Amsterdam, 23 February 2023
EMA/29478/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report for paediatric studies submitted in accordance with article 46 of regulation (EC) No 1901/2006, as amended

Volibris

International non-proprietary name: ambrisentan

Procedure no.: EMA/H/C/000839/P46/029

Marketing authorisation holder (MAH): Glaxo Group Limited

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Status of this report and steps taken for the assessment				
Current step[1]	Description	Planned date	Actual Date	Need for discussion[2]
☐	Start of procedure	26/12/2022	26/12/2022	☐
☐	CHMP Rapporteur Assessment Report	30/01/2023	30/01/2023	☐
☐	CHMP members comments	13/02/2023	n/a	☐
☐	Updated CHMP Rapporteur Assessment Report	16/02/2023	n/a	☐
☒	CHMP adoption of conclusions:	23/02/2023	23/02/2023	☐

Abbreviation Description of abbreviated term

6MWD	6-minute walk distance
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ALP	Alkaline phosphatase
AST	Aspartate aminotransferase
COVID-19	Coronavirus disease 2019
d	Day
ECG	Electrocardiogram
ERA	Endothelin receptor antagonist
EMA/EMEA	European Medicines Agency
EOS	End of Study
EU	European Union
FSH	Follicle-stimulating hormone
g/L	Grams per litre
GGT	Gamma glutamyl transferase
ITT	Intention-to-Treat
kg	Kilogram
LDH	Lactate dehydrogenase
LH	Luteinizing hormone
m	Metre
Max	Maximum
Min	Minimum
mmHg	Millimetres of mercury
n or N	Number of participants
ng/L	Nanograms per litre
NT-proBNP	N-terminal pro-B-type natriuretic peptide
PAH	Pulmonary arterial hypertension
PCC	Potential clinical concern
PDE-5i	Phosphodiesterase type 5 inhibitor
PIP	Paediatric Investigation Plan
SAE	Serious adverse event
SAS	Statistical Analysis System
SD	Standard deviation
SF-10	Short Form – 10-item
SHBG	Sex hormone binding globulin
SmPC	Summary of Products Characteristics
TEAE	Treatment-emergent adverse event
US	United States
WHO	World Health Organization
yr	Year

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1. Introduction

On 18 November 2022, the MAH submitted a completed paediatric study (ID AMB114588) for ambrisentan (Volibris), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

Background on the product and disease/condition

Ambrisentan is an orally active, propanoic acid-class, endothelium receptor antagonist (ERA) selective for the endothelin type A receptor. Endothelin plays a significant role in the pathophysiology of pulmonary arterial hypertension (PAH).

Ambrisentan is currently approved by the European Commission under the brand name Volibris as 2.5 mg, 5 mg and 10 mg film-coated tablets for oral use for the following indications:

> *Volibris is indicated for treatment of pulmonary arterial hypertension (PAH) in adult patients of WHO Functional Class (FC) II to III, including use in combination treatment (see section 5.1). Efficacy has been shown in idiopathic PAH (IPAH) and in PAH associated with connective tissue disease.*
>
> *Volibris is indicated for treatment of PAH in adolescents and children (aged 8 to less than 18 years) of WHO Functional Class (FC) II to III including use in combination treatment. Efficacy has been shown in IPAH, familial, corrected congenital and in PAH associated with connective tissue disease (see section 5.1).*

PAH is a rare, progressive, highly debilitating disorder characterized by angioproliferative vasculopathy in the pulmonary arterioles, leading to endothelial and smooth muscle proliferation and dysfunction, inflammation and thrombosis. These changes increase pulmonary vascular resistance and subsequent pulmonary arterial pressure, causing right ventricular failure which leads to eventual death if untreated. Similar to adults, paediatric PAH is defined as a mean pulmonary arterial pressure (mPAP) ≥25 mmHg at rest with a normal pulmonary artery wedge pressure (PAWP) ≤15 mmHg and an increased pulmonary vascular resistance >3 Wood units x m2 (≈240 dyn s cm–5) in the absence of lung disease. However, there are important known differences in vascular function, foetal origins of disease, growth and development, genetics, natural history, underlying disease, responses of the right ventricle, responsiveness to PAH-specific therapies, and gaps in knowledge, particularly in the youngest age groups.

Paediatric development

On 21 April 2008, ambrisentan was firstly approved by the EC as 5 mg and 10 mg film-coated tablets for oral use for the treatment of PAH in adult patients of WHO Functional Class II to III, including use in combination treatment.

On 22 July 2021, the CHMP issued a positive opinion on an application (Procedure No. EMEA/H/C/000839/X/0061/G) consisting of an extension of the marketing authorisation to introduce a new strength (2.5 mg film-coated tablet), grouped with an extension of indication to include treatment of PAH in adolescents and children (8 to less than 18 years). For the submission of this application, the MAH submitted a pivotal phase 2b study (ID AMB112529, which is part of the agreed PIP) and its ongoing extension study (ID AMB114588; data cut-off date for the interim report: 23 Aug 2019).

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the referred paediatric indication application included an EMA Decision (P/0370/2019) on the agreement of a paediatric investigation plan (PIP) (EMEA-000434-PIP01-08-M06) for oral use of ambrisentan as film-coated tablet and dispersible tablet for the treatment of idiopathic (IPAH) and familial (FPAH) pulmonary hypertension as well as the treatment of associated pulmonary hypertension (APAH).

In accordance with Article 46 of the regulation (EC) No. 1901/2006, Glaxo Group Ltd hereby submits to the EMA a final study report for study AMB114588 which is not part of the PIP agreed to ambrisentan.

The MAH stated that study AMB114588 (EudraCT Number: 2010-021572-29) titled “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” is part of a clinical development program. The variation application consisting of the full relevant data package (i.e., containing several studies) is expected to be submitted by second quartile 2023. A line listing of all the concerned studies has not been submitted by the applicant.

2.2. Information on the pharmaceutical formulation used in the study

Ambrisentan is authorised in the European Union to be used in adult patients and adolescents and children (aged 8 to less than 18 years) as 2.5 mg, 5 mg and 10 mg film-coated tablets for oral use. The approved posology for the paediatric indication is:

Body weight (kg)	Initial once daily dose (mg)	Subsequent once daily dose titration (mg)*
≥50 ≥35 to <50 ≥20 to <35	5 5 2.5	10 7.5 5
* =dependent on clinical response and tolerability		

In paediatric patients, when co-administered with cyclosporine A, the dose of ambrisentan for patients ≥50 kg should be limited to 5 mg once daily, or for patients ≥20 to <50 kg should be limited to 2.5 mg once daily. The patient should be carefully monitored.

In the hereby submitted study, ambrisentan was provided to study centers at the following dosage forms and strengths:

- Commercially available 10 mg tablet
- Commercially available 5 mg tablet
- Manufactured 2.5 mg tablet of equivalent. The 2.5 mg tablet was developed for use in paediatric populations (see procedure No. EMEA/H/C/000839/X/0061/G).

Participants in study AMB114588 could receive 2.5 mg, 5 mg, 7.5 mg, or 10 mg of ambrisentan per day, dosed orally (tablet[s] in 2.5 mg, 5 mg, and 10 mg strengths swallowed whole), once daily.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final reports for:

- Study AMB114588 (EudraCT Number: 2010-021572-29) – "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"

Please note that an interim analysis of this extension study (ID AMB114588) was submitted to the European Medicines Agency (EMA) to support regulatory activities (Procedure No. EMEA/H/C/000839/X/0061/G).

2.3.2. Clinical study

Study AMB114588 (EudraCT Number: 2010-021572-29) – "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"

Description

Study AMB114588 was a phase 2b, open-label, multi-center, long term extension to study AMB112529 which was only open to patients who had previously participated in the pivotal phase 2b study AMB112529, a 24-week (6-month), randomised, open label study comparing safety and efficacy parameters for a High dose (7.5 mg or 10 mg, adjusted for body weight) and a Low dose (2.5 mg or 5 mg, adjusted for body weight) of ambrisentan for the treatment of PAH in paediatric patients aged 8 years up to 18 years, and in whom continued treatment with ambrisentan was warranted. The primary objective was to continue to monitor the safety and tolerability of ambrisentan at 1 of the 4 dose levels (2.5 mg, 5 mg, 7.5 mg, or 10 mg) studied in study AMB112529 over an extended period of time. The secondary objective was to obtain supportive efficacy data on the paediatric use of ambrisentan.

Participants could remain in study AMB114588 for a minimum of 6 months. Beyond the 6-month period, participants could continue in the extension study until one of the following conditions was met:

- The subject turned 18 years of age (when the subject could receive marketed product) or the reached pubertal maturity before 18 years of age (ambrisentan could be supplied through a named patient or expanded access program until the participant reached 18 years of age).

• The product was approved and available for use in the subject's age group.

• Development for use in the paediatric population was discontinued.

• The subject decided he/she no longer wanted to participate in the study.

• The investigator considered it in the best interest of the subject to discontinue ambrisentan (e.g., for safety reasons).

Participants were followed for 30 days post their last dose of ambrisentan for the monitoring of AEs/SAEs.

Methods

Study participants

Eligible participants for this study had participated in AMB112529, which included the following criteria for enrolment: males or females at least 8 years of age and not yet 18 years of age (at the time of randomization); a diagnosis of PAH (WHO Group 1) with WHO Class II or III symptoms that were idiopathic, familial, secondary to connective tissue disease, or persistent PAH despite surgical repair; not taking an ERA; and, no changes to their baseline drug therapy for PAH for the duration of the study.

Inclusion criteria

- Had to have complied with the protocol for AMB112529 and completed the Week 24 Visit in that study. For participants who did not complete the Week 24 Visit, 1 of 3 criteria had to be met:
    - Had required additional targeted treatment for PAH due to inadequate response to the current treatment or worsening of their clinical condition prior to Week 24 in AMB112529.
    - Had required a reduction in dose of baseline targeted treatment for PAH after ambrisentan was added to the treatment regimen.
    - In the opinion of the investigator, continued treatment with ambrisentan was warranted.
- Females had to be of non-childbearing potential (physiologically incapable of becoming pregnant) or, for those with child-bearing potential and sexually active, 2 reliable methods of contraception were to be used until study completion and for at least 30 days following the last dose of study drug.
- Participant or participant's legal guardian had to be able and willing to give written informed consent. As part of the consent and as aligned with the product label, female participants of

childbearing potential were informed of the risk of teratogenicity and were required to be counselled in a developmentally appropriate manner on the importance of pregnancy prevention; male participants were informed of the potential risk of testicular tubular atrophy and aspermia.

Exclusion criteria

- Participants withdrawn from ambrisentan in AMB112529 or whom did not comply with that study's protocol.

- Females who were pregnant or breastfeeding.

- Had severe renal impairment (estimated creatinine clearance <30 mL/min) at the point of transition from AMB112529 into this study.

