22 July 2021
EMA/CHMP/476747/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Volibris

International non-proprietary name: ambrisentan

Procedure No. EMEA/H/C/000839/X/0061/G

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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List of abbreviations

6MWD	6-Minute walking distance
AE	Adverse event
ANCOVA	Analysis of Covariance
AUCss	Area under the plasma drug concentration-time curve from pre-dose to the end of the dosing interval at steady state
bpm	Beats per minute
CI	Confidence interval
cm	Centimetres
Cmax,ss	Maximum plasma concentration at steady-state
CQA	Critical Quality Attribute
EM(E)A	European Medicines (Evaluation) Agency
ER	Exposure–response
ERAs	Endothelium receptor antagonists
ES	Epoprostenol sodium
EU	European Union
EU	European Union
GMP	Good Manufacturing Practices
GSK	GlaxoSmithKline
HDPE	High density polyethylene
HPAH	Heritable pulmonary arterial hypertension
HPLC	High performance liquid chromatography
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICP-MS	Inductively coupled plasma mass spectrometry
IDMC	Independent Data Monitoring Committee
IPAH	Idiopathic pulmonary arterial hypertension
ITT	Intent-to-Treat
kg	Kilograms
L	Litre
LEVDP	Left ventricular end diastolic pressure
LFTs	Liver function tests
m	Metre
m^2	Square metres
MAA	Marketing Authorisation Application
MCID	Minimal clinically important difference
mg	Milligram
MIAH	Manufacturer and Importer Authorisation Holder
min	Minute
mL	Millilitre
mmHg	Millimetres of mercury
MMRM	Mixed Model with Repeated Measures
mPAP	Mean pulmonary arterial pressure

ng	Nanogram
NMT	Not more than
NT-proBNP	N-terminal pro-B-type natriuretic peptide
NYHA	New York Heart Association
PA	Pulmonary arterial
PAH	Pulmonary arterial hypertension
PCWP	Pulmonary capillary wedge pressure
PD	Pharmacodynamic
PDCO	Paediatric Committee
PDE	Permitted Daily Exposure
PDE-5(i)	Phosphodiesterase-5 inhibitor
Ph.Eur.	European Pharmacopoeia
PIP	Paediatric Investigation Plan
PK	Pharmacokinetic
PVR	Pulmonary vascular resistance
QP	Qualified Person
RA	Right atrial
RH	Relative Humidity
RV	Right ventricular
s(ec)	Seconds
SC	Sildenafil citrate
SDAC	Statistics and Data Analysis Centre
SF-10	Short Form 10
TAMC	Total Aerobic Microbial Count
TAPSE	Tricuspid annular plane systolic excursion
TRJ	Tricuspid regurgitant jet
TYMC	Total Combined Mould And Yeasts Count
UK	United Kingdom
ULN	Upper limit of normal
US	United States
UV	Ultraviolet
UV-Vis	Ultraviolet-visible
WHO	World Health Organisation

1. Background information on the procedure

1.1. Submission of the dossier

GlaxoSmithKline (Ireland) Limited submitted on 23 April 2020 a group of variation(s) consisting of an extension of the marketing authorisation and the following variation(s) concerning:

a new strength: 2.5 mg film-coated tablet

In addition, CHMP recommends the variation(s) to the terms of the marketing authorisation, concerning the following change(s):

Variation(s) requested		Type
A.7	A.7 - Administrative change - Deletion of manufacturing sites	IA
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Extension application to introduce a new strength (2.5 mg film-coated tablet), grouped with an extension of indication to include treatment of PAH in adolescents and children (8 to less than 18 years). Version 9.0 of the RMP has been submitted.
Type IA category A.7, to delete the following manufacturing sites:
"Aspen Bad Oldesloe GmbH, Industriestrasse 32-36, 23843 Bad Oldesloe, Germany" as a site responsible for batch release of the finished product and "Patheon, Inc., Burlington Century Operations, 977 Century Drive, Burlington, ON L7L5J8 Canada" as a quality control release testing site of the finished product.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

The legal basis for this application refers to Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I of Regulation (EC) No 1234/2008, 2 point (c) - Extensions of marketing authorisations.

The grouped application is submitted under Article 7.2(b), of Annex III of the variation regulation (EC) 1234/2008 – Group of variations.

1.3. Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) EMA Decision P/0370/2019 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP EMEA-000434-PIP01-08-M06 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

1.3.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH submitted a critical report addressing the possible similarity with authorised orphan medicinal products.

1.4. Scientific advice

The MAH did not seek Scientific advice at the CHMP.

1.5. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Maria Concepcion Prieto Yerro Co-Rapporteur: Tomas Radimersky

CHMP Peer reviewer(s): N/A

The Rapporteur appointed by the PRAC was:

PRAC Rapporteur: Eva A. Segovia

The application was received by the EMA on	23 April 2020
The procedure started on	21 May 2020
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	10 August 2020
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	14 August 2020
The PRAC Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	18 August 2020
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	03 September 2020
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	17 September 2020
The MAH submitted the responses to the CHMP consolidated List of Questions on	17 March 2021
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	21 April 2021
The PRAC Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	23 April 2021
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	06 May 2021
The CHMP agreed on a list of outstanding issues in writing to be sent to the MAH on	20 May 2021
The MAH submitted the responses to the CHMP List of Outstanding Issues on	18 June 2021
The CHMP Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC	7 July 2021

members on	
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Volibris on	22 July 2021
The CHMP adopted a report on similarity of Volibris with Opsumit (macitentan) and Adempas (riociguat) the authorised orphan medicinal product(s) on (see Appendix on similarity)	22 July 2021

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The claimed therapeutic indication is:

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

PAH is a rare, progressive, highly debilitating disorder characterized by angioproliferative vasculopathy in the pulmonary arterioles, leading to endothelial and smooth muscle proliferation and dysfunction, inflammation and thrombosis. These changes increase pulmonary vascular resistance and subsequent pulmonary arterial pressure, causing right ventricular failure which leads to eventual death if untreated [Lan et al. Diseases 2018, 6: 38].

Similar to adults, paediatric PAH is defined as a mean pulmonary arterial pressure (mPAP) ≥25 mmHg at rest with a normal pulmonary artery wedge pressure (PAWP) ≤15 mmHg and an increased pulmonary vascular resistance >3 Wood units x m2 (≈240 dyn s cm−5) in the absence of lung disease [Beghetti et al. Paediatric
Pulmonology, 2019 Oct;54(10):1516-1526]. However, there are important known differences in vascular function, foetal origins of disease, growth and development, genetics, natural history, underlying disease, responses of the right ventricle, responsiveness to PAH-specific therapies, and gaps in knowledge, particularly in the youngest age groups [Abman et al. Circulation. 2015; 132: 2037–99].

The most frequent causes of PAH in children are idiopathic (IPAH), heritable gene defects, and congenital heart disease (CHD); however, connective tissue disease, human immunodeficiency virus (HIV), drugs, and portopulmonary hypertension are also rare causes in this population [Beghetti et al., 2019].

2.1.2. Epidemiology and risk factors, screening tools/prevention

Large scale epidemiology studies of PAH in children have not been conducted and there is no or limited outcome data in paediatric PAH patients. In the United Kingdom (UK), survival in treated children with idiopathic PAH at 1, 3 and 5 years was 89%, 84%, and 75% respectively; whilst transplant free survival was 89%, 76%, and 57% respectively [Moledina et al. Heart 2010; 96: 1401–06].

