EMA/120148/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Volibris

International non-proprietary name: Ambrisentan

Procedure No. EMEA/H/C/000839/II/0067

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	13 Nov 2023	13 Nov 2023	☐
☐	CHMP Rapporteur Assessment Report	18 Dec 2023	15 Dec 2023	☐
☐	CHMP members comments	03 Jan 2024	n/a	☐
☐	Updated CHMP Rapporteur Assessment Report	05 Jan 2024	n/a	☐
☐	Start of written procedure	09 Jan 2024	09 Jan 2024	☐
☐	Request for Supplementary Information	11 Jan 2024	11 Jan 2024	☐
☐	Re-start of procedure	14 Feb 2024	14 Feb 2024	☐
☐	CHMP Rapporteur Assessment Report	28 Feb 2024	28 Feb 2024	☐
☐	CHMP members comments	04 Mar 2024	04 Mar 2024	☐
☐	Updated CHMP Rapporteur Assessment Report	07 Mar 2024	07 Mar 2024	☐
☐	Start of written procedure	12 Mar 2024	12 Mar 2024	☐
☒	Opinion	14 Mar 2024	14 Mar 2024	☐

[1] Tick the box corresponding to the applicable step – do not delete any of the steps. If not applicable, add n/a instead of the date.

[2] Criteria for CHMP plenary discussion: substantial disagreement between the Rapporteur and other CHMP members and/or at the request of the Rapporteur or the Chair

Procedure resources	
PRAC Rapporteur:	Maria Concepcion Prieto Yerro

Declarations

☒The assessor confirms that reference to ongoing assessments or development plans for other products is not included in this assessment report, including in the Product Information, if any.

Whenever the above box is un-ticked please indicate section and page where confidential information is located here:

ABBREVIATIONS

6MWD	6-Minute walking distance
AE	Adverse event
AESI	Adverse Events of Interest
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
AUCss	Area under the plasma drug concentration-time curve from pre-dose to the end of the dosing interval at steady state
AUCss	Area Under the Curve at Steady State
BLQ	Below the Lower Limit of Quantification for a Bioassay
BMI	Body Mass Index
bpm	Beats per minute
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CL/F	Apparent clearance
cm	Centimetres
Cmax,ss	Maximum plasma concentration at steady-state
CRCL	Creatinine Clearance
CrI	Credible Interval
CSR	Clinical study report
CV	Cardiovascular
C_T	Concentration at the End of a Dosing Interval
ECG	Electrocardiogram
ECHO	Echocardiogram
eCRF	Electronic case report form
eGFR	Estimated Glomerular Filtration Rate
EMA/EMEA	European Medicines Agency
ER	Exposure–response
ERA	Endothelin Receptor Antagonist
ERA	Environmental Risk Assessment
ES	Epoprostenol sodium
EU	European Union
FC	Functional Class
Fpen	Fraction of Market Penetration
FSH	FollicleStimulating Hormone
GGT	Gamma-Glutamyl Transferase
GI	Gastrointestinal
GSK	GlaxoSmithKline
HPAH	Heritable pulmonary arterial hypertension
hr	Hours
IDMC	Independent Data Monitoring Committee
IPAH	Idiopathic pulmonary arterial hypertension
ITT	Intent-to-Treat
IU	International Unit
kg	Kilogram
L	Litre
LFT	Liver Function Test
LH	Luteinizing Hormone
LSM	Least squared mean
LVEDP	Left ventricular end diastolic pressure
m	Metre
m2	Square metres
MAA	Marketing Authorization Application
MCH	Mean Corpuscular Haemoglobin
MCHC	Mean Corpuscular Haemoglobin Concentration

MCID	Minimal clinically important difference
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
min	Minute
mL	Millilitre
mmHg	Millimetres of mercury
MMRM	Mixed Model with Repeated Measures
mPAP	Mean pulmonary arterial pressure
NA	Not Applicable
ng	Nanogram
NONMEM	Non-Linear Mixed-Effects Modelling
NR	Normal Reference Range
NT-proBNP	N-terminal pro-B-type natriuretic peptide
NYHA	New York Heart Association
PAH	Pulmonary arterial hypertension
PBRERs	Periodic Benefit Risk Evaluation Reports
PBT	Persistance, Bioaccumulation and Toxicity
PCC	Potential Clinical Concern
pc-VPC	prediction-corrected visual predictive check
PCWP	Pulmonary capillary wedge pressure
PD	Pharmacodynamic
PDCO	Paediatric Committee
PDE-5	phosphodiesterase-5
PDE-5(i)	Phosphodiesterase-5 inhibitor
PEC	Predicted Environmental Concentration
PI	Product Information
PIP	Paediatric Investigation Plan
PK	Pharmacokinetic(s)
PVE	Pharmacovigilance and Epidemiology
PVR	Pulmonary vascular resistance
RA	Right atrial
RAP	Reporting and Analysis Plan
RBC	Red Blood Cell
RV	Right ventricular
s(ec)	Seconds
SAE	Serious Adverse Event
SBGH	Sex Hormone Binding Globulin
SC	Sildenafil citrate
SD	Standard deviation
SDAC	Statistics and Data Analysis Centre
SF-10	Short Form 10
SF-36	Short Form 10
SOC	System Organ Class
TAPSE	Tricuspid annular plane systolic excursion
TRJ	Tricuspid regurgitant jet
UK	United Kingdom
ULN	Upper limit of normal
US	United States
US	The United States
V/F	Apparent volume of distribution
WHO	World Health Organisation

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1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, GlaxoSmithKline (Ireland) Limited submitted to the European Medicines Agency on 22 June 2023 an application for a variation.

The following changes were proposed:

Variation requested		**Type**	**Annexes affected**
C.I.3.b	C.I.3.b - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Change(s) with new additional data submitted by the MAH	Type II	I, II and IIIB

To update sections 4.8 and 5.1 of the SmPC following the assessment of Art 46 procedure (EMEA/H/C/000839) based on final results from study AMB114588; this is 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. In addition, the MAH took the opportunity to implement minor editorial changes to Annex II and to the Package Leaflet.

The requested variation proposed amendments to the Summary of Product Characteristics, Annex II and Package Leaflet.

2. Overall conclusion and impact on the benefit/risk balance

This Type II Variation application is based on the final results from study AMB114588 submitted by the MAH. This is 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. Compared with the interim analysis, the final study report includes the same number of children (n=38) but a slightly longer mean follow-up (i.e.: 3.4 years in the interim analysis vs. 4.0 years in the final analysis) and similar survival.

Of the 41 paediatric subjects enrolled in the initial study, 38 transitioned into the long-term extension study. Time to all-cause death and change from baseline in 6MWD were the primary analyses to demonstrate efficacy of ambrisentan in this study. There were 6 subjects who had a clinical worsening resulting in death during this study, and the mean/median time to death was 4.2 years from the start of treatment in Study AMB112529. There was evidence at the Entry Visit to this study of clinically relevant improvements from Study AMB112529 Baseline in exercise capacity for subjects from all dose groups as demonstrated by the 6MWD test, which represented an improved status observed across the initial AMB112529 study. Change from Baseline in this long-term extension study continued to show a similar magnitude of mean improvement in all dose groups at End of Study. Mean percentage change from baseline in 6MWD at end of study was approximately 34.4%, 12.7%, 2.4%, and 7% in the ambrisentan 2.5 mg, 5 mg, 7.5 mg and 10 mg groups respectively. At the End of Study Visit, all subjects reported no change or an improvement from Study AMB112529 Baseline in WHO FC with 1 subject showing an improvement from Baseline by more than 1 category. At the Entry Visit to this long-term extension study, the majority of subjects had reported either the same WHO FC category or a shift that indicated improvement, with 2 subjects reporting a worsening (one from a WHO FC category of II to III who remained category III for the duration of the extension study, and one from II to IV who subsequently died from cardiac failure acute). 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 (n=29).

With respect to safety, based on pooled data from 38 subjects, ambrisentan was generally well tolerated with no new clinically relevant safety findings. The most frequently reported TEAEs were upper respiratory tract infection and nasopharyngitis. No AESI led to permanent discontinuation of ambrisentan or withdrawal from the study. None of the SAEs (including deaths) reported were regarded as related to

ambrisentan and all deaths (excluding one subject who died from COVID-19 infection) were due to events associated with the natural progression profile and known characteristics of children with PAH disease. Observed small changes in renal parameters are generally consistent with the long-term nature of this extension study and the increasing age of the participants. A small mean reduction from Baseline in haemoglobin, haematocrit, and platelet count was observed for all dose groups combined, consistent with safety findings in the adult population.

In summary, the final results of the extension study AMB114588 are consistent with those of the interim analysis submitted previously and with the known efficacy and safety profile of ambrisentan, and do not raise any new efficacy or safety concern.

In the response to the RSI, the MAH has provided a revised and improved version of the description of the extension study AMB114588 in section 5.1 of the SmPC (see Product Information attached with track changes). The revised product information is deemed acceptable, and therefore the variation is recommended for approval.

The benefit-risk balance of Volibris, remains positive.

3. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation requested		**Type**	**Annexes affected**
C.I.3.b	C.I.3.b - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Change(s) with new additional data submitted by the MAH	Type II	I, II and IIIB

To update sections 4.8 and 5.1 of the SmPC following the assessment of Art 46 procedure (EMEA/H/C/000839) based on final results from study AMB114588; this is 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. In addition, the MAH took the opportunity to implement minor editorial changes to Annex II and to the Package Leaflet.

☒is recommended for approval.

Grounds for refusal

N/A

Amendments to the marketing authorisation

N/A

Annex: Rapporteur’s assessment comments on the type II variation

4. Introduction

Ambrisentan is approved for the treatment of PAH in adult patients in idiopathic PAH and in PAH associated with connective tissue disease. Ambrisentan is also approved in children over the age of 8 years of WHO Functional Class (FC) II to III with efficacy having been shown in idiopathic PAH (IPAH), familial PAH, corrected congenital PAH as well as and in PAH associated with connective tissue disease. Ambrisentan has been approved for marketing in the EU through the centralised procedure.

This Type II Variation application is based on the final results from study AMB114588 submitted by the MAH. This is 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.

Study AMB114588 (Study Report TMF-14398819) is an extension study to support the initial 24-week study (Study AMB112529), whereby Study AMB112529 had been conducted in accordance with the Paediatric Investigation Plan (PIP), procedure number: EMEA- 00044-PIP0l-08 agreed with the European Medicines Agency's Paediatric Committee (PDCO).

GlaxoSmithKline (GSK) performed an interim analysis for this long-term extension study to support regulatory activities for the submission of a type II variation to update sections 4.8 (Undesirable effect) and section 5.1(Pharmacodynamic properties) of the Product Information (PI) to provide posology for the treatment of children with pulmonary arterial hypertension (PAH) aged 8 years and over (Interim Clinical Study Report (CSR); dated 03 April 2020). A description of the interim analysis was already included in the currently approved Volibris SmPC.

Within this Type II variation, sections 4.8 and 5.1 of the SmPC are updated to reflect the final study results provided. In addition, the MAH took the opportunity to implement minor editorial changes to Annex II and to the Package Leaflet.

Non-clinical critical assessment

No new clinical data regarding pharmacology, pharmacokinetics or toxicology have been submitted in this variation. The only new data submitted were related to ERA.

The Environmental Risk Assessment for Volibris™ Film Coated Tablets 2.5, 5 and 10 mg (referred to as ambrisentan tablets 5 and 10 mg), containing 2.5, 5 or 10 mg ambrisentan, is required for both the product and packaging by Directive 2001/83/EC, as amended.

Ambrisentan, 5 or 10 mg tablets for once daily dosing, was first approved on 15 June 2007 in the US and on 21 April 2008 in the European Union (EU) and is currently approved in in all European Economic Area countries as well as Japan and 20 further countries. In the US, ambrisentan is approved under the trade name Letairis and licensed by Gilead [Letairis® US Prescribing Information (SPC), 2019]. In the EU and other countries, ambrisentan is approved under the trade name Volibris and the marketing authorization holder is GSK. Cumulative patient exposure to marketed ambrisentan since first marketing approval to 31 July 2022 is estimated to be 209974 patient-years.

The present application is being made to support updates to the Patient Information following completion of clinical study AMB114588, an open label, long term extension study to AMB112529.

The current adult and paediatric dosing regime are detailed in the table below. Patients would continue to take ambrisentan tablets for as long as they continue to gain clinical benefit or until such time as their disease progresses. The average duration of treatment is likely to be between 2 to 3 years.