- Had clinically significant fluid retention or clinically significant anemia in the opinion of the investigator, or participants who were to enter another clinical trial or be treated with another investigational product after exiting AMB112529.

Treatments

Participants received 2.5 mg, 5 mg, 7.5 mg, or 10 mg of ambrisentan per day, dosed orally (tablet[s] in 2.5 mg, 5 mg, and 10 mg strengths swallowed whole), once daily.

At the time the participant exited AMB112529, the investigator was told the dose of ambrisentan that the participant was receiving. Based on the investigator's best judgement, participant could continue on the same dose, the dose could be adjusted downward or upward in 2.5 mg increments to not less than 2.5 mg per day and not more than the lesser of 10 mg per day or 0.25 mg/kg per day.

Whenever the dose of ambrisentan was changed, 1 of the following reasons for the change was required to be recorded:

- Change in body weight.
- Deterioration of clinical condition.
- Tolerability issues.
- Other.

Objectives

- The primary objective of this open-label, long-term extension study was to continue to monitor the safety and tolerability of ambrisentan at dose levels studied in study AMB112529 over an extended period of time in a paediatric (aged 8 years up to 18 years) PAH population.

- The secondary objective was to obtain supportive efficacy data on the paediatric use of ambrisentan in PAH.

Outcomes/endpoints

Primary Safety Assessments:

In order to meet the primary objectives of the long-term safety and tolerability of ambrisentan in a paediatric PAH population at dose levels studied in study AMB112529 over an extended period of time, the safety endpoints stated below were measured monthly, every 3 months, or every 6 months, as required for each parameter of interest. Assessments marked with an asterisk (*) were pre-specified to be evaluated as changes from AMB112529 Baseline:

- Adverse Events (AEs) (AMB114588 Study Entry and every 3 months through to End of Study [EOS]).
- Serious Adverse Events (SAEs) (AMB114588 Study Entry and every 3 months through to EOS).
- Hematology and clinical chemistry (AMB114588 Study Entry and every 3 months through to EOS).
- Liver function tests – ALT, AST, GGT, and total bilirubin (AMB114588 Study Entry and monthly through to EOS; following Protocol Amendment 03 implementation, schedule changed to every 3 months, unless clinically indicated).
- Physical examination – liver size, jugular venous pressure, oxygen saturation, and the presence of peripheral edema and/or ascites (AMB114588 Study Entry and every 6 months through to EOS).
- Vital signs – systolic and diastolic blood pressure, heart rate, weight, height, body mass index, and body surface area (AMB114588 Study Entry and every 3 months through to EOS).
- Pubertal development* – males: right and left testicular volume (Prader's orchidometer) and genital and pubic hair development (Tanner criteria); females: breast and pubic hair development (Tanner criteria) (AMB114588 Study Entry and every 6 months through to EOS).
- Endocrinology assessments* – males: total testosterone, FSH, inhibin B, LH, and SHBG; females: estriol, estrone, estradiol, FSH, inhibin B, LH, and SHBG (AMB114588 Study Entry and every 6 months through to EOS).
- Time to a change in the dose of ambrisentan or other targeted PAH therapeutic agents (prostanoids, PDE-5i) due to tolerability issues.
- 12-lead ECGs were performed at AMB114588 Study Entry and every 6 months through to EOS.

AE information volunteered by the participant, discovered by investigator questioning, or detected by other means, was collected from the start of study treatment until follow-up. The following information on AEs was obtained:

- Duration (start and stop dates).
- Severity (mild, moderate, severe).
- Causality (reasonable possibility as yes/no).
- Actions taken and outcome.

Secondary Efficacy Assessments:

To meet the secondary objective of obtaining supportive efficacy data on the paediatric use of ambrisentan in PAH, the efficacy endpoints stated below were measured every 3 months or 6 months, as required for each parameter of interest. Assessments marked with an asterisk (*) were pre-specified to be evaluated as changes from AMB112529 Baseline:

- 6-minute walk distance (6MWD)* (AMB114588 Study Entry and every 6 months through to EOS; following Protocol Amendment 03 implementation, 6MWD became an optional assessment). Participants with a 20% decrease in 6MWD from AMB112529 Baseline were required to return in 1 week to repeat the test to confirm PAH deterioration. Time to clinical worsening of PAH, defined as the time to the first occurrence of:
  - death (all cause) or placement on active list for lung transplant and/or atrial septostomy;
  - hospitalization due to PAH deterioration;
  - addition of another targeted PAH therapeutic agent (prostanoids, PDE-5i) due to deterioration of clinical condition;
  - change in dose of ambrisentan or other targeted PAH therapeutic agent (prostanoids, PDE-5i) due to deterioration of clinical condition;
  - PAH-related deterioration, identified by: increase in WHO Functional Class, deterioration in exercise testing (i.e., a 20% decrease in 6MWD on 2 consecutive tests 1 week apart), and/or 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).
- Time to addition of another targeted PAH therapeutic agent(s) (prostanoids, PDE-5i).
- Time to change in dose of ambrisentan or other targeted PAH therapeutic agents (prostanoids, PDE-5i) due to deterioration of clinical condition.

- WHO Functional Class* (AMB114588 Study Entry and every 6 months through to EOS).
- Plasma NT-proBNP* (AMB114588 Study Entry and every 6 months through to EOS).
- Health outcomes assessments*
    - SF-10 Health Survey for Children (AMB114588 Study Entry and every 3 months through to EOS).
    - Missed school days (AMB114588 Study Entry and every 3 months through to EOS).
- Echocardiograms* – pericardial effusion, right atrial pressure, tricuspid annular plane systolic excursion, eccentricity index (systolic and diastolic), right ventricular pressure, and tricuspid regurgitant jet velocity (AMB114588 Study Entry and every 6 months through to EOS).

Sample size

Sample size was based on the number of participants who had previously completed AMB112529. No sample size calculations were performed.

Randomisation and blinding (masking)

This was a non-randomized study where the treatment assignment was based on the investigator's best judgement. There was no blinding as AMB114588 was an open-label study.

Statistical Methods

Statistical Analyses

All programming of tables, figures and listings were performed using Statistical Analysis System (SAS) version 8.2 or higher.

There were no hypothesis tests or formal comparisons planned for this study. All safety, efficacy, and other data were presented descriptively with summary statistics and graphically (where applicable) by dose group (2.5 mg, 5 mg, 7.5 mg, or 10 mg) and overall (for the total population). Where available, data were summarized by visit.

For endpoints analyzed as changes from baseline, baseline values were those collected prior to the first dose in AMB112529.

A log transformation was applied to NT-proBNP data and summary measures were based on an analysis of log-transformed data which included the geometric mean.

Analysis Sets

The Safety Population, used to analyze safety parameters, consisted of all participants who received at least 1 dose of study drug. In the Safety Population, participants belonged to a treatment group according to the highest ambrisentan dose received in the extension study (ID AMB114588). The Intention-to-Treat (ITT) Population, used to analyse study population and efficacy parameters, consisted of all participants who received at least 1 dose of study drug. In the ITT population, participants belonged to a treatment group according to the ambrisentan dose received at the start of the extension study (ID AMB114588). The Idiopathic group included participants from the ITT Population with an idiopathic etiology of PAH at the start of study treatment in AMB112529. The Non-idiopathic group included participants from the ITT Population with an etiology of PAH (at the start of study treatment in AMB112529) defined as familiar, persistent PAH despite surgical repair, or secondary to connective tissue disease.

Interim Analyses

There were no planned interim analyses for this study. However, an unplanned interim analysis was conducted to support regulatory activities (Procedure No. EMEA/H/C/000839/X/0061/G). All data collected by a pre-determined clinical cut-off date of 23 August 2019 were analyzed in that interim analysis.

Results

Participant flow

Of the 41 participants randomized into a Low dose (N=21) or High dose (N=20) group in AMB112529, 38 participants (93%) entered this long-term extension study. Overall, just over half (55%; n=21) of the participants who entered this extension study completed it. Across the dose groups, the proportion of completers ranged from 42% (8 of 19 participants for 5 mg group) to 100% (5 of 5 participants for 10 mg group).

Just under half of all participants withdrew from the extension study (45%; n=17). The most frequently reported reasons for study withdrawal were investigator discretion (18%; n=7) and the report of AEs (16%; n=6). The 6 participants withdrawn from the study due to AEs experienced SAEs that led to death.

Patient disposition is shown in table 1:

Table 1. Summary of Subject Disposition (ITT Population)

	Ambrisentan Dose Group				Total
	2.5 mg (N=9)	5 mg (N=19)	7.5 mg (N=5)	10 mg (N=5)	(N=38)
	n (%)				
Status					
Completed	5 (56)	8 (42)	3 (60)	5 (100)	21 (55)
Withdrawn	4 (44)	11 (58)	2 (40)	0	17 (45)
Ongoing	0	0	0	0	0
Died	0	5 (26)	1 (20)	1 (20)	7 (18)[a]
Primary reason for study withdrawal					
Adverse event	0	5 (26)	1 (20)	0	6 (16)[b]
Lost to follow-up	0	2 (11)	0	0	2 (5)
Investigator discretion	3 (33)	3 (16)	1 (0)	0	7 (18)
Withdrew consent	1 (11)	1 (5)	0	0	2 (5)

Source: Table 1.1
Abbreviations: N= Number of participants, ()= percentage
a. All 7 deaths were due to SAEs with 1 of the deaths (5 mg) due to COVID-19 complications
b. These 6 participants who were withdrawn from the study due to an AE experienced SAEs that led to death.

Recruitment

A total of 38 participants, who had previously completed AMB112529, were enrolled into this extension study AMB114588.

Participants were recruited across 9 countries: US (n=7 participants), Russian Federation (n=7), Argentina (n=5), Hungary (n=5), Japan (n=5), France (n=3), Germany (n=2), Italy (n=2), Spain (n=2) during the study period (21 Jun 2011 [date of first subject roll-over from study AMB112529] – 12 Nov 2013 [last subject rolled over to this long-term extension study]). The investigational sites were the same as those used in AMB112529.

Baseline data

Demographic characteristics:

At AMB112529 Baseline, the majority of the study population was 12 to <18 years of age (63%; 24 of 38 participants), which was also the age stratum represented by the majority of participants in the 5 mg (63%; 12 of 19 participants), 7.5 mg (80%; 4 of 5 participants), and 10 mg (100%; 5 of 5 participants) dose groups. The majority of participants (67%; 6 of 9 participants) in the lowest dose group (ambrisentan 2.5 mg) were represented by the younger age stratum (8 to 11 years of age). The mean/median age of the study population was 11.9/12.5 years (range: 8 to 16 years). The majority was female (66%; 25 of 38 participants) and of White/Caucasian/European Heritage (71%; 27 of 38 participants) with approximately one-third (32%; 12 of 38 participants) of Hispanic/Latino ethnicity. Five of 38 participants (13%) were of Japanese heritage, 2 of 38 participants (5%) were African American/African heritage, and single participants had other geographic ancestry.

