.06572)	-0.0610 (± 0.10235)	-0.0004 (± 0.04543)

Notes:

[37] - Safety Population

[38] - Safety Population

[39] - Safety Population

[40] - Safety Population

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Hematology parameters: Basophils, Eosinophils, Lymphocytes, Monocytes, Total neutrophils, White Blood Cells (WBC), Platelet count

End point title	Change from Baseline in Hematology parameters: Basophils, Eosinophils, Lymphocytes, Monocytes, Total neutrophils, White Blood Cells (WBC), Platelet count[41]

End point description:

Blood samples were collected from participants for analysis of following hematology parameters: Basophils, eosinophils, lymphocytes, monocytes, total neutrophils, WBC, platelet count. Baseline was the last value recorded prior to start of study treatment from AMB112529. Change from Baseline was calculated by subtracting the Baseline value from the end of study post-dose visit value. Only those participants with available data at the specified time points were analyzed (represented by n=X in category titles).

End point type	Primary

End point timeframe:

Baseline (Day 1) and up to 10 years and 11 months

Notes:

[41] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There are no statistical data to report

End point values	Ambrisentan 7.5 mg (Safety)	Ambrisentan 10 mg (Safety)	Ambrisentan 2.5 mg (Safety)	Ambrisentan 5 mg (Safety)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	5[42]	9[43]	3[44]	9[45]
Units: Giga cells per Liter				
arithmetic mean (standard deviation)				
Basophils, n=3, 9, 5, 9	-0.006 (± 0.0152)	-0.002 (± 0.0148)	-0.007 (± 0.0153)	0.019 (± 0.0417)
Eosinophils, n=3, 9, 5, 9	-0.026 (± 0.0602)	0.009 (± 0.0746)	-0.210 (± 0.4139)	0.034 (± 0.1096)
Lymphocytes, n=3, 9, 5, 9	-0.152 (± 0.6937)	-0.394 (± 1.1063)	-1.107 (± 0.7310)	-0.329 (± 1.1373)
Monocytes, n=3, 9, 5, 9	-0.006 (± 0.1635)	0.037 (± 0.1986)	-0.013 (± 0.1550)	0.040 (± 0.1273)
Total neutrophils, n= 3, 9, 5, 9	0.412 (± 0.6278)	0.524 (± 2.0030)	0.677 (± 1.9014)	-0.974 (± 1.2239)
WBC, n=3, 9, 5, 9	0.22 (± 0.421)	0.18 (± 2.787)	-0.67 (± 2.616)	-1.22 (± 2.072)
Platelet count, n=3, 9, 5, 7	-9.2 (± 30.87)	-0.4 (± 64.78)	-34.0 (± 27.18)	-29.3 (± 50.03)

Notes:

[42] - Safety Population

[43] - Safety Population

[44] - Safety Population

[45] - Safety Population

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Hematology parameter: Mean Corpuscle Hemoglobin

End point title	Change from Baseline in Hematology parameter: Mean

	Corpuscle Hemoglobin[46]

End point description:

Blood samples were collected from participants for analysis of following hematology parameter: Mean Corpuscle Hemoglobin. Baseline was the last value recorded prior to start of study treatment from AMB112529. Change from Baseline was calculated by subtracting the Baseline value from the end of study post-dose visit value. Only those participants with available data at the specified time points were analyzed.

End point type	Primary

End point timeframe:

Baseline (Day 1) and up to 10 years and 11 months

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: There are no statistical data to report

End point values	Ambrisentan 7.5 mg (Safety)	Ambrisentan 10 mg (Safety)	Ambrisentan 2.5 mg (Safety)	Ambrisentan 5 mg (Safety)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	5[47]	9[48]	3[49]	9[50]
Units: Picograms				
arithmetic mean (standard deviation)	-0.70 (± 1.512)	0.11 (± 1.981)	-1.70 (± 3.315)	-1.46 (± 2.823)

Notes:

[47] - Safety Population

[48] - Safety Population

[49] - Safety Population

[50] - Safety Population

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Hematology parameter: Mean Corpuscle Volume

End point title	Change from Baseline in Hematology parameter: Mean Corpuscle Volume[51]

End point description:

Blood samples were collected from participants for analysis of following hematology parameter: Mean Corpuscle Volume. Baseline was the last value recorded prior to start of study treatment from AMB112529. Change from Baseline was calculated by subtracting the Baseline value from the end of study post-dose visit value. Only those participants with available data at the specified time points were analyzed.

End point type	Primary

End point timeframe:

Baseline (Day 1) and up to 10 years and 11 months

Notes:

[51] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There are no statistical data to report

End point values	Ambrisentan 7.5 mg (Safety)	Ambrisentan 10 mg (Safety)	Ambrisentan 2.5 mg (Safety)	Ambrisentan 5 mg (Safety)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	5[52]	9[53]	3[54]	9[55]
Units: Femtoliters				
arithmetic mean (standard deviation)	-0.8 (± 2.68)	0.8 (± 5.61)	-2.3 (± 6.66)	-1.0 (± 5.52)

Notes:

[52] - Safety Population

[53] - Safety Population

[54] - Safety Population

[55] - Safety Population

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Hematology parameters: Red Blood Cell count, Reticulocytes

End point title	Change from Baseline in Hematology parameters: Red Blood Cell count, Reticulocytes[56]

End point description:

Blood samples were collected from participants for analysis of following hematology parameters: Red Blood Cell count, reticulocytes. Baseline was the last value recorded prior to start of study treatment from AMB112529. Change from Baseline was calculated by subtracting the Baseline value from the end of study post-dose visit value. Only those participants with available data at the specified time points were analyzed.

End point type	Primary

End point timeframe:

Baseline (Day 1) and up to 10 years and 11 months

Notes:

[56] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: There are no statistical data to report

End point values	Ambrisentan 7.5 mg (Safety)	Ambrisentan 10 mg (Safety)	Ambrisentan 2.5 mg (Safety)	Ambrisentan 5 mg (Safety)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	5[57]	9[58]	3[59]	9[60]
Units: Trillion cells per liter				
arithmetic mean (standard deviation)				
Red Blood Cell count	0.14 (± 0.251)	0.00 (± 0.497)	-0.57 (± 0.862)	0.07 (± 0.387)
Reticulocytes	0.00906 (± 0.013265)	0.01843 (± 0.041832)	0.01427 (± 0.024625)	-0.00816 (± 0.043615)

Notes:

[57] - Safety Population

[58] - Safety Population

[59] - Safety Population

[60] - Safety Population

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants with abnormal values for physical examination parameter: Liver size

End point title	Number of participants with abnormal values for physical examination parameter: Liver size[61]

End point description:

Physical examination included measurement of liver size. Any abnormal enlargement or reduction in the size of the liver is reported. Liver size was assessed as normal or abnormal. Data for abnormal (improved, worsened and unchanged) liver size is presented. End of study visit data is presented. Only those participants with available data at the specified time points were analyzed.

End point type	Primary

End point timeframe:

Up to 10 years and 11 months

Notes:

[61] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There are no statistical data to report

End point values	Ambrisentan 2.5 mg (Safety)	Ambrisentan 5 mg (Safety)	Ambrisentan 7.5 mg (Safety)	Ambrisentan 10 mg (Safety)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	4[62]	10[63]	5[64]	10[65]
Units: Participants				
Liver Size: Abnormal: Improved	0	0	0	0
Liver Size: Abnormal: Worsened	0	0	0	0
Liver Size: Abnormal: Unchanged	0	0	0	2

Notes:

[62] - Safety Population

[63] - Safety Population

[64] - Safety Population

[65] - Safety Population

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants with abnormal values for physical examination parameter: Jugular Venous Pressure

End point title	Number of participants with abnormal values for physical examination parameter: Jugular Venous Pressure[66]

End point description:

Physical examination included measurement of Jugular venous pressure. Jugular venous pressure was assessed as normal or abnormal. Data for abnormal (improved, worsened and unchanged) jugular venous pressure is presented. End of study visit data is presented. Only those participants with available data at the specified time points were analyzed.

End point type	Primary

End point timeframe:

Up to 10 years and 11 months

Notes:

[66] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There are no statistical data to report

End point values	Ambrisentan 2.5 mg (Safety)	Ambrisentan 5 mg (Safety)	Ambrisentan 7.5 mg (Safety)	Ambrisentan 10 mg (Safety)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	4[67]	10[68]	5[69]	10[70]
Units: Participants				
Jugular Venous Pressure: Abnormal: Improved	0	0	0	0
Jugular Venous Pressure: Abnormal: Worsened	0	0	0	0
Jugular Venous Pressure: Abnormal: Unchanged	0	0	0	2

Notes:

[67] - Safety Population

[68] - Safety Population

[69] - Safety Population

[70] - Safety Population

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants with abnormal values for physical examination parameters: Ascites

End point title	Number of participants with abnormal values for physical examination parameters: Ascites[71]

End point description:

Physical examination included measurement of ascites. Ascites were assessed as present or absent. Data for ascites present with improved, worsened and unchanged is presented. End of study visit data is presented. Only those participants with available data at the specified time points were analyzed.

End point type	Primary

End point timeframe:

Up to 10 years and 11 months

Notes:

[71] - 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: here are no statistical data to report

End point values	Ambrisentan 2.5 mg (Safety)	Ambrisentan 5 mg (Safety)	Ambrisentan 7.5 mg (Safety)	Ambrisentan 10 mg (Safety)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	4[72]	10[73]	5[74]	10[75]
Units: Participants				
Ascites: Present: Improved	0	0	0	0
Ascites: Present: Worsened	0	0	0	0
Ascites: Present: Unchanged	0	0	0	2

Notes:

[72] - Safety Population

[73] - Safety Population

[74] - Safety Population

[75] - Safety Population

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants with abnormal values for physical examination parameter: Peripheral edema

End point title	Number of participants with abnormal values for physical examination parameter: Peripheral edema[76]

End point description:

Physical examination included measurement of peripheral edema. Peripheral edema were assessed as present or absent. Data for peripheral edema present with improved, worsened and unchanged is presented. End of study visit data is presented. Only those participants with available data at the specified time points were analyzed.