Recent data from registries have shed light on the prevalence and incidence of paediatric PH. In the Netherlands, the incidence and prevalence of IPAH is 0.7 and 4.4 per million children, respectively [van Loon et al. Circulation 2011; 124: 1755–64]. Similar numbers have been observed in the UK, with annual cases of IPAH of 0.48 per million and a prevalence of 2.1 per million [Barst et al. Circulation. 2012; 125: 113–122]. National and large-scale registries either including children [Barst et al. Circulation. 2012; 125: 113–122] or exclusively dedicated to paediatrics have described the different aetiologies of PH, with IPAH, HPAH and CHD-PAH as the most common [Moledina et al. Heart 2010; 96: 1401–06] [Berger et al. Lancet 2012; 379: 537–46]. However, PH associated with respiratory disease is also noted to be important and may be underreported [Berger et al. Lancet 2012; 379: 537–46].

2.1.3. Biologic features, Aetiology and pathogenesis

PH can present at any age from the neonatal period to adulthood. Paediatric PH has some unique features that are not found in adult PH, including prenatal aetiological factors, and postnatal parenchymal and vascular abnormalities in lung development [Barst et al. Eur Respir J. 2011; 37: 665–677].

Three signalling pathways (nitric oxide, prostacyclin-thromboxane and endothelin-1) involved in the pathogenesis of PAH have been targeted for therapeutic intervention by the following classes of PAH medicines [Humbert, 2004; Frank, 2018]: phosphodiesterase type 5 (PDE-5) inhibitors (sildenafil, tadalafil); soluble guanylate cyclase stimulators (riociguat); ERAs (ambrisentan, bosentan, and macitentan); and prostanoids (epoprostenol, iloprost, beraprost, and treprostinil).

2.1.4. Clinical presentation, diagnosis and stage/prognosis

PH is defined as an increase in mean pulmonary arterial pressure (PAPm) ≥25 mmHg at rest as assessed by right heart catheterization (RHC) [Hoeper MM, et al. J Am Coll Cardiol 2013; 62(Suppl):D42–D50]. Available data have shown that the normal PAPm at rest is 14 ± 3 mmHg with an upper limit of normal of approximately 20 mmHg [Hoeper et al, 2013] [Kovacs et al. Eur Respir J 2009; 34: 888–894].

There are 5 groups in the PH classification [Galie et al, 2015]. The term PAH (Group 1 of the PH classification), describes a group of PH patients characterized haemodynamically by the presence of pre-capillary PH, defined by a pulmonary artery wedge pressure (PAWP) ≥15 mmHg and a PVR >3 Wood units (WU) in the absence of other causes of pre-capillary PH such as PH due to lung diseases, chronic thromboembolic pulmonary hypertension (CTEPH) or other rare diseases [Hoeper et al, 2013].

Dyspnoea, fatigue and failure to thrive are common symptoms; syncope is more common in children, but overt RV failure is a late event and the child may die of sudden death before the occurrence of RV failure.

PAH disease aetiologies are described in the following table [Galie et al 2015]. The more frequent aetiologies in children are idiopathic, heritable, associated with connective tissue disease and associated with congenital heart disease (underlined in the following table). PPHN remains in the PAH group but has been moved to a subgroup (Subgroup 1'' within group 1), as it is considered to be a specific entity with a more transient course in most cases [Galie et al, 2015].

GROUP 1. Pulmonary arterial hypertension
1.1 Idiopathic
1.2 Heritable (familial)
1.2.1 BMPR2 mutation

1.2.2 Other mutations
1.3 Drugs and toxins induced
1.4 Associated with:
1.4.1 Connective tissue disease
1.4.2 HIV infection
1.4.3 Portal hypertension
1.4.4 Congenital heart disease
1.4.4.1. Eisenmenger's syndrome
Includes all large intra- and extra-cardiac defects which begin as systemic-to-pulmonary shunts and progress with time to severe elevation of PVR and to reversal (pulmonary-to-systemic) or bidirectional shunting; cyanosis, secondary erythrocytosis, and multiple organ involvement are usually present.
1.4.4.2. PAH associated with prevalent systemic-to-pulmonary shunts
• Correctable
• Non-correctable: Includes moderate to large defects; PVR is mildly to moderately increased, systemic-to-pulmonary shunting is still prevalent, whereas cyanosis at rest is not a feature.
1.4.4.3. PAH with small/coincidental defects
Marked elevation in PVR in the presence of small cardiac defects (usually ventricular septal defects <1 cm and atrial septal defects <2 cm of effective diameter assessed by echo), which themselves do not account for the development of elevated PVR; the clinical picture is very similar to idiopathic PAH. Closing the defects is contra-indicated.
1.4.4.4. PAH after defect correction
Congenital heart disease is repaired, but PAH either persists immediately after correction or recurs/develops months or years after correction in the absence of significant postoperative haemodynamic lesions.
1.4.5 Schistosomiasis

GROUP 1'. Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis

GROUP 1". Persistent pulmonary hypertension of the newborn

BMPR2 = bone morphogenetic protein receptor, type 2; HIV = human immunodeficiency virus; PAH = pulmonary arterial hypertension; PVR = pulmonary vascular resistance;

Source: Galie et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Respir J. 2015; 46: 903–75

Before the epoprostenol era, the prognosis had been worse in children, with a median survival estimated at 10 months, compared to 2.8 years in adults; however, with new targeted therapies the outcome has improved significantly [Galie et al. Eur Respir J. 2015; 46: 903–75].

2.1.5. Management

Detailed, consensus, evidence-based guidelines for the treatment of PAH have been published [Galie et al. Eur Respir J. 2015; 46: 903–75]. Pharmacological approaches are divided into those regarded as supportive or background treatment (aimed at alleviating vasoconstriction, breathlessness, and thromboembolic complications) and those (such as endothelium receptor antagonist [ERAs]) that target the underlying pathophysiology.

Only bosentan (EMA and FDA) and sildenafil (EMA) have been approved for use in children [Farhat, 2019]. Bosentan pharmacokinetics have been assessed in two studies, and several uncontrolled studies have shown positive results similar to adults, with survival rates around 80–90% at 1 year [Rosenzweig et al. J Am Coll Cardiol 2005; 46: 697–704]. A paediatric formulation is available in Europe. Bosentan is subject to clinically significant drug-drug interactions with several important concomitant medications and is also associated with potential hepatotoxicity. Sildenafil has shown efficacy and has been approved in Europe for children 1–17 years of age. Increased mortality using high doses has raised concerns; therefore high doses should not be used in children (high individual doses of sildenafil on a three daily dosing not recommended: >10 mg/dose with a bodyweight of 8–20 kg, >20 mg/dose in children with a bodyweight >20 kg or >1 mg/kg/dose in infants and small children) [301].

Although not approved for use in the paediatric population, there is evidence that prostanoid therapies are effective in children [Frank, 2018]. However, in common with their use in adults, the pharmacokinetic (PK) properties of these drugs and routes of administration (e.g., intravenous [IV]), present substantial challenges to their successful use in a paediatric population. Therefore, there is an unmet need for an approved treatment that provides clear clinical benefit without the complexities associated with managing potential issues.

Sequential combination therapy is the most widely utilised strategy both in RCTs and in clinical practice: from monotherapy with a PDE5-i or ERA, there is an addition of a second (ERA+PDE5i) and then a third drug (normally a prostanoid) in cases of inadequate clinical results or in cases of deterioration [Galie et al, 2015].