For the summary of Demographic Characteristics at start of AMB112529 and at entry to AMB114588, see Table 2.

Table 2 Summary of Demographic Characteristics (ITT Population)

	Ambrisentan Dose Group				Total (N=38)
	2.5 mg (N=9)	5 mg (N=19)	7.5 mg (N=5)	10 mg (N=5)	
Age (yrs)[a]					
Mean (SD)	9.7 (2.29)	11.9 (2.57)	12.6 (2.61)	15.2 (0.84)	11.9 (2.81)
Median	8.0	13.0	12.0	15.0	12.5
Min to Max	8 to 13	8 to 16	9 to 16	14 to 16	8 to 16
Age stratum; n (%)[a]					
8 to 11 yrs	6 (67)	7 (37)	1 (20)	0	14 (37)
12 to <18 yrs	3 (33)	12 (63)	4 (80)	5 (100)	24 (63)
Sex; n (%)[a]					
Female	7 (78)	9 (47)	4 (80)	5 (100)	25 (66)
Male	2 (22)	10 (53)	1 (20)	0	13 (34)
Childbearing potential for females; n (%)[b]					
n	7	9	4	5	25
Pre-menarcheal	6 (86)	6 (67)	2 (50)	0	14 (56)
Potentially able to bear children	1 (14)	3 (33)	2 (50)	5 (100)	11 (44)
Weight (kg)[b]					
Mean (SD)	30.11 (4.457)	40.39 (13.711)	42.74 (5.874)	60.30 (10.040)	40.88 (13.789)
Median	29.60	38.00	39.80	58.70	37.50
Min to Max	25.2 to 37.0	20.1 to 70.8	36.7 to 50.0	50.4 to 77.2	20.1 to 77.2
Weight category; n (%)[b]					
20 to <35 kg	7 (78)	9 (47)	0	0	16 (42)
35 to <50 kg	2 (22)	5 (26)	4 (80)	0	11 (29)
≥50 kg	0	5 (26)	1 (20)	5 (100)	11 (29)

Source: Table 1.5
a. At AMB112529 Baseline.
b. At AMB114588 Study Entry.

Other Baseline Characteristics:

At AMB112529 Baseline, the majority of the study population (84%) and the majority in each dose group (79% to 100%) were classified as WHO Functional Class II with the remaining participants (16%) meeting WHO Functional Class III. The median (range) 6MWD for the study population was 438 m (160 m to 600 m).

For the summary of Baseline Characteristics at start of AMB112529 and at entry to AMB114588, see Table 3.

Table 3. Summary of WHO Functional Class and 6MWD (ITT Population)

	Ambrisentan Dose Group				Total (N=38)
	2.5 mg (N=9)	5 mg (N=19)	7.5 mg (N=5)	10 mg (N=5)	
AMB112529 Baseline - WHO Functional Class; n (%)					
Class II	9 (100)	15 (79)	4 (80)	4 (80)	32 (84)
Class III	0	4 (21)	1 (20)	1 (20)	6 (16)
AMB114588 Study Entry - WHO Functional Class; n (%)					
Class I	4 (44)	2 (11)	3 (60)	0	9 (24)
Class II	5 (56)	12 (63)	1 (20)	4 (80)	22 (58)
Class III	0	4 (21)	1 (20)	1 (20)	6 (16)
Class IV	0	1 (5)	0	0	1 (3)
AMB112529 Baseline - 6MWD (m)					
Mean (SD)	393.32 (99.393)	433.96 (123.120)	484.56 (89.889)	460.00 (94.170)	434.42 (110.371)
Median	420.50	453.00	500.00	450.00	438.00
Min to Max	168.0 to 486.0	160.0 to 600.0	370.0 to 592.8	330.0 to 580.0	160.0 to 600.0
AMB114588 Study Entry - 6MWD (m)[a]					
Mean (SD)	485.38 (75.619)	464.52 (125.709)	538.04 (119.203)	465.80 (99.329)	479.70 (109.686)
Median	480.00	455.50	580.00	477.00	477.00
Min to Max	333.5 to 561.0	160.0 to 710.0	365.0 to 640.0	300.0 to 560.0	160.0 to 710.0

Source: Table 1.5
a. For 5 mg group, 6MWD data was based on 18 and not 19 participants.

Number analysed

A total of 38 patients were enrolled from the AMB112529 study. At entry to the extension study AMB114588, all 38 participants were included in the Safety Population and the ITT Population. Study population and efficacy parameters were summarized using the ITT Population which utilized the dose group at entry into this extension study, whereas all safety parameters were summarized using the Safety Population, which utilized the highest dose received in the extension study. In total, there were 12 participants who presented in a different dose group for the study population and efficacy parameters (ITT Population) compared with the safety parameters (Safety Population) since they were titrated up during this extension study and had a 'highest dose' of ambrisentan above that of the 'initial dose' at entry.

Table 4. Initial Dose of Ambrisentan at Entry to AMB114588 and Highest Dose Received in AMB114588

ITT Population (N=38)	Safety Population (N=38)			
Initial Ambrisentan Dose	Highest Ambrisentan Dose			
	2.5 mg (N=4)	5 mg (N=16)	7.5 mg (N=6)	10 mg (N=12)
2.5 mg (N=9)	4	2	1	2
5 mg (N=19)	0	14	2	3
7.5 mg (N=5)	0	0	3	2
10 mg (N=5)	0	0	0	5

Source: Table 1.13

Abbreviations: N= Number of participants; () =percentage

Efficacy results

All efficacy results are presented by the initial ambrisentan dose group (2.5 mg, 5 mg, 7.5 mg or 10 mg) at entry into this extension study (ID AMB114588) in accordance with the analysis population criteria for the ITT Population.

6MWD:

From AMB112529 Baseline to AMB114588 End of Study, for the total population at the end of the study (n=29 participants in whom data were available), 6MWD increased by a mean/median of 58.4 m/55.5 m, representing mean and median increases of 17.0% and 13.9%, respectively. 6MWD increases were greatest in the 2.5 mg and 5 mg groups.

For the summary of 6MWD (ITT Population) at start of AMB112529, at entry to AMB114588 and AMB114588 End of Study, see Table 5.

Table 5 Summary of 6MWD (ITT Population)

	Ambrisentan Dose Group				Total (N=38)
	2.5 mg (N=9)	5 mg (N=19)	7.5 mg (N=5)	10 mg (N=5)	
	Walking distance (m)				
AMB112529 Baseline[a]					
n	9	19	5	5	38
Mean (SD)	393.32 (99.393)	433.96 (123.120)	484.56 (89.889)	460.00 (94.170)	434.42 (110.371)
Median	420.50	453.00	500.0	450.00	438.00
Min to Max	168.0 to 486.0	160.0 to 600.0	370.0 to 592.8	330.00 to 580.00	160.0 to 600.0
AMB114588 Entry Visit					
n	9	18	5	5	37
Mean (SD)	485.38 (75.619)	464.52 (125.709)	538.04 (119.203)	465.80 (99.329)	479.70 (109.686)
Median	480.00	455.50	580.00	477.00	477.00
Min to Max	333.5 to 561.0	160.0 to 710.0	365.0 to 640.0	300.0 to 560.0	160.0 to 710.0
AMB114588 End of Study					
n	9	11	4	5	29
Mean (SD)	491.86 (114.580)	504.98 (146.375)	516.25 (54.482)	494.24 (126.599)	500.61 (118.680)
Median	450.00	542.00	529.50	540.00	528.00
Min to Max	380.4 to 660.0	137.5 to 650.0	442.0 to 564.0	300.0 to 637.0	137.5 to 660.0
Change from AMB112529 Baseline to AMB114588 End of Study (m)					
n	9	11	4	5	29
Mean (SD)	98.53 (115.355)	56.74 (58.069)	3.05 (94.659)	34.24 (72.135)	58.42 (88.149)
Median	80.00	57.00	-36.90	27.00	55.50
Min to Max	-81.6 to 282.0	-41.0 to 142.6	-58.0 to 144.0	-40.0 to 123.0	-81.6 to 282.0
Change from AMB112529 Baseline to AMB114588 End of Study (%)					
n	9	11	4	5	29
Mean (SD)	34.468 (54.0742)	12.715 (17.2296)	2.435 (21.3867)	6.910 (15.1262)	17.047 (34.3063)
Median	19.510	12.100	-6.475	6.340	13.900
Min to Max	-17.66 to 167.86	-14.06 to 41.72	-11.60 to 34.29	-9.09 to 23.93	-17.66 to 167.86

Source: Table 2.2, Table 2.3, and Table 2.4

Note: 6MWD results apply to all participants who completed the assessment at the respective timepoint whether or not oxygen was used. For the total population, the number of participants requiring oxygen for the 6MWD was 4 of 38 participants at AMB112529 Baseline, 4 of 37 participants at AMB114588 Study Entry, and 2 of 29 participants at AMB114588 End of Study.

a. At AMB112529 Baseline, there were 5 participants across 3 dose groups (2.5 mg, 5 mg, 10 mg) who could not complete the 6-minute test (range: 2.3 to 5.8 minutes); however, their data contributed to the summary statistics.

Over half of the study population (58%; 22 of 38 participants) achieved a clinically significant improvement in 6MWD (defined as an increase in walk distance by at least 20 m) from AMB112529 Baseline to last observation, with a comparable proportion in those with an idiopathic etiology of PAH at AMB112529 Baseline (58%; 14 of 24 participants) or a non-idiopathic etiology (57%; 8 of 14 participants).

The number of participants requiring oxygen for 6MWD was 4 of 37 participants at AMB114588 Study Entry (2 each from the 2.5 mg and 5 mg groups), and 2 of 29 participants at AMB114588 End of Study (2 from the 2.5 mg group).