End point type	Primary

End point timeframe:

Up to 10 years and 11 months

Notes:

[76] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There are no statistical data to report

End point values	Ambrisentan 2.5 mg (Safety)	Ambrisentan 5 mg (Safety)	Ambrisentan 7.5 mg (Safety)	Ambrisentan 10 mg (Safety)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	4[77]	10[78]	5[79]	10[80]
Units: Participants				
Peripheral edema: Present: Improved	0	0	0	0
Peripheral edema: Present: Worsened	0	0	0	0
Peripheral edema: Present: Unchanged	0	0	0	0

Notes:

[77] - Safety Population

[78] - Safety Population

[79] - Safety Population

[80] - Safety Population

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Saturated Oxygen Level (Physical Examination Parameter)

End point title	Percentage of Saturated Oxygen Level (Physical Examination Parameter)[81]

End point description:

Physical examination included measurement of saturated oxygen. End of study visit data is presented. Only those participants with available data at the specified time points were analyzed.

End point type	Primary

End point timeframe:

Up to 10 years and 11 months

Notes:

[81] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There are no statistical data to report

End point values	Ambrisentan 2.5 mg (Safety)	Ambrisentan 5 mg (Safety)	Ambrisentan 7.5 mg (Safety)	Ambrisentan 10 mg (Safety)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	4[82]	10[83]	5[84]	10[85]
Units: Percentage of oxygen saturation				
arithmetic mean (standard deviation)	95.5 (± 4.20)	96.8 (± 2.04)	97.4 (± 1.34)	96.9 (± 1.97)

Notes:

[82] - Safety Population

[83] - Safety Population

[84] - Safety Population

[85] - Safety Population

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in vital signs parameter: Systolic blood pressure (SBP) and Diastolic blood pressure (DBP)

End point title	Change from Baseline in vital signs parameter: Systolic blood pressure (SBP) and Diastolic blood pressure (DBP)[86]

End point description:

SBP and DBP was measured for the participants at indicated time points. Baseline was the last value recorded prior to start of study treatment from AMB112529. Change from Baseline was calculated by subtracting the Baseline value from the end of study post-dose visit value. Only those participants with available data at the specified time points were analyzed.

End point type	Primary

End point timeframe:

Baseline (Day 1) and up to 10 years and 11 months

Notes:

[86] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There are no statistical data to report

End point values	Ambrisentan 2.5 mg (Safety)	Ambrisentan 5 mg (Safety)	Ambrisentan 7.5 mg (Safety)	Ambrisentan 10 mg (Safety)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	4[87]	10[88]	5[89]	10[90]
Units: Millimeters of mercury				
arithmetic mean (standard deviation)				
SBP	16.3 (± 16.38)	8.4 (± 17.99)	1.2 (± 18.63)	8.5 (± 12.22)
DBP	1.5 (± 5.80)	2.3 (± 12.70)	3.6 (± 16.96)	2.1 (± 9.67)

Notes:

[87] - Safety Population

[88] - Safety Population

[89] - Safety Population

[90] - Safety Population

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in vital signs parameter: Heart rate

End point title	Change from Baseline in vital signs parameter: Heart rate[91]

End point description:

Heart rate was measured for the participants at indicated time points. Baseline was the last value recorded prior to start of study treatment from AMB112529. Change from Baseline was calculated by subtracting the Baseline value from the end of study post-dose visit value. Only those participants with available data at the specified time points were analyzed.

End point type	Primary

End point timeframe:

Baseline (Day 1) and up to 10 years and 11 months

Notes:

[91] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There are no statistical data to report

End point values	Ambrisentan 2.5 mg (Safety)	Ambrisentan 5 mg (Safety)	Ambrisentan 7.5 mg (Safety)	Ambrisentan 10 mg (Safety)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	4[92]	10[93]	5[94]	10[95]
Units: Beats per minute				
arithmetic mean (standard deviation)	-9.0 (± 13.44)	-4.0 (± 8.08)	-3.8 (± 11.50)	-6.0 (± 15.06)

Notes:

[92] - Safety Population

[93] - Safety Population

[94] - Safety Population

[95] - Safety Population

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in vital signs parameter: Weight

End point title	Change from Baseline in vital signs parameter: Weight[96]

End point description:

Weight was measured for the participants at indicated time points. Baseline was the last value recorded prior to start of study treatment from AMB112529. Change from Baseline was calculated by subtracting the Baseline value from the end of study post-dose visit value. Only those participants with available data at the specified time points were analyzed.

End point type	Primary

End point timeframe:

Baseline (Day 1) and up to 10 years and 11 months

Notes:

[96] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There are no statistical data to report

End point values	Ambrisentan 2.5 mg (Safety)	Ambrisentan 5 mg (Safety)	Ambrisentan 7.5 mg (Safety)	Ambrisentan 10 mg (Safety)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	4[97]	10[98]	5[99]	10[100]
Units: Kilograms				
arithmetic mean (standard deviation)	17.43 (± 12.695)	10.73 (± 8.628)	7.12 (± 5.346)	12.17 (± 16.300)

Notes:

[97] - Safety Population

[98] - Safety Population

[99] - Safety Population

[100] - Safety Population

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Vital Sign Parameter: Height

End point title	Change from Baseline in Vital Sign Parameter: Height[101]

End point description:

Height was measured for the participants at indicated time points. Baseline was the last value recorded prior to start of study treatment from AMB112529. Change from Baseline was calculated by subtracting the Baseline value from the end of study post-dose visit value. Only those participants with available data at the specified time points were analyzed.

End point type	Primary

End point timeframe:

Baseline (Day 1) and up to 10 years and 11 months

Notes:

[101] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There are no statistical data to report

End point values	Ambrisentan 2.5 mg (Safety)	Ambrisentan 5 mg (Safety)	Ambrisentan 7.5 mg (Safety)	Ambrisentan 10 mg (Safety)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	4[102]	10[103]	5[104]	10[105]
Units: Centimeters				
arithmetic mean (standard deviation)	25.3 (± 19.99)	9.9 (± 9.92)	7.2 (± 9.47)	12.1 (± 17.55)

Notes:

[102] - Safety Population

[103] - Safety Population

[104] - Safety Population

[105] - Safety Population

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Vital Sign Parameter: Body mass index

End point title	Change from Baseline in Vital Sign Parameter: Body mass index[106]

End point description:

Body mass index was measured for the participants at indicated time points. Body mass index was calculated as weight in kilograms (kg) divided by the square of their height in meters (m^2). Baseline was the last value recorded prior to start of study treatment from AMB112529. Change from Baseline was calculated by subtracting the Baseline value from the end of study post-dose visit value. Only those participants with available data at the specified time points were analyzed.

End point type	Primary

End point timeframe:

Baseline (Day 1) and up to 10 years and 11 months

Notes:

[106] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There are no statistical data to report

End point values	Ambrisentan 2.5 mg (Safety)	Ambrisentan 5 mg (Safety)	Ambrisentan 7.5 mg (Safety)	Ambrisentan 10 mg (Safety)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	4[107]	10[108]	5[109]	10[110]
Units: Kilogram per meter square				
arithmetic mean (standard deviation)	2.65 (± 2.195)	2.45 (± 1.828)	1.52 (± 1.633)	1.99 (± 2.642)

Notes:

[107] - Safety Population

[108] - Safety Population

[109] - Safety Population

[110] - Safety Population

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Vital Sign Parameter: Body surface area

End point title	Change from Baseline in Vital Sign Parameter: Body surface area[111]

End point description:

Body surface area was measured for the participants at indicated time points. Baseline was the last value recorded prior to start of study treatment from AMB112529. Change from Baseline was calculated by subtracting the Baseline value from the end of study post-dose visit value. Only those participants with available data at the specified time points were analyzed.

End point type	Primary

End point timeframe:

Baseline (Day 1) and up to 10 years and 11 months

Notes:

[111] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There are no statistical data to report

End point values	Ambrisentan 2.5 mg (Safety)	Ambrisentan 5 mg (Safety)	Ambrisentan 7.5 mg (Safety)	Ambrisentan 10 mg (Safety)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	4[112]	10[113]	5[114]	10[115]
Units: Meter square				
arithmetic mean (standard deviation)	0.398 (± 0.3024)	0.207 (± 0.1744)	0.144 (± 0.1254)	0.236 (± 0.3163)

Notes:

[112] - Safety Population

[113] - Safety Population

[114] - Safety Population

[115] - Safety Population

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants with abnormal electrocardiogram (ECG) findings

End point title	Number of participants with abnormal electrocardiogram (ECG) findings[116]

End point description:

12-lead ECG was measured in a semi-supine position using an automated ECG machine. Abnormal findings were categorized as clinically significant (CS) and not clinically significant (NCS). Data for any time till end of study were presented. Only those participants with available data at the specified time points were analyzed.

End point type	Primary

End point timeframe:

Up to 10 years and 11 months

Notes:

[116] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There are no statistical data to report

End point values	Ambrisentan 2.5 mg (Safety)	Ambrisentan 5 mg (Safety)	Ambrisentan 7.5 mg (Safety)	Ambrisentan 10 mg (Safety)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	4[117]	16[118]	6[119]	12[120]
Units: Participants				
Abnormal, not clinically significant	4	14	3	9
Abnormal, clinically significant	0	2	1	3

Notes:

[117] - Safety Population

[118] - Safety Population

[119] - Safety Population

[120] - Safety Population

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Plasma Endocrine Parameters - Female: Follicle Stimulating Hormone (FSH) and Luteinizing Hormone (LH) at End of study

End point title	Change from Baseline in Plasma Endocrine Parameters - Female: Follicle Stimulating Hormone (FSH) and Luteinizing Hormone (LH) at End of study[121]

End point description:

FSH and LH level of participants were measured. Only those parameters having status as overall were presented. Baseline was the last value recorded prior to start of study treatment from AMB112529. Change from Baseline was calculated by subtracting the Baseline value from the end of study post-dose visit value. Only those participants with available data at the specified time points were analyzed.