Table 1 Current adult and paediatric dosing regime

Patient Population	**Initial once daily (mg)[a]**	**Subsequent dose titration (mg)[b]**
Adults	5	10
Paediatrics (aged 8-18) Bodyweight: ≥ 50 kg 5 10 Bodyweight: ≥ 35 kg but <50 kg Bodyweight: <35 kg	 5 5 2.5	 10 7.5 5

[a] = with or without food. [b] = dependent on clinical response and tolerability

Therefore, a Environmental Risk Assessment(ERA) on the impact of ambrisentan 2.5, 5 and 10 mg tablets on the environment is provided according to current guidance, EMEA/CHMP/SWP/4447/00, 2006.

Screening for Persistence, Bioaccumulation and Toxicity (PBT)

The measured octanol-water partition coefficient for the neutral species was calculated to be log P = 1.20. The measured n-octanol/water partition coefficient for the negative species was determined to be log P = -0.84.

This data indicates that the Log Kow for Ambrisentan is significantly less than 4.5 and that a PBT assessment is not warranted.

Calculation of the Predicted Environmental Concentration (PEC) in surface water.

The PEC has been calculated, according to the formula established in the guideline EMEA/CHMP/SWP/4447/00 corr 2:

$PEC_{SURFACEWATER}$ = (DOSEai * F_{PEN}) / (default WASTEWinhab * default DILUTION)

The maximum recommended daily dose for ambrisentarn is 10 mg/day. Then,

= (10 mg/inhabitant/day * 0.01) / (200 L/inhabitant/day * 10)
= 0.00005 mg/L = 0.05 µg/L

Therefore, the action limit of 0.01 µg/L is exceeded, and risk assessment should be continue in a Phase II. However, according to the current guidance the $PEC_{SURFACEWATER}$ may be calculated on the basis of a refined figure for Market Penetration (Fpen).

$F_{pen} = P_{region}\ t_{TREATMENT} \times n_{TREATMENT,p}) / Nd$

$= (0.01 \times 1 \times 26) \div 365 = 0.00071$

P_{region} = Prevalence of this condition in the population (less than 5 in 10,000. This is a worst-case scenario for this indication as data from the literature suggests that prevalence is significantly lower than 5 in 10,000)

$t_{treatment}$ = Duration of one treatment period (6 days)

$n_{treatment}$ = Number of treatment period per year (13 $year^{-1}$)
N_d = Number of days per year (365 days/year)
F_{pen} = 0.0005

The refined $PEC_{SURFACEWATER}$ is calculated as follows:

$PEC_{SURFACEWATER}$ = (DOSEai * $F_{PEN-REFINED}$ / default WASTEWinhab * default DILUTION

= (10 × 0.0005) / (200 × 10) = **0.0000025 mg/L or 0.0025 µg/**L

Since the $PEC_{SURFACEWATER}$ for ambrisentan as calculated in line with the EMA ERA guidelines is below than the nominal value of 0.01 µg/l, and no other environmental concerns are noted, the Applicant assumed that Phase II Tier A ERA is not required for ambrisentan.

Moreover, the calculated PECSURFACEWATER for ambrisentan for actual sales in 2021 ($PEC_{SURFACEWATER}$ = 18 x 109/365 x 5.14 x 108 x 200 x 10 **= 0.000048 µg/L)** is significantly below the nominal Tier 1 trigger value (0.01 µg/L) quoted in the EMA Guidance on Environmental Risk Assessment. Therefore,the Applicant concluded that there is no need for further refinement of the PEC for ambrisentan and no further evaluation is required.

Discussion on nonclinical aspects

No new non clinical data have been submitted in this application which is considered acceptable by the assessors.

According to the current *Guideline on the environmental risk assessment of medicinal products for human use* (EMA/CHMP/SWP/4447/00 corr 2[1*]), an update of the evaluation of the environmental impact should be made if there is an increase in the environmental exposure. In the current type II variation for Volibris 2.5 mg, 5 mg, and 10 mg film coated tablets, the MAH intention is to update sections 4.8 (Undesirable effect) and section 5.1(Pharmacodynamic properties) of the product information (PI) for the treatment of children with pulmonary arterial hypertension (PAH) aged 8 years and over following the final Clinical Study Report (CSR) for study AMB114588.

No new studies have been carried out to asses the environmental risk.
An estimation of exposure of ambrisentan in the environment, taking into account the prevalence of the disease, has been provided. In this way, the applicant has calculated a PEC using a refined Fpen, which, as mentioned, follows the postulates of the ERA guidance.

Since the $PEC_{SURFACEWATER}$ value for ambrisentan is less than 0.01 µg/L, and no other environmental concerns have been reported, it is assumed that the medicinal product is unlikely to pose a risk for the environment following indications listed in the SmPC.
No further assessment is needed to characterise the risk of ambrisentan to the environment.

Conclusion on the non-clinical aspects

Based on the updated data submitted in this application, the indications of ambrisentan do not lead to a significant increase in environmental exposure further to the use of Volibris.

Considering the above data, Volibris is not expected to pose a risk to the environment.

5. Clinical Pharmacology aspects

N/A.

6. Clinical Efficacy aspects

6.1. Methods – analysis of data submitted

Study AMB114588 (Study Report TMF-14398819; EudraCT Number: 2010-021572-29)
Study Title: 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

Study Objectives

The primary objective of Study AMB114588 was to evaluate the long-term safety and tolerability of ambrisentan in the paediatric PAH population. The secondary objective of Study AMB114588 was to obtain supportive efficacy data on the paediatric use of ambrisentan in PAH.

In Study AMB114588, efficacy was primarily assessed from all-cause mortality and from change from baseline in the 6MWD test at 6-monthly intervals.

Study Design

Study AMB114588 was an open label, long-term extension to Study AMB112529 that had a minimum duration of 6 months although subjects could remain in the extension study until any of the following were met:

- Subject turned 18 years of age and thus able to receive marketed ambrisentan or the participant reached pubertal maturity before 18 years of age and ambrisentan could be supplied through a named patient or expanded access program until the participant reached 18 years of age
- Ambrisentan was finally approved and available for use in the subject's age group
- Development of ambrisentan for use in the paediatric population was discontinued
- Subject decided they no longer wanted to participate in the study
- The investigator considered it was in the best interest of the subject to discontinue ambrisentan (e.g. for safety reasons).

Both Study AMB112529 and its extension Study AMB114588 utilized an IDMC to conduct external objective medical and/or statistical review of safety, exposure (ambrisentan plasma concentration) and/or efficacy issues to protect the ethical and safety interests of subjects and to protect the scientific validity of each study. A SDAC provided predefined summary tables and listings to the IDMC to aid review. The remit of the SDAC and the IDMC was outlined in an IDMC charter.

Selection of Study Population

Study AMB114588 was only open to paediatric subjects who had participated in Study AMB112529 and in whom continued treatment with ambrisentan was warranted. Specifically, subjects had to meet at least one of the following criteria in order to participate in the extension study: completed the Week 24 visit in AMB112529; 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; required reduction in dose of baseline targeted treatment for PAH after ambrisentan was added to the treatment regimen; continued treatment with ambrisentan was warranted in the opinion of the investigator.

Subjects were excluded from participation in the extension study if they were withdrawn from ambrisentan therapy or did not comply with the Study AMB112529 protocol, had severe renal impairment (estimated creatinine clearance <30 mL/min assessed within the previous 45 days) at the

point of transition into the extension study, had clinically significant fluid retention/anaemia, were pregnant or breastfeeding, or were about to participate in another trial with another investigational product. Study AMB112529 enrolled male or female subjects aged 8 up to 18 years with a current diagnosis of PAH (WHO Group 1) with WHO Class II or III symptoms in one of the following categories: IPAH; HPAH; secondary to connective tissue disease; or persistent PAH despite surgical repair. Subjects with right heart catheterisation also had to meet the following hemodynamic criteria: mean pulmonary arterial pressure of ≥25 mmHg; pulmonary vascular resistance of ≥240 dyne sec/cm^5; and left ventricular end diastolic pressure or pulmonary capillary wedge pressure of ≤15 mmHg. Subjects were either to be treatment naïve or within the previous month had discontinued treatment with another ERA such as bosentan due to elevated LFTs of <3 x ULN or were on a stable dose of drug therapy for PAH, which was not permitted to change for the duration of the treatment period. Subjects were excluded from participation in Study AMB112529 if they were taking an ERA, cyclosporine A, had body weight <20 kg, or had not tolerated PAH therapy due to adverse effects that may have been related to their mechanism of action (except liver abnormalities for those subjects who were receiving another ERA). Subjects with a diagnosis of active hepatitis (hepatitis B surface antigen and hepatitis C antibody), or clinically significant hepatic enzyme elevation at Screening were also excluded, as well as subjects with severe renal impairment, clinically significant fluid retention or anaemia.

Study Treatment

Commercially available ambrisentan 5 mg and 10 mg tablets were used and ambrisentan 2.5 mg tablets were manufactured for use in both studies AMB112529 and AMB114588. In Study AMB114588 subjects were dosed orally once daily at a dose individually tailored for each subject in the range of 2.5 mg to 10 mg but was not to exceed 0.25 mg/kg/day. The investigator was informed of the dose the subject was receiving in Study AMB112529 and the dose of ambrisentan could remain the same or be adjusted up or down in increments of 2.5 mg at the discretion of the investigator.

Methods to Reduce Bias

Both the AMB112529 and AMB114588 studies were open-label. However, in Study AMB112529, subjects were randomized to either a Low Dose group or a High Dose group of ambrisentan as summarized in Table 1. The 2.5 mg, 5mg, and 10 mg ambrisentan tablets differed in size and colour. Over-encapsulating the tablets to disguise the dose strengths was impractical and may have been difficult for the younger subjects to swallow. Using all 2.5 mg tablets (with matching placebo) to disguise the dose would have required every subject to take 4 tablets at each dose and could have resulted in an unacceptable risk of subjects receiving the wrong dose (i.e., the wrong mix of active and placebo tablets). Therefore, the study was conducted with an open-label design because the risks and inconveniences to the subjects associated with blinding the dose outweighed any benefit of conducting the study in a blinded fashion.

However, to minimise bias, blinding measures were taken at the investigative site; a person not involved in subject assessments was designated to dispense the investigational product and to perform the subsequent compliance checks (pill counts). Subjects and their parents (or legal guardian) were asked not to comment on the number of tablets taken with the individual performing the assessments. Therefore, the individual making the subject assessments would be unbiased.

After each subject had completed the study, the randomized treatment was unblinded to the investigators to allow for informed dose adjustments and follow-up treatment as necessary.

Efficacy Endpoints

Study AMB114588 utilized the same endpoints as Study AMB112529 but also included time to all-cause mortality, time to addition of another targeted therapeutic agent for PAH and time to a change in ambrisentan dose for the treatment of PAH. An overview of the efficacy endpoints utilized in the extension study is provided in Table 1.

Table1. Efficacy Endpoints Utilized in Study AMB114588

Efficacy endpoint	**Study AMB114588**
Primary	
All-cause mortality	Collected as part of worsening of PAH

Secondary	
6MWD	Every 6 months (or 4 to 6 weeks after discontinuing ambrisentan)
Time to clinical worsening of PAH	As required
Change from Baseline in WHO functional class	Every 6 months (or 4 to 6 weeks after discontinuing ambrisentan)
Change from Baseline in plasma NT-proBNP concentration	Every 6 months or early withdrawal
Health outcomes (SF-10 and school days missed)	Every 3 months (or 4 to 6 weeks after discontinuing ambrisentan)
Time to addition of another targeted PAH therapeutics agent	As required
Time to change in dose[b]	As required
Exploratory	
Change from Baseline in major prognostic factors[c] based on echocardiograms: pericardial effusion, RA pressure, TAPSE, eccentricity index (systolic and diastolic), and RV pressure by TRJ velocity	Every 6 months (or 4 to 6 weeks after discontinuing ambrisentan)
Other	
Change from Baseline in cardiopulmonary hemodynamics[d]	Assessments taken only if part of subject's standard care

a. Subjects with a 20% decrease in 6MWD were required to return in 1 week to repeat the test, to confirm PAH deterioration in Studies AMB112529 and AMB114588
b. Of ambrisentan or other targeted PAH therapeutic agents (prostanoids, PDE-5 inhibitors) due to deterioration of clinical condition
c. Based on echocardiograms: pericardial effusion, RA pressure, TAPSE, eccentricity index (systolic and diastolic), and RV pressure by TRJ velocity
d. Collected in subjects in whom hemodynamic data was considered part of the standard of care

6-Minute Walk Distance

The 6MWD endpoint has been shown in the adult PAH population to correlate with longterm clinical outcome [Enright, 2003], and there is evidence that it can be used in children as young as 6 years [Geiger, 2007] and is generally used to follow exercise tolerance in paediatric PAH patients of appropriate age. In IPAH, exercise capacity correlates with RA pressure, pulmonary arterial pressure, and cardiac index. Interventional clinical trials in adults with PAH have commonly used the 6MWD test to demonstrate efficacy for drug approval [Ollivier, 2019].