Table 6. Summary of use of Oxygen during 6 Minute Walking exercise (L/min)

Treatment	Planned Relative Time	Number of Subjects who attempted the 6 minute walk	n	Mean	SD	Q1	Median	Q3	Min.	Max.
Total (N=38)	Baseline**	38	4 (11%)	1.38	0.750	1.00	1.00	1.75	1.0	2.5
	Entry Visit*	37	4 (11%)	1.38	0.750	1.00	1.00	1.75	1.0	2.5
	Month 6	34	3 (9%)	1.50	0.866	1.00	1.00	2.50	1.0	2.5
	Month 12	30	3 (10%)	1.50	0.866	1.00	1.00	2.50	1.0	2.5
	Month 18	27	3 (11%)	1.50	0.866	1.00	1.00	2.50	1.0	2.5
	Month 24	27	3 (11%)	1.50	0.866	1.00	1.00	2.50	1.0	2.5
	Month 30	23	3 (13%)	1.50	0.866	1.00	1.00	2.50	1.0	2.5
	Month 36	20	3 (15%)	1.50	0.866	1.00	1.00	2.50	1.0	2.5
	Month 42	17	2 (12%)	1.00	0.000	1.00	1.00	1.00	1.0	1.0
	Month 48	17	2 (12%)	1.25	0.354	1.00	1.25	1.50	1.0	1.5
	Month 54	11	2 (18%)	1.25	0.354	1.00	1.25	1.50	1.0	1.5
	Month 60	9	2 (22%)	1.25	0.354	1.00	1.25	1.50	1.0	1.5
	Month 66	8	2 (25%)	1.25	0.354	1.00	1.25	1.50	1.0	1.5
	End of Study	29	2 (7%)	1.25	0.354	1.00	1.25	1.50	1.0	1.5

Note:** Baseline is the last value recorded prior to start of study treatment from AMB112529.
* Entry Visit is at entry to AMB114588.
Q1 = 1st quartile, Q3 = 3rd quartile.
Subjects are considered as belonging to their treatment group at the start of study AMB114588.

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Time to Clinical Worsening of PAH:

In the extension study (ID AMB114588), 11 of 38 participants (29%) across all 4 dose groups experienced an occurrence of clinical worsening of PAH based on at least 1 of 5 pre-specified criteria, with more than 1 clinical worsening criterion met by 5 of 11 participants (45%). The most frequently reported reasons for clinical worsening of PAH were death (6 of 38 participants; 16%) and PAH-related deterioration (4 of 38 participants; 11%); PAH-related deterioration was due to an increase from AMB112529 baseline in WHO Functional Class (2 participants) and/or clinical signs or symptoms of right-sided heart failure (3 participants). Following randomization in AMB112529, the mean/median time to clinical worsening of PAH in the extension study was approximately 2.2 years/1.5 years with a range of approximately 3 months to 5.2 years. Approximately 70% of the clinical worsening occurrences (for 8 of 11 participants) were within 3 years following randomization in AMB112529. In this extension study, 7 participants died approximately 3 months to 8 years following randomization in AMB112529 with a mean/median time to death of approximately 4.2 years/5.2 years from the start of treatment in AMB112529.

Table 7. Summary of Clinical Worsening of PAH (ITT Population)

		Ambrisentan Dose Group				Total (N=38)
		2.5 m (N=9)	5 mg (N=19)	7.5 mg (N=5)	10 mg (N=5)	
Participants meeting at least one criterion (n [%])[a]		2 (22)	5 (26)	3 (60)	1 (20)	11 (29)
Clinical Worsening Criteria Met by Participants (n [%])[b]						
Death (all-cause) or placed on an active list for a lung transplant or atrial septostomy[c]		0	4 (21)	1 (20)	1 (20)	6 (16)
Hospitalization for worsening of PAH		0	1 (5)	1 (20)	0	2 (5)
Addition of another targeted PAH therapeutic agent[d]		2 (22)	0	1 (20)	0	3 (8)
Change in dose of ambrisentan or other targeted PAH therapeutic agents		0	0	1 (20)	0	1 (3)
PAH-related deterioration		1 (11)	2 (11)	0	1 (20)	4 (11)
Reasons for PAH-related deterioration[e]	Increase from baseline in WHO functional class	0	1 (50)	0	1 (100)	2 (50)
	Deterioration in exercise testing[f]	0	0	0	0	0
	Clinical signs or symptoms of right-sided heart failure[g]	1 (100)	1 (50)	0	1 (100)	3 (75)

Abbreviations: N= Number of participants; ()=percentage
Source: Table AMB114588 2.8

a. Participants who experienced clinical worsening of PAH in AMB114588 based on at least one criterion.
b. More than one criterion could have been met by participants.
c. One additional participant who died was not entered as a clinical worsening prior to site closure.
d. Prostanoids and/or PDE-5i.
e. For the reasons for PAH-related deterioration, the denominator used for the percentage derivation was the number of participants experiencing 'PAH-related deterioration' in each dose group or overall – i.e., 2.5 mg (n=1), 5 mg (n=2), 10 mg (n=1), total (n=4).
f. Defined as a 20% decrease in 6MWD on 2 consecutive tests conducted 1 week apart.
g. Clinical signs or symptoms of right-sided heart failure were new peripheral edema, increase in liver size, ascites, increase in jugular venous pressure, pericardial effusion, increased dyspnea.

Table 8. Summary of Time to Clinical Worsening of PAH (ITT Population)

	Ambrisentan Dose Group				Total (N=38)
	2.5 mg (N=9)	5 mg (N=19)	7.5 mg (N=5)	10 mg (N=5)	
n (%)[a]	2 (22)	5 (26)	3 (60)	1 (20)	11 (29)
Mean (SD) (d)[b]	315.5 (2.12)	896.2 (721.33)	1122.0 (704.09)	228.0	791.5 (650.07)
Median (d)	315.5	868.0	909.0	228.0	549.0
Min to Max (d)	314 to 317	101 to 1884	549 to 1908	228 to 228	101 to 1908

Abbreviations: N= Number of participants; ()= percentage
Source: Table AMB114588 2.7

a. Participants who experienced clinical worsening of PAH in AMB114588 based on at least 1 criterion. One additional participant who died was not entered as a clinical worsening prior to site closure.
b. Time to clinical worsening was estimated from AMB112529 Baseline.

Time to the Addition of Another Targeted PAH Therapeutic Agent:

Over the course of this extension study (ID AMB114588), 17 of 38 participants (45%) across all 4 dose groups required the addition of another targeted PAH therapeutic agent (prostanoids, PDE-i) due to deterioration of clinical condition (6 participants), lack of beneficial effect with previous therapy (3 participants), and/or other reason (i.e., 'other', 'electively') (12 participants). Of these 17 participants, 8 had additions due to deterioration in clinical condition and/or lack of beneficial effect with previous therapy. Overall, considering all reasons for the addition of a PAH therapy, the mean/median time to the addition of a PAH therapy was 1.8 years/1.2 years (range of approximately 3 months to 5.2 years) from the start of ambrisentan dosing in AMB112529.

Table 9. Summary of Time to the Addition of Another Targeted PAH Therapeutic Agent (Prostanoids, PDE-5i) (ITT Population)

	Ambrisentan Dose Group				Total (N=38)
	2.5 mg (N=9)	5 mg (N=19)	7.5 mg (N=5)	10 mg (N=5)	
Due to deterioration of clinical condition					
n (%)[a]	1 (11)	2 (11)	1 (20)	2 (40)	6 (16)
Mean (SD) (d)[b]	510.0	697.5 (863.38)	909.0	345.5 (109.60)	584.2 (449.01)
Median (d)	510.0	697.5	909.0	345.5	466.5
Min to Max (d)	510 to 510	87 to 1308	909 to 909	268 to 423	87 to 1308
Due to lack of beneficial effect with previous therapy					
n (%)[a]	2 (22)	1 (5)	0	0	3 (8)
Mean (SD) (d)[b]	315.5 (2.12)	173.0	-	-	268.0 (82.29)
Median (d)	315.5	173.0	-	-	314.0
Min to Max	314 to 317	173 to 173	-	-	173 to 317
Overall[c]					
n (%)[a]	5 (56)	8 (42)	2 (40)	2 (40)	17 (45)
Mean (SD) (d)[b]	802.8 (786.58)	466.4 (394.75)	1381.5 (668.22)	345.5 (109.60)	658.8 (595.03)
Median (d)	314.0	396.5	1381.5	345.5	423.0
Min to Max (d)	160 to 1882	87 to 1308	909 to 1854	268 to 423	87 to 1882

Abbreviations: N= Number of participants; ()= percentage
Source: Table AMB114588 2.9

a. Participants who required the addition of another targeted PAH therapeutic agent in AMB114588.
b. Time to the addition of another targeted PAH therapeutic agent was estimated from AMB112529 Baseline.
c. 'Overall' includes reasons related to deterioration of clinical condition, lack of beneficial effect with previous therapy, or PAH therapeutic agents (prostanoids, PDE-5i) started for other reasons (i.e., 'Other', 'Electively').

Time to Change in Dose of Ambrisentan or Other Targeted PAH Therapeutic Agent due to Deterioration of Clinical Condition:

Over the course of this extension study (ID AMB114588), 9 of 38 participants (24%) across all 4 dose groups required a change in the dose of ambrisentan or another targeted PAH therapeutic agent (prostanoids, PDE-5i) due to deterioration of clinical condition. From the start of ambrisentan dosing in AMB112529, the mean/median time to a dose change in ambrisentan or a PAH therapeutic agent due to deterioration of clinical condition was 2.6 years/2.1 years (range of approximately 3 months to 6.7 years). Dose changes appeared to occur earlier in the highest ambrisentan dose group (10 mg) which had the lowest median time (approximately 1 year) compared with the other 3 dose groups (2.5 mg, 5 mg, 7.5 mg) with median times of approximately 2.1 years to 3.6 years.

Table 10. Summary of Time to Change in Dose of Ambrisentan or Other Targeted PAH Therapeutic Agent (Prostanoids, PDE-5i) due to Deterioration of Clinical Condition (ITT Population)

	Ambrisentan Dose Group				Total (N=38)
	2.5 mg (N=9)	5 mg (N=19)	7.5 mg (N=5)	10 mg (N=5)	
n (%)[a]	3 (33)	3 (16)	1 (20)	2 (40)	9 (24)
Mean (SD) (d)[b]	1247.3 (1051.97)	1097.0 (922.77)	909.0	345.5 (109.60)	959.2 (789.79)
Median (d)	780.0	1308.0	909.0	345.5	780.0
Min to Max (d)	510 to 2452	87 to 1896	909 to 909	268 to 423	87 to 2452

Abbreviations: N= Number of participants; () = percentage
Source: Table AMB114588 2.10
a. Participants who required a change in dose of ambrisentan or other targeted PAH therapeutic agent due to deterioration of clinical condition in AMB114588.
b. Time to change in dose of ambrisentan or other targeted PAH therapeutic agent was estimated from AMB112529 Baseline.

WHO Functional Class:

Changes from AMB112529 Baseline to AMB114588 End of Study showed an improvement (n=13; 45%) or no change (n=16; 55%), and no deterioration, in WHO Functional Class for study participants in whom data were available (n=29). Of those participants who experienced an improvement, most improved by 1 WHO Functional Class category (11 of 13 participants).