End point type	Primary

End point timeframe:

Baseline (Day 1) and up to 10 years and 11 months

Notes:

[121] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There are no statistical data to report

End point values	Ambrisentan 2.5 mg (Safety)	Ambrisentan 5 mg (Safety)	Ambrisentan 7.5 mg (Safety)	Ambrisentan 10 mg (Safety)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	3[122]	6[123]	3[124]	7[125]
Units: International units per Liter				
arithmetic mean (standard deviation)				
FSH	0.200 (± 1.2490)	3.217 (± 4.0455)	0.100 (± 3.6042)	-0.336 (± 3.7053)
LH	0.03 (± 0.058)	5.17 (± 9.665)	4.17 (± 9.563)	0.61 (± 9.778)

Notes:

[122] - Safety Population

[123] - Safety Population

[124] - Safety Population

[125] - Safety Population

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Plasma Endocrine Parameters - Female: Follicle Stimulating Hormone (FSH) and Luteinizing Hormone (LH) at 20 years of age of participants

End point title	Change from Baseline in Plasma Endocrine Parameters - Female: Follicle Stimulating Hormone (FSH) and Luteinizing Hormone (LH) at 20 years of age of participants[126]

End point description:

FSH and LH level of participants were measured. Only those parameters having status as overall were presented. Baseline was the last value recorded prior to start of study treatment from AMB112529.Change from Baseline was calculated by subtracting the Baseline value from the specified time point value. Only participants with data at 20 year visit is presented. When participants reached pubertal maturity prior to being 20 years of age then these tests were not repeated at 20-years of age of participants. Only those participants with available data at the specified time points were analyzed.99999 indicates standard deviation could not be calculated due to single participant.

End point type	Primary

End point timeframe:

Baseline (Day 1) and at 20 years of age of participants

Notes:

[126] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There are no statistical data to report

End point values	Ambrisentan 2.5 mg (Safety)	Ambrisentan 5 mg (Safety)	Ambrisentan 7.5 mg (Safety)	Ambrisentan 10 mg (Safety)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	1[127]	3[128]	1[129]	3[130]
Units: International units per Liter				
arithmetic mean (standard deviation)				
FSH	35.800 (± 99999)	0.800 (± 1.2530)	-2.500 (± 99999)	0.967 (± 0.3055)
LH	8.60 (± 99999)	6.17 (± 16.717)	-6.30 (± 99999)	5.10 (± 4.597)

Notes:

[127] - Safety Population

[128] - Safety Population

[129] - Safety Population

[130] - Safety Population

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Plasma Endocrine Parameters - Female: Inhibin B at end of study

End point title	Change from Baseline in Plasma Endocrine Parameters - Female: Inhibin B at end of study[131]

End point description:

Inhibin B level of participants was measured. Only those parameters having status as overall were presented. Baseline was the last value recorded prior to start of study treatment from AMB112529. Change from Baseline was calculated by subtracting the Baseline value from the end of study post-dose visit value. Only those participants with available data at the specified time points were analyzed.

End point type	Primary

End point timeframe:

Baseline (Day 1) and up to 10 years and 11 months

Notes:

[131] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There are no statistical data to report

End point values	Ambrisentan 2.5 mg (Safety)	Ambrisentan 5 mg (Safety)	Ambrisentan 10 mg (Safety)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	2[132]	5[133]	4[134]	
Units: Nanogram per liter				
arithmetic mean (standard deviation)	0.0 (± 11.31)	14.0 (± 67.48)	-29.0 (± 27.60)	

Notes:

[132] - Safety Population

[133] - Safety Population

[134] - Safety Population

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Plasma Endocrine Parameters - Female: Inhibin B at 20 years of age of participants

End point title	Change from Baseline in Plasma Endocrine Parameters - Female: Inhibin B at 20 years of age of participants[135]

End point description:

Inhibin B level of participants was measured. Only those parameters having status as overall were presented. Baseline was the last value recorded prior to start of study treatment from AMB112529.Change from Baseline was calculated by subtracting the Baseline value from the specified time point value. Only participants with data at 20 year visit is presented. When participants reached pubertal maturity prior to being 20 years of age then these tests were not repeated at 20-years of age of participants. Only those participants with available data at the specified time points were analyzed. 99999 indicates standard deviation could not be calculated due to single participant.

End point type	Primary

End point timeframe:

Baseline (Day 1) and at 20 years of age of participants

Notes:

[135] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There are no statistical data to report

End point values	Ambrisentan 2.5 mg (Safety)	Ambrisentan 7.5 mg (Safety)	Ambrisentan 5 mg (Safety)	Ambrisentan 10 mg (Safety)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	1[136]	1[137]	2[138]	2[139]
Units: Nanogram per liter				
arithmetic mean (standard deviation)	0.0 (± 99999)	37.0 (± 99999)	49.0 (± 110.31)	7.5 (± 70.00)

Notes:

[136] - Safety Population

[137] - Safety Population

[138] - Safety Population

[139] - Safety Population

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Plasma Endocrine Parameters - Female: Sex Hormone Binding Globulin at end of study

End point title	Change from Baseline in Plasma Endocrine Parameters - Female: Sex Hormone Binding Globulin at end of study[140]

End point description:

Sex hormone binding globulin level of participants was measured. Only those parameters having status as overall were presented. Baseline was the last value recorded prior to start of study treatment from AMB112529. Change from Baseline was calculated by subtracting the Baseline value from the end of study post-dose visit value. Only those participants with available data at the specified time points were analyzed.

End point type	Primary

End point timeframe:

Baseline (Day 1) and up to 10 years and 11 months

Notes:

[140] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There are no statistical data to report

End point values	Ambrisentan 5 mg (Safety)	Ambrisentan 2.5 mg (Safety)	Ambrisentan 10 mg (Safety)	Ambrisentan 7.5 mg (Safety)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	6[141]	2[142]	4[143]	2[144]
Units: Nanomoles per liter				
arithmetic mean (standard deviation)	11.8 (± 14.22)	-10.0 (± 1.41)	17.3 (± 22.31)	0.5 (± 0.71)

Notes:

[141] - Safety Population

[142] - Safety Population

[143] - Safety Population

[144] - Safety Population

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Plasma Endocrine Parameters - Female: Sex Hormone Binding Globulin at 20 years of age of participants

End point title	Change from Baseline in Plasma Endocrine Parameters - Female: Sex Hormone Binding Globulin at 20 years of age of participants[145]

End point description:

Sex hormone binding globulin level of participants was measured. Only those parameters having status as overall were presented. Baseline was the last value recorded prior to start of study treatment from AMB112529.Change from Baseline was calculated by subtracting the Baseline value from the specified time point value. Only participants with data at 20 year visit is presented. When participants reached pubertal maturity prior to being 20 years of age then these tests were not repeated at 20-years of age of participants. Only those participants with available data at the specified time points were analyzed. 99999 indicates standard deviation could not be calculated due to single participant

End point type	Primary

End point timeframe:

Baseline (Day 1) and at 20 years of age of participants

Notes:

[145] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There are no statistical data to report

End point values	Ambrisentan 2.5 mg (Safety)	Ambrisentan 5 mg (Safety)	Ambrisentan 7.5 mg (Safety)	Ambrisentan 10 mg (Safety)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	1[146]	3[147]	1[148]	2[149]
Units: Nanomoles per liter				
arithmetic mean (standard deviation)	49.0 (± 99999)	1.7 (± 54.37)	10.0 (± 99999)	-15.5 (± 2.12)

Notes:

[146] - Safety Population

[147] - Safety Population

[148] - Safety Population

[149] - Safety Population

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Plasma Endocrine Parameters - Female: Estrone at end of study

End point title	Change from Baseline in Plasma Endocrine Parameters - Female: Estrone at end of study[150]

End point description:

Estrone level of female participants was measured. Only those parameters having status as overall were presented. Baseline was the last value recorded prior to start of study treatment from AMB112529. Change from Baseline was calculated by subtracting the Baseline value from the end of study post-dose

visit value. Only those participants with available data at the specified time points were analyzed.99999 indicates standard deviation could not be calculated due to single participant.

End point type	Primary

End point timeframe:

Baseline (Day 1) and up to 10 years and 11 months

Notes:

[150] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There are no statistical data to report

End point values	Ambrisentan 2.5 mg (Safety)	Ambrisentan 5 mg (Safety)	Ambrisentan 7.5 mg (Safety)	Ambrisentan 10 mg (Safety)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	1[151]	5[152]	2[153]	5[154]
Units: Picomole per milliliter				
arithmetic mean (standard deviation)	0.00 (± 99999)	-6.80 (± 178.361)	-26.00 (± 209.304)	17.00 (± 125.913)

Notes:

[151] - Safety Population

[152] - Safety Population

[153] - Safety Population

[154] - Safety Population

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Plasma Endocrine Parameters - Female: Estrone at 20 years of age of participants

End point title	Change from Baseline in Plasma Endocrine Parameters - Female: Estrone at 20 years of age of participants[155]

End point description:

Estrone level of female participants was measured. Only those parameters having status as overall were presented. Baseline was the last value recorded prior to start of study treatment from AMB112529.Change from Baseline was calculated by subtracting the Baseline value from the specified time point value. Only participants with data at 20 year visit is presented. When participants reached pubertal maturity prior to being 20 years of age then these tests were not repeated at 20-years of age of participants. Only those participants with available data at the specified time points were analyzed. 99999 indicates standard deviation could not be calculated due to single participant.