2.2. About the product

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

- Ambrisentan is a potent (Ki 0.016 nM) and highly selective ETA antagonist (approximately 4000-fold more selective for ETA as compared to ETB).
- Ambrisentan blocks the ETA receptor subtype, localized predominantly on vascular smooth muscle cells and cardiac myocytes. This prevents endothelin-mediated activation of second messenger systems that result in vasoconstriction and smooth muscle cell proliferation.
- The selectivity of ambrisentan for the ETA over the ETB receptor is expected to retain ETBreceptor mediated production of the vasodilators nitric oxide and prostacyclin.

Ambrisentan belongs to the pharmacotherapeutic group of anti-hypertensives, other anti-hypertensives (ATC code: C02KX02).
Ambrisentan is currently approved for treatment of pulmonary arterial hypertension (PAH) in adult patients of WHO Functional Class (FC) II to III, including use in combination treatment. Efficacy has been shown in idiopathic PAH (IPAH) and in PAH associated with connective tissue disease. The claimed the therapeutic indication is:
Volibris is indicated for treatment of PAH in adolescents and children (aged 8 to less than 18 years) of WHO Functional Class (FC) II to III including use in combination treatment. Efficacy has been shown in IPAH, familial, corrected congenital and in PAH associated with connective tissue disease.

2.3. Type of Application and aspects on development

This application for ambrisentan (Volibris) EMEA/H/C/000839 is an extension of Marketing Authorisation to register 2.5 mg film coated tablets, grouped with Type II variation for a new paediatric (8 to < 18 years) indication and a Type IA deletion of product release site and quality control release testing site.

Ambrisentan is currently approved for the treatment of PAH in adults. It was first approved in the US on 15 June 2007. Ambrisentan is currently approved in the US, all European Economic Area countries, and Japan as well as over 20 further countries. Ambrisentan is marketed in the EU and other countries as VOLIBRIS by GlaxoSmithKline (GSK), and in the US as Letairis by Gilead Sciences Inc.
Ambrisentan is available as 2.5 (Japan only), 5 and 10 mg film-coated tablets for once daily oral administration.

GSK submitted an initial Marketing Authorization Application (MAA) (EMEA/H/C/000839/0000) under Article 8.3 of Directive 2001/83/EC as a full dossier in adults for the treatment of PAH. The application was approved in the EU on 21 April 2008. This product was withdrawn from the Community Register of

designated orphan medicinal products in April 2018 at the end of the 10-year period of market exclusivity.

The current approved indication wording for ambrisentan in adults with PAH is as follows:
Volibris is indicated for the treatment of pulmonary arterial hypertension (PAH) in adult patients of WHO Functional Class (FC) II and III, including use in combination treatment to improve exercise capacity, decrease the symptoms of PAH and delay clinical worsening. Efficacy has been shown in idiopathic PAH (IPAH) and in PAH associated with connective tissue disease.

The proposed indication for ambrisentan for the paediatric population is as follows:
Volibris is indicated for treatment of PAH in adolescents and children (aged 8 to less than 18 years) of WHO Functional Class (FC) II to III, including use in combination treatment. Efficacy has been shown in IPAH, familial, corrected congenital and in PAH associated with connective tissue disease.

For the submission of this variation application, the MAH submitted 4 completed studies and 1 ongoing extension study (ID AMB114588). Data from the completed studies were also submitted as part of an agreed paediatric investigation plan (EMEA-000434-PIP01-08-M06; EMA Decision P/0370/2019) for ambrisentan (Volibris), which contained a waiver in paediatric subjects from birth to less than one year of age. At the time of submission of the application, the PIP number EMEA-000434-PIP01-08-M06 was not yet completed as some measures were deferred.

2.4. Quality aspects

2.4.1. Introduction

Volibris 5 and 10 mg film coated tablets are already authorised medicinal products in the EU (EU/1/08/451/001-004). This is a line extension to register a new strength (2.5 mg).

The finished product is presented as film coated tablets containing 2.5 mg of ambrisentan as active substance.

Other ingredients are:

Tablet core: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, magnesium stearate

Film coat: polyvinyl alcohol, talc (E553b), titanium dioxide (E171), macrogol, and lecithin (soya) (E322)

The product is available in white high-density polyethylene (HDPE) bottles closed with polypropylene child-resistant closures as described in section 6.5 of the SmPC.

2.4.2. Active Substance

The active substance used to manufacture the new strength 2.5 mg is the same as that used in the manufacture of the currently authorised strengths 5 mg and 10 mg (EU/1/08/451/001-004). The information presented by the applicant in the dossier was already assessed in the original submission and includes updates from any subsequent variations. The active substance is sourced from the same manufacturer, is manufactured by the same process and is released in accordance with the same active substance specification.

2.4.3. Finished Medicinal Product

Description of the product and Pharmaceutical development

The proposed 2.5 mg strength can be differentiated from the approved Volibris 5 and 10 mg strengths by colour, shape and printed marks. The 2.5 mg strength is presented as white, 7 mm round, convex, film-coated tablet with "GS" debossed on one side and "K11" on the other side. The finished product has been developed as an immediate-release tablet dosage form for oral administration.

The 2.5 mg tablet has been developed for use in paediatric populations. It contains the active substance ambrisentan and the excipients are the same as those contained in the 5 and 10 mg tablet except for the kind of Opadry selected.

The 2.5 mg strength uses the same formulation as that contained in the 5 and 10 mg tablet except Opadry® OY-S film coat is replaced by Opadry® II. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no additional requirements to assure consistent product performance. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

The finished product has been developed as an immediate-release tablet dosage form for oral administration. Tablets in 2.5 mg, 5 mg, and 10 mg strengths were manufactured by direct compression of dry blends.

The excipients in the dry blends, croscarmellose sodium, lactose monohydrate, magnesium stearate, and microcrystalline cellulose were selected based on their common use in pharmaceutical manufacturing. The manufacturing process for the finished product consists of a dry blend direct compression process where a pre-blend of lactose and active substance are dry mixed and co-milled followed by an intermediate blend of remaining lactose. Croscarmellose sodium and microcrystalline cellulose are then added and blended followed by a final blend with magnesium stearate. The final blend is then compressed using a rotary tablet press to the required specifications. Bulk tablets are then film coated to a specified weight gain.

The primary packaging is high density polyethylene (HDPE) bottles closed with polypropylene child-resistant closures. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The commercial manufacturing process uses direct compression of a dry blend followed by film coating of the core tablets

The manufacturing process consists of 4 main steps: blending of the active substance and excipients, compression of the core tablets, film coating, and packaging. The process is considered to be a non-standard manufacturing process since the proportion of the active substance in the formula is below 2 % (i.e. 1.70 %).

Major steps of the manufacturing process have been validated using 3 consecutive commercial scale batches of the 2.5 mg tablets. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

In addition, a Technical Risk Assessment was conducted reviewing the identified finished product failure modes against the current operating and process controls. Trending and process capability data of commercial batches of 2.5 mg, 5 mg and 10 mg strength tablets are provided from commercial batches

collected as part of lifecycle management to demonstrate that the current control strategy is appropriate and robust.

The in-process controls are adequate for this pharmaceutical form.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: physical appearance (visual), identification (HPLC, UV), identification of colorants (UV-VIS spectrum), ambrisentan content (assay by HPLC), related substances (HPLC), content uniformity (HPLC), dissolution (HPLC), and microbial limit test (Ph. Eur.).

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Batch analysis data on 3 batches using a validated ICP-MS method was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data, it can be concluded that it is not necessary to include any elemental impurity controls.

A risk evaluation concerning the presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided it is accepted that no risk of presence of nitrosamine impurities in the active substance or the related finished product was identified. Therefore, no additional control measures are deemed necessary.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for testing has been presented.