Plasma NT-proBNP:

From AMB112529 Baseline to AMB114588 End of Study, there was a geometric mean/median percent decrease in NT-proBNP for the total population in whom data was available (n=25), which was largely driven by NT-proBNP reductions in the 2 lower ambrisentan dose groups (2.5 mg and 5 mg). NT-proBNP levels were below 1200 ng/L at last observation for the majority of the study population (87%; 33 of 38 participants) with no apparent difference in this finding based on PAH etiology at AMB112529 Baseline: idiopathic group (83%; 20 of 24 participants) versus non-idiopathic group (93%; 13 of 14 participants). At any point in the extension study, NT-proBNP levels rose above 1200 ng/L for approximately one-third of the study population (29%; 11 of 38 participants) with an apparent difference in this finding based on PAH etiology at AMB112529 Baseline: idiopathic group (42%; 10 of 24 participants) versus non-idiopathic group (7%; 1 of 14 participants).

SF-10 and Missed School Days:

From AMB112529 Baseline to AMB114588 End of Study, mean/median changes in Physical Health and Psychosocial Summary scores from the SF-10 were minimal for the total population in whom data was available (n=26) and there was an overall decrease, or no change of school days missed due to PAH for participants.

Safety results

All safety results are presented according to the highest ambrisentan dose received in the extension study (ID AMB114588; 2.5 mg, 5 mg, 7.5 mg or 10 mg).

Treatment-emergent adverse events (TEAEs) were included in summary tables and were defined as events that started on or after the date of the first ambrisentan dose in AMB112529 and continued (i.e., were unresolved) into this extension study (ID AMB114588) or started on or after the date of the first ambrisentan dose in this extension study. Recurring TEAEs (i.e., successive TEAEs classified with the same preferred term) for a given participant were only counted once according to maximum intensity.

Extent of Exposure:

Exposure by duration for the Safety Population was estimated from the start of dosing in AMB112529. For the total population, the range in exposure was approximately 3 months (100 days) to approximately 10 years (3640 days) with a median exposure of approximately 3.5 years (1292 days). The median number of days of exposure was similar across dose groups; based on these data and the interval of days of exposure, there was no apparent trend regarding length of exposure to ambrisentan and dose group. The majority of participants in each dose group attending a visit were treatment compliant (75% to 100%), defined as receiving ≥80% and ≤120% of planned investigational product. The overall percentage of visits at which participants were treatment-compliant was 97.9%, with a similar result observed across dose groups (93.4% to 100%).

For the summary of Exposure to Investigational Product (Safety Population), see Table 11.

Table 11. Summary of Exposure to Investigational Product (Safety Population)

	Ambrisentan Dose Group				Total (N=38)
	2.5 mg (N=4)	5 mg (N=16)	7.5 mg (N=6)	10 mg (N=12)	
Number of days of exposure starting from AMB112529 Baseline					
Mean (SD)	1793.0 (1369.48)	1274.1 (832.87)	1278.2 (674.77)	1684.8 (976.87)	1459.1 (909.50)
Median	1569.5	1276.0	1321.0	1420.0	1291.5
Min to Max	393 to 3640	100 to 2829	476 to 2106	440 to 3559	100 to 3640
Interval of exposure starting from AMB112529 Baseline; n (%)[a]					
≤180 d (≤0.5 yr)	0	1 (6)	0	0	1 (3)
181 to 360 d (>0.5 to 1 yr)	0	2 (13)	0	0	2 (5)
361 to 540 d (>1 to 1.5 yrs)	1 (25)	2 (13)	1 (17)	1 (8)	5 (13)
541 to 720 d (>1.5 to 2 yrs)	0	0	1 (17)	1 (8)	2 (5)
721 to 900 d (>2 to 2.5 yrs)	0	1 (6)	0	0	1 (3)
901 to 1080 d (>2.5 to 3 yrs)	0	0	0	2 (17)	2 (5)
1081 to 1260 d (>3 to 3.5 yrs)	0	2 (13)	1 (17)	1 (8)	4 (11)
1261 to 1440 d (>3.5 to 4 yrs)	1 (25)	1 (6)	0	1 (8)	3 (8)
1441 to 1620 d (>4 to 4.5 yrs)	0	1 (6)	1 (17)	1 (8)	3 (8)
1621 to 1800 d (>4.5 to 5 yrs)	0	1 (6)	0	0	1 (3)
1801 to 1980 d (>5 to 5.5 yrs)	1 (25)	1 (6)	1 (17)	1 (8)	4 (11)
1981 to 2160 d (>5.5 to 6 yrs)	0	2 (13)	1 (17)	1 (8)	4 (11)
2161 to 2340 d (>6 to 6.5 yrs)	0	0	0	1 (8)	1 (3)
2341 to 2520 d (>6.5 to 7 yrs)	0	1 (6)	0	0	1 (3)
2521 to 2700 d (>7 to 7.5 yrs)	0	0	0	0	0
2701 to 2880 d (>7.5 to 8 yrs)	0	1 (6)	0	0	1 (3)
2881 to 3060 d (>8 to 8.5 yrs)	0	0	0	0	0
3061 to 3240 d (>8.5 to 9 yrs)	0	0	0	0	0
3241 to 3420 d (>9 to 9.5 yrs)	0	0	0	1 (8)	1 (3)
3421 to 3600 d (>9.5 to 10 yrs)	0	0	0	1 (8)	1 (3)
3601 to 3780 d (>10 to 10.5 yrs)	1 (25)	0	0	0	1 (3)

Abbreviations: N= Number of participants; () = percentage
Source: Table 3.1
a. Since 360 days was used in the source output to establish intervals of exposure, a conversion factor of 360 was used to estimate years from days for the purpose of this table

Treatment-Emergent Adverse Events Overall:

TEAEs were experienced by the majority of the study population (89%; n=34) and the majority in each dose group (81% to 100%). Overall, the occurrence of TEAEs did not appear to be dose-dependent.

TEAE occurrence did not appear to be dependent on PAH etiology at AMB112529 Baseline given the similar occurrence of TEAEs in the idiopathic group (92%; 22 of 24 participants) and non-idiopathic group (86%; 12 of 14 participants). There appeared to be a higher occurrence of TEAEs in participants on a PAH therapy (PDE-5i and/or prostanoids) during the extension study (97%; 28 of 29 participants) versus those not on a PAH therapy (67%; 6 of 9 participants).

One TEAE (swelling face; 10 mg) led to a dose decrease; no other TEAEs led to a dose decrease or increase. TEAEs that led to a dose interruption/delay were all reported for the same participant (2.5 mg): deafness (non-serious), and atrioventricular block complete, ALT increased, and hypotension (all serious).

There were 6 participants across 3 ambrisentan dose groups (5 mg, 7.5 mg and 10 mg) who were withdrawn from the extension study due to a TEAE; all of these TEAEs were serious and led to death. Aside from participants who experienced fatal serious TEAEs, no other participants permanently discontinued the study or investigational product due to TEAEs.

Most Frequent Treatment-Emergent Adverse Events:

Common TEAEs were defined as occurring in ≥5% of the study population (i.e., at least 2 participants, irrespective of dose group). The most common TEAEs in this extension study were upper respiratory tract infection (11 of 38 participants; 29%), nasopharyngitis (9 of 38 participants; 24%), and headache (7 of 38 participants; 18%). Their onset in the extension study was within the first 2 years (headache) or 4 years (upper respiratory tract infection, nasopharyngitis) of dosing starting from AMB112529 Baseline.

Table 12. Summary of TEAEs by Preferred Term Occurring in at least 5% of the Total Population (Safety Population)

Preferred Term	Ambrisentan Dose Group				Total (N=38)
	2.5 mg (N=4)	5 mg (N=16)	7.5 mg (N=6)	10 mg (N=12)	
	n (%)				
Any event	4 (100)	13 (81)	6 (100)	11 (92)	34 (89)
Upper respiratory tract infection	2 (50)	3 (19)	4 (67)	2 (17)	11 (29)
Nasopharyngitis	0	5 (31)	1 (17)	3 (25)	9 (24)
Headache	0	3 (19)	2 (33)	2 (17)	7 (18)
Anaemia[a]	0	2 (13)	0	4 (33)	6 (16)
Pharyngitis	1 (25)	3 (19)	0	2 (17)	6 (16)
Pyrexia	0	2 (13)	2 (33)	2 (17)	6 (16)
Gastroenteritis	1 (25)	2 (13)	0	2 (17)	5 (13)
Influenza	0	3 (19)	1 (17)	1 (8)	5 (13)
Nausea	0	2 (13)	2 (33)	1 (8)	5 (13)
Oropharyngeal pain	0	3 (19)	1 (17)	1 (8)	5 (13)
Epistaxis	0	1 (6)	2 (33)	1 (8)	4 (11)
Pain in jaw	0	2 (13)	2 (33)	0	4 (11)
Pulmonary arterial hypertension	0	0	1 (17)	3 (25)	4 (11)
Vomiting	1 (25)	2 (13)	1 (17)	0	4 (11)
Abdominal pain	0	1 (6)	0	2 (17)	3 (8)
Back pain	0	1 (6)	2 (33)	0	3 (8)
Constipation	1 (25)	1 (6)	0	1 (8)	3 (8)
Dermatitis contact[a]	0	1 (6)	1 (17)	1 (8)	3 (8)
Diarrhoea	0	1 (6)	2 (33)	0	3 (8)
Dysmenorrhoea	0	2 (13)	0	1 (8)	3 (8)
Erythema[a]	1 (25)	1 (6)	1 (17)	0	3 (8)
Iron deficiency anaemia[a]	0	3 (19)	0	0	3 (8)
Non-cardiac chest pain	0	2 (13)	0	1 (8)	3 (8)
Pain in extremity	0	0	2 (33)	1 (8)	3 (8)
Pneumonia	1 (25)	1 (6)	1 (17)	0	3 (8)
Rash[a]	0	1 (6)	2 (33)	0	3 (8)
Rhinitis allergic[a]	0	2 (13)	0	1 (8)	3 (8)
Toothache	0	1 (6)	0	2 (17)	3 (8)
Animal bite	0	0	0	2 (17)	2 (5)
Arthralgia	0	1 (6)	1 (17)	0	2 (5)
Aspartate aminotransferase increased[a]	1 (25)	0	0	1 (8)	2 (5)
Bronchitis	0	1 (6)	1 (17)	0	2 (5)
Cardiac failure acute	0	2 (13)	0	0	2 (5)
Chest pain	0	1 (6)	1 (17)	0	2 (5)
Conjunctivitis allergic[a]	0	1 (6)	0	1 (8)	2 (5)
Dizziness[a]	0	0	2 (33)	0	2 (5)
Dyspepsia	0	1 (6)	0	1 (8)	2 (5)
Eczema[a]	0	1 (6)	0	1 (8)	2 (5)
Fatigue	0	1 (6)	1 (17)	0	2 (5)
Gastroenteritis viral	0	2 (13)	0	0	2 (5)
Gastrooesophageal reflux disease	0	1 (6)	1 (17)	0	2 (5)
Hordeolum	0	1 (6)	1 (17)	0	2 (5)
Hot flush	0	1 (6)	1 (17)	0	2 (5)
Hypoaesthesia	0	0	1 (17)	1 (8)	2 (5)
Insomnia	0	1 (6)	1 (17)	0	2 (5)
Limb injury	0	0	0	2 (17)	2 (5)