End point type	Primary

End point timeframe:

Baseline (Day 1) and at 20 years of age of participants

Notes:

[155] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There are no statistical data to report

End point values	Ambrisentan 2.5 mg (Safety)	Ambrisentan 7.5 mg (Safety)	Ambrisentan 5 mg (Safety)	Ambrisentan 10 mg (Safety)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	1[156]	1[157]	2[158]	2[159]
Units: Picomole per milliliter				
arithmetic mean (standard deviation)	-7.00 (± 99999)	11.00 (± 99999)	179.00 (± 196.576)	89.00 (± 73.539)

Notes:

[156] - Safety Population

[157] - Safety Population

[158] - Safety Population

[159] - Safety Population

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Plasma Endocrine Parameters - Female: Estradiol at end of study

End point title	Change from Baseline in Plasma Endocrine Parameters - Female: Estradiol at end of study[160]

End point description:

Estradiol level of female participants was measured. Only those parameters having status as overall were presented. Baseline was the last value recorded prior to start of study treatment from AMB112529. Change from Baseline was calculated by subtracting the Baseline value from the end of study post-dose visit value. Only those participants with available data at the specified time points were analyzed. Only those participants with available data at the specified time points were analyzed.99999 indicates standard deviation could not be calculated due to single participant.

End point type	Primary

End point timeframe:

Baseline (Day 1) and up to 10 years and 11 months

Notes:

[160] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There are no statistical data to report

End point values	Ambrisentan 2.5 mg (Safety)	Ambrisentan 7.5 mg (Safety)	Ambrisentan 10 mg (Safety)	Ambrisentan 5 mg (Safety)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	1[161]	2[162]	5[163]	4[164]
Units: Picomoles per liter				
arithmetic mean (standard deviation)	-11.00 (± 99999)	-255.50 (± 427.800)	44.80 (± 264.452)	-77.25 (± 211.435)

Notes:

[161] - Safety Population

[162] - Safety Population

[163] - Safety Population

[164] - Safety Population

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Plasma Endocrine Parameters - Female: Estradiol at 20 years of age of participants

End point title	Change from Baseline in Plasma Endocrine Parameters - Female: Estradiol at 20 years of age of participants[165]

End point description:

Estradiol level of female participants was measured. Only those parameters having status as overall were presented. Baseline was the last value recorded prior to start of study treatment from AMB112529.Change from Baseline was calculated by subtracting the Baseline value from the specified time point value. Only participants with data at 20 year visit is presented. When participants reached

maturity prior to being 20 years of age then these tests were not repeated at 20-years of age of participants. Only those participants with available data at the specified time points were analyzed. 99999 indicates standard deviation could not be calculated due to single participant.

End point type	Primary

End point timeframe:

Baseline (Day 1) and at 20 years of age of participants

Notes:

[165] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There are no statistical data to report

End point values	Ambrisentan 2.5 mg (Safety)	Ambrisentan 7.5 mg (Safety)	Ambrisentan 10 mg (Safety)	Ambrisentan 5 mg (Safety)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	1[166]	1[167]	2[168]	1[169]
Units: Picomoles per liter				
arithmetic mean (standard deviation)	55.50 (± 99999)	15.00 (± 99999)	387.50 (± 375.474)	-107.00 (± 99999)

Notes:

[166] - Safety Population

[167] - Safety Population

[168] - Safety Population

[169] - Safety Population

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Plasma Endocrine Parameters - Male: FSH and LH at end of study

End point title	Change from Baseline in Plasma Endocrine Parameters - Male: FSH and LH at end of study[170]

End point description:

FSH and LH level of participants were measured. Only those parameters having status as overall were presented. Baseline was the last value recorded prior to start of study treatment from AMB112529. Change from Baseline was calculated by subtracting the Baseline value from the end of study post-dose visit value. Only those participants with available data at the specified time points were analyzed.99999 indicates standard deviation could not be calculated due to single participant.

End point type	Primary

End point timeframe:

Baseline (Day 1) and up to 10 years and 11 months

Notes:

[170] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There are no statistical data to report

End point values	Ambrisentan 2.5 mg (Safety)	Ambrisentan 5 mg (Safety)	Ambrisentan 10 mg (Safety)	Ambrisentan 7.5 mg (Safety)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	1[171]	3[172]	2[173]	2[174]
Units: International units per Liter				
arithmetic mean (standard deviation)				
FSH	6.000 (± 99999)	0.267 (± 0.3215)	0.850 (± 2.4749)	3.250 (± 3.4648)
LH	3.20 (± 99999)	1.70 (± 1.473)	3.55 (± 4.738)	3.55 (± 2.333)

Notes:

[171] - Safety Population

[172] - Safety Population

[173] - Safety Population

[174] - Safety Population

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Plasma Endocrine Parameters - Male: FSH and LH at 20 years of age of participants

End point title	Change from Baseline in Plasma Endocrine Parameters - Male: FSH and LH at 20 years of age of participants[175]

End point description:

FSH and LH level of participants were measured. Only those parameters having status as overall were presented. Baseline was the last value recorded prior to start of study treatment from AMB112529.Change from Baseline was calculated by subtracting the Baseline value from the specified time point value. Only participants with data at 20 year visit is presented. When participants reached pubertal maturity prior to being 20 years of age then these tests were not repeated at 20-years of age of participants. Only those participants with available data at the specified time points were analyzed. 99999 indicates standard deviation could not be calculated due to single participant.

End point type	Primary

End point timeframe:

Baseline (Day 1) and at 20 years of age of participants

Notes:

[175] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There are no statistical data to report

End point values	Ambrisentan 7.5 mg (Safety)	Ambrisentan 10 mg (Safety)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	2[176]	1[177]		
Units: International units per Liter				
arithmetic mean (standard deviation)				
FSH	2.350 (± 3.6062)	0.500 (± 99999)		
LH	2.90 (± 2.828)	0.60 (± 99999)		

Notes:

[176] - Safety Population

[177] - Safety Population

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Plasma Endocrine Parameters - Male: Inhibin B at end of study

End point title	Change from Baseline in Plasma Endocrine Parameters - Male: Inhibin B at end of study[178]

End point description:

Inhibin B level of participants was measured. Only those parameters having status as overall were presented. Baseline was the last value recorded prior to start of study treatment from AMB112529. Change from Baseline was calculated by subtracting the Baseline value from the end of study post-dose

visit value. Only those participants with available data at the specified time points were analyzed.

End point type	Primary

End point timeframe:

Baseline (Day 1) and up to 10 years and 11 months

Notes:

[178] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There are no statistical data to report

End point values	Ambrisentan 5 mg (Safety)	Ambrisentan 10 mg (Safety)	Ambrisentan 7.5 mg (Safety)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	2[179]	2[180]	2[181]	
Units: Nanogram per liter				
arithmetic mean (standard deviation)	15.0 (± 5.66)	73.0 (± 175.36)	8.5 (± 6.36)	

Notes:

[179] - Safety Population

[180] - Safety Population

[181] - Safety Population

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Plasma Endocrine Parameters - Male: Inhibin B at 20 years of age of participants

End point title	Change from Baseline in Plasma Endocrine Parameters - Male: Inhibin B at 20 years of age of participants[182]

End point description:

Inhibin B level of participants was measured. Only those parameters having status as overall were presented. Baseline was the last value recorded prior to start of study treatment from AMB112529.Change from Baseline was calculated by subtracting the Baseline value from the specified time point value. Only participants with data at 20 year visit is presented. When participants reached pubertal maturity prior to being 20 years of age then these tests were not repeated at 20-years of age of participants. Only those participants with available data at the specified time points were analyzed. 99999 indicates standard deviation could not be calculated due to single participant.

End point type	Primary

End point timeframe:

Baseline (Day 1) and at 20 years of age of participants

Notes:

[182] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There are no statistical data to report

End point values	Ambrisentan 7.5 mg (Safety)	Ambrisentan 10 mg (Safety)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	2[183]	1[184]		
Units: Nanogram per liter				
arithmetic mean (standard deviation)	23.0 (± 21.21)	-47.0 (± 99999)		

Notes:

[183] - Safety Population

[184] - Safety Population

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Plasma Endocrine Parameters - Male: Sex Hormone Binding Globulin at end of study

End point title	Change from Baseline in Plasma Endocrine Parameters - Male: Sex Hormone Binding Globulin at end of study[185]

End point description:

Sex hormone binding globulin level of participants was measured. Only those parameters having status as overall were presented. Baseline was the last value recorded prior to start of study treatment from AMB112529. Change from Baseline was calculated by subtracting the Baseline value from the end of study post-dose visit value. Only those participants with available data at the specified time points were analyzed.

End point type	Primary

End point timeframe:

Baseline (Day 1) and up to 10 years and 11 months

Notes:

[185] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There are no statistical data to report

End point values	Ambrisentan 5 mg (Safety)	Ambrisentan 10 mg (Safety)	Ambrisentan 7.5 mg (Safety)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	2[186]	2[187]	2[188]	
Units: Nanomoles per liter				
arithmetic mean (standard deviation)	-28.5 (± 28.99)	-11.0 (± 39.60)	-11.5 (± 3.54)	

Notes:

[186] - Safety Population

[187] - Safety Population

[188] - Safety Population

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Plasma Endocrine Parameters - Male: Sex Hormone Binding Globulin at 20 years of age of participants

End point title	Change from Baseline in Plasma Endocrine Parameters - Male: Sex Hormone Binding Globulin at 20 years of age of participants[189]

End point description:

Sex hormone binding globulin level of participants was measured. Only those parameters having status as overall were presented. Baseline was the last value recorded prior to start of study treatment from AMB112529.Change from Baseline was calculated by subtracting the Baseline value from the specified time point value. Only participants with data at 20 year visit is presented. When participants reached pubertal maturity prior to being 20 years of age then these tests were not repeated at 20-years of age

of participants. Only those participants with available data at the specified time points were analyzed. 99999 indicates standard deviation could not be calculated due to single participant.