The 6MWD test was primarily used to demonstrate the efficacy of ambrisentan in the paediatric population in both Study AMB112529 and its long-term safety and efficacy Study AMB114588. In addition, a separate Bayesian analysis of data from the 6MWD from Study AMB112529 was performed. A population PK modelling and simulation analysis was performed to explore the potential relationship between ambrisentan PK and change from baseline in 6MWD at 12 and 24 weeks in the paediatric population in Study AMB112529 and if required, develop an ER model relating ambrisentan PK to change from baseline in 6MWD.

At the VOLIBRIS Paediatric Pre-submission meeting in December 2019 the Spanish Rapporteur requested an additional assessment of subject response to therapy using a MCID criteria for the 6MWD to further demonstrate the clinical relevance of the treatment effect in paediatric subjects.

For the 6MWD, the proportion of subjects with a change from baseline in 6MWD of ≥20 metres (which the value suggested in the Rapporteur discussion) was calculated by randomized group and overall at Weeks 12 and 24 in Study AMB112529 and at 12 months and last observation in Study AMB114588. A subgroup analysis by PAH aetiology (idiopathic versus non-idiopathic PAH) was also performed.

Time to Clinical Worsening

Time to clinical worsening of PAH was defined as the time from randomisation to the first occurrence of:

- Death (all cause) or placement on active list for lung transplant;
- Hospitalization due to PAH deterioration;
- Addition or increased dose of other targeted PAH therapeutic agents (prostanoids,
- PDE-5 inhibitors) and/or atrial septostomy;
- 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).

Change in WHO Functional Class

The WHO classification of functional capacity, an adaptation of the NYHA classification, is routinely used to qualitatively assess activity tolerance. The WHO FC assesses the severity of an individual's symptoms and how they impact on day-to-day activities, with a higher classification indicating greater severity/impact. This classification system, presented in Table 2, is useful to monitor disease progression and response to treatment [McGoon, 2004].

Table 2. World Health Organization Classification of Functional Status of Patients with Pulmonary Hypertension

WHO Class	Description
I	Patients with pulmonary hypertension in whom there is no limitation of usual physical activity; ordinary physical activity does not cause increased dyspnea, fatigue, chest pain, or presyncope.
II	Patients with pulmonary hypertension who have mild limitation of physical activity. There is no discomfort at rest, but normal physical activity causes increased dyspnea, fatigue, chest pain, or presyncope.
III	Patients with pulmonary hypertension who have a marked limitation of physical activity. There is no discomfort at rest, but less than ordinary activity causes increased dyspnea, fatigue, chest pain, and presyncope.
IV	Patients with pulmonary hypertension who are unable to perform any physical activity at rest and who may have signs of right ventricular failure. Dyspnea and/or fatigue may be present at rest, and symptoms are increased by almost any physical activity.

N-terminal Pro-B-type Natriuretic Peptide

Blood samples for determination of N-Terminal pro-B-type Natriuretic Peptide plasma concentrations were collected in both Study AMB112529 and Study AMB114588.

Cardiopulmonary Hemodynamics

Cardiopulmonary hemodynamics were not scheduled assessments as part of Study AMB112529 or Study AMB114588 but were collected in those subjects in whom collecting hemodynamic data was considered part of the standard of care.

Health Outcomes

The 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 aged 5 years and over. In addition to the SF-10, specific questions were asked regarding number of scheduled school days missed and how many were missed due to symptoms of PAH. These health outcome measures were collected in both Study AMB112529 and Study AMB114588.

Time to Addition of Another Targeted PAH Therapeutics Agent

The time to addition of another targeted therapeutic agent for PAH was collected as required in long-term safety Study AMB114588. Time to addition of other targeted PAH therapeutic agents was defined as the time from randomisation to the first occurrence of:

- Deterioration of clinical condition;
- Lack of beneficial effect with previous therapy (not reaching set treatment goals).

Time to a Change in Ambrisentan Dose

The time to a change in ambrisentan dose for the treatment of PAH was collected as required in long-term safety Study AMB114588. Time to change in dose of ambrisentan or other targeted PAH therapeutic agents (prostanoids, PDE-5 inhibitors) was defined as the time from randomisation to the first occurrence of a dose change due to deterioration of clinical condition.

Statistical Considerations

Sample Size

Sample size in extension study AMB114588 was based on feasibility and the number of subjects who entered and completed study AMB112529. No sample size calculations were performed in Study AMB114588.

Efficacy Analyses

Efficacy endpoints in the extension study were analysed in a similar manner to the initial study. The ITT population for the extension study considered subjects as belonging to their treatment group at the start of study AMB114588 and not as belonging to their treatment group at the time of the visit/event in the protocol. All subjects from the ITT population were included in the analysis of efficacy data. The ITT population consisted of all randomized subjects who received at least 1 dose of study drug. Given the small sample size, all efficacy data were summarized descriptively and graphically. Data were summarized by dose group (Low and High) and overall. For key efficacy endpoints, data were also summarized by age strata (8 to 11 years and 12 to <18 years). Baseline values in the extension study were those collected prior to the first dose (from

Study AMB112529). Therefore, if a subject had no pre-dose data for a parameter on Day 1 (defined as the day of first dose in Study AMB112529), then the data from their last pre-treatment assessment from Study AMB112529 was used.

6.2. Results

In total, 38 subjects (93%), 19 in each ambrisentan dose group, entered the long-term extension study AMB114588 (Source AMB112529 CSR Table 1.11).

At AMB114588 End of Study, 21 subjects had completed the study and 17 had been withdrawn (mainly at the discretion of the investigator or because of death from recorded AEs) (Table 3). All of the 6 subjects withdrawn for AEs died as a result of the event although none were suspected to be related to ambrisentan treatment. One further subject who completed the study treatment period subsequently died from an AE that started during the study (death due to deterioration of PAH).

Table 3. Subject Disposition in Study AMB114588 (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 (%)				
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: AMB114588 CSR Table 1.1

a. All 7 deaths were due to SAEs (AMB114588 CSR Section 6.2.1) 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.

Demographic and Baseline Characteristics

Most of the subjects who transitioned into the long-term extension study were of White/ Caucasian/European heritage, and two-thirds of subjects were in the 12 to <18 years age stratum, were female, were potentially of child-bearing potential, and had idiopathic PAH (Table 4Table 4).

The mean/median age of subjects in the extension study increased with each increment in ambrisentan dose and this incremental increase by dose was also observed for subject weight and for female subjects reported as being of child-bearing potential (Table 4). The increasing mean age and weight with each incremental ambrisentan dose group reflected the intended study design for higher doses dependent on weight at entry to AMB112529.

Table 4. Demographic Characteristics in Study AMB114588 (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

	Ambrisentan Dose Group				Total (N=38)
	2.5 mg (N=9)	5 mg (N=19)	7.5 mg (N=5)	10 mg (N=5)	
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: AMB114588 CSR Table 1.5

a. At AMB112529 Baseline.

b. At AMB114588 Study Entry.

Most of the subjects who transitioned into the long-term extension had idiopathic aetiology at baseline in Study AMB112529, with approximately 80% of all subjects receiving ongoing PAH therapy at the start of ambrisentan treatment (mainly were prostanoids and PDE-5 inhibitors) (Table 5). Background therapy for PAH in the longterm extension study is discussed further in Section 6.

The range of duration of PAH (0 to 4189 days) also showed a general relationship of increased duration for subjects by incremental dose group (Table 5).

Table 5. Baseline Characteristics in Study AMB114588 (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)	
Aetiology of PAH; n (%)					
Idiopathic	4 (44)	14 (74)	4 (80)	2 (40)	24 (63)
Familial[a]	0	1 (5)	0	1 (20)	2 (5)
Persistent PAH despite surgical repair[a]	3 (33)	3 (16)	1 (20)	1 (20)	8 (21)
Secondary to connective tissue disease[a]	2 (22)	1 (5)	0	1 (20)	4 (11)
Duration of PAH (d)					
Mean (SD)	1022.4 (1059.02)	1313.5 (1448.93)	64.6 (124.44)	2248.2 (1291.72)	1203.2 (1335.23)
Median	668.0	450.0	12.0	2017.0	508.5
Min to Max	11 to 2800	0 to 4189	0 to 287	728 to 4065	0 to 4189
PAH Therapy Use; n (%)					
Ongoing PAH therapy	8 (89)	15 (79)	3 (60)	4 (80)	30 (79)
Prior PAH therapy, not ongoing	0	1 (5)	0	0	1 (3)
No PAH therapy	1 (11)	3 (16)	2 (40)	1 (20)	7 (18)

Source: AMB114588 CSR Table 1.5

a. Considered non-idiopathic.

All subjects entered into the long-term extension study were classified as WHO functional Class II or III at baseline in Study AMB112529 in accordance with the protocol requirements. At entry to this long-term extension study, approximately one quarter of subjects had an improvement in functional class and were classified as WHO FC I (Table 6). The remainder of subjects were FC II or III at the Entry Visit except for 1 subject with FC IV. In general, there was an improvement in 6MWD at entry into the long-term extension study compared with the baseline values in Study AMB112529 (Table 6).

Table 6. Baseline WHO Functional Class and 6MWD Characteristics in Study AMB114588 (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: AMB114588 CSR Table 1.5

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

Background PAH Therapy in Studies AMB112529 and AMB114588

The proportion of subjects receiving background therapy for PAH (prostanoids or PDE-5 inhibitors only) at entry to this long-term extension study was similar across all dose groups and was 68% for the overall population (Table 7). The most frequently received medication was sildenafil followed by combination therapy with a PDE-5i and prostanoids (Source AMB114588 CSR Listing 1.8).

Table 7. Ongoing Background PAH Therapy in Study AMB114588 (ITT Population)

PAH Therapy	Ambrisentan Dose Group				Total (N=38)
	2.5 mg (N=9)	5 mg (N=19)	7.5 mg (N=5)	10 mg (N=5)	
AMB114588 Entry Visit; n (%)					
Any medication	7 (78)	12 (63)	3 (60)	4 (80)	26 (68)
PDE-5i (monotherapy)					
Any medication	4 (44)	6 (32)	3 (60)	4 (80)	17 (45)
Sildenafil	4 (44)	5 (26)	3 (60)	4 (80)	16 (42)
Sildenafil citrate (SC)	0	1 (5)	0	0	1 (3)
Prostanoid (monotherapy)					
Any medication	0	1 (5)	0	0	1 (3)
Epoprostenol sodium (ES)	0	1 (5)	0	0	1 (3)
PDE-5i and Prostanoid in combination					
Any medication	3 (33)	5 (26)	0	0	8 (21)
SC + ES	0	2 (11)	0	0	2 (5)
Tadalafil + beraprost sodium	1 (11)	1 (5)	0	0	2 (5)
Sildenafil + iloprost	0	1 (5)	0	0	1 (3)
SC + beraprost sodium	1 (11)	0	0	0	1 (3)
SC + treprostinil	1 (11)	0	0	0	1 (3)
Tadalafil + treprostinil sodium (TS)	0	1 (5)	0	0	1 (3)
AMB114588 Final Visit; n (%)					

PAH Therapy	Ambrisentan Dose Group				Total (N=38)
	2.5 mg (N=9)	5 mg (N=19)	7.5 mg (N=5)	10 mg (N=5)	
Any medication	8 (89)	13 (68)	3 (60)	3 (60)	27 (71)
PDE-5i (monotherapy)					
Any medication	4 (44)	5 (26)	3 (60)	3 (60)	15 (39)
Sildenafil	3 (33)	5 (26)	3 (60)	3 (60)	14 (37)
Tadalafil	1 (11)	0	0	0	1 (3)
Prostanoid (monotherapy)					
Any medication	0	2 (11)	0	0	2 (5)
Epoprostenol sodium (ES)	0	1 (5)	0	0	1 (3)
Treprostinil	0	1 (5)	0	0	1 (3)
PDE-5i and Prostanoid in combination					
Any medication	4 (44)	6 (32)	0	0	10 (26)
SC + beraprost sodium	1 (11)	1 (5)	0	0	2 (5)
Sildenafil + iloprost	0	1 (5)	0	0	1 (3)
Sildenafil + SC + treprostinil + TS	1 (11)	0	0	0	1 (3)
Sildenafil + TS	0	1 (5)	0	0	1 (3)
SC + ES	0	1 (5)	0	0	1 (3)
Tadalafil + beraprost sodium	0	1 (5)	0	0	1 (3)
Tadalafil + ES	1 (11)	0	0	0	1 (3)
Tadalafil + selexipag	1 (11)	0	0	0	1 (3)
Tadalafil + TS	0	1 (5)	0	0	1 (3)

Source: Study AMB114588 CSR Table 1.9, Table 1.10

Clinical Worsening of Pulmonary Arterial Hypertension in Study AMB114588

Only events of clinical worsening that occurred in the extension study are reported here. Subjects could experience more than one reason for clinical worsening of PAH, and the most frequently reported reason for first worsening of PAH was death and PAH related deterioration (Table 8). In the extension study, 11 participants (29%) across all 4 dose groups experienced an occurrence of clinical worsening of PAH based on at least 1 criterion (Table 8), with more than 1 clinical worsening criterion met by 5 of 11 participants (45%) (Source: AMB114588 CSR Listing 2.3). One additional subject from the 7.5 mg group died but was inadvertently not captured as a clinical worsening on the eCRF prior to site closure (as required by protocol), and hence is not included in this table.