Nevertheless, it was indicated that one reference marker is no longer used in the assay and related substances for ambrisentan active substance method, therefore the CHMP recommended to submit a post approval variation within 6 months of approval of this line extension application to update the analytical procedure for ambrisentan assay and related substances across the 2.5 mg, 5 mg and 10 mg strengths to remove reference to the obsolete marker. Batch analysis results are provided for 3 commercial scale batches of the 2.5 mg strength confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the above release specifications.

Stability of the product

Stability data from 3 production scale batches of finished product stored for up to 18 months under long term conditions (30 ºC / 75% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of the medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for appearance, ambrisentan content, drug related impurities content, dissolution and microbial limits. The analytical procedures used are stability indicating. No significant changes were observed under long term and accelerated conditions and all results complied with the specifications.

Data have also been presented from forced degradation and photostability studies. Based on the results, the finished product does not require additional protection from light and the chemical and physical stability of the finished product has been demonstrated.

Based on available stability data, the proposed shelf-life of 2 years without any special storage conditions as stated in the SmPC (section 6.3) is acceptable.

Adventitious agents

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

At the time of the CHMP opinion, there was a minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product which pertains to the redundant reference marker. The applicant should submit a post-approval variation within 6 months of approval of this line extension application to update the analytical procedure for ambrisentan assay and related substances across the strengths to remove reference to the redundant reference marker. This point is put forward and agreed as a recommendation for future quality development.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this new strength (2.5 mg) is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.4.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

2.5. - to submit a post approval variation within 6 months of approval of this line extension application to update the analytical procedure for ambrisentan assay and

related substances across the 2.5 mg, 5 mg and 10 mg strengths to remove reference to a redundant reference marker. Non-clinical aspects

2.5.1. Pharmacology

No additional pharmacology studies have been performed specifically to support the paediatric indication. This is considered acceptable since a complete battery of pharmacology studies was provided for initial MAA.

2.5.2. Pharmacokinetics

No new nonclinical pharmacokinetics studies have been submitted in this application. The known pharmacokinetic profile of ambrisentan in humans and nonclinical species (metabolism and excretion principally by liver/bile) does not raise grounds to presuppose greater systemic exposure in children/adolescents (8 to less than18 years), compared to adults. Furthermore, data from clinical study AMB112529 demonstrated that systemic exposure to ambrisentan in patients 8 to less than 18 years is expected to be consistent with that seen in adults, when adjusted for body weight.

Currently available safety margins were agreed on via type II variation procedure in 2018 (EMEA/H/C/000839/II/0054) and reflected in section 5.3 of SmPC. These were calculated based on published data with paediatric exposures (9 to 15 years old children treated with 10 mg of ambrisentan, once daily) as described by Takatsuki [Takatsuki, 2013].

2.5.3. Toxicology

All relevant nonclinical reports for ambrisentan (including nonclinical data generated to support paediatric development including PIP studies 3 and 4) have been reviewed as part of previous submissions. No further nonclinical data has been generated specifically to support the paediatric indication (8 to <18 years).

For PIP (EMEA-000434-PIP01-08-M06) two juvenile animal studies were conducted: 2-week juvenile animal study to determine tolerability and toxicokinetics of ambrisentan and 8-week juvenile animal study to determine oral toxicology and toxicokinetic of ambrisentan including an 8 weeks recovery period. Additionally, investigative juvenile rat studies were conducted, one to further histologically evaluate brain tissues from the definitive juvenile study and another two separate investigative studies to assess respiratory function and recovery in juvenile rats.

The key target organs of toxicity were identified as testis and nasal cavity, with the rat being the more sensitive species in terms of both oral dose and systemic exposure. In the rat toxicity studies (1 to 6 months in duration), the rats were 5-6 weeks of age at start of dosing. In a toxicity study in juvenile rats (dosed from 7 days old), ambrisentan was associated with a decrement in brain weight gain and noisy respiration. However, when 5-week old rats (corresponding to an age of 8 years in humans) were treated, brain-weight decrease was observed only at very high doses.

A discussion of these target organs of toxicity and their relevance to the intended paediatric population has been provided. The presence of sustained hypoxemia in juvenile rats is considered by the MAH as a likely mechanism for the decrease in brain weight gain. However, the mechanism for the decrease in brain weight has already been reviewed in (Type II variation EMEA/H/C/000839/II/0054) and altered postnatal development of the rat soft palate, pharynx or larynx as a cause of hypoxia was inconclusive in the mechanistic study. It is still unclear whether the decrease in brain weight observed after

administration of ambrisentan in the juvenile rat toxicity studies is caused by hypoxemia due to ETA receptor antagonist-induced altered postnatal development of the upper respiratory tract.

No new data were provided by the applicant to further elaborate on the mechanism behind the decrease in brain weight observed in juvenile animals. Consequently, clinical relevance of brain weight decreases remains unclear, especially for children younger than 8 years old.

Section 5.3 of SmPC has been updated to include the age range in children that is covered by the juvenile rat study, which supports that the finding would likely not be meaningful for children age 8 and above.

2.5.4. Ecotoxicity/environmental risk assessment

In accordance with Article 8(3) of Directive 2001/83, the applicant has submitted an environmental risk assessment for for Volibris™ Film Coated Tablets 2.5, 5 and10 mg (referred to as ambrisentan tablets 5 and 10 mg), containing 2.5, 5 or 10 mg ambrisentan.

This assessment has been conducted in accordance to guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00).

Following the low PEC values estimated for Volibris™ film-coated tablets 5 and 10 mg on the basis of the refined Fpen values, it can be concluded that the market authorization of the medicinal product is unlikely to adversely impact the environment. The results of the environmental risk assessment are summarized in the table below.

Table 5 Summary of main study results

Substance (INN/Invented Name): Volibris/ Ambrisentan			
CAS-number (if available): 177036-94-1			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	for the neutral species, log P = 1.20. for the negative species, log P = -0.84.	Potential PBT (N)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	ND	NA
	BCF	ND	NA
Persistence	DT50 or ready biodegradability	ND	NA
Toxicity	NOEC or CMR		not T
PBT-statement :	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)		0.0025 µg/L 0.000032 µg/L 0.000086 µg/L	> 0.01 threshold (N)
Other concerns (e.g. chemical class)			(N)

2.5.5. Discussion on non-clinical aspects

No further nonclinical data has been generated specifically to support the paediatric indication (8 to <18 years) in this variation. However, the applicant was requested to discuss the need to update the safety margins safety margins in section 5.3 of the SmPC in line with newly provided paediatric studies. The applicant provided calculation for animal-to-human exposure ratios in comparison to the paediatric data obtained in study AMB112529; geometric mean AUC = 9.15 µg.h/mL in children ages 8 and above administered up to 10 mg) and in comparison, to the values calculated from literature (Takatsuki, 2013; 12.0 mcg.h/mL).

CHMP agreed to maintain the animal-to-human exposure ratios in the SmPC in line with literature data as these values provide lower safety margins, thus leaving extra safety margins in comparison to the conducted study. The worst-case scenario approach with a more conservative safety margins is acceptable. Furthermore, available non-clinical data do not allow an understanding of the risk of brain weight decrement to the paediatric population, especially for children younger than 8 years old, this is taken into account in the SmPC.

An updated Environmental Risk Assessment has been provided. Following the low PEC values estimated for Volibris film-coated tablets 5 and 10 mg on the basis of the refined Fpen values, it can be concluded that the market authorization of the medicinal product is unlikely to adversely impact the environment.

2.5.6. Conclusion on the non-clinical aspects

There are no new safety concerns for paediatric indication (8 to <18 years) based on available non-clinical data. Section 5.3 of SmPC has been updated to include the age range in children that is covered by the juvenile rat study, which supports the finding would likely not be meaningful for children age 8 and above.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

This application is based on the phase IIb clinical trial AMB112529 and its open-label extension AMB112588. The summary of both studies is shown in table below.

Table 6 Synopses of individual studies.

Protocol No.	Type of Study	Study Objective(s)	Study Design	Key Inclusion Criteria of Subjects	No. of Subjects: Gender M/F: Mean Age (Range)	Treatment Details (Drug/Dose/Form/ Route/Frequency/ Duration)	Study Status; Type of Report	Location of Study Report
AMB112529	Safety and efficacy	Evaluate Safety and tolerability of ambrisentan in paediatric PAH PK assessment PK/PD modelling Efficacy assessments being 6MWD, clinical worsening of PAH, SF-10, WHO functional class, NT-ProBNP	O,UC,R, PRL	Paediatrics: 8 years to less than 18 years Current diagnosis of PAH (WHO Group 1) with WHO class II or III symptoms in one of the following categories: idiopathic; heritable (familial); secondary to connective tissue disease; persistent PAH despite surgical repair of atrial septal defects, ventricular septal defects, atrio-ventricular septal defects, and persistent patent ductus Treatment naïve OR discontinued another ERA due to elevated LFTs, OR on stable dose of PAH drug therapy	41 (14/27) 12.0 years 8-16 years	Low dose group: Tablet, 2.5 mg or 5 mg (adjusted for body weight); single dose, oral, daily, 24 weeks High dose group: Tablet, 5, 7.5 mg or 10 mg (adjusted for body weight); single dose, oral, daily, 24 weeks	Complete; CSR (2019N407876_02) CPSR (2019NE411467_00) 2019N411696_00 (EXP19004) (combined analysis AMB 112529, 112565, AMB-220, AMB-320 and AMB-321))	5.3.5.1 5.3.3.5 5.3.5.3
AMB114588	Long term safety and tolerability	Evaluate long term safety and tolerability in paediatric PAH Pubertal development every 6 months up to 20 years of age Time to change in dose of ambrisentan or other targeted PAH agents due to tolerability issues or deterioration of clinical condition Time to addition of another targeted PAH therapeutic agent due to deterioration of clinical condition or lack of beneficial effect with previous therapy Efficacy assessments being all cause mortality, 6MWD, clinical worsening of PAH, SF-10, WHO functional class, NNT-ProBNP	O, UC, NR	Paediatrics: 8 years to less than 18 years Had participated in and complied, to the best of their ability, with the protocol for Study AMB112529 and completed the Week 24 Visit in Study AMB112529. For subjects who did not complete the week 24 visit, one of the following was required to have been met: required additional targeted treatment for PAH due to inadequate response to the current treatment or worsening of their clinical condition prior to week 24, or required reduction in dose of baseline targeted treatment for PAH after ambrisentan was added, or in the opinion of the investigator continued treatment with ambrisentan was warranted	38 (13/25) 11.9 years 8 to16y	All subjects received a tailored dose of ambrisentan (range 2.5 mg to 10 mg) as a tablet per oral, daily. Dose was continued from study AMB112529 and/or adjusted based on investigator discretion. First subject rolled over from study AMB112529 21 June 2011 Last subject rolled over from study AMB112529 Up to interim cut-off date 23 Aug 2019	Ongoing ICSR (2019N418957_01)	5.3.5.2
Degree of Blinding O = Open SB = Single Blind DB = Double	**Degree of Control** UC = Uncontrolled PLC = Placebo AC = Active	**Treatment Assignment** R = Random NR = Nonrandom	**Treatment Sequence** PRL = Parallel XO = Crossover DR =	M – Male F = Female				

Blind	control		Dose Rising					

CPSR = Clinical Pharmacology Study Report | CSR = Clinical Study Report | ERA = Endothelium Receptor Antagonist | ICSR – Interim Clinical Study Report | LFTs = Liver Function Tests

NT-ProBNP = N-terminal pro-B-type natriuretic peptide | 6MWD = 6-Minute Walking Distance | PAH = Pulmonary Arterial Hypertension | PD = Pharmacodynamic | PK = Pharmacokinetic

SF-10 = Short Form 10 | WHO = World Health Organisation

2.6.2. Pharmacokinetics

Analytical methods

Sample analysis and assay validation for ambrisentan (GSK1325760) supporting study AMB112529 was submitted. Updated experimental with additional stability data was also submitted. The results indicate that GSK1325760 is stable in human plasma stored at -20 ºC for 1106 days.

The performance of the bioanalytical method was demonstrated in the validation.

The in-study accuracy and precision results of calibration standards and the QCs were acceptable. The reasons for the re-analysis of samples are considered acceptable.

The samples were analyzed within the appropriate stability period (i.e., at least 1106 days at -20 ºC.

The incurred sample re-analysis was performed. It was observed that more than 67% of the ambrisentan repeat results and original results were within 20% of the mean of the two values.

A POP-PK analysis of PK data from Study AMB112529 was used to characterize the PK of ambrisentan in paediatrics aged 8 to less than 18 years with PAH given Low and High doses of ambrisentan adjusted for body weight. The ambrisentan PK from this paediatric population was compared to the known PK of ambrisentan in an adult population of healthy subjects and subjects with PAH. The effects of covariates on PK parameters was also assessed.

Table 7 Ambrisentan Weight-Group Based Doses for AMB112529

Body Weight	Low Dose		High Dose	
	Starting dose dispensed at Baseline	Dispensed at Week 2 onwards	Starting dose dispensed at Baseline	Dispensed at Week 2 onwards
≥50 kg	5 mg	5 mg	5 mg	10 mg
≥35 kg and <50 kg	5 mg	5 mg	5 mg	7.5 mg
≥20 kg and <35 kg	2.5 mg	2.5 mg	2.5 mg	5 mg

Bioequivalence

As a consequence of the extension of the PAH indication to include children aged 8 to less than 18 years the registration of an additional strength (2.5 mg) of the ambrisentan immediate-release film coated tablet is also submitted.

The manufacturing process is direct compression. Commercially available ambrisentan 5 and 10 mg tablets were used in the paediatric Study AMB112529 and its ongoing long-term extension Study AMB114588. The ambrisentan 2.5 mg tablets had the same qualitative composition and tablet weight as the 5 and 10 mg tablets.

Phase appropriate in vitro dissolution methodology was developed and used to test ambrisentan tablets throughout the clinical program. The introduction of the final quality-controlled method was selected

based on its discriminatory capacity in response to bioequivalence study AMB-103 in adults. The 2.5, 5 and 10 mg ambrisentan tablets exhibit similar dissolution profiles.

Study AMB-103

This Phase 1, open-label, randomized, 2-period (for 2.5 mg and 5 mg tablets) or 3-period (for 10 mg tablets) crossover, single-center study evaluated the bioequivalence of ambrisentan tablets manufactured by Abbott and used in clinical studies with ambrisentan tablets manufactured by Patheon that are representative of the proposed commercial dosage forms.

The primary objectives of this study were:

• To compare the clinical trial and commercial formulations of ambrisentan 2.5 mg tablets for bioequivalence.

• To compare the clinical trial and commercial formulations of ambrisentan 5 mg tablets for bioequivalence.

• To compare the clinical trial and commercial formulations of ambrisentan 10 mg tablets for bioequivalence.

Pharmacokinetics Results:

The PK parameters of ambrisentan were comparable between Treatments A1 (commercial 2.5 mg formulation) and R1 (clinical 2.5 mg formulation). The geometric mean ratios of Cmax, AUC0-last and AUC0–∞ were 94.1%, 104.5%, and 105.9%, respectively, and the 90% CI were all within the range of 80-125%, indicating Treatments A1 and R1 were bioequivalent.

Table 8 Comparison of Ambrisentan Pharmacokinetic Parameters Following Treatment A1 (2,5mg Test Drug A) and Treatment R1 (2,5mg Reference Drug)

PK Parameter	Treatment	Arithmetic Mean (SD)	Geometric Mean	Geometric Mean Ratio and 90% CI (A1/R1)
C_{max} (ng/mL)	A1	203.5 (56.8) n = 20	199.1 n = 20	94.1 (83.4, 106.2)
	R1	217.1 (49.7) n = 20	211.5 n = 20	
$AUC_{0\text{-last}}$ (ng*hr/mL)	A1	1833.3 (353.0) n = 20	1800.3 n = 20	104.5 (97.3, 112.3)
	R1	1762.5 (404.0) n = 20	1722.7 n = 20	
$AUC_{0-\infty}$ (ng*hr/mL)[1, 2]	A1	2110.0 (362.0) n = 17	2096.3 n = 16	105.9 (98.8, 113.5)
	R1	2008.0 (376.3) n = 18	1980.0 n = 16	
t_{max} (hr)[3]	A1	2.0 (1.0, 6.0) n = 20	NA	p = 0.27
	R1	1.5 (1.0, 6.0) n = 20	NA	
$t_{1/2}$ (hr)[1]	A1	16.2 (5.0) n = 17	NA	NA
	R1	15.0 (3.7) n = 18	NA	

Demographics and PK Concentration Data

The POP-PK analysis dataset for Study AMB112529 consisted of a total of 211 observations from 39 paediatric subjects with PAH, of which only 3% of the samples had values below level of quantification (BLQ) (<5 ng/mL). The subjects were generally well matched between the 2 dose groups as summarized in Table 9.

Table 9 Selected Demographic and Covariate Summary in Study AMB112529 Population PK Dataset

Covariate	Statistic	Low dose	High dose	Overall
Number of Subjects (%)	.	20 (51)	19 (49)	39
Age (years)	Mean (SD)	12 (2.63)	12.2 (2.85)	12.1 (2.7)
	Median (Min-Max)	13 (8-16)	12 (8-16)	13 (8-16)
Gender N (%)	Male	8 (40)	5 (26.3)	13 (33.3)
	Female	12 (60)	14 (73.7)	26 (66.7)
Baseline Weight (kg)	Mean (SD)	39.4 (11.9)	39.7 (15.3)	39.6 (13.5)
	Median (Min-Max)	38.0 (20.9-67.0)	36.1 (20.1-77.0)	36.1 (20.1-77.0)
Baseline BMI (kg/m^2)	Mean (SD)	17.8 (2.70)	17.9 (3.75)	17.8 (3.21)
	Median (Min-Max)	18.4 (12.8-21.2)	15.9 (13.7-28.6)	17.5 (12.8-28.6)
Race N (%)				
Whites	White/Caucasian/European Heritage	10 (50)	18 (94.7)	28 (71.8)
Total East Asian	Asian-East Asian Heritage	1 (5)	.	1 (2.6)
	Asian-Japanese Heritage	5 (25)	.	5 (12.8)
Others	American Indian or Alaskan Native	1 (5)	.	1 (2.6)
	Asian-Central/South Asian Heritage	1 (5)	.	1 (2.6)
	Asian-South East Asian Heritage	.	1 (5.3)	1 (2.6)
	African American/African Heritage	2 (10)	.	2 (5.1)
Ethnicity N (%)	Hispanic/Latino	5 (25)	7 (36.8)	12 (30.8)
	Non-Hispanic/Latino	15 (75)	12 (63.2)	27 (69.2)

Figure 2 Observed Ambrisentan Concentration-Time Data, Stratified by Dose and Weight Groups

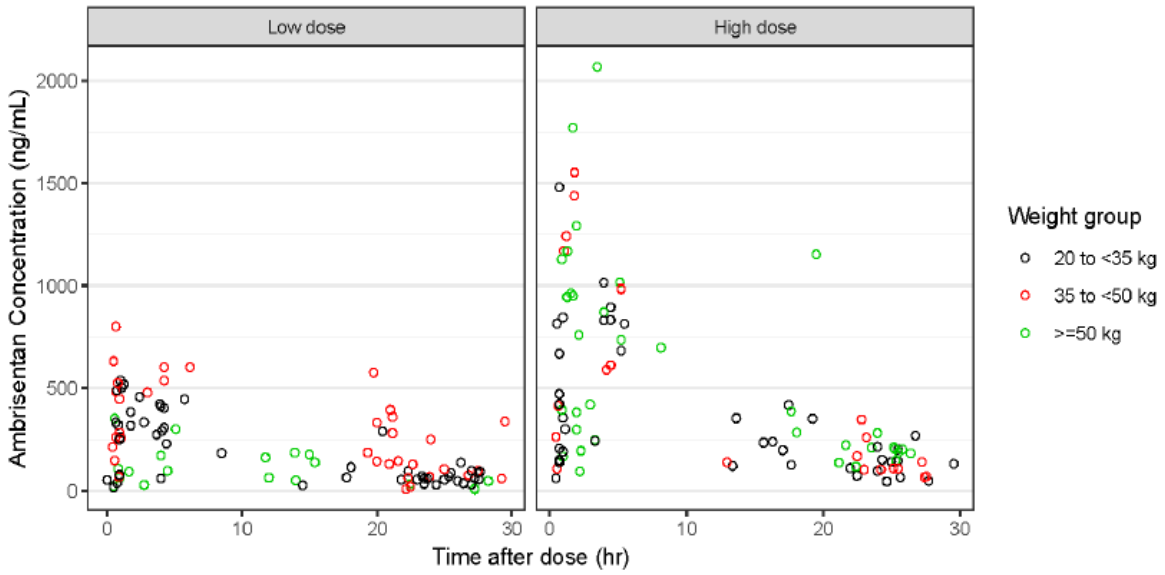
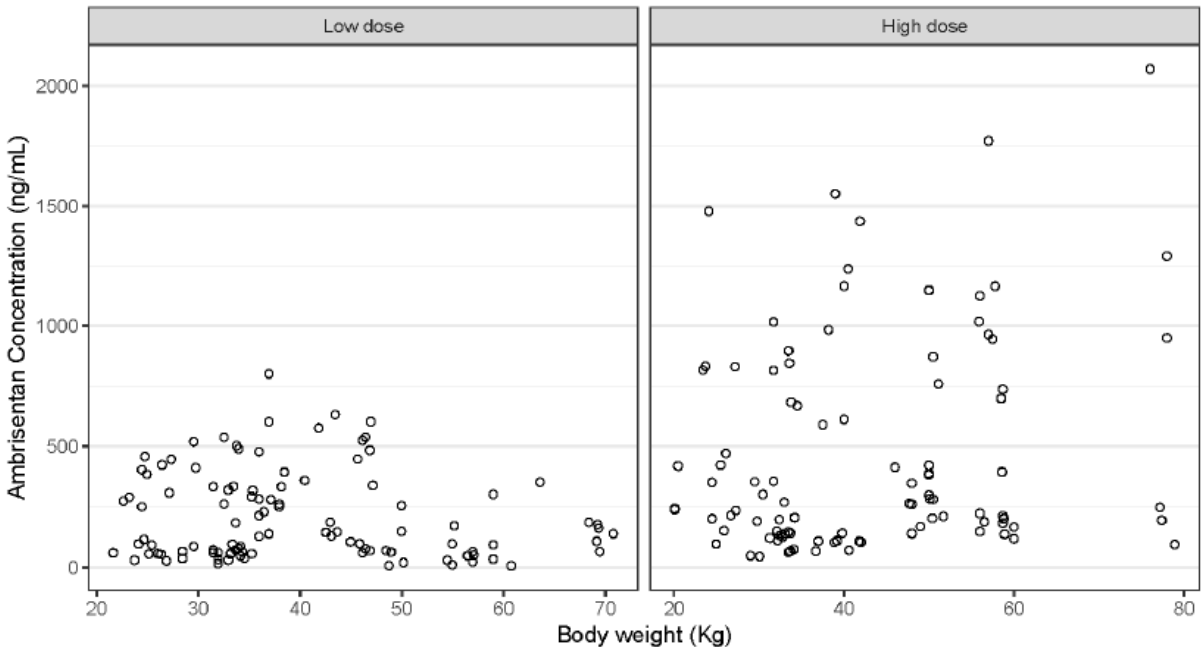


Figure 3 Observed Ambrisentan Concentrations-versus Body Weight, Stratified by Dose Groups in Study AMB112529



Final Population PK model in paediatric subjects

The PK of ambrisentan concentration-time data from Study AMB112529 was well-described by a two-compartment model with first-order absorption, first-order elimination and a lag time. The only covariate found to be statistically significant was body weight and was fixed to allometric coefficients. Key parameters for this POP-PK final model are shown in Table 10. For comparative purposes, estimates from the previously developed adult model are also presented in in the table. Comparison shows that the ambrisentan parameter estimates for CL/F, Vc/F, Ka and ALAG using the data from Study AMB112529 are comparable to those reported in the adult population PK report for adult

ambrisentan final model confirming similar PK behaviour for ambrisentan between children and adults when differences in body size was accounted for.

Table 10 Comparison of the Final Ambrisentan Pharmacokinetic Models in Paediatric and Adult PAH population

	Paediatric final model (AMB112529)			Adult final model		
Parameter	**Estimate**	**%RSE**	**Interindividual %CV**	**Estimate**	**%RSE**	**Interindividual %CV**
CL/F [L/hr]	1.17	6.33	21.8	1.56	7.82	32.1
Vc/F [L]	12.3	16.1	94.1	9.52	2.75	20.5
Q/F [L/hr]	0.457	21.1	42.5	0.928	6.99	-
Vp/F [L]	81.3	24.5	33.2	8.51	4.83	25.3
Ka [hr^{-1}]	2.46	25.7	133	1.72	5.87	82.6
ALAG [hr]	0.525	14.7	31.2	0.423	1.82	0.036
CL/F ~WT	0.75 FIX	-	-	0 FIXED	-	-
Vc/F ~WT	1 FIX	-	-	0.740	9.77	-
Q/F ~WT	0.75 FIX	-	-	-	-	-
Vp/F ~WT	1 FIX	-	-	-	-	-
σ^2prop (%)	45.8	14.2	-	27.6[1]	5.89	-

Data Source: Table 7.5-1 and Table 7.5-2 from PK-PD report (GSK Document Number 2019N411467_00) and Table 10.20 from the adult population PK Report (Run 411) [GSK Document number HM2007/00511/00]

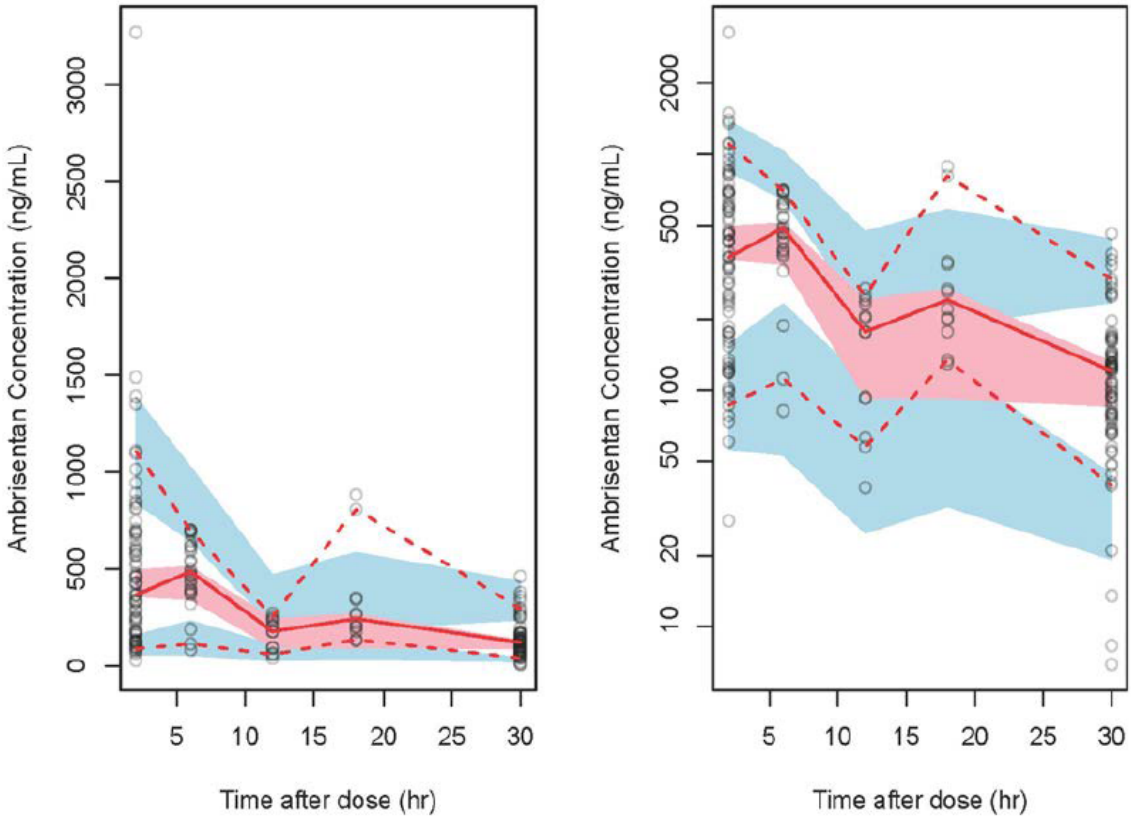
RSE = Relative standard error; CV = coefficient of variation; CL/F = Apparent clearance; Vc/F = Apparent volume of central compartment; Q/F = Apparent inter-compartmental clearance; Vp/F = Apparent volume of peripheral compartment, ALAG=Absorption lag-time, Ka=Absorption rate constant, CL/F~WT=Weight effect on CL/F, Vc/F~WT= Weight effect on Vc/F, Vp/F= Weight effect on Vp/F, Q/F~WT=Weight effect on Q/F, σ^2prop (%): CV% for proportional residual error model.

1: the adult error model also incorporated an IIV term (ηi) in the residual error model with the following estimated values CV% (%RSE) = 18.2 (29.9).

The goodness-of-fit (GoF) plots for the final model for all data from Study AMB112529 indicated that the final model adequately described the observed data with no obvious systematic bias in the model predictions.

Results of the pc-VPC of the final POP-PK model indicated an overall good agreement for the 5th, median, and 95th percentiles of ambrisentan concentrations between observation and predictions (Figure 4).

Figure 4 Predication-Corrected Visual Predictive Check for the Final Developed Adult Population PK Model



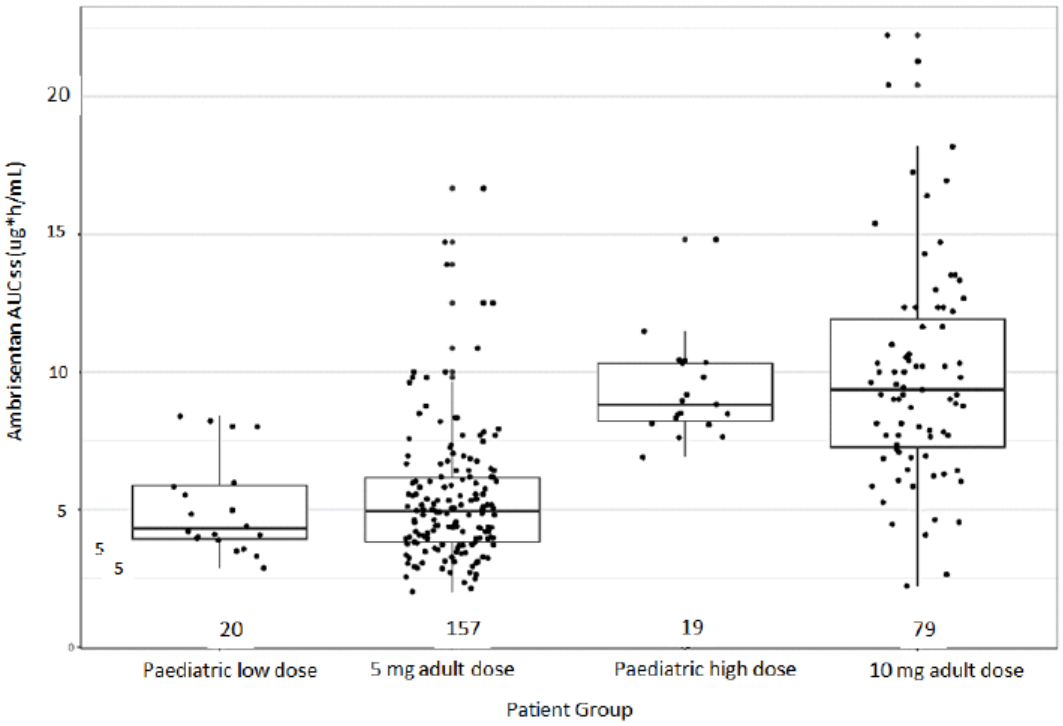
Data Source: Figure 7.5-3 from PK-PD report (GSK Document Number 2019N411467_00)
Shaded areas represent 90% PI of the median of predicted concentrations (pink) and 5th and 95th percentiles of the predicted data (blue) for the previously developed adult POP-PK model. Red lines indicate the median (solid) and 5th and 95th percentiles (dashed) of the observed data from Study AMB112529; Left plot: linear; Right plot: log-linear.

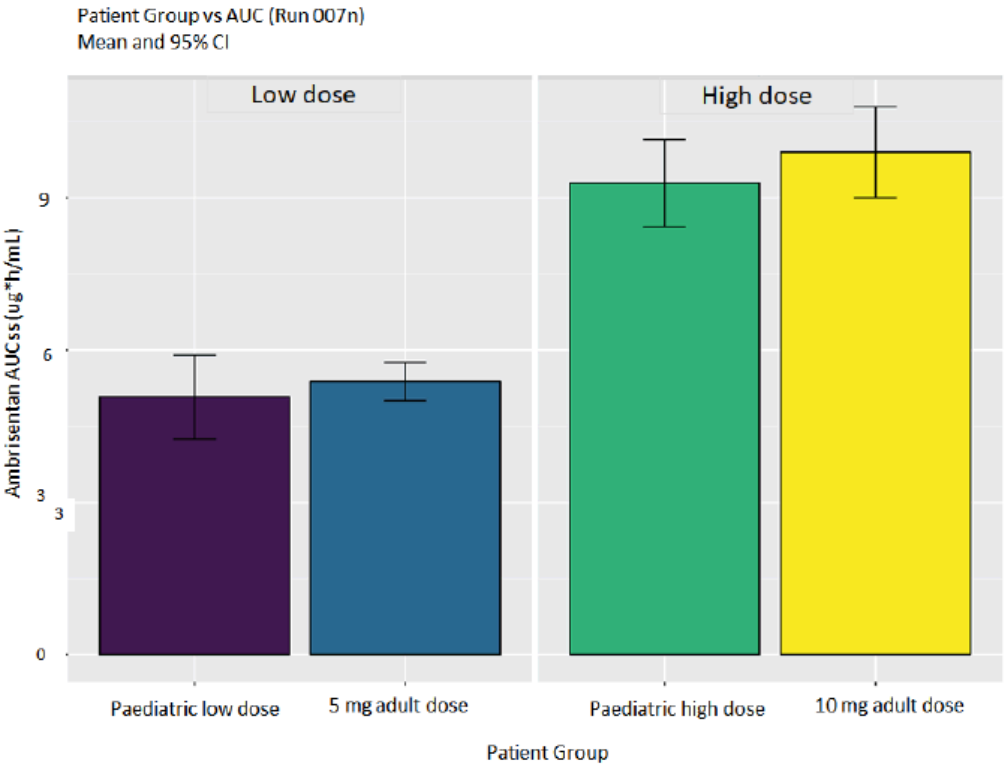
Final Population PK Model Derived Exposure

Table 11 Comparison of Model-Derived Ambrisentan Exposure Following Administration of Ambrisentan in Paediatric Population (8 to less than 18 years) and Adult Population

Subject group	Dose group	Weight Group (kg)	N	Geometric mean (95% CI)	
				AUC_{ss} (µg*hr/mL)	$C_{max,ss}$ (ng/mL)
Adults	5 mg (Low)	-	157	4.98 (4.68-5.29)	469 (447-493)
Adults	10 mg (High)	-	79	9.12 (8.30-10.0)	830 (757-909)
Paediatric	Low dose	-	20	4.82 (4.14-5.61)	519 (458-589)
Paediatric	High dose	-	19	9.15 (8.41-9.96)	981 (894-1080)
Paediatric	Low dose	≥20-<35	8	4.03 (3.48-4.68)	478 (401-568)
Paediatric	Low dose	≥35-<50	8	6.42 (5.09-8.11)	516 (408-651)
Paediatric	Low dose	≥50	4	3.87 (2.73-5.48)	624 (369-1060)
Paediatric	High dose	≥20-<35	9	8.73 (7.75-9.83)	953 (850-1070)
Paediatric	High dose	≥35-<50	4	8.70 (7.62-9.92)	1100 (679-1790)
Paediatric	High dose	≥50 kg	6	10.2 (8.04-12.8)	948 (791-1140)

Figure 5 Comparison of Model derived Ambrisentan AUCss Following Administration of Ambrisentan in Paediatric Population (8 to less than 18 Year) and adult population, stratified by subject and dose





Black Circles (paediatrics aged 8 to less than 18 years) are the final paediatric POP-PK model derived AUCss; Black circles (adults)are the final adult POP-PK model derived AUC ss. Number below each boxplot represents the number of subjects in the respective boxplot.

Figure 6 Comparison of Model Derived Ambrisentan Cmax,ss Following Administration of Ambrisentan in Paediatric Population (8 to less than 18 years) and Adult population,

Stratified by subject and Dose