End point type	Primary

End point timeframe:

Baseline (Day 1) and at 20 years of age of participants

Notes:

[189] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There are no statistical data to report

End point values	Ambrisentan 7.5 mg (Safety)	Ambrisentan 10 mg (Safety)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	2[190]	1[191]		
Units: Nanomoles per liter				
arithmetic mean (standard deviation)	-2.5 (± 12.02)	12.0 (± 99999)		

Notes:

[190] - Safety Population

[191] - Safety Population

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Plasma Endocrine Parameters - Male: Total Testosterone at end of study

End point title	Change from Baseline in Plasma Endocrine Parameters - Male: Total Testosterone at end of study[192]

End point description:

Total Testosterone level of participants was measured. Only those parameters having status as overall were presented. Baseline was the last value recorded prior to start of study treatment from AMB112529. Change from Baseline was calculated by subtracting the Baseline value from the end of study post-dose visit value. Only those participants with available data at the specified time points were analyzed. 99999 indicates standard deviation could not be calculated due to single participant.

End point type	Primary

End point timeframe:

Baseline (Day 1) and up to 10 years and 11 months

Notes:

[192] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There are no statistical data to report

End point values	Ambrisentan 2.5 mg (Safety)	Ambrisentan 5 mg (Safety)	Ambrisentan 10 mg (Safety)	Ambrisentan 7.5 mg (Safety)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	1[193]	3[194]	2[195]	2[196]
Units: Nanomoles per liter				
arithmetic mean (standard deviation)	10.650 (± 99999)	2.900 (± 7.1190)	17.175 (± 0.1061)	7.300 (± 1.6971)

Notes:

[193] - Safety Population

[194] - Safety Population

[195] - Safety Population

[196] - Safety Population

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Plasma Endocrine Parameters - Male: Total Testosterone at 20 years of age of participants

End point title	Change from Baseline in Plasma Endocrine Parameters - Male: Total Testosterone at 20 years of age of participants[197]

End point description:

Total Testosterone level of participants was measured. Only those parameters having status as overall were presented. Baseline was the last value recorded prior to start of study treatment from AMB112529.Change from Baseline was calculated by subtracting the Baseline value from the specified time point value. Only participants with data at 20 year visit is presented. When participants reached pubertal maturity prior to being 20 years of age then these tests were not repeated at 20-years of age of participants. Only those participants with available data at the specified time points were analyzed. 99999 indicates standard deviation could not be calculated due to single participant.

End point type	Primary

End point timeframe:

Baseline (Day 1) and at 20 years of age of participants

Notes:

[197] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There are no statistical data to report

End point values	Ambrisentan 7.5 mg (Safety)	Ambrisentan 10 mg (Safety)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	2[198]	1[199]		
Units: Nanomoles per liter				
arithmetic mean (standard deviation)	4.000 (± 10.7480)	6.600 (± 99999)		

Notes:

[198] - Safety Population

[199] - Safety Population

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline of Pubertal Development in Male: Testicular volume at end of study

End point title	Change From Baseline of Pubertal Development in Male: Testicular volume at end of study[200]

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. Baseline was the last value recorded prior to start of study treatment from AMB112529. Change from Baseline was calculated by subtracting the Baseline value from the end of study post-dose visit value. Only those participants with data available at the specified data points were analyzed (represented by n=X in category titles).99999 indicates standard deviation could not be calculated due

to single participant.Data reported for left and right testicular volume.

End point type	Primary

End point timeframe:

Baseline (Day 1) and up to 10 years and 11 months

Notes:

[200] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There are no statistical data to report

End point values	Ambrisentan 5 mg (Safety)	Ambrisentan 10 mg (Safety)	Ambrisentan 7.5 mg (Safety)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	2[201]	2[202]	2[203]	
Units: Milliliter				
arithmetic mean (standard deviation)				
Right TV, n=1, 2, 2	0.0 (± 99999)	11.5 (± 16.26)	15.0 (± 7.07)	
Left TV, n= 2, 2, 2	6.0 (± 8.49)	13.0 (± 14.14)	16.5 (± 4.95)	

Notes:

[201] - Safety Population

[202] - Safety Population

[203] - Safety Population

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline of Pubertal Development in Male: Testicular volume at 20 years of age of participants

End point title	Change From Baseline of Pubertal Development in Male: Testicular volume at 20 years of age of participants[204]

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 as overall were presented. Baseline was the last value recorded prior to start of study treatment from AMB112529.Change from Baseline was calculated by subtracting the Baseline value from the specified time point value. Only participants with data at 20 year visit is presented. When participants reached pubertal maturity prior to being 20 years of age then these tests were not repeated at 20-years of age of participants. Only those participants with data available at the specified data points were analyzed (represented by n=X in category titles). 99999 indicates standard deviation could not be calculated due to single participant.88888 indicates data is not available as no participants were analyzed. Data reported for left and right testicular volume.

End point type	Primary

End point timeframe:

Baseline (Day 1) and at 20 years of age of participants

Notes:

[204] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There are no statistical data to report

End point values	Ambrisentan 7.5 mg (Safety)	Ambrisentan 5 mg (Safety)	Ambrisentan 10 mg (Safety)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	2[205]	1[206]	1[207]	
Units: Milliliter				
arithmetic mean (standard deviation)				
Right TV, n=0, 2, 1	15.0 (± 7.07)	88888 (± 88888)	8.0 (± 99999)	
Left TV, n= 1, 2, 1	16.5 (± 4.95)	17.0 (± 99999)	8.0 (± 99999)	

Notes:

[205] - Safety Population

[206] - Safety Population

[207] - Safety Population

Statistical analyses

No statistical analyses for this end point

Primary: Time to change in dose of ambrisentan or other targeted PAH therapeutic agents (prostanoids, Phosphodiesterase type 5 [PDE-5] inhibitors) due to tolerability issues

End point title	Time to change in dose of ambrisentan or other targeted PAH therapeutic agents (prostanoids, Phosphodiesterase type 5 [PDE-5] inhibitors) due to tolerability issues[208]

End point description:

Time to change in dose of ambrisentan or other targeted PAH therapeutic agents (prostanoids, Phosphodiesterase type 5 [PDE-5] inhibitors) due to tolerability issues was defined as the time from randomization to the first occurrence of a dose change due to tolerability issues.

End point type	Primary

End point timeframe:

Baseline (Day 1) and up to 10 years and 11 months

Notes:

[208] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There are no statistical data to report

End point values	Ambrisentan 2.5 mg (Safety)	Ambrisentan 7.5 mg (Safety)	Ambrisentan 10 mg (Safety)	Ambrisentan 5 mg (Safety)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	1[209]	1[210]	3[211]	2[212]
Units: Days				
arithmetic mean (standard deviation)	393.0 (± 99999)	354.0 (± 99999)	1448.7 (± 745.09)	468.5 (± 41.72)

Notes:

[209] - Safety Population

[210] - Safety Population

[211] - Safety Population

[212] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with all-cause death

End point title	Number of participants with all-cause death

End point description:

Number of participants with all-cause death is presented.

End point type	Secondary

End point timeframe:

Up to 10 years and 11 months

End point values	Ambrisentan 2.5 mg (Safety)	Ambrisentan 5 mg (Safety)	Ambrisentan 7.5 mg (Safety)	Ambrisentan 10 mg (Safety)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	4[213]	16[214]	6[215]	12[216]
Units: Participants	0	4	1	2

Notes:

[213] - Safety Population

[214] - Safety Population

[215] - Safety Population

[216] - 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 6 MWD data has been presented into three categories as overall, with oxygen use and without oxygen use. The 6-minute walk test measures the distance that a participant can walk in 6 minutes. All participants were given standardized instructions and the distance walked was measured.Baseline which is the last value recorded prior to start of study treatment in AMB112529. Change from Baseline was calculated by subtracting the Baseline value from the end of study post-dose visit value. Intent-to-Treat (ITT) Population consisted of all participants who received at least 1 dose of study drug. Participants were considered as belonging to their treatment group at the start of study AMB114588. Only those participants with data available at the specified data points were analyzed (represented by n=X in category titles). 88888 indicates data is not available as no participants were

End point type	Secondary

End point timeframe:

Baseline (Day 1) and up to 10 years and 11 months

End point values	Ambrisentan 2.5 mg (ITT)	Ambrisentan 5 mg (ITT)	Ambrisentan 7.5 mg (ITT)	Ambrisentan 10 mg (ITT)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9[217]	11[218]	4[219]	5[220]
Units: Meters				
arithmetic mean (standard deviation)				
Overall, n=9, 11, 4, 5	98.53 (± 115.355)	56.74 (± 58.069)	3.05 (± 94.659)	34.24 (± 72.135)
With oxygen use, n=2, 0, 0, 0	-13.05 (± 96.944)	88888 (± 88888)	88888 (± 88888)	88888 (± 88888)

Without oxygen use, n=7, 11, 4, 5	130.41 (± 104.115)	56.74 (± 58.069)	3.05 (± 94.659)	34.24 (± 72.135)

Notes:

[217] - ITT Population

[218] - ITT Population

[219] - ITT Population

[220] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Time to the First Clinical Worsening of PAH

End point title	Time to the First Clinical Worsening of PAH

End point description:

Time to clinical worsening of PAH is defined as time from randomization to first occurrence of death(all cause),placed on active list for lung transplant, &/or atrial septostomy,hospitalization due to PAH deterioration,addition of another targeted PAH therapeutic agents (prostanoids,PDE-5 inhibitors) due to deterioration of clinical condition,change in dose of ambrisentan/other targeted PAH therapeutic agents(prostanoids, PDE-5 inhibitors) due to deterioration of clinical condition, PAH related deterioration identified by increase in WHO functional class,deterioration in exercise testing (i.e.20% decrease in 6MWD on 2 consecutive tests -1 week apart, clinical signs or symptoms of right sided heart failure (i.e.new peripheral edema,increase in liver size,ascites,increase in jugular venous pressure, pericardial effusion increased dyspnea).Only participants with available data at specified time points were analyzed.99999 indicate SD could not be calculated due to single participant.