Preferred Term	Ambrisentan Dose Group				Total (N=38)
	2.5 mg (N=4)	5 mg (N=16)	7.5 mg (N=6)	10 mg (N=12)	
	n (%)				
Motion sickness	0	1 (6)	0	1 (8)	2 (5)
Myalgia	0	1 (6)	1 (17)	0	2 (5)
Oedema peripheral[a]	0	1 (6)	0	1 (8)	2 (5)
Otitis externa	0	2 (13)	0	0	2 (5)
Otitis media	1 (25)	0	0	1 (8)	2 (5)
Otitis media chronic	1 (25)	0	0	1 (8)	2 (5)
Palpitations	0	1 (6)	1 (17)	0	2 (5)
Pharyngotonsillitis	0	0	0	2 (17)	2 (5)
Pruritus[a]	0	1 (6)	0	1 (8)	2 (5)
Puncture site pain	0	1 (6)	1 (17)	0	2 (5)
Respiratory tract infection	0	0	1 (17)	1 (8)	2 (5)
Rhinitis	0	1 (6)	0	1 (8)	2 (5)
Rhinorrhoea	1 (25)	1 (6)	0	0	2 (5)
Sinusitis	0	1 (6)	0	1 (8)	2 (5)
Tonsillitis	0	0	0	2 (17)	2 (5)
Vertigo	0	0	0	2 (17)	2 (5)

Abbreviations: N= Number of participants; ()= percentage
Source: Table AMB114588 3.3

Treatment-Emergent Adverse Events by Maximum Intensity:

TEAEs were rated as mild or moderate in maximum intensity for the majority of the study population (58%) and by at least half of participants in each dose group (50% to 75%). A total of 26 moderate TEAEs were experienced by 12 of 38 participants (32%) across all 4 dose groups; none were regarded as related to the investigational product and their occurrence did not appear to be dose-dependent. Of the 26 severe TEAEs, 18 were considered SAEs (6 of which had a fatal outcome).

Table 13. Summary of TEAEs by Maximum Intensity (Safety Population)

Maximum Intensity for Any Event	Ambrisentan Dose Group				Total (N=38)
	2.5 mg (N=4)	5 mg (N=16)	7.5 mg (N=6)	10 mg (N=12)	
	n (%)				
Mild	2 (50)	4 (25)	1 (17)	1 (8)	8 (21)
Moderate	1 (25)	4 (25)	3 (50)	6 (50)	14 (37)
Severe	1 (25)	5 (31)	2 (33)	4 (33)	12 (32)

Abbreviations: N= Number of participants; ()= percentage
Source: Table AMB114588 3.4

Treatment-Emergent Adverse Events Related to the Investigational Product:

Approximately 39% (15 of 38 patients) of the study population and 25% to 50% in each dose group experienced a TEAE that was considered related to the investigational product. Related TEAEs were more common in the higher ambrisentan dose groups (7.5 mg [50%] and 10 mg [50%]) as compared

with the lower ambrisentan dose groups (2.5 mg [25%] and 5 mg [31%]; differences in frequency did not appear to apply to a system organ class or TEAE specifically.

Table 14. Summary of TEAEs Related to the Investigational Product (Safety Population)

System Organ Class Preferred Term	Ambrisentan Dose Group				Total (N=38)
	2.5 mg (N=4)	5 mg (N=16)	7.5 mg (N=6)	10 mg (N=12)	
	n (%)				
Any event	1 (25)	5 (31)	3 (50)	6 (50)	15 (39)
Infections and infestations					
Any event	1 (25)	1 (6)	0	2 (17)	4 (11)
Gastroenteritis	1 (25)	0	0	1 (8)	2 (5)
Bronchitis	0	1 (6)	0	0	1 (3)
Nasopharyngitis	0	0	0	1 (8)	1 (3)
Pharyngotonsillitis	0	0	0	1 (8)	1 (3)
Sinusitis	0	1 (6)	0	0	1 (3)
Nervous system disorders					
Any event	0	2 (13)	2 (33)	0	4 (11)
Headache	0	1 (6)	2 (33)	0	3 (8)
Presyncope[a]	0	1 (6)	0	0	1 (3)
Syncope[a]	0	1 (6)	0	0	1 (3)
Ear and labyrinth disorders					
Any event	1 (25)	1 (6)	0	1 (8)	3 (8)
Deafness	1 (25)	0	0	0	1 (3)
Motion sickness	0	1 (6)	0	0	1 (3)
Vertigo	0	0	0	1 (8)	1 (3)
Skin and subcutaneous tissue disorders					
Any event	0	1 (6)	2 (33)	0	3 (8)
Alopecia	0	0	1 (17)	0	1 (3)
Angioedema[a]	0	0	1 (17)	0	1 (3)
Eczema[a]	0	1 (6)	0	0	1 (3)
Erythema[a]	0	0	1 (17)	0	1 (3)
Blood and lymphatic system disorders					
Any event	0	1 (6)	0	1 (8)	2 (5)
Anaemia[a]	0	1 (6)	0	1 (8)	2 (5)
General disorders and administration site conditions					
Any event	0	1 (6)	0	1 (8)	2 (5)
Oedema peripheral[a]	0	1 (6)	0	0	1 (3)
Swelling face[a]	0	0	0	1 (8)	1 (3)
Vascular disorders					
Any event	0	0	1 (17)	1 (8)	2 (5)
Hot flush	0	0	1 (17)	0	1 (3)
Hyperaemia	0	0	0	1 (8)	1 (3)
Cardiac disorders					
Any event	0	1 (6)	0	0	1 (3)
Cardiac failure congestive	0	1 (6)	0	0	1 (3)
Gastrointestinal disorders					
Any event	0	0	1 (17)	0	1 (3)
Abdominal pain upper	0	0	1 (17)	0	1 (3)
Dry mouth	0	0	1 (17)	0	1 (3)
Gastrooesophageal reflux disease	0	0	1 (17)	0	1 (3)
Nausea	0	0	1 (17)	0	1 (3)
Injury, poisoning, and procedural complications					
Any event	0	0	0	1 (8)	1 (3)
Skin laceration	0	0	0	1 (8)	1 (3)
Investigations					

System Organ Class Preferred Term	Ambrisentan Dose Group				Total (N=38)
	2.5 mg (N=4)	5 mg (N=16)	7.5 mg (N=6)	10 mg (N=12)	
	n (%)				
Any event	0	0	0	1 (8)	1 (3)
Aspartate aminotransferase increased[a]	0	0	0	1 (8)	1 (3)
Blood bilirubin increased[a]	0	0	0	1 (8)	1 (3)
Metabolism and nutrition disorders					
Any event	0	0	1 (17)	0	1 (3)
Decreased appetite	0	0	1 (17)	0	1 (3)
Musculoskeletal and connective tissue disorders					
Any event	0	0	1 (17)	0	1 (3)
Pain in jaw	0	0	1 (17)	0	1 (3)
Respiratory, thoracic, and mediastinal disorders					
Any event	0	0	1 (17)	0	1 (3)
Nasal obstruction	0	0	1 (17)	0	1 (3)

Abbreviations: N= Number of participants; ()= percentage
Source: Table AMB114588 3.7

Deaths:

In the extension study, TEAEs that were fatal were experienced by 7 participants across 3 dose groups (Safety Population; 5 mg, 7.5 mg, and 10 mg). Fatal serious TEAEs were PAH (n=2; 10 mg), cardiac failure acute (n=2; 5 mg; for 1 of these participants, the SAE began in AMB112529), acute right ventricular failure (n=1; 5 mg), COVID-19 (n=1; 5 mg), and failure to thrive (n=1; 7.5 mg). All serious TEAEs that resulted in death led to withdrawal from the study (n=6) with the exception of 1 participant who died from PAH after completing the treatment period and the study due to reaching the age of 18. None of the deaths were considered related to the investigational product by the investigator.

Other Serious Adverse Events:

In this extension study (ID AMB114588), 42 SAEs were experienced by just over half of the study population (21 participants; 55%) across all dose groups. A greater proportion of participants experienced SAEs in the higher ambrisentan dose groups (7.5 mg [67%] and 10 mg [67%]) as compared with the lower ambrisentan dose groups (2.5 mg [50%] and 5 mg [44%]). SAEs occurred more commonly in the idiopathic group (63%; 15 of 24 participants) as compared with the non-idiopathic group (43%; 6 of 14 participants) and more commonly in participants on a PAH therapy (prostanoids and/or PDE-5i) during the extension study (62%; 18 of 29 participants) versus those not on a PAH therapy (33%; 3 of 9 participants). None of the SAEs were considered related to the investigational product by the investigator. Excluding the 7 SAEs that were fatal, the remaining SAEs, all non-fatal, resolved during the study with the exception of the following SAEs, which occurred for the same participant (5 mg) and were considered ‘not recovered/not resolved’: pulmonary hemorrhage, disseminated intravascular coagulation, and gastric hemorrhage. This participant subsequently died from COVID-19 which was diagnosed prior to the onset of these 3 SAEs.

Table 15. Summary of Serious TEAEs (Safety Population)

System Organ Class Preferred Term	Ambrisentan Dose Group				Total (N=38)
	2.5 mg (N=4)	5 mg (N=16)	7.5 mg (N=6)	10 mg (N=12)	
	n (%)				
Any event	2 (50)	7 (44)	4 (67)	8 (67)	21 (55)
Cardiac disorders					
Any event	1 (25)	3 (19)	1 (17)	2 (17)	7 (18)
Cardiac failure acute	0	2 (13)	0	0	2 (5)
Acute right ventricular failure	0	1 (6)	0	0	1 (3)
Atrioventricular block complete	1 (25)	0	0	0	1 (3)
Atrioventricular block first degree	0	0	0	1 (8)	1 (3)
Conduction disorder	0	0	0	1 (8)	1 (3)
Right ventricular failure	0	0	1 (17)	0	1 (3)
Supraventricular tachycardia	0	0	0	1 (8)	1 (3)
Wandering pacemaker	0	0	0	1 (8)	1 (3)
Infections and infestations					
Any event	0	2 (13)	2 (33)	3 (25)	7 (18)
Pneumonia	0	1 (6)	1 (17)	0	2 (5)
Appendicitis	0	0	0	1 (8)	1 (3)
COVID-19	0	1 (6)	0	0	1 (3)
Influenza	0	0	1 (17)	0	1 (3)
Myringitis	0	0	0	1 (8)	1 (3)
Otitis media acute	0	1 (6)	0	0	1 (3)
Otitis media chronic	0	0	0	1 (8)	1 (3)
Sinusitis	0	0	0	1 (8)	1 (3)
Respiratory, thoracic, and mediastinal disorders					
Any event	0	2 (13)	0	3 (25)	5 (13)
Pulmonary arterial hypertension	0	0	0	3 (25)	3 (8)
Hyperventilation	0	1 (6)	0	0	1 (3)
Pulmonary haemorrhage	0	1 (6)	0	0	1 (3)
Pulmonary hypertension	0	0	0	1 (8)	1 (3)
Blood and lymphatic disorders					
Any event	0	2 (13)	0	1 (8)	3 (8)
Anaemia[a]	0	1 (6)	0	1 (8)	2 (5)
Disseminated intravascular coagulation	0	1 (6)	0	0	1 (3)
General disorders and administration site conditions					
Any event	1 (25)	0	0	2 (17)	3 (8)
Complication associated with device	0	0	0	1 (8)	1 (3)
Illness	1 (25)	0	0	0	1 (3)
Non-cardiac chest pain	0	0	0	1 (8)	1 (3)
Gastrointestinal disorders					
Any event	1 (25)	1 (6)	0	0	2 (5)
Gastric haemorrhage	0	1 (6)	0	0	1 (3)
Vomiting	1 (25)	0	0	0	1 (3)
Congenital, familial, and genetic disorders					
Any event	0	1 (6)	0	0	1 (3)
Autoimmune lymphoproliferative syndrome	0	1 (6)	0	0	1 (3)
Investigations					
Any event	1 (25)	0	0	0	1 (3)
Alanine aminotransferase increased[a]	1 (25)	0	0	0	1 (3)
Metabolism and nutrition disorders					

System Organ Class Preferred Term	Ambrisentan Dose Group				Total (N=38)
	2.5 mg (N=4)	5 mg (N=16)	7.5 mg (N=6)	10 mg (N=12)	
	n (%)				
Any event	0	0	1 (17)	0	1 (3)
Failure to thrive	0	0	1 (17)	0	1 (3)
Musculoskeletal and connective tissue disorders					
Any event	0	0	1 (17)	0	1 (3)
Scoliosis	0	0	1 (17)	0	1 (3)
Nervous system disorders					
Any event	0	0	1 (17)	0	1 (3)
Migraine	0	0	1 (17)	0	1 (3)
Reproductive system and breast disorders					
Any event	0	1 (6)	0	0	1 (3)
Dysmenorrhoea	0	1 (6)	0	0	1 (3)
Vascular disorders					
Any event	1 (25)	0	0	0	1 (3)
Hypotension[a]	1 (25)	0	0	0	1 (3)

Abbreviations: N= Number of participants; () = percentage
Source: Table AMB114588 3.9

Adverse Events of Special Interest:

Adverse events of special interest (AESI) were anemia, hepatotoxicity, hypersensitivity, hypotension, male infertility, edema, and fluid retention. AESI were experienced by approximately half of the study population (53%; n=20) and at least half of participants in each dose group (50% to 58%). No AESI led to an ambrisentan dose change or permanent discontinuation of ambrisentan or withdrawal from the study. The most common AESI was anemia (6 participants [16%], 11 events) which occurred across 2 dose groups (5 mg and 10 mg). For 2 participants, 3 events of anemia were considered related to the investigational product. The majority of events resolved (all but 1, which was considered intermittent and occurred in a participant with a past medical history of anemia prior to ambrisentan exposure).

Table 16. Summary of TEAEs of Special Interest (Safety Population)

System Organ Class Preferred Term	Ambrisentan Dose Group				Total (N=38)
	2.5 mg (N=4)	5 mg (N=16)	7.5 mg (N=6)	10 mg (N=12)	
	n (%)				
Any event	2 (50)	8 (50)	3 (50)	7 (58)	20 (53)
Skin and subcutaneous tissue disorders					
Any event	1 (25)	3 (19)	3 (50)	2 (17)	9 (24)
Dermatitis contact	0	1 (6)	1 (17)	1 (8)	3 (8)
Erythema	1 (25)	1 (6)	1 (17)	0	3 (8)
Rash	0	1 (6)	2 (33)	0	3 (8)
Eczema	0	1 (6)	0	1 (8)	2 (5)
Pruritus	0	1 (6)	0	1 (8)	2 (5)
Angioedema	0	0	1 (17)	0	1 (3)
Dermatitis atopic	0	0	1 (17)	0	1 (3)
Urticaria	0	0	1 (17)	0	1 (3)
Blood and lymphatic system disorders					
Any event	0	4 (25)	0	4 (33)	8 (21)
Anaemia	0	2 (13)	0	4 (33)	6 (16)
Iron deficiency anaemia	0	3 (19)	0	0	3 (8)
Investigations					
Any event	1 (25)	3 (19)	0	1 (8)	5 (13)
Aspartate aminotransferase increased	1 (25)	0	0	1 (8)	2 (5)
Alanine aminotransferase increased	1 (25)	0	0	0	1 (3)
Aspartate aminotransferase abnormal	1 (25)	0	0	0	1 (3)
Blood alkaline phosphatase increased	1 (25)	0	0	0	1 (3)
Blood bilirubin increased	0	0	0	1 (8)	1 (3)
Blood lactate dehydrogenase increased	1 (25)	0	0	0	1 (3)
Blood pressure diastolic decreased	0	1 (6)	0	0	1 (3)
Haemoglobin decreased	0	1 (6)	0	0	1 (3)
Transaminases increased	0	1 (6)	0	0	1 (3)
General disorders and administration site conditions					
Any event	0	1 (6)	1 (17)	2 (17)	4 (11)
Oedema peripheral	0	1 (6)	0	1 (8)	2 (5)
Localised oedema	0	0	1 (17)	0	1 (3)
Swelling face	0	0	0	1 (8)	1 (3)
Respiratory, thoracic, and mediastinal disorders					
Any event	0	2 (13)	1 (17)	1 (8)	4 (11)
Rhinitis allergic	0	2 (13)	0	1 (8)	3 (8)
Asthma	0	0	0	1 (8)	1 (3)
Bronchospasm	0	0	1 (17)	0	1 (3)
Eye disorders					
Any event	0	1 (6)	1 (17)	1 (8)	3 (8)
Conjunctivitis allergic	0	1 (6)	0	1 (8)	2 (5)
Eye swelling	0	0	1 (17)	0	1 (3)
Eyelid oedema	0	1 (6)	0	0	1 (3)
Nervous system disorders					
Any event	0	1 (6)	2 (33)	0	3 (8)
Dizziness	0	0	2 (33)	0	2 (5)
Presyncope	0	1 (6)	0	0	1 (3)
Syncope	0	1 (6)	0	0	1 (3)
Vascular disorders					
Any event	1 (25)	2 (13)	0	0	3 (8)

System Organ Class Preferred Term	Ambrisentan Dose Group				Total (N=38)
	2.5 mg (N=4)	5 mg (N=16)	7.5 mg (N=6)	10 mg (N=12)	
	n (%)				
Cyanosis	0	1 (6)	0	0	1 (3)
Flushing	0	1 (6)	0	0	1 (3)
Hypotension	1 (25)	0	0	0	1 (3)
Gastrointestinal disorders					
Any event	0	0	1 (17	0	1 (3)
Ascites	0	0	1 (17	0	1 (3)
Hepatobiliary disorders					
Any event	0	1 (6)	0	0	1 (3)
Hepatomegaly	0	1 (6)	0	0	1 (3)
Infections and infestations					
Any event	0	0	0	1 (8)	1 (3)
Conjunctivitis	0	0	0	1 (8)	1 (3)

Abbreviations: N= Number of participants; ()= percentage
Source: Table AMB114588 3.17

Liver Events:

Protocol-defined liver chemistry stopping criteria for ALT was met by 1 participant (2.5 mg) in the extension study. The ALT elevation was reported as severe in intensity and as a SAE and occurred approximately 2 years following the first dose. Two other SAEs that were also severe in intensity contemporaneously occurred for this participant (atrioventricular block complete and hypotension). All 3 SAEs led to a temporary dose interruption and resolved within 23 days; none were regarded as related to the investigational product by the investigator. Four participants had a TEAE related to liver function tests (AST, ALT, ALP, bilirubin, LDH, and transaminases) or hepatobiliary disorders. Elevated AST and bilirubin (both mild in intensity and non-serious) reported for 1 participant (10 mg) were considered related to the study drug. Two of these 4 participants met laboratory values of potential clinical concern (PCC) for ALT and GGT (participant who met protocol-defined stopping criteria) or ALT and AST.

Neutropenia:

One participant (5 mg group) experienced a TEAE of neutropenia that was mild in intensity, non-serious, not regarded as related to the investigational product and did not lead to a dose change. Onset of neutropenia was in the initial AMB112529 study approximately 49 days after the first dose and was intermittent, continuing into the extension study, with a reported duration of 144 days. Total neutrophils returned to normal by the End of Study.

Clinical Chemistry Changes of Potential Clinical Concern:

Values of Potential Clinical Concern (PCC) were determined for ALT, AST, total bilirubin, creatinine, and GGT. Over the course of this extension study (Study Entry to End of Study), 6 participants (16%) across 3 dose groups (2.5 mg, 5 mg, 10 mg) reached levels of PCC (i.e., fell above pre-defined PCC reference ranges) for ALT, AST, total bilirubin, and/or GGT with no participants reaching levels of PCC for creatinine. Two of these participants had TEAEs related to liver function tests with the remaining 4 participants not reporting corresponding TEAEs.

Hematological Changes of Potential Clinical Concern:

Values of PCC were determined for hemoglobin, hematocrit, and platelet count. Over the course of this extension study (Study Entry to End of Study), 9 participants (24%) across 2 ambrisentan dose groups (5 mg, 10 mg) reached levels of PCC (i.e., fell above and/or below predefined PCC reference ranges) for hemoglobin, hematocrit, and platelet count. Four participants (11%) had low hemoglobin and/or hematocrit of PCC, with low values of both parameters observed in 3 of these participants.

Physical Examination:

No clinically relevant findings were observed related to physical examinations. At the end of the extension study, 93% of the remaining participants (27 of 29 participants) had normal liver size and jugular venous pressure and no participants had peripheral edema. Ascites was reported for 2 of 29 participants (7%). The mean oxygen saturation level for the remaining 29 participants was 96.8% (range: 90% to 100%).

Vital Sign Changes of Potential Clinical Concern:

Levels of PCC were determined for systolic and diastolic blood pressure, heart rate, and weight. Over the course of this extension study (Entry to End of Study), values of PCC for vital signs were observed for 7 participants (5 mg, 7.5 mg, 10 mg) for heart rate (2 participants exceeded the reference range and 4 participants fell below the reference range) and systolic blood pressure (2 participants fell below the reference range). For the remaining 2 parameters (diastolic blood pressure and weight), no participants reached levels of PCC.