Table 8. Time to the First Clinical Worsening of PAH - All Cause in Study AMB114588 (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 (allcause) 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	0	1 (50)	0	1 (100)	2 (50)

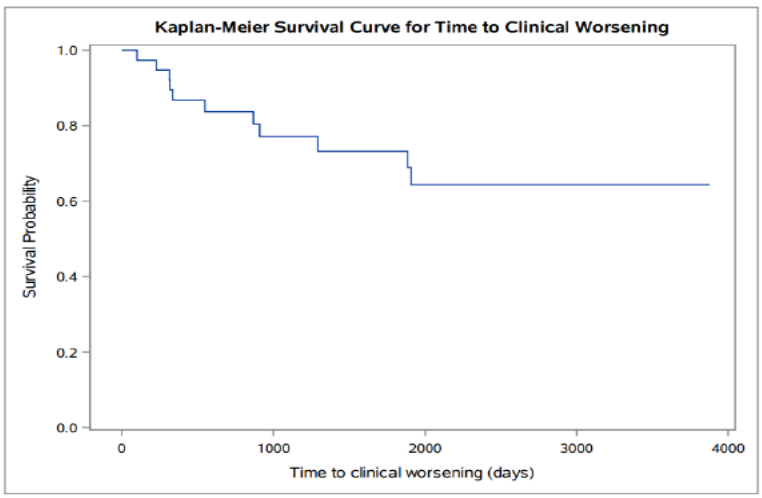
	WHO functional class					
	Deterioration in exercise testing[f]	0	0	0	0	0
	Clinical signs or symptoms of right-sided heart failure[g]	1 (100)	1 (50)	0	1 (100)	3 (75)

Source: AMB114588 CSR Table 2.7, Table 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.

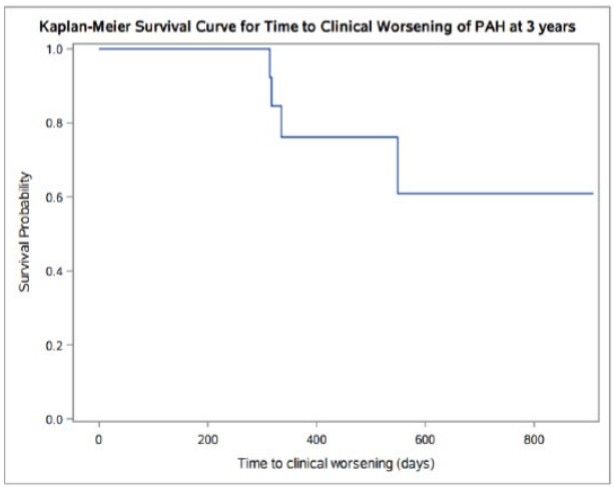
The time to first clinical worsening of PAH was variable across subjects and dose groups, with the highest mean time reported for subjects in the 5 mg and 7.5 mg groups. The Kaplan-Meier analysis showed most events occurred within 3 years of Study AMB112529 Baseline (Figure 1).

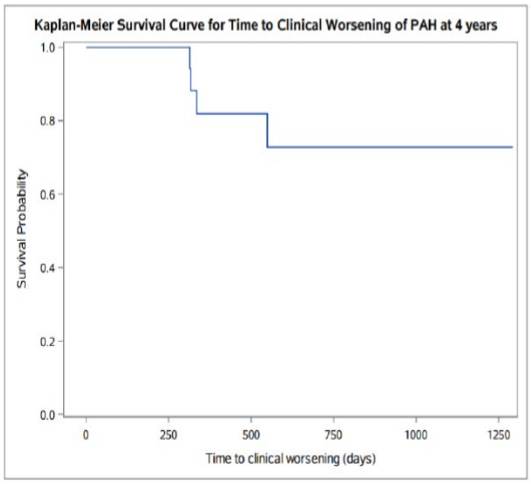
Figure 1. Kaplan-Meier Survival Curves with 95% Confidence Bands of Time to First Clinical Worsening of PAH in Study AMB114588 (ITT Population)



Kaplan-Meier event-free survivor estimate for worsening of PAH at 3 and 4 years after the start of treatment were 73.33% and 78.95% respectively (Figure 2). Kaplan-Meier event-free survivor estimate for worsening of PAH at end of study treatment is 71.05%.

Figure 2. Kaplan-Meier Survival Curves with 95% Confidence Bands of Time to First Clinical Worsening of PAH for overall, at 3 years, at 4 years in Study AMB114588 (ITT Population)





All-cause death in Study AMB114588 (ITT Population)

All-cause death (primary study endpoint) was analysed as the main component of clinical worsening.

Seven participants across 3 dose groups (5 mg, 7.5 mg, 10 mg) 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 (Source AMB114588 CSR Table 2.12).

Table). There were 6 participants who experienced clinical worsening resulting in death during this extension study. One additional death was inadvertently not entered onto the eCRF as a clinical worsening prior to site closure and this event is not included in the efficacy analysis of time to death.

Table 9. Summary of Time to Death (All-cause) (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)	
Number of deaths[a]	0	5	1	1	7
Mean (SD) (d)[b]	-	1605.2 (1004.24)	2232.0	473.0	1533.0 (972.30)
Median (d)	-	1884.0	2232.0	473.0	1884.0
Min to Max (d)	-	101 to 2829	2232 to 2232	473 to 473	101 to 2829

Source: AMB114588 CSR Table 2.1

a. Number of deaths occurring in AMB114588. The distribution of deaths across 2 dose groups (5 mg and 10 mg) differs from AMB114588 CSR Section 6.2.1 due to different populations used for the analysis (ITT versus Safety). However, both populations equally show 7 deaths.

b. Time to death was estimated from AMB112529 Baseline.

Kaplan-Meier estimates of survival were 94.74% and 92.11% at 3 and 4 years after the start of treatment, respectively. Kaplan-Meier estimates of survival is 81.58% at the end of study.

Change from Baseline in 6MWD in Extension Study AMB114588

From AMB112529 Baseline to AMB114588 Study Entry, mean and median 6MWD increased for the total population (increases of 13.3% and 6.4%, respectively) and across all 4 dose groups (mean increases of 1.3% to 33.8% and median increases of 5.6% to 17.1%), indicative of an improvement in exercise capacity across the initial AMB112529 study. Increases were greatest in the 2.5 mg group (mean/median increase of 33.8% and 17.1%, respectively) (Table 10).

Table 10. Change from Baseline in Six-Minute Walking Distance in Study AMB114588 (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: AMB114588 CSR 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.

Of the 38 subjects who attempted the 6MWD test either at AMB112529 Baseline, AMB114588 Study Entry through to the end of the extension study, or at follow-up, 7 subjects could not complete the full

duration of the test (Source AMB114588 CSR Table 2.5); 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. Of these 5 participants, 3 participants (2.5 mg, 5 mg, 10 mg) completed the full 6-minute test from AMB114588 Study Entry through to End of Study with 2 exceptions (Month 12 for 1 participant [5 mg] and follow-up for another [10 mg]). The remaining 2 participants (5 mg) completed the full test at AMB114588 Study Entry through to Month 6 or Month 36 (no End of Study assessments were conducted). Two additional participants were not able to complete the 6MWD at either Month 12 (7.5 mg; 5.3 minutes) or Follow-up (10 mg; 3.1 minutes) whilst they were able to complete it at all other visits, including AMB112529 Baseline, AMB114588 Study Entry and End of Study. The number of participants requiring oxygen for 6MWD was 4 of 38 participants at AMB112529 Baseline (2 each from the 2.5 mg and 5 mg groups), 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).

World Health Organisation Functional Class

At AMB114588 Study Entry, all 4 WHO Functional Classes (I, II, III and IV) were represented by participants with over half meeting Class II (n=22; 58%) and the remaining participants meeting Class I (n=9; 24%), Class III (n=6; 16%) or Class IV (n=1; 3%) (Source: AMB114588 CSR Table 1.5 and Section 5.4). At AMB114588 Study Entry, WHO Functional Classes represented no change (n=26; 68%) or an improvement (n=10; 26%) from AMB112529 Baseline for the majority of participants, and a deterioration for 2 participants (5%) (Source: AMB114588 CSR Table 2.14). 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 (n=29) (Table 11). Of those participants who experienced an improvement, most improved by one WHO Functional Class category (11 of 13 participants). (Source AMB114588 CSR Table 2.13, Table 2.14). There was no clinically relevant mean change from Baseline in the WHO functional class based on summary statistics (Source AMB114588 CSR Table 2.12).

Table 11. World Health Organisation Functional Class Change from Baseline Categorization at Study Entry and End of Study in Study AMB114588 (ITT Population)

WHO Category Change [a]	Ambrisentan Dose Group				Total (N=38)
	2.5 mg (N=9)	5 mg (N=19)	7.5 mg (N=5)	10 mg (N=5)	
Change from AMB112529 Baseline to AMB114588 End of Study; n (%)					
N	9	11	4	5	29
Improved	5 (56)	5 (45)	3 (75)	0	13 (45)
No Change	4 (44)	6 (55)	1 (25)	5 (100)	16 (55)
Deteriorated	0	0	0	0	0
-2	0	2 (18)	0	0	2 (7)
-1	5 (56)	3 (27)	3 (75)	0	11 (38)
0	4 (44)	6 (55)	1 (25)	5 (100)	16 (55)
+1	0	0	0	0	0
+2	0	0	0	0	0

Source: AMB114588 CSR Table 2.14

a. -1 and -2 represent a decrease in WHO Functional Class category by 1 or 2 class categories, respectively, indicative of an 'improvement'; 0 represents no change in WHO Functional Class category; +1 and +2 represent an increase in WHO Functional Class category by one 1 or 2 class categories, respectively, indicative of 'deterioration'.

Plasma N-terminal pro-B-type Natriuretic Peptide Concentration

For the subjects who entered the long-term extension study, the geometric mean NT-proBNP concentration at Study AMB112529 Baseline was variable across subjects and dose groups (Table 12). Variable changes from Baseline in concentrations were also evident at the Entry Visit. From AMB112529 Baseline to AMB114588 End of Study, there was a geometric mean/median percent decrease in NT-proBNP for the total population, which was largely driven by NT-proBNP reductions in the 2 lower dose groups (2.5 mg and 5 mg) (Table 12).

Table 12. Ratio to Baseline in Plasma NT-proBNP Concentration (ng/L) in Study AMB114588 (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					
n	9	19	4	5	37
Geometric mean (SD [logs]) (ng/L)	265.69 (1.505)	244.77 (1.638)	106.55 (0.707)	213.72 (1.647)	224.09 (1.504)
Median (ng/L)	275.00	169.00	98.35	105.00	175.00
Min to Max (ng/L)	22.0 to 2878.0	21.0 to 5738.0	56.0 to 238.0	32.0 to 1657.0	21.0 to 5738.0
AMB114588 Entry Visit					
n	5	12	4	5	26
Geometric mean (SD [logs]) (ng/L)	245.78 (0.395)	169.13 (1.372)	66.90 (0.576)	186.90 (1.842)	160.63 (1.265)
Median (ng/L)	220.00	290.73	78.99	175.00	202.83
Min to Max (ng/L)	158.0 to 378.0	16.0 to 713.0	30.0 to 107.0	18.0 to 2335.0	16.0 to 2335.0
AMB114588 End of Study					
n	7	11	3	5	26
Geometric mean (SD [logs]) (ng/L)	99.45 (1.322)	101.22 (1.091)	81.22 (0.714)	431.62 (1.980)	129.80 (1.388)
Median (ng/L)	150.00	77.00	61.00	213.00	93.00
Min to Max (ng/L)	6.5 to 367.0	26.0 to 1117.0	48.0 to 183.0	62.0 to 5210.0	6.5 to 5210.0
Percent Change from AMB112529 Baseline to AMB114588 End of Study					
n	7	11	2	5	25
Geometric mean (SD [logs]) (%)	-62.59 (1.496)	-56.02 (2.021)	59.06 (1.018)	101.96 (0.454)	-36.81 (1.683)
Median (%)	-47.52	-62.93	59.06	102.86	-22.58
Min to Max (%)	-97.6 to 116.3	-99.0 to 2227.1	-22.6 to 226.8	-2.1 to 214.4	-99.0 to 2227.1

Source: AMB114588 CSR Table 2.15 and Table 2.16

Cardiopulmonary Hemodynamics

Addition of Another Targeted PAH Therapeutic Agent

The time to addition of another targeted PAH therapeutic agent was analysed in Study AMB114588 only. Over the course of this extension study, 17 participants (45%) across all 4 dose groups required the addition of another targeted PAH therapeutic agent (prostanoids, PDE5i), whereby six subjects, evenly distributed across the 4 ambrisentan dose groups required the addition of another targeted therapeutic agent for PAH (prostanoids and PDE-5i) due to deterioration of clinical condition (Table 13).