End point type	Secondary

End point timeframe:

Up to 10 years and 11 months

End point values	Ambrisentan 2.5 mg (ITT)	Ambrisentan 5 mg (ITT)	Ambrisentan 7.5 mg (ITT)	Ambrisentan 10 mg (ITT)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2[221]	5[222]	3[223]	1[224]
Units: Days				
arithmetic mean (standard deviation)	315.5 (± 2.12)	896.2 (± 721.33)	1122.0 (± 704.09)	228.0 (± 99999)

Notes:

[221] - ITT Population

[222] - ITT Population

[223] - ITT Population

[224] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Time to the addition of another targeted PAH therapeutic agent due to deterioration of clinical condition

End point title	Time to the addition of another targeted PAH therapeutic agent due to deterioration of clinical condition

End point description:

Time to addition of another targeted PAH therapeutics agents due to deterioration of clinical condition was defined as the time from randomization to the first occurrence of deterioration of clinical condition.

End point type	Secondary

End point timeframe:

Up to 10 years and 11 months

End point values	Ambrisentan 2.5 mg (ITT)	Ambrisentan 5 mg (ITT)	Ambrisentan 7.5 mg (ITT)	Ambrisentan 10 mg (ITT)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1[225]	2[226]	1[227]	2[228]
Units: Days				
arithmetic mean (standard deviation)	510.0 (± 99999)	697.5 (± 863.38)	909.0 (± 99999)	345.5 (± 109.60)

Notes:

[225] - ITT Population

[226] - ITT Population

[227] - ITT Population

[228] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Time to the addition of another targeted PAH therapeutic agent due to lack of beneficial effect with previous therapy

End point title	Time to the addition of another targeted PAH therapeutic agent due to lack of beneficial effect with previous therapy[229]

End point description:

The time to addition of another targeted PAH therapeutic agents due to lack of beneficial effect with previous therapy was defined as the time from randomization to the first occurrence of lack of beneficial effect with previous therapy (not reaching set treatment goals).Only those participants with available data at the specified time points were analyzed.99999 indicates standard deviation could not be calculated due to single participant.

End point type	Secondary

End point timeframe:

Up to 10 years and 11 months

Notes:

[229] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only reporting on a subset of the arms that are contained in the baseline period

End point values	Ambrisentan 2.5 mg (ITT)	Ambrisentan 5 mg (ITT)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2[230]	1[231]		
Units: Days				
arithmetic mean (standard deviation)	315.5 (± 2.12)	173.0 (± 99999)		

Notes:

[230] - ITT Population

[231] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Time to change in dose of ambrisentan or other targeted PAH therapeutic agents (prostanoids, PDE-5 inhibitors) due to deterioration of clinical condition

End point title	Time to change in dose of ambrisentan or other targeted PAH therapeutic agents (prostanoids, PDE-5 inhibitors) due to deterioration of clinical condition

End point description:

Time to change in dose of ambrisentan or other targeted PAH therapeutic agents (prostanoids, PDE-5 inhibitors) due to deterioration of clinical condition was defined as the time from randomization to the first occurrence of a dose change due to deterioration of clinical condition. Only those participants with available data at the specified time points were analyzed.99999 indicates standard deviation could not be calculated due to single participant.

End point type	Secondary

End point timeframe:

Up to 10 years and 11 months

End point values	Ambrisentan 2.5 mg (ITT)	Ambrisentan 5 mg (ITT)	Ambrisentan 7.5 mg (ITT)	Ambrisentan 10 mg (ITT)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3[232]	3[233]	1[234]	2[235]
Units: Days				
arithmetic mean (standard deviation)	1247.3 (± 1051.97)	1097.0 (± 922.77)	909.0 (± 99999)	345.5 (± 109.60)

Notes:

[232] - ITT Population

[233] - ITT Population

[234] - ITT Population

[235] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Subject Global Assessment (SF-10) Health Survey for Children

End point title	Change from Baseline in Subject Global Assessment (SF-10) Health Survey for Children

End point description:

The short-form 10 (SF-10) Health Survey for children is a 10-item, 4-week recall, parent-completed health assessment that measures physical and psychosocial functioning for children ages five and over. 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. The aggregate score was then standardized and transformed to a norm-based scoring metric in accordance with the developer's guidelines. 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. Baseline was the last value recorded prior to start of study treatment from AMB112529. Change from Baseline was calculated by subtracting the Baseline value from the end of study post-dose visit value.Only those participants with available data at the specified time points were analyzed.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and up to 10 years and 11 months

End point values	Ambrisentan 2.5 mg (ITT)	Ambrisentan 5 mg (ITT)	Ambrisentan 7.5 mg (ITT)	Ambrisentan 10 mg (ITT)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8[236]	9[237]	4[238]	5[239]
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Physical health summary	-1.618 (± 7.4650)	-0.967 (± 16.4890)	-1.788 (± 12.0104)	-0.272 (± 15.1029)
Psychosocial summary	-0.336 (± 5.4290)	-1.880 (± 7.9810)	2.225 (± 6.2357)	6.766 (± 6.5080)

Notes:

[236] - ITT Population

[237] - ITT Population

[238] - ITT Population

[239] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with change from Baseline in World Health Organization (WHO) Functional Class of PAH

End point title	Number of participants with change from Baseline in World Health Organization (WHO) Functional Class of PAH

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 mapped to numeric scale for which scores ranged from 1-4 (i.e. Class I=1 and IV=4). Change categorization was based on change from Baseline scores: -2, -1, 0, +1, +2. Data was categorized as No Change (0), Improved (-1,-2), Deteriorated (+1,+2). Higher score indicated higher severity.Baseline was the last value recorded prior to start of study treatment from AMB112529. Change from Baseline was calculated by subtracting the Baseline value from the end of study post-dose visit value. Only those participants with available data at the specified time points were analyzed.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and up to 10 years and 11 months

End point values	Ambrisentan 2.5 mg (ITT)	Ambrisentan 5 mg (ITT)	Ambrisentan 7.5 mg (ITT)	Ambrisentan 10 mg (ITT)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9[240]	11[241]	4[242]	5[243]
Units: Participants				
Improved	5	5	3	0
No Change	4	6	1	5
Deteriorated	0	0	0	0

Notes:

[240] - ITT Population

[241] - ITT Population

[242] - ITT Population

[243] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage change from Baseline in Plasma N-terminal pro-B-type natriuretic peptide (NT-Pro BNP) concentration

End point title	Percentage change from Baseline in Plasma N-terminal pro-B-type natriuretic peptide (NT-Pro BNP) concentration

End point description:

Blood samples were collected to analyze NT-Pro BNP concentration at specific time points. Baseline was the last value recorded prior to start of study treatment from AMB112529. Change from Baseline was calculated by subtracting Baseline value from the specified time point value. Only those participants with available data at the specified time points were analyzed.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and up to 10 years and 11 months

End point values	Ambrisentan 2.5 mg (ITT)	Ambrisentan 5 mg (ITT)	Ambrisentan 7.5 mg (ITT)	Ambrisentan 10 mg (ITT)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7[244]	11[245]	2[246]	5[247]
Units: Percentage Change				
geometric mean (full range (min-max))	-62.59 (-97.6 to 116.3)	-56.02 (-99.0 to 2227.1)	59.06 (-22.6 to 226.8)	101.96 (-2.1 to 214.4)

Notes:

[244] - ITT Population

[245] - ITT Population

[246] - ITT Population

[247] - ITT Population

Statistical analyses

No statistical analyses for this end point

Adverse events information

Timeframe for reporting adverse events:

All-cause mortality, non-STEAEs and STEAEs were collected from the start of study treatment up to 10 years and 11 months

Adverse event reporting additional description:

All-cause mortality, non-STEAEs and STEAEs were collected in Safety Population which consisted of all participants who received at least 1 dose of study drug. Participants were considered as belonging to the treatment group according to the highest dose received in the extension study (AMB114588).

Assessment type	Systematic

Dictionary used

Dictionary name	25.0
Dictionary version	25.0

Reporting groups

Reporting group title	Ambrisentan 2.5 mg (Safety)

Reporting group description:

Participants received ambrisentan 2.5 mg tablet orally once daily. The Safety Population consisted of all participants who received at least 1 dose of study drug. Participants were considered as belonging to the treatment group according to the highest dose received in the extension study (AMB114588).

Reporting group title	Ambrisentan 5 mg (Safety)

Reporting group description:

Participants received ambrisentan 5 mg tablet orally once daily. The Safety Population consisted of all participants who received at least 1 dose of study drug. Participants were considered as belonging to the treatment group according to the highest dose received in the extension study (AMB114588).

Reporting group title	Ambrisentan 7.5 mg (Safety)

Reporting group description:

Participants received ambrisentan 7.5 mg tablet orally once daily. The Safety Population consisted of all participants who received at least 1 dose of study drug. Participants were considered as belonging to the treatment group according to the highest dose received in the extension study (AMB114588).

Reporting group title	Ambrisentan 10 mg (Safety)

Reporting group description:

Participants received ambrisentan 10 mg tablet orally once daily. The Safety Population consisted of all participants who received at least 1 dose of study drug. Participants were considered as belonging to the treatment group according to the highest dose received in the extension study (AMB114588).