12-lead Electrocardiograms:

Over the course of this extension study (Entry to End of Study), 'abnormal, clinically significant' 12-lead ECGs were recorded for a total of 6 participants (16%) across 3 dose groups (5 mg, 7.5 mg, 10 mg). Abnormal, clinically significant 12-lead ECGs were also observed for the majority of these participants (4 of 6) at AMB112529 Baseline. At End of Study, no remaining participants had 'abnormal, clinically significant' 12-ECG assessments.

Pubertal Development and Plasma Endocrinology Parameters:

While 40% of females and 38% of males were pre-adolescent at the start of the initial study (ID AMB112529), the proportion reduced to 5% of females and no males by the end of the extension study. Pubertal assessments conducted at 20 years of age showed that all females (n=10) were at Stage 4 or Stage 5 for pubertal development and all males (n=4) were at Stage 5. No clinically relevant changes in plasma endocrinology parameters were observed from AMB112529 Baseline to the end of the extension study for both females and males.

Time to Change in Dose of Ambrisentan or Other Targeted PAH Therapeutic Agent due to Tolerability:

Over the course of this extension study (ID AMB114588), 7 participants (18%) across all 4 dose groups were reported as having a change in their dose of ambrisentan or another targeted PAH therapeutic agent (prostanoids, PDE-5i) due to tolerability issues. Based on the data of 6 participants

who had a dose change in ambrisentan (n=2) or a PAH agent (n=4) during the extension study due to tolerability issues (and excluding the 1 participant [2.5 mg] who discontinued ambrisentan due to tolerability but had no dose changes in the extension study), dose changes were initiated after approximately 1 year and up to 6 years of dosing from the start of dosing in AMB112529. Time to a dose change was notably higher in the 10 mg group (median of approximately 4 years) as compared to lower dose groups (medians of approximately 1 year).

2.3.3. Discussion on clinical aspects

Ambrisentan is a selective endothelium receptor antagonist (ERA) currently approved by the European Comission as 2.5 mg, 5 mg and 10 mg film-coated tablets for oral use for the treatment of PAH in adults, adolescents and children (aged 8 to less than 18 years) of WHO Functional Class (FC) II to III including use in combination treatment.

This Article 46 procedure of Regulation (EC) No 1901/2006, concerns the submission of a final study report for study AMB114588 (EudraCT Number: 2010-021572-29) titled “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” is part of a clinical development program. The variation application consisting of the full relevant data package (i.e., containing several studies) is expected to be submitted by second quartile 2023. Please note that a final study report for the pivotal study AMB112529 as well as an interim report for its extension study AMB114588 (data cut-off date: 23 Aug 2019) was previously submitted for the procedure No. EMEA/H/C/000839/X/0061/G, consisting of an extension of the marketing authorisation to introduce a new strength (2.5 mg film-coated tablet), grouped with an extension of indication to include treatment of PAH in adolescents and children (8 to less than 18 years). The approval of the paediatric indication was issued on 22 July 2021.

AMB114588 was a phase 2b, open-label, long-term extension study of the pivotal phase 2b, 24-week (6-month), randomized, open-label study AMB112529. This extension study was performed to monitor the safety and tolerability as well as obtaining supportive efficacy data of ambrisentan film-coated tablet[s] in 2.5 mg, 5 mg, and 10 mg strengths, at 1 of the 4 dose levels (2.5 mg or 5 mg for the Low dose group and 7.5 mg or 10 mg for the High dose group; adjusted for body weight) studied in study AMB112529, in subjects aged 8 years up to 18 years with PAH who have participated in AMB112529. Participants could remain in study AMB114588 for a minimum of 6 months. Beyond the 6-month period, participants could continue in the extension study until it was met 1 of 5 pre-specified conditions. Participants were followed for 30 days post their last dose of ambrisentan for the monitoring of AEs/SAEs. The safety endpoints were Adverse Events (AEs), Serious Adverse Events (SAEs), Hematology and clinical chemistry, Liver function tests (ALT, AST, GGT, and total bilirubin), physical examination, vital signs, pubertal development, endocrinology assessments and time to a change in the dose of ambrisentan or other targeted PAH therapeutic agents (prostanoids, PDE-5i) due to tolerability issues. The efficacy endpoints measured were 6-minute walk distance (6MWD) from baseline to End of the Study, time to clinical worsening of PAH, time to addition of another targeted PAH therapeutic agent(s), time to change in dose of ambrisentan or other targeted PAH therapeutic agents (prostanoids, PDE-5i) due to deterioration of clinical condition, WHO Functional Class, Plasma NT-proBNP and other Health outcomes assessments as SF-10 Health Survey for Children and missed school days. The study design and duration as well as the proposed objectives seem adequate for an extension study to describe the long-term effects of ambisentran in a target population.

Of the 41 participants randomized into a Low dose or High dose group in AMB112529, 38 participants (93%) entered this long-term extension study. The majority of the study population was 12 to <18 years of age (63%; 24/38 participants), which was also the age stratum represented by the majority

of participants in the 5 mg (63%; 12/19 participants), 7.5 mg (80%; 4/5 participants), and 10 mg (100%; 5/5 participants) dose groups. The majority of participants (67%; 6/9 participants) in the lowest ambrisentan dose group (ambrisentan 2.5 mg) were represented by the younger age stratum (8 to 11 years of age). The mean/median age of the study population was 11.9/12.5 years (range: 8 to 16 years). The majority was female (66%) and of White/Caucasian/European Heritage (71%) with approximately one-third (32%) of Hispanic/Latino ethnicity.

Overall, just over half (55%; n=21) of the participants who entered this extension study completed it. The most frequently reported reasons for study withdrawal were investigator discretion (18%; n=7) and the report of AEs (16%; n=6).

Regarding the safety and tolerability of ambrisentan data in the long-term treatment, the most reported TEAEs were upper respiratory tract infection (11 of 38 participants; 29%), nasopharyngitis (9 of 38 participants; 24%), and headache (7 of 38 participants; 18%). These TEAEs were previously reported in the initial study and are consistent with product labelling for the adult population. Despite affecting a large number of patients, none of these adverse effects represented a serious health problem. A total of 26 severe TEAEs were experienced by 12 of 38 participants (32%) across all 4 dose groups. Of the 26 severe TEAEs, 18 were considered SAEs (6 of which had a fatal outcome). None were regarded as related to the investigational product as it could be considered they were due to events that reflect the underlying disease features and complications arising during the natural disease course. On the other hand, approximately 39% (15 of 38 patients) of the study population and 25% to 50% in each dose group experienced a TEAE that was considered related to the investigational product. Related TEAEs were more common in the higher dose groups (7.5 mg [50%] and 10 mg [50%]) as compared with the lower dose groups (2.5 mg [25%] and 5 mg [31%], so these AEs seem dose-dependent. The most frequently reported AESI was anemia (6 participants [16%], 11 events), with the majority resolving and none leading to withdrawal from ambrisentan treatment or the study. The range of time to death (approximately 3 months to 8 years from AMB112529 Baseline) is in line with the population studied and there was no evidence of a contemporaneous or dose relationship. No clinically relevant findings were observed related to physical examinations and pubertal assessments.

Regarding the efficacy measures, change from baseline of the initial study (ID AMB112529) to the end of the extension study, in participants in whom data were available (n=29), 6MWD increased by a mean/median of 58.4 m/55.5 m, representing mean and median increases of 17.0% and 13.9%, respectively. Moreover, half of the study population (58%) achieved a clinically significant improvement in 6MWD with a comparable proportion in those with an idiopathic etiology of PAH (58%) or non-idiopathic etiology (57%). Although the obtained efficacy results appear to support an improvement in the measured efficacy endpoints, the limited sample size and the lack of a control group makes interpretation difficult.

The clinical course of the population studied showed approximately 29% of participants (11/38 participants), across all 4 dose groups, experienced an occurrence of clinical worsening of PAH based on at least 1 of 5 pre-specified criteria, with more than 1 clinical worsening criterion met by 45% participants (5/11 participants). Over half of the 11 participants met the clinical worsening criterion of death (6/11 participants), and over one-third (4/11 participants) met the criterion of PAH-related deterioration. Moreover, almost one half of participants (45%; 17/38 participants) required addition of another PAH targeted therapy (for any reason) alongside their ambrisentan treatment, of which 8 participants had additions due to deterioration in clinical condition and/or lack of beneficial effect with previous therapies. Time to clinical worsening was variable, with no evidence of a contemporaneous or dose relationship. Change in the dose of ambrisentan or concurrent targeted PAH therapy in the extension study due to deterioration of clinical condition was reported for approximately one quarter of participants (24%; 9/38 participants) with changes in dose occurring over a wide range of time from the start of ambrisentan treatment in the initial study (approximately 3 months to 6.7 years). Changes

from AMB112529 Baseline to AMB114588 End of Study showed an improvement (n=13; 45%) or no change (n=16; 55%), and no deterioration, in WHO Functional Class for study participants in whom data were available (n=29). From AMB112529 Baseline to AMB114588 End of Study, there was a geometric mean/median percent decrease in NT-proBNP for the total population in whom data was available (n=25), which was largely driven by NT-proBNP reductions in the 2 lower ambrisentan dose groups (2.5 mg and 5 mg). From AMB112529 Baseline to AMB114588 End of Study, mean/median changes in Physical Health and Psychosocial Summary scores from the SF-10 were minimal for the total population in whom data was available (n=26) and there was an overall decrease, or no change of School Days Missed due to PAH for participants. However, despite the positive trend for benefit in these secondary outcomes, the significant amount of missing data (29%, 34% and 12% respectively), precludes a definitive conclusion on the effect of ambrisentan on improvement in respiratory function or decrease in NT-proBNP or in Physical Health-School Days Missed respectively.

In summary, the observed safety and efficacy results of the study AMB114588 are in line with the EU SmPC of ambrisentan. As such, no regulatory action required at this time.

3. Rapporteur's overall conclusion and recommendation

In accordance with Article 46 of Regulation (EC) No 1901/2006, the MAH submitted a final study report for study AMB114588 (EudraCT Number: 2010-021572-29) titled "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".

A final study report for the pivotal study AMB112529 as well as an interim report for its extension study AMB114588 (data cut-off date: 23 Aug 2019) was previously submitted for the procedure No. EMEA/H/C/000839/X/0061/G, consisting of an extension of the marketing authorisation to introduce a new strength (2.5 mg film-coated tablet), grouped with an extension of indication to include treatment of PAH in adolescents and children (8 to less than 18 years). The approval of the paediatric indication was issued on 22 July 2021.

Since the provided results for ambrisentan are in line with the approved product information in the EU, no regulatory action required at this point.

A variation application consisting of the full relevant data package (i.e., containing several studies) is expected to be submitted by second quartile 2023, which is agreed by the Rapporteur.

☒ Fulfilled:

No regulatory action required.