The mean time to addition of another targeted therapeutic agent for PAH due to deterioration of clinical condition varied across the treatment groups and was highest in the 7.5 mg group and lowest in the 10 mg group.

No subjects in the ambrisentan 7.5 mg and 10 mg groups and 2 and 1 subjects in the ambrisentan 2.5 mg and 5 mg groups, respectively required the addition of another targeted therapeutic agent for PAH due to lack of beneficial effect with previous therapy (Table 13). The mean time to addition of another targeted therapy for PAH due to lack of beneficial effect was higher in the 2.5mg ambrisentan dose group compared with the 5 mg dose group.

One subject was recorded with both reasons due to multiple new therapeutic agent additions at different visits in the study. The median time to addition of another targeted therapeutic agent for PAH overall was broadly similar across the ambrisentan 2.5 mg, 5 mg and 10 mg groups but was higher in the 7.5 mg group.

Table 13. Time to the Addition of Another Targeted PAH Therapeutic Agent – Prostanoids, PDE-5 Inhibitors in Study AMB114588 (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)
tMedian (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

Source: Ambrisentan CSR AMB1145888 Table 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').

Change in Dose of Ambrisentan or Other Targeted PAH Therapeutic Agents

A total of 9 subjects required a change in dose of ambrisentan or other targeted PAH therapeutic agents (prostanoids, PDE-5i) due to deterioration of clinical condition in Study AMB114588 (Table 14). The time to change in dose in ambrisentan or another targeted PAH therapeutic agent due to deterioration of clinical condition ranged from approximately 3 months to 6.7 years. There was no clear relationship observed between ambrisentan dose group at study entry and time to change in dose of ambrisentan or other PAH agents.

Table 14. Summary of Time to Change in Dose of Ambrisentan or Other Targeted PAH Therapeutic Agents (Prostanoids, PDE-5 Inhibitors) due to Deterioration of Clinical Condition in Study AMB114588 (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

Source: AMB114588 CSR Table 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.

Subject Global Assessment – Physical Health and Psychosocial Summary Scores

At AMB112529 Baseline, the mean/median Physical Health Summary score was higher in the 2.5 mg group compared with all higher dose groups whilst mean/median Psychosocial Summary scores were similar across all dose groups. From AMB112529 Baseline to AMB114588 End of Study, mean/median changes in Physical Health and Psychosocial Summary scores were minimal for the total population.

6.3. Discussion

GSK has submitted the final results of the extension study AMB114588, which is part of the EU PIP for ambrisentan (interim results were submitted previously, and the SmPC already included study results, but corresponding to the interim analysis). The final results are consistent with those of the interim analysis. However, a label update in section 4.8 (Undesirable effect) and section 5.1 (Pharmacodynamic properties) for the treatment of children with PAH aged 8 years and over has been proposed to reflect the final study results. Compared with the interim analysis, the final study report includes the same number of children (n=38) but a slightly longer mean follow-up (i.e.: 3.4 years in the interim analysis vs. 4.0 years in the final analysis) and similar survival.

Of the 41 paediatric subjects enrolled in the initial study, 38 transitioned into the long-term extension study. Exposure estimates showed ambrisentan treatment was received by subjects for a duration of 3 months up to approximately 10 years. During the initial study, subjects were randomized to 24 weeks of treatment at a specified 'Low dose' or 'High dose' as determined by subject weight at study entry. Despite investigators having the option to change the dose of ambrisentan on entry to the AMB114588 study, the finding that the majority of subjects (66%) continued throughout the open-label extension study at the dose allocated during the initial study, is supportive of the tolerability and clinical benefit afforded by the dosing strategy employed in these studies for this age group. Most of the up-titrations of ambrisentan dose were due to weigh increases consistent with childhood growth with the majority of subjects finishing the study on either the 5 mg or 10 mg dose of ambrisentan. Two subjects had a final dose that was lower than their dose at study entry: 1 subject had a reduction in ambrisentan dose from 7.5 mg to 5 mg after 1 year at the discretion of the investigator and 1 subject was uptitrated from 5 mg to 7.5 mg in line with a gain in weight but was reduced back to 5 mg due to AEs before finishing the study on a dose of 2.5 mg.

Time to all-cause death and change from baseline in 6MWD were the primary analyses to demonstrate efficacy of ambrisentan in this study. Baseline for all efficacy endpoints in the long-term extension was defined as the time of randomization to ambrisentan in the AMB112529 study.

There were 6 subjects who had a clinical worsening resulting in death during this study (whilst one additional participant who died was not entered as a clinical worsening prior to site closure), and the mean/median time to death was 4.2 years from the start of treatment in Study AMB112529.

There was evidence at the Entry Visit to this study of clinically relevant improvements from Study AMB112529 Baseline in exercise capacity for subjects from all dose groups as demonstrated by the 6MWD test, which represented an improved status observed across the initial AMB112529 study. Change from Baseline in this long-term extension study continued to show a similar magnitude of mean improvement in all dose groups at at End of Study. Mean percentage change from baseline in 6MWD at end of study was approximately 34.4%, 12.7%, 2.4%, and 7% in the ambrisentan 2.5 mg, 5 mg, 7.5 mg and 10 mg groups respectively (Source AMB114588 CSR Table 2.4).

At the End of Study Visit, all subjects reported no change or an improvement from Study AMB112529 Baseline in WHO FC with 1subject showing an improvement from Baseline by more than 1 category. At the Entry Visit to this long-term extension study, the majority of subjects had reported either the same WHO FC category or a shift that indicated improvement, with 2 subjects reporting a worsening (one from a WHO FC category of II to III who remained category III for the duration of the extension study, and one from II to IV who subsequently died from cardiac failure acute). 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 (n=29).

In summary, the final results of the extension study AMB114588 are consistent with those of the interim analysis submitted previously and with the known efficacy/effectiveness profile of ambrisentan, and do not raise any new concern.

7. Clinical Safety aspects

7.1. Methods – analysis of data submitted

Study AMB114588 was an open label, long-term extension study to Study AMB112529. All subjects were required to participate in Study AMB112529 and were to remain in the extension study for a minimum of 6-month, beyond which they could continue until either the subject reached 18 years of age (and could receive marketed ambrisentan), or ambrisentan was approved and available for use in the subject's age group, or development for use in the paediatric population was discontinued, or the subject decided to no longer participate in the study, or the investigator considered it is in the best interest of the subject to discontinue ambrisentan (e.g., for safety reasons).

Safety was assessed by both clinical and laboratory evaluations. AEs and SAEs were defined in the Protocol Amendment 4 (Section 6.2.8) and were collected throughout the study including follow-up as appropriate following discontinuation of study medication. Clinical laboratory testing was done via both the central and local laboratories. The results reported in this document are the central laboratory data, unless otherwise specified. Haematology included platelet count, red blood cell (RBC) count, reticulocyte count, haematocrit, haemoglobin, RBC indices (mean corpuscular volume [MCV], mean corpuscular haemoglobin [MCH], and mean corpuscular haemoglobin concentration [MCHC]), white blood cell (WBC) count, and automated WBC differential (neutrophils-total, lymphocytes, monocytes, eosinophils, and basophils). Clinical chemistry included sodium, magnesium, potassium, calcium, glucose, chloride, bicarbonate, phosphorus-inorganic, total protein, albumin, lactate dehydrogenase, creatine phosphokinase, alkaline phosphatase (ALP), blood urea nitrogen (BUN), uric acid, creatinine, and estimated glomerular filtration rate (eGFR; Schwartz formula). Liver function tests (LFTs) included ALT, AST, gamma-glutamyl transferase (GGT), and total bilirubin. Baseline values were those collected prior to the first dose of ambrisentan in Study AMB112529. The baseline values recorded in Study AMB112529 were also the baseline values for the extension study.

The time to change in dose of ambrisentan or other targeted PAH therapeutic agents (prostanoids and PDE-5 inhibitors) due to tolerability issues (e.g. AEs) was assessed as well. Physical examination, 12-lead ECG, and echocardiogram were assessed every 6 months. Pubertal development was assessed every 6 months, as well as at 20 years of age. Vital signs and central laboratory assessments were assessed every 3 months. All safety assessments were also performed at Study End Visit and at 4-6 weeks following early discontinuation of study medication.

The analysis populations were:

- The ITT Population consisted of all subjects who received at least 1 dose of study drug. The ITT population was used for efficacy and study population analyses. For the ITT population, subjects were considered as belonging to their treatment group at the start of the extension study.

- The Safety Population was defined as all subjects who received at least 1 dose of study drug. The Safety Population was used for safety analyses. Subjects were considered as belonging to the treatment group according to the highest dose received.

7.2. Results

Number of Subjects in the Analysis Population

All 38 subjects who transitioned from Study AMB112529 to Study AMB114588 were included in the Safety and ITT populations.

Extent of Exposure and Treatment Compliance

For AMB114588, 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 (Table 15).

At least 75% of subjects in each dose group were treatment-compliant (defined as receiving ≥80% and ≤120% of planned study treatment) at each visit (Source: AMB114588 CSR Table 1.11). The overall

percentage of visits at which a subject was compliant was 97.8% with a similar mean percentage compliance for all dose groups (93.1% to 100.0%) (Source: AMB114588 CSR Table 1.12).

Table 15. Exposure to Ambrisentan in Study AMB114588 (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)

Source: AMB114588 CSR 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.

The majority of subjects (25 subjects [66%]) remained on the same dose initiated in Study AMB112529 throughout the long-term extension study with no up or down titrations (Source AMB114588 CSR Listing 3.1). Of the remaining 13 subjects who had at least 1 dose adjustment during the study, 11 subjects had dose increases alone, 1 subject had a dose reduction, and 1 subject had both increases and decreases in dose (Table). Dose adjustments were more common in the 2 higher dose groups (7.5 mg [67%] and 10 mg [58%]) as compared with the 2 lower dose groups (5 mg [13%] and 2.5 mg [0%] (Table 16).

A total of 11 subjects, regardless of the initial dose, were on 10 mg for their final dose. (Source AMB114588 Listing 3.1). Two subjects had a final dose that was lower than their dose at study entry (Table 16).

Of the 34 subjects with complete exposure data for the interim analysis of the extension study, the majority finished the study on either 5 mg (18 subjects) or 10 mg (11 subjects) (Table 16).

Table16. Initial Ambrisentan Dose at Entry into Study AMB114588 and Highest Dose Received and Final Dose Received in Study AMB114588 (ITT Population)

ITT Population (N=38)	Safety Population (N=38)
	Highest Ambrisentan Dose

Initial 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: AMB114588 CSR Table 1.13

The majority of subjects who up-titrated or down-titrated (or both) during this long-term extension study were from the 2.5 mg or 5 mg group at entry to the study (Table 17).

Table 17. Initial, Highest, and Final Doses of Ambrisentan in Study AMB114588 (ITT Population)

Initial Dose (mg/d)	Highest Dose (mg/d)	Final Dose (mg/d)	Number of Participants
2.5	2.5	2.5	4
	5	5	2[a]
	7.5	7.5	1[a]
	10	10	2[a]
5	5	5	14
	7.5	2.5	1[a]
	7.5	7.5	1[a]
	10	5	1[a]
	10	10	2[a]
7.5	7.5	7.5	2
	7.5	5	1
	10	10	2[a]
10	10	10	5

Source: CSR AMB114588 Listing 1.11

a. Twelve participants in total up-titrated from their 'initial dose' at AMB114588 study entry and thus have a higher 'highest dose' (used for Safety Population) compared to their initial dose (used for ITT Population).

Adverse events (AEs)

As the number of subjects in each dose group was determined by the subjects rolled-over from Study AMB112529 and some dose groups had small numbers, interpretation using overall subjects has been predominantly employed in this document.

Treatment-Emergent Common AEs

Overall, 89% of subjects reported at least 1 treatment-emergent AE, with a lowest incidence (81%) observed in the 5 mg group (Table 18). The most frequently reported treatment-emergent AE for overall subjects was upper respiratory tract infection (11 subjects, 29%) followed by nasopharyngitis (9 subjects, 24%). The most frequently reported treatment-emergent AEs in each dose group were: upper respiratory tract infection in the 2.5 mg and 7.5 groups, nasopharyngitis in the 5 mg group, and anaemia in the 10 mg group. SOCs with the highest incidence of treatment-emergent AEs were those relating Infections and Infestations (63%) for all dose groups and are further presented in Section 0.

Table 18. Treatment-Emergent AEs Occurring in >2 Total Subjects, Study AMB114588 (Safety Population)

Preferred Term	Ambrisentan[1]				
	2.5 mg N=4	5 mg N=16	7.5 mg N=6	10 mg N=12	Total N=38
Any event[2]	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	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	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	1 (25)	1 (6)	1 (17)	0	3 (8)
Iron deficiency anaemia	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	0	1 (6)	2 (33)	0	3 (8)
Rhinitis allergic	0	2 (13)	0	1 (8)	3 (8)
Toothache	0	1 (6)	0	2 (17)	3 (8)

Data Source: Study AMB114588 CSR Table 3.3

1. Subjects were considered as belonging to the treatment group according to the highest dose received.
2. Treatment-emergent AEs were those events either starting in AMB112529 and continuing into the extension study or starting in the extension study.

Treatment-Emergent AEs by Intensity

Overall, the majority of treatment-emergent AEs were reported mild (21%) or moderate (37%) in intensity. Overall, 26 severe treatment-emergent AEs were reported in 12 subjects (32%): cardiac failure acute (2), pulmonary arterial hypertension (2) and ALT increased, anaemia, acute right ventricular failure, right ventricular failure, atrioventricular block complete, autoimmune lymphoproliferative syndrome, cataract, conduction disorder, conductive deafness, conjunctivitis, disseminated intravascular coagulation, dyspepsia, eustachian tube dysfunction, failure to thrive, gastric haemorrhage, hypotension, hepatomegaly, oedema peripheral, migraine, pulmonary haemorrhage, pulmonary hypertension, and tension headache (1 each) (Date Source: Study AMB114588 CSR Table 3.4).

Treatment-Emergent AEs by Relationship to Ambrisentan

A drug-related AE was recorded by the investigator as having a reasonable possibility of being caused by the treatment with ambrisentan. The overall incidence of drug-related AEs was 39% (Table 19). Drug-related AEs which occurred in more than 1 subject were headache (3), anaemia, and gastroenteritis (2 each).

Table 19. Drug-Related Treatment-Emergent AEs, Study AMB114588 (ITT Population)

Preferred Term	Ambrisentan[1]				
	2.5 mg N=4	5 mg N=16	7.5 mg N=6	10 mg N=12	Total N=38
Any event[2]	1 (25)	5 (31)	3 (50)	6 (50)	15 (39)
Headache	0	1 (6)	2 (33)	0	3 (8)
Anaemia	0	1 (6)	0	1 (8)	2 (5)
Gastroenteritis	1 (25)	0	0	1 (8)	2 (5)
Abdominal pain upper	0	0	1 (17)	0	1 (3)
Alopecia	0	0	1 (17)	0	1 (3)
Angioedema	0	0	1 (17)	0	1 (3)
Aspartate aminotransferase increased	0	0	0	1 (8)	1 (3)
Blood bilirubin increased	0	0	0	1 (8)	1 (3)
Bronchitis	0	1 (6)	0	0	1 (3)
Cardiac failure congestive	0	1 (6)	0	0	1 (3)
Deafness	1 (25)	0	0	0	1 (3)
Decreased appetite	0	0	1 (17)	0	1 (3)
Dry mouth	0	0	1 (17)	0	1 (3)
Eczema	0	1 (6)	0	0	1 (3)
Erythema	0	0	1 (17)	0	1 (3)
Gastrooesophageal reflux disease	0	0	1 (17)	0	1 (3)
Hot flush	0	0	1 (17)	0	1 (3)
Hyperaemia	0	0	0	1 (8)	1 (3)
Motion sickness	0	1 (6)	0	0	1 (3)
Nasal obstruction	0	0	1 (17)	0	1 (3)
Nasopharyngitis	0	0	0	1 (8)	1 (3)
Nausea	0	0	1 (17)	0	1 (3)
Oedema peripheral	0	1 (6)	0	0	1 (3)
Pain in jaw	0	0	1 (17)	0	1 (3)
Pharyngotonsillitis	0	0	0	1 (8)	1 (3)
Presyncope	0	1 (6)	0	0	1 (3)
Sinusitis	0	1 (6)	0	0	1 (3)
Skin laceration	0	0	0	1 (8)	1 (3)
Swelling face	0	0	0	1 (8)	1 (3)
Syncope	0	1 (6)	0	0	1 (3)
Vertigo	0	0	0	1 (8)	1 (3)

Data Source: Study AMB114588 CSR Table 3.7

1. Subjects were considered as belonging to the treatment group according to the highest dose received.
2. Treatment-emergent AEs were those events either starting in AMB112529 and continuing into the extension study or starting in the extension study.

Deaths in study AMB114588

7 subjects died due to an SAE and are tabulated in Table 20. For these 7 deaths, 4 were in the 5 mg dose group, 1 in the 7.5 mg dose group, and 2 in the 10 mg dose group. The causes of deaths were due to acute cardiac failure in 3 subjects (including acute right ventricular failure in 1 subject), worsening of PAH in 2 subjects, failure to thrive in 1 subject and COVID-19 in 1 subject. Treatment with ambrisentan was recorded as discontinued in 3 subjects and "not applicable" in 4 subjects; all 4 subjects were recorded having the last dose of ambrisentan 1 or 2 days before they died. None of the deaths were considered by the investigator to be related to ambrisentan treatment (Data Source: Study AMB114588 CSR Listing 3.1 and Listing 3.6).

An SAE of cardiac failure acute was reported in 1 subject in the study AMB112529 and the event was continued in the extension study. The subject had an early withdrawal visit in that study after they had been enrolled in the extension study. The subject subsequently died from the ongoing SAE in the extension study.
All deaths, with a mean time to death of more than 3 years from treatment initiation, were recorded as resulting in withdrawal from the study (as was intended by the protocol), with the exception of 1 subject with an event of PAH (deterioration of) with onset during participation in the study, who

subsequently reached the age of 18 and hence completed the treatment period and the study prior to the final event outcome of death.

From the start of dosing in AMB112529 through to the end of the extension study (AMB114588), there were a total of 8 deaths, 7 deaths which occurred in the extension study and 1 death which occurred in AMB112529 (pneumonia; low dose group).

Table 20. Deaths, Study AMB114588 (Safety Population)

Subject ID	Age (year)/ Gender	Preferred Term	SAE (yes/no)	Relate to Drug (yes/no)	Drug-Withdrawn (yes/no)	Study-Withdrawn (yes/no)
Ambrisentan 5 mg Group[1]						
		Cardiac failure acute	Y	N	Y	Y
[2]		Cardiac failure acute	Y	N	Not applicable	Y
		COVID-19	Y	N	Y	Y
		Acute right ventricular failure	Y	N	Not applicable	Y
Ambrisentan 7.5 mg Group[1]						
[3]		Failure to thrive	Y	N	Y	Y
Ambrisentan 10 mg Group[1]						
[4]		Pulmonary arterial hypertension	Y	N	Not applicable	N
		Pulmonary arterial hypertension	Y	N	Not applicable	Y

Data Source: Study AMB114588 CSR Listing 3.6

1. Subjects were considered as belonging to the treatment group according to the highest dose received.
2. An SAE of cardiac failure acute was reported in the study AMB112529 and the event was continued in the extension study. The subject had an early withdrawal visit in that study after they had been enrolled in the extension study. The subject subsequently died from the ongoing SAE in the extension study.
3. The subject had an SAE of failure to thrive which resulted in death over 5 years from start of ambrisentan treatment (Study Day 1885) and was inadvertently not entered onto the eCRF as a clinical worsening prior to site closure.
4. The subject reached the age of 18 and hence completed the treatment period and the study prior to the final event outcome of death.

Other Serious Adverse Events in study AMB114588

A total of 42 treatment-emergent SAEs were reported in 21 subjects (55%) (Table 21). SAEs which occurred in more than 2 subjects each were: PAH (3 in the 10 mg dose group), anaemia (2; 1 each in the 5 mg and 10 mg dose groups), cardiac failure acute (2 in the 5 mg dose group), and pneumonia (2; 1 each in the 5 mg and 7.5 mg dose groups). Two SAEs (cardiac failure acute and failure to thrive) led to discontinuation of ambrisentan. Three SAEs (ALT increased, atrioventricular block complete, and hypotension) in 1 subject led to ambrisentan treatment being temporarily interrupted. None of the SAEs were considered by the investigator to be related to ambrisentan treatment (Data Source: Study AMB114588 CSR Listing 3.5).

Table 21. Treatment-Emergent SAEs, Study AMB114588 (Safety Population)

Preferred Term	Ambrisentan[1] 2.5 mg N=4	5 mg N=16	7.5 mg N=6	10 mg N=12	Total N=38
Any event[2]	2 (50)	7 (44)	4 (67)	8 (67)	21 (55)
Pulmonary arterial hypertension	0	0	0	3 (25)	3 (8)
Anaemia	0	1 (6)	0	1 (8)	2 (5)
Cardiac failure acute	0	2 (13)	0	0	2 (5)
Pneumonia	0	1 (6)	1 (17)	0	2 (5)
Acute right ventricular failure	0	1 (6)	0	0	1 (3)
ALT increased	1 (25)	0	0	0	1 (3)
Appendicitis	0	0	0	1 (8)	1 (3)
Atrioventricular block complete	1 (25)	0	0	0	1 (3)
Atrioventricular block first degree	0	0	0	1 (8)	1 (3)
Autoimmune lymphoproliferative syndrome	0	1 (6)	0	0	1 (3)
Conduction disorder	0	0	0	1 (8)	1 (3)
Complication associated with device	0	0	0	1 (8)	1 (3)
Dysmenorrhoea	0	1 (6)	0	0	1 (3)
Failure to thrive	0	0	1 (17)	0	1 (3)
Hyperventilation	0	1 (6)	0	0	1 (3)
Hypotension	1 (25)	0 0	0	0	1 (3)
Influenza	0	0	1 (17)	0	1 (3)
Illness	1 (25)	0	0	0	1 (3)
Migraine	0	0	1 (17)	0	1 (3)
Myringitis	0	0	0	1 (8)	1 (3)
Non-cardiac chest pain	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)
Pulmonary hypertension	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)
Sinusitis	0	0	0	1 (8)	1 (3)
Scoliosis	0	0	1 (17)	0	1 (3)
Vomiting	1 (25)	0	0	0	1 (3)
Wandering pacemaker	0	0	0	1 (8)	1 (3)

Data Source: Study AMB114588 CSR Table 3.9

1. Subjects were considered as belonging to the treatment group according to the highest dose received.
2. Treatment-emergent AEs were those events either starting in AMB112529 and continuing into the extension study or starting in the extension study.

Adverse Events of Special Interest in study AMB114588

Overall, treatment-emergent AESIs were reported in 20 subjects (53%) with a comparable percentage of subjects who had at least 1 event in each dose group (Table 22).

Anaemia was the most frequently reported AESI, with 11 events in 6 subjects (all in the 5 mg and 10 mg dose groups). An SAE of anaemia was reported in 2 subjects. Three events of anaemia in 2 subjects were considered by the investigator to be related to ambrisentan treatment (Data Source: Study AMB114588 CSR Listing 3.2).

Oedema-related events (including terms of oedema peripheral, angioedema, ascites, eyelid oedema, eye swelling, localised oedema, and swelling face) were reported in 6 subjects with 9 events. One subject had events of localised oedema, ascites, and angioedema. Events of oedema peripheral, angioedema and swelling face were considered by the investigator to be related to ambrisentan treatment.

Liver function laboratory abnormalities (including terms of ALT increased, AST increased, AST abnormal, blood bilirubin increased, and transaminases increased) were reported as AEs/SAEs in 3 subjects and are further presented in Section 0. One subject had an SAE of ALT increased that met protocol defined investigational product stopping criteria and led to drug interruption. Two mild AEs of

AST abnormal and AST increased were also reported for this subject. The second subject had the events of AST increased and blood bilirubin increased and both events were considered by the investigator to be related to ambrisentan treatment. The third subject reported 2 moderate AEs of transaminases increased separately and none were considered by the investigator to be related to ambrisentan treatment. (Data Source: Study AMB114588 CSR Table 3.17, Listing 3.2, and Listing 3.11).

A severe AE of hepatomegaly reported in 1 subject with no associated liver function laboratory abnormality during the study.

Events of hypotension (including terms of syncope, presyncope, and hypotension) were reported in 2 subjects. One subject had events of syncope and presyncope; both events were considered by the investigator to be related to ambrisentan treatment. An event of hypotension in 1 subject was reported as an SAE*.

No AESIs led to permanent discontinuation of ambrisentan treatment or withdrawal from the study (Data Source: Study AMB114588 CSR Table 3.18).

The majority of AESIs were resolved. There was no correlation between the time on treatment and the first occurrence of an AESI (Data Source: Study AMB114588 CSR Table 3.19 and Listing 3.2).

Table 22. Treatment-Emergent Adverse Events of Special Interest, Study AMB114588 (Safety Population)

Preferred Term	Ambrisentan[1]				
	2.5 mg N=4	5 mg N=16	7.5 mg N=6	10 mg N=12	Total N=38
Any event[2]	2 (50)	8 (50)	3 (50)	7 (58)	20 (53)
Anaemia	0	2 (13)	0	4 (33)	6 (16)
Dermatitis contact	0	1 (6)	1 (17)	1 (8)	3 (8)
Erythema	1 (25)	1 (6)	1 (17)	0	3 (8)
Iron deficiency anaemia	0	3 (19)	0	0	3 (8)
Rash	0	1 (6)	2 (33)	0	3 (8)
Rhinitis allergic	0	2 (13)	0	1 (8)	3 (8)
Eczema	0	1 (6)	0	1 (8)	2 (5)
AST increased	1 (25)	0	0	1 (8)	2 (5)
Conjunctivitis allergic	0	1 (6)	0	1 (8)	2 (5)
Dizziness	0	0	2 (33)	0	2 (5)
Oedema peripheral	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)
ALT increased	1 (25)	0	0	0	1 (3)
Ascites	0	0	1 (17)	0	1 (3)
AST abnormal	1 (25)	0	0	0	1 (3)
Asthma	0	0	0	1 (8)	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)
Bronchospasm	0	0	1 (17)	0	1 (3)
Conjunctivitis	0	0	0	1 (8)	1 (3)
Eyelid oedema	0	1 (6)	0	0	1 (3)
Eye swelling	0	0	1 (17)	0	1 (3)
Flushing	0	1 (6)	0	0	1 (3)
Hepatomegaly	0	1 (6)	0	0	1 (3)
Hypotension	1 (25)	0	0	0	1 (3)
Localised oedema	0	0	1 (17)	0	1 (3)
Presyncope	0	1 (6)	0	0	1 (3)
Swelling face	0	0	0	1 (8)	1 (3)
Syncope	0	1 (6)	0	0	1 (3)
Transaminases increased	0	1 (6)	0	0	1 (3)
Urticaria	0	0	1 (17)	0	1 (3)

Data Source: Study AMB114588 CSR Table 3.17

1. Subjects were considered as belonging to the treatment group according to the highest dose received.
2. Treatment-emergent AEs were those events either starting in AMB112529 and continuing into the extension study or starting in the extension study.

Adverse Events Leading to Premature Discontinuation of Investigational Product and/or Study in Study AMB114588

Six subjects were recorded as withdrawn due to an SAE (4 in the 5 mg dose group and 1 each in the 7.5 mg and 10 mg dose groups). These events were as follows: cardiac failure acute (2 subjects), acute right ventricular failure (1) and COVID-19 in the 5 mg dose group, failure to thrive (1) in the 7.5 mg dose group, and pulmonary arterial hypertension (1) in the 10 mg dose group. All 6 events led to a fatal outcome (

Table) and none were considered by the investigator to be related to ambrisentan treatment (Data Source: Study AMB114588 CSR Table 3.6, Table 3.13, and Listing 3.7).

AEs/SAEs led to an interruption in ambrisentan treatment in 1 subject with 4 events in the 2.5 mg dose group. SAEs of ALT increased, hypotension, and atrioventricular block complete are presented in Section 0 and Section 0. A drug-related AE of deafness (moderate in intensity) also led to a temporary interruption in ambrisentan treatment.

A dose of ambrisentan was reduced in 2 subjects due to their AEs: an AE of fatigue and a drug-related AE of erythema in 1 subject in the 7.5 mg dose group and a drug-related AE of swelling face in 1 subject on the 10 mg dose group. All 3 events were mild in intensity (Data Source: Study AMB114588 CSR Table 3.5 and Listing 3.2).

Analysis of Adverse Events by Organ System or Syndrome in Study AMB114588

SOCs with the highest incidence of AEs (≥30% of overall subjects) included Infections and Infestations, General Disorders and Administration Site Conditions, Respiratory, Thoracic and mediastinal Disorders, GI Disorders, and Nervous System Disorders (Table 23).

Table 23. Treatment-emergent AEs by SOCs, Study AMB114588 (Safety Population)

	Ambrisentan[1]				
SOCs, n (%)	**2.5 mg N=4**	**5 mg N=16**	**7.5 mg N=6**	**10 mg N=12**	**Overall N=38**
Treatment-emergent AEs ≥30% of Overall Subjects					
Infections and infestations	3 (75%)	8 (50%)	5 (83%)	8 (67%)	24 (63%)
General disorders and administration site conditions	2 (50%)	5 (31%)	4 (67%)	6 (50%)	17 (45%)
Respiratory, thoracic and mediastinal disorders	1 (25%)	6 (38%)	3 (50%)	4 (33%)	14 (37%)
Gastrointestinal disorders	2 (50%)	7 (44%)	3 (50%)	3 (25%)	15 (39%)
Nervous system disorders	1 (25%)	6 (38%)	3 (50%)	3 (25%)	13 (34%)
Drug-related Treatment-emergent AEs ≥10% of Overall Subjects					
Infections and infestations	1 (25%)	1 (6%)	0	2 (17%)	4 (11%)
Nervous system disorders	0	2 (13%)	2 (33%)	0	4 (11%)
Treatment-emergent SAEs ≥10% of Overall Subjects					
Cardiac disorders	1 (25%)	3 (19%)	1 (17%)	2 (17%)	7 (18%)
Infections and infestations	0	2 (13%)	2 (33%)	3 (25%)	7 (18%)
Respiratory, thoracic and mediastinal disorders	0	2 (13%)	0	3 (25%)	5 (13%)

Data Source: Study AMB114588 CSR Table 3.2, Table 3.7, and Table 3.9.

1. Subjects were considered as belonging to the treatment group according to the highest dose received.

Clinical Laboratory Evaluations in Study AMB114588

Haematology and clinical chemistry were assessed every 3-month throughout the study and at the end of study visit.

Haematology Values Over Time:

Mean values of haematology parameters were generally within the normal reference range throughout the study. There were small mean reductions from baseline in haemoglobin, haematocrit, and platelet count for overall subjects. The mean reductions continued to be observed by Month 36. Fewer than half of subjects remained at Month 36 visit and onward in the study, and there were too few subjects in each dose group to provide a meaningful interpretation. The mean decreases from baseline at the end of study visit were -3.7 G/L in haemoglobin, -0.39% in haematocrit, and -17.3 GI/L in platelet count. Mean reductions in red blood cell (RBC) count were observed at most post-baseline visits (<-0.35 TI/L). There were also small mean reductions in red blood cell indices, as well as lymphocytes

(%). The mean decreases from baseline at the end of study visit were -6.9 G/L in MCHC, -0.8 pg/cell in MCH, 0.5 FL in MCV, and lymphocytes (-5.18%) (Data Source: Study AMB114588 CSR Table 3.22).

Haematology Abnormalities of Potential Clinical Concern:

Overall, few subjects (≤4 in a specific lab parameter) had haematology (haemoglobin, haematocrit, and platelet count) values of clinical concern at any post-baseline. None of these values of potential clinical concern were observed at the entry visit to the extension study (Table 24).

Table 24. Incidence of Haematology Values of Potential Clinical Concern, Study AMB114588 (Safety Population)

Haematology Parameter	Respect to Clinical Concern Value	Number (%) of Subjects		
		Ambrisentan[1], N=38		
		Entry Visit[2]	Any Visit[3,4]	Note
Haemoglobin[5] (G/L)	n	29	37	
	above	0	1 (3)	in the 10 mg group
	below	0	4 (11)	3 in the 5 mg group and 1 in the 10 mg group
Haematocrit[6] (%)	n	29	37	
	above	0	3 (8)	all 3 in the 10 mg group
	below	0	3 (8)	2 in the 5 mg group and 1 in the 10 mg group
Platelets[7] (GI/L)	n	29	37	
	above	0	2 (5)	both in the 5 mg group
	below	0	1 (3)	in the 5 mg group

Data Source: Study AMB114588 CSR Table 3.23

1. Subjects were considered as belonging to the treatment group according to highest dose received.
2. At entry to the extension study.
3. Any post post-baseline visit.
4. Subjects with both Normal and Low values were counted once under their worst case (Low); Subjects with both Normal and High values were counted once under their worst case (High); Subjects with both High and Low values were counted under both categories.
5. Haemoglobin values of clinical concern: Males: <98 G/L or >180 G/L, Females: <91 G/L or >161 G/L.
6. Haematocrit values of clinical concern: male: <0.32 or >0.54, Females: <0.29 or >0.506.
7. Platelet value of clinical concern: <100 GI/L or >500 GI/L.

Laboratory abnormalities were reported as AEs in 10 subjects including anaemia (6), iron deficiency anaemia (3), and neutropenia (1). AEs of anaemia in 2 subjects were considered by the investigator to be related to ambrisentan treatment (Data Source: Study AMB114588 CSR Table 3.2 and Listing 3.2).

Clinical Chemistry and Liver Function Test from Study AMB112529 Baseline:

The mean values, including ALT, AST, GGT, bilirubin, alkaline phosphatase, BUN, creatinine, and eGFR* observed for overall subjects were all within the testing laboratory's reference range throughout the extension study.

In general, there was little change in mean clinical chemistry parameters over the course of the study, with the exception of creatinine (Table 25). A small mean increase in creatinine from baseline was observed at entry to the extension study which continued to be observed to a larger magnitude at subsequent visits. This corresponded with a small mean decrease in eGFR and stable BUN values.

There were no other clinically relevant changes from baseline or trends in clinical chemistry parameters.
Clinical chemistry values of clinical concern at any post-baseline visit included the following parameters: ALT ≥3X upper limit of normal (ULN) in 1 subject in the 5 mg dose group, AST ≥3X ULN in 1 subject in the 5 mg dose group, total bilirubin >34.2μmol/L in 3 subjects (1 each in the 2.5 mg, 5

mg, and 10 mg groups). No subjects had a value of potential clinical concern for these parameters at Study AMB112529 baseline or at the entry to the extension study (Data Source: Study AMB114588 CSR Table 3.26 and Listing 3.10).

There were no subjects with values of potential clinical concern for creatinine* and all other protocol-specified clinical chemistry parameters.

Hepatic laboratory test abnormalities (including terms of ALT increased, AST increased, AST abnormal, blood bilirubin increased, and transaminases increased) were reported as AEs/SAEs in 3 subjects.

A fourth subject had a severe AE of hepatomegaly with a concurrent fatal SAE of cardiac failure acute. Both events were considered by the investigator to be unrelated to ambrisentan treatment. The event of cardiac failure acute was reported in the study AMB112529 and continued in the extension study. The subject subsequently died from the ongoing SAE in the extension study. Study AMB112529 baseline values of ALT, AST, and bilirubin were within the normal reference range. ALT was 51 IU/L (NR = 0-45 IU/L) at Week 8 in Study AMB112529 and AST values were from 57-62 IU/L (NR = 0-42 IU/L) at Week 4 and onward. No LFT was performed in the extension study. (Data Source: Study AMB112529 CSR Listing 3.10; Study AMB114588 CSR Listing 3.2 and Listing 3.10).

Vital Signs, Physical Findings, and Other Observations Related to Safety

Overall, 89% of subjects (34/38) had normal liver size on physical examination and 84% of subjects (32/38) had normal jugular venous pressure at the entry visit to the extension study. One subject had peripheral oedema and 2 had ascites. The mean saturated oxygen value was 97% (Data Source: Study AMB114588 CSR Table 3.34).

Physical examination parameters remained generally stable or improved at subsequent visits with no clear pattern of change. At the end of study visit, 93% of the remaining subjects (27/29) had normal liver size and jugular venous pressure with mean saturated oxygen level of 96.8%; no peripheral oedema reported, and ascites was reported in 2 subjects.

Overall, an increase in systolic blood pressure from baseline in Study AMB112529 was observed at all visits from Month 3, with an end of study visit mean/median increase of 8.3/6.0 mmHg. A progressive increase in mean/median height and weight from the entry visit was also observed, which may reflect the paediatric population under study. There were no other clinically relevant or consistent mean changes from baseline in vital signs (Data Source: Study AMB114588 CSR Table 3.31). Few subjects had systolic blood pressure, diastolic blood pressure, or heart rate value of clinical concern at any post-baseline visit (≤7subjects for each measure).

Pubertal development in male and female subjects were assessed using Tanner criteria [Marshall, 1969; Marshall, 1970; Cameron, 2004]. In addition, blood samples were obtained to measure follicle-stimulating hormone (FSH), luteinizing hormone (LH), testosterone, sex hormone binding globulin (SBGH) and inhibin B levels. A total of 25 female subjects and 13 male subjects in the extension study had pubertal assessments at Study AMB112529 baseline and at the entry visit to the extension study. A total of 14 subjects (10 females and 4 males) had their 20-year old pubertal assessment. No clinically relevant change from baseline was observed at the end of study visit in female/male plasma endocrine parameters (Data Source: Study AMB114588 CSR Table 3.41 and Table 3.42).

ECG

The results of a 12-lead ECG were categorized as normal, abnormal not clinically significant, or abnormal clinically significant in the medical and scientific judgement of the investigator for both studies. No further details on ECG findings are available. The majority of subjects had abnormal but not clinically significant ECG findings at Study AMB112529 baseline, at entry visit to the extension study, and at post-baseline visits (71%, 79%, and 86% of subjects, respectively). A total of 6 subjects had a clinically significant abnormal ECG at any post-baseline visit. Of these, 4 had a clinically significant abnormal ECG at baseline, at entry visit to the extension study, as well as at most post-baseline visits. Of the 6 participants, 2 experienced fatal SAEs (cardiac failure acute and acute right ventricular failure) and did not have End of Study 12-ECG data; of the remaining 4 participants

by End of Study, 12-ECG assessments were 'abnormal, not clinically significant'. At End of Study, no remaining participants had 'abnormal, clinically significant' 12-ECG assessments.

Echocardiogram

Overall, 84% of subjects (31/37) who were entered into the extension study had no pericardial infusion at baseline in Study AMB112529 and the incidence was similar across the ambrisentan dose groups (Data Source: Study AMB11458 CSR Table 2.17). At the end of study, with the exception of right ventricular pressure, mean changes from baseline in all parameters were small. With the exception of the 5 mg dose group, a mean reduction in right ventricular pressure was observed across all dose groups.

Change in Ambrisentan or Targeted PAH Therapeutic Agent Dose Due to Tolerability

There were 7 subjects who had a change in dose of ambrisentan, prostanoids or PDE-5 inhibitors as a result of tolerability issues. There was no clear relationship between dose group and time to PAH medication dose change, with overall median time of 498.0 days (ranged from 354 to 2187 days) (Data Source: Study AMB114588 CSR Table 3.43).

Treatment-Emergent AEs by Age in Study AMB114588

A total of 14 subjects aged 8-11 years and 24 subjects aged 12 to <18 years were enrolled in the extension study. In the 8-11 years age stratum, all subjects but 1 reported at least 1 treatment-emergent AEs. AEs that occurred in more than 2 subjects were nasopharyngitis (4), pharyngitis (4), upper respiratory tract infection (4), gastroenteritis (3), influenza (3) (Data Source: Study AMB114588 Age 8-11 Years Subset Table 3.3002). In the 12 to <18 years age stratum, the majority of subjects reported at least 1 treatment-emergent AE. The most frequently reported AEs were headache and upper respiratory tract infection (6 subjects each).

Treatment-Emergent AEs by Relationship to Ambrisentan

In the 8-11 years age stratum, treatment-emergent AEs that were considered by the investigator to be related to ambrisentan treatment were reported in 4 subjects with 6 events (2 subjects with 4 events in the 10 mg group and 1 each in the 2.5 mg and 5 mg groups). An AE of gastroenteritis was reported in 2 subjects (1 each in the 2.5 mg and 10 mg groups). The rest of the events included deafness (2.5 mg group) oedema peripheral (5 mg group), nasopharyngitis, skin laceration, and swelling face (all in the 10 mg group) (Data Source: Study AMB114588 Age 8-11 Years Subset Table 3.7002).
In the 12 to <18 years age stratum, treatment-emergent AEs that were considered by the investigator to be related to ambrisentan treatment were reported in 11 subjects (46%). Drug-related AEs occurring in more than 1 subject were headache (3) and anaemia (2).

AEs Leading to Premature Discontinuation of Investigational Product and/or Study

In the 8-11 years age stratum, 4 subjects were withdrawn from the study or were withdrawn from ambrisentan treatment due to an AE: cardiac failure acute (2) and acute right ventricular failure (1) in the 5 mg dose group and pulmonary arterial hypertension (1) in the 10 mg dose group (Data Source: Study AMB114588 Age 8-11 Years Subset Table 3.6002). In the 12 to <18 years age stratum, 1 subject in the 7.5 mg dose group was withdrawn from the study and was withdrawn from ambrisentan treatment due to an SAE of failure to thrive (Data Source: Study AMB114588 Age 12-18 Years Subset Table 3.6003).

Use in Pregnancy and Lactation

No pregnancies were reported. It is not known whether ambrisentan is transferred to breast milk. Breastfeeding during ambrisentan therapy is contraindicated.

7.3. Discussion

GSK has submitted the final results of the extension study AMB114588, which is part of the EU PIP for ambrisentan (interim results were submitted previously, and the SmPC already included study results, but corresponding to the interim analysis). The final results are consistent with those of the interim

analysis. However, a label update in section 4.8 (Undesirable effect) and section 5.1 (Pharmacodynamic properties) for the treatment of children with PAH aged 8 years and over has been proposed to reflect the final study results.

Based on pooled data from 38 subjects, ambrisentan was generally well tolerated with no new clinically relevant safety findings, including from physical examination and pubertal development assessments. The most frequently reported TEAEs were upper respiratory tract infection and nasopharyngitis. No AESI led to permanent discontinuation of ambrisentan or withdrawal from the study. None of the SAEs (including 7 deaths) reported were regarded as related to ambrisentan and all 7 deaths (excluding one subject who died from COVID-19 infection) were due to events associated with the natural progression profile and known characteristics of children with PAH disease. Observed small changes in renal parameters are generally consistent with the long-term nature of this extension study and the increasing age of the participants. A small mean reduction from Baseline in haemoglobin, haematocrit, and platelet count was observed for all dose groups combined, consistent with safety findings in the adult population.

In summary, the final results of the extension study AMB114588 are consistent with those of the interim analysis submitted previously and with the known safety profile of ambrisentan, and do not raise any new safety concern.

7.4. Direct Healthcare Professional Communication

N/A.

8. PRAC advice

N/A.

9. Changes to the Product Information

The MAH sent the final study report of the extension study AMB114588 (Study Report TMF-14398819) within current variation application. As a result, section(s) 4.8 and 5.1 of the SmPC are being updated.

Some additional amendments are needed to improve the description of the populations, ambrisentan doses, concomitant PAH medications and results of the AMB114588 extension study in section 5.1, while the proposed amendment to section 4.8 is agreed. On the other hand, minor editorial changes to Annex II and to the Package Leaflet are acceptable.

Please refer to Attachment 1 which includes all agreed changes and all the proposed changes by the Rapporteur to the Product Information.

9.1.1. Additional monitoring

N/A.

9.1.2. Quick Response (QR) code

N/A.

10. Request for supplementary information

10.1. Major objections

None.

10.2. Other concerns

Non Clinical aspects

None.

Clinical aspects

1. Some changes are necessary in section 5.1 of the SmPC to improve the description of the extension study AMB114588 (see Product Information with Rapporteur's comments and proposed amendments included).

11. Assessment of the responses to the request for supplementary information

11.1. Major objections

N/A.

11.2. Other concerns

Clinical aspects

Question 1: Some changes are necessary in section 5.1 of the SmPC to improve the description of the extension study AMB114588 (see Product Information with Rapporteur's comments and proposed amendments included).

Summary of the MAH's response

The applicant has carefully evaluated the suggested changes by the Rapporteur to the EU SmPC Section 5.1 with regards to the description of AMB114588 and has detailed individual responses for each proposed amendment below:

1. The applicant accepts the inclusion of the proposed text by the Rapporteur: Most of the subjects who transitioned into this long-term extension had idiopathic or heritable PAH (68%). However, the applicant has proposed additional text to highlight that the aetiology status is described as per AMB112529 Baseline as follows: Most of the subjects who transitioned into this long-term extension had idiopathic or heritable PAH (68%) as per AMB112529 Baseline.

2. The applicant does not agree with the inclusion of the proposed text by the Rapporteur: Most children received the ambrisentan 5 mg dose (n=16), followed by the 10 mg dose (n=12), the 7.5 mg dose (n=6) and the 2.5 mg dose (n=4). Given that participants were allowed to up or down-titrate during the duration of the extension study, which has been appropriately described in section 5.1, adding individual patient numbers for each dose would neither be accurate (without indicating if these are highest dose received or relating to a particular visit in the extension study), nor would this additional text be meaningful given the complexity of individual dose titrations for some participants throughout the extension study.

3. The applicant does not agree with the following edits by the Rapporteur to existing text: Original GSK proposed text: Overall, 66% of patients who continued in the extension study remained on the same dose of ambrisentan used in AMB112529. Proposed text by the Rapporteur: The majority of subjects (n=25; 66%) remained on the same dose initiated in study AMB112529 throughout the long-term extension study. This update is incorrect. In AMB112529 participants were randomised into either a low or high dose group. Within each body weight group, participants were then started at the lower dose for that group and then, at Week 2, those randomised to the high dose group received the higher dose. The proposed amendment by the Rapporteur suggests that most subjects remained on the same dose on which they were 'initiated' on in study AMB112529, which is inaccurate. The applicant has

therefore proposed to re-instate the original text.

4. The applicant accepts the addition of the standard deviation for the mean duration of exposure by the Rapporteur but does not agree with the lower limit of the range: The mean duration (± standard deviation) of exposure to ambrisentan treatment was 4.0 ± 2.5 years (range: 0.3 to 10.0 years). In the extension study, the minimum exposure was 100 days (~3 months) and not 0.3 years (~3.6 months). The applicant has therefore proposed a correction of the exposure range in section 5.1.

5. The applicant does not agree with the inclusion of the proposed text by the Rapporteur: All cause death (primary study endpoint) was analysed as the main component of clinical worsening. This is incorrect, as all-cause mortality was included in the 'time to clinical worsening' endpoint, which was a secondary efficacy endpoint for this study.

6. The applicant accepts the inclusion of the proposed text by the Rapporteur: […], while 11 participants (29%) across all 4 dose groups experienced an occurrence of clinical worsening CONFIDENTIAL of PAH based on at least 1 criterion, with more than 1 clinical worsening criterion met by 5 of 11 participants (45%).

7. The applicant does not agree with the inclusion of the suggested text by the Rapporteur: There were 6 subjects who had a clinical worsening resulting in death during this study (whilst one additional participant who died was not entered as a clinical worsening prior to site closure), and the mean/median time to death was 4.2 years from the start of treatment in Study AMB112529. Based on EMA guidelines (https://www.ema.europa.eu/en/human-regulatoryoverview/marketing-authorisation/product-information-requirements/how-prepare-andreview-summary-product-characteristics), section 5.1 should provide a concise summary of statistically compelling and clinically relevant data for the primary endpoint(s), with secondary endpoints only being added on a case-by-case basis. Given that all-cause mortality was a secondary efficacy endpoint in the extension study, the applicant does not agree with the inclusion of the text. This is also in line with section 5.1 for another endothelin receptor antagonist. Specifically, section 5.1 in the SmPC for bosentan does not include detailed information on deaths in the paediatric clinical trials and only describes Kaplan-Meier estimates for survival. The applicant has therefore proposed the re-instatement of the updated KaplanMeier estimates for survival accordingly.

8. The applicant accepts the proposed amendment by the Rapporteur with respect to re-ordering the efficacy results; whereby Clinical Worsening is described first, followed by results for 6MWD and WHO Functional Class.

9. The applicant accepts the amendments to the proposed text by the Rapporteur to include the mean increase and standard deviation for 6MWD.

10. The applicant accepts the inclusion of the proposed amendment by the Rapporteur: At AMB114588 Study Entry, all 4 WHO Functional Classes (I, II, III and IV) were represented by participants with over half meeting Class II (n=22; 58%) and the remaining participants meeting Class I (n=9; 24%), Class III (n=6; 16%) or Class IV (n=1; 3%).

Assessment of the MAH's response

The Company has accepted most of the proposed changes and has provided appropriate justifications for not including the other proposed changes (see attached the PI with track changes).

Issue solved.

Conclusion

☐Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☒No need to update overall conclusion and impact on benefit-risk balance