Serious adverse events	Ambrisentan 2.5 mg (Safety)	Ambrisentan 5 mg (Safety)	Ambrisentan 7.5 mg (Safety)
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 4 (50.00%)	7 / 16 (43.75%)	4 / 6 (66.67%)
number of deaths (all causes)	0	4	1
number of deaths resulting from adverse events			
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 4 (25.00%)	0 / 16 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration			

site conditions			
Complication associated with device			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Illness			
subjects affected / exposed	1 / 4 (25.00%)	0 / 16 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Hyperventilation			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary arterial hypertension			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary haemorrhage			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary hypertension			

subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 4 (25.00%)	0 / 16 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Autoimmune lymphoproliferative syndrome			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute right ventricular failure			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Atrioventricular block complete			
subjects affected / exposed	1 / 4 (25.00%)	0 / 16 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block first degree			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure acute			
subjects affected / exposed	0 / 4 (0.00%)	2 / 16 (12.50%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0
Conduction disorder			

subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Right ventricular failure			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Supraventricular tachycardia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wandering pacemaker			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Migraine			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disseminated intravascular coagulation			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Gastric haemorrhage			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Vomiting			
subjects affected / exposed	1 / 4 (25.00%)	0 / 16 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Scoliosis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Influenza			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myringitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Otitis media acute			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Sinusitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Otitis media chronic			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Failure to thrive			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1

Serious adverse events	Ambrisentan 10 mg (Safety)		
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 12 (66.67%)		
number of deaths (all causes)	2		
number of deaths resulting from adverse events			
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Complication associated with device			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Illness			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Non-cardiac chest pain			

subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Hyperventilation			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pulmonary arterial hypertension			
subjects affected / exposed	3 / 12 (25.00%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 2		
Pulmonary haemorrhage			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pulmonary hypertension			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Congenital, familial and genetic disorders			
Autoimmune lymphoproliferative syndrome			

subjects affected / exposed	0 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Acute right ventricular failure				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Atrioventricular block complete				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Atrioventricular block first degree				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac failure acute				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Conduction disorder				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Right ventricular failure				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Supraventricular tachycardia				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Wandering pacemaker				

subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Migraine			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Disseminated intravascular coagulation			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Gastric haemorrhage			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Scoliosis			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Appendicitis			

subjects affected / exposed	1 / 12 (8.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
COVID-19				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Influenza				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Myringitis				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Otitis media acute				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sinusitis				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Otitis media chronic				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Failure to thrive				

subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Ambrisentan 2.5 mg (Safety)	Ambrisentan 5 mg (Safety)	Ambrisentan 7.5 mg (Safety)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 4 (75.00%)	13 / 16 (81.25%)	5 / 6 (83.33%)
Vascular disorders			
Cyanosis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Flushing			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Hot flush			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Hyperaemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Surgical and medical procedures			
Therapeutic procedure			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Catheter site discharge			
subjects affected / exposed	1 / 4 (25.00%)	0 / 16 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Catheter site pain			

subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Chest discomfort			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Chest pain			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	1 / 6 (16.67%)
occurrences (all)	0	1	2
Chills			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Fatigue			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	1 / 6 (16.67%)
occurrences (all)	0	2	1
Influenza like illness			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Localised oedema			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Non-cardiac chest pain			
subjects affected / exposed	0 / 4 (0.00%)	2 / 16 (12.50%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Oedema peripheral			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Puncture site pain			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	1 / 6 (16.67%)
occurrences (all)	0	1	3
Pyrexia			
subjects affected / exposed	0 / 4 (0.00%)	2 / 16 (12.50%)	2 / 6 (33.33%)
occurrences (all)	0	2	3
Swelling face			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Immune system disorders			

Allergy to vaccine			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Immunisation reaction			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Erection increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Bronchospasm			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	4
Cough			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Dyspnoea exertional			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Epistaxis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	2 / 6 (33.33%)
occurrences (all)	0	1	3
Hypoxia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Nasal congestion			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Nasal inflammation			

subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Nasal obstruction			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Oropharyngeal pain			
subjects affected / exposed	0 / 4 (0.00%)	3 / 16 (18.75%)	1 / 6 (16.67%)
occurrences (all)	0	3	1
Pleurisy			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Pulmonary arterial hypertension			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Respiratory symptom			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Rhinitis allergic			
subjects affected / exposed	0 / 4 (0.00%)	2 / 16 (12.50%)	0 / 6 (0.00%)
occurrences (all)	0	3	0
Rhinorrhoea			
subjects affected / exposed	1 / 4 (25.00%)	1 / 16 (6.25%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Tonsillar hypertrophy			
subjects affected / exposed	1 / 4 (25.00%)	0 / 16 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Upper respiratory tract inflammation			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Adenoidal hypertrophy			
subjects affected / exposed	1 / 4 (25.00%)	0 / 16 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Abnormal behaviour			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	0 / 6 (0.00%)
occurrences (all)	0	1	0

Automatism			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Hallucination			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Insomnia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Panic attack			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Product issues			
Device breakage			
subjects affected / exposed	1 / 4 (25.00%)	0 / 16 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Device leakage			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Investigations			
Aspartate aminotransferase abnormal			
subjects affected / exposed	1 / 4 (25.00%)	0 / 16 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 4 (25.00%)	0 / 16 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 4 (25.00%)	0 / 16 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Blood bilirubin increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Blood lactate dehydrogenase increased			
subjects affected / exposed	1 / 4 (25.00%)	0 / 16 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0

Blood parathyroid hormone increased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Blood pressure diastolic decreased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Haemoglobin decreased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Transaminases increased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Vitamin D decreased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Weight decreased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
Animal bite			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Foot fracture			
subjects affected / exposed	1 / 4 (25.00%)	0 / 16 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Gingival injury			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hand fracture			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Joint injury			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Ligament sprain			

subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Limb injury			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Procedural pain			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Skin laceration			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Upper limb fracture			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Ear procedural complication			
subjects affected / exposed	1 / 4 (25.00%)	0 / 16 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Cardiac failure congestive			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Palpitations			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Pulmonary valve stenosis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	2 / 6 (33.33%)
occurrences (all)	0	0	4
Facial paralysis			

subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Headache			
subjects affected / exposed	0 / 4 (0.00%)	3 / 16 (18.75%)	2 / 6 (33.33%)
occurrences (all)	0	3	3
Hypoaesthesia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Lethargy			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Petit mal epilepsy			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Presyncope			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Seizure			
subjects affected / exposed	1 / 4 (25.00%)	0 / 16 (0.00%)	0 / 6 (0.00%)
occurrences (all)	5	0	0
Somnolence			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Speech disorder			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Syncope			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Tardive dyskinesia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Tension headache			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			

Lymphadenopathy			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Iron deficiency anaemia			
subjects affected / exposed	0 / 4 (0.00%)	3 / 16 (18.75%)	0 / 6 (0.00%)
occurrences (all)	0	3	0
Lymphoid tissue hyperplasia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Neutropenia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Anaemia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Ear and labyrinth disorders			
Conductive deafness			
subjects affected / exposed	1 / 4 (25.00%)	0 / 16 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Deafness			
subjects affected / exposed	1 / 4 (25.00%)	0 / 16 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Ear congestion			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Ear haemorrhage			
subjects affected / exposed	1 / 4 (25.00%)	0 / 16 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Eustachian tube dysfunction			
subjects affected / exposed	1 / 4 (25.00%)	0 / 16 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Motion sickness			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Vertigo			

subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Astigmatism			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Cataract			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Conjunctivitis allergic			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Eye pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Eye swelling			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Eyelid oedema			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Ocular hyperaemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Strabismus			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Visual impairment			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Abdominal pain			

subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Abdominal pain lower			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Abdominal pain upper			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	3
Aphthous ulcer			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Ascites			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Constipation			
subjects affected / exposed	1 / 4 (25.00%)	1 / 16 (6.25%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Diarrhoea			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	2 / 6 (33.33%)
occurrences (all)	0	1	3
Dry mouth			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Dyspepsia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Gastritis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Nausea			
subjects affected / exposed	0 / 4 (0.00%)	2 / 16 (12.50%)	2 / 6 (33.33%)
occurrences (all)	0	5	3
Stomatitis			

subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Tooth disorder			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Toothache			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Vomiting			
subjects affected / exposed	0 / 4 (0.00%)	2 / 16 (12.50%)	1 / 6 (16.67%)
occurrences (all)	0	2	2
Hepatobiliary disorders			
Hepatomegaly			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Angioedema			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Dermatitis atopic			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Dermatitis contact			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Eczema			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Eczema asteatotic			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Erythema			

subjects affected / exposed	1 / 4 (25.00%)	1 / 16 (6.25%)	1 / 6 (16.67%)
occurrences (all)	1	1	1
Lichen sclerosus			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Pruritus			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Rash			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	2 / 6 (33.33%)
occurrences (all)	0	1	2
Urticaria			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Proteinuria			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Back pain			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	2 / 6 (33.33%)
occurrences (all)	0	1	2
Bone cyst			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Coccydynia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Fistula			

subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Muscle spasms			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Musculoskeletal chest pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Myalgia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Osteonecrosis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Pain in extremity			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	2 / 6 (33.33%)
occurrences (all)	0	0	3
Pain in jaw			
subjects affected / exposed	0 / 4 (0.00%)	2 / 16 (12.50%)	2 / 6 (33.33%)
occurrences (all)	0	2	2
Sacral pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Systemic lupus erythematosus			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Bone pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	1 / 6 (16.67%)
occurrences (all)	0	7	1
Bronchitis viral			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	0 / 6 (0.00%)
occurrences (all)	0	1	0

Conjunctivitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Ear infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Epididymitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	2
Folliculitis			
subjects affected / exposed	1 / 4 (25.00%)	0 / 16 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Gastroenteritis			
subjects affected / exposed	1 / 4 (25.00%)	2 / 16 (12.50%)	0 / 6 (0.00%)
occurrences (all)	1	3	0
Gastroenteritis viral			
subjects affected / exposed	0 / 4 (0.00%)	2 / 16 (12.50%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Herpes virus infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Hordeolum			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Influenza			
subjects affected / exposed	0 / 4 (0.00%)	3 / 16 (18.75%)	0 / 6 (0.00%)
occurrences (all)	0	3	0
Nasopharyngitis			
subjects affected / exposed	0 / 4 (0.00%)	5 / 16 (31.25%)	1 / 6 (16.67%)
occurrences (all)	0	18	3
Oral candidiasis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Otitis externa			
subjects affected / exposed	0 / 4 (0.00%)	2 / 16 (12.50%)	0 / 6 (0.00%)
occurrences (all)	0	2	0

Otitis media			
subjects affected / exposed	1 / 4 (25.00%)	0 / 16 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Otitis media chronic			
subjects affected / exposed	1 / 4 (25.00%)	0 / 16 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Periodontitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Pharyngitis			
subjects affected / exposed	1 / 4 (25.00%)	3 / 16 (18.75%)	0 / 6 (0.00%)
occurrences (all)	2	4	0
Pharyngotonsillitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Pneumonia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 16 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Respiratory tract infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	3
Respiratory tract infection viral			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Rhinitis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	0 / 6 (0.00%)
occurrences (all)	0	3	0
Sinusitis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Tinea pedis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Tonsillitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0

Tooth infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Tracheobronchitis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Upper respiratory tract infection			
subjects affected / exposed	2 / 4 (50.00%)	3 / 16 (18.75%)	4 / 6 (66.67%)
occurrences (all)	4	8	7
Urinary tract infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Viral infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	3
Vulvovaginal candidiasis			
subjects affected / exposed	1 / 4 (25.00%)	0 / 16 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Pharyngitis streptococcal			
subjects affected / exposed	1 / 4 (25.00%)	0 / 16 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Hyperglycaemia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Hyperuricaemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Iron deficiency			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Type 1 diabetes mellitus			

subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	0 / 6 (0.00%)
occurrences (all)	0	1	0

Non-serious adverse events	Ambrisentan 10 mg (Safety)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 12 (83.33%)		
Vascular disorders			
Cyanosis			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Flushing			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Hot flush			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Hyperaemia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Surgical and medical procedures			
Therapeutic procedure			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Catheter site discharge			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Catheter site pain			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Chest discomfort			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		

Chest pain			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Chills			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Fatigue			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Influenza like illness			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Localised oedema			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Non-cardiac chest pain			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Oedema peripheral			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Puncture site pain			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Pyrexia			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Swelling face			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Immune system disorders			
Allergy to vaccine			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	2		
Immunisation reaction			

subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Erection increased			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Bronchospasm			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Cough			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Dyspnoea exertional			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Epistaxis			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Hypoxia			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Nasal congestion			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Nasal inflammation			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Nasal obstruction			

subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Oropharyngeal pain			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Pleurisy			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Pulmonary arterial hypertension			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Respiratory symptom			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Rhinitis allergic			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Rhinorrhoea			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Tonsillar hypertrophy			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Upper respiratory tract inflammation			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Adenoidal hypertrophy			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Abnormal behaviour			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Automatism			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		

Hallucination			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Insomnia			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Panic attack			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Product issues			
Device breakage			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Device leakage			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Investigations			
Aspartate aminotransferase abnormal			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Blood bilirubin increased			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Blood parathyroid hormone increased			

subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Blood pressure diastolic decreased			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Haemoglobin decreased			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Transaminases increased			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Vitamin D decreased			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Weight decreased			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Injury, poisoning and procedural complications			
Animal bite			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Foot fracture			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Gingival injury			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Hand fracture			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Joint injury			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Ligament sprain			

subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	3		
Limb injury			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Procedural pain			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Skin laceration			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Upper limb fracture			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Ear procedural complication			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Cardiac failure congestive			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Palpitations			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Pulmonary valve stenosis			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Facial paralysis			

subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Headache			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	7		
Hypoaesthesia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Lethargy			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Petit mal epilepsy			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Presyncope			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Seizure			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Somnolence			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Speech disorder			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Syncope			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Tardive dyskinesia			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Tension headache			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Blood and lymphatic system disorders			

Lymphadenopathy			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Iron deficiency anaemia			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Lymphoid tissue hyperplasia			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Neutropenia			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Anaemia			
subjects affected / exposed	4 / 12 (33.33%)		
occurrences (all)	9		
Ear and labyrinth disorders			
Conductive deafness			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Deafness			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Ear congestion			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Ear haemorrhage			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Eustachian tube dysfunction			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Motion sickness			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	2		
Vertigo			

subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Eye disorders			
Astigmatism			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Cataract			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Conjunctivitis allergic			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	3		
Eye pain			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Eye swelling			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Eyelid oedema			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Ocular hyperaemia			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Strabismus			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Visual impairment			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Abdominal pain			

subjects affected / exposed	2 / 12 (16.67%)			
occurrences (all)	3			
Abdominal pain lower				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences (all)	0			
Abdominal pain upper				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences (all)	0			
Aphthous ulcer				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences (all)	0			
Ascites				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences (all)	0			
Constipation				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	1			
Diarrhoea				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences (all)	0			
Dry mouth				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences (all)	0			
Dyspepsia				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	1			
Gastritis				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences (all)	0			
Gastrooesophageal reflux disease				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences (all)	0			
Nausea				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	1			
Stomatitis				

subjects affected / exposed	0 / 12 (0.00%)			
occurrences (all)	0			
Tooth disorder				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences (all)	0			
Toothache				
subjects affected / exposed	2 / 12 (16.67%)			
occurrences (all)	2			
Vomiting				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences (all)	0			
Hepatobiliary disorders				
Hepatomegaly				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences (all)	0			
Skin and subcutaneous tissue disorders				
Alopecia				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences (all)	0			
Angioedema				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences (all)	0			
Dermatitis atopic				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences (all)	0			
Dermatitis contact				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	1			
Eczema				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	1			
Eczema asteatotic				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	1			
Erythema				

subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Lichen sclerosus			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Pruritus			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Rash			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Urticaria			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Proteinuria			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Back pain			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Bone cyst			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Coccydynia			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Fistula			

subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Muscle spasms			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Musculoskeletal chest pain			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Myalgia			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Osteonecrosis			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Pain in extremity			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Pain in jaw			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Sacral pain			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Systemic lupus erythematosus			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Bone pain			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Bronchitis viral			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		

Conjunctivitis				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	1			
Ear infection				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	1			
Epididymitis				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences (all)	0			
Folliculitis				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences (all)	0			
Gastroenteritis				
subjects affected / exposed	2 / 12 (16.67%)			
occurrences (all)	3			
Gastroenteritis viral				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences (all)	0			
Herpes virus infection				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences (all)	0			
Hordeolum				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences (all)	0			
Influenza				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	1			
Nasopharyngitis				
subjects affected / exposed	3 / 12 (25.00%)			
occurrences (all)	9			
Oral candidiasis				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences (all)	0			
Otitis externa				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences (all)	0			

Otitis media				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	3			
Otitis media chronic				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences (all)	0			
Periodontitis				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	2			
Pharyngitis				
subjects affected / exposed	2 / 12 (16.67%)			
occurrences (all)	4			
Pharyngotonsillitis				
subjects affected / exposed	2 / 12 (16.67%)			
occurrences (all)	4			
Pneumonia				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences (all)	0			
Respiratory tract infection				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	4			
Respiratory tract infection viral				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	1			
Rhinitis				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	1			
Sinusitis				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences (all)	0			
Tinea pedis				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	1			
Tonsillitis				
subjects affected / exposed	2 / 12 (16.67%)			
occurrences (all)	5			

Tooth infection			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Tracheobronchitis			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Upper respiratory tract infection			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	5		
Urinary tract infection			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	2		
Viral infection			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Vulvovaginal candidiasis			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Pharyngitis streptococcal			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Hyperglycaemia			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Hyperuricaemia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Iron deficiency			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Type 1 diabetes mellitus			

subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 October 2010	Amendment 01: The intents of this amendment are to clarify procedural issues to insure a better global understanding of intent of the protocol and to correctly categorize alkaline phosphatase as a clinical chemistry parameter rather than a liver function test.
08 February 2011	Amendment 02: The intents of this amendment are to add oestrogen and remove testosterone from laboratory assessments being conducted on female participants and to align the storage conditions requirements in the protocol with those that are printed on the study medication package.
10 June 2020	Amendment 03: The intents of this amendment are primarily to modify the testing schedule for liver functions tests and to modify the locale for performing monthly pregnancy tests that do not occur at the quarterly visits, in light of the Coronavirus disease 2019 (COVID-19) pandemic to minimize the participants need to travel to the site while maintaining appropriate monitoring to ensure participant safety. In addition, the amendment seeks to clarify protocol language on the 30-day follow-up and on the dose groups to which the participants will be considered to belong for the analysis displays, as well as updating the Medical Monitor and Sponsor Signatory
25 May 2021	Amendment 04: The primary intent of this amendment is to include changes to when participants can leave the study and the timing of the pubertal development assessment. Specifically, the amendment seeks to clarify that any participants who reached pubertal maturity before 18 years of age and ambrisentan can be supplied through a named participant or expanded access program until the participant reaches 18 years of age will complete their end of study visit at the investigator site. No further pubertal development assessments will be required for these participants. All participants who have reached the age of 18 and who have reached pubertal maturity at a previous visit will complete their final study visit in the form of a telephone follow-up in order to notify the participants of the end of the study and that no further study visits and assessments will take place. All participants who have reached the age of 18 and who have not reached pubertal maturity in previous visits will complete their final study visit at the investigator site and will have their pubertal development assessed. These participants may return at any point and do not need to wait until 20 years of age to have their pubertal maturity evaluated.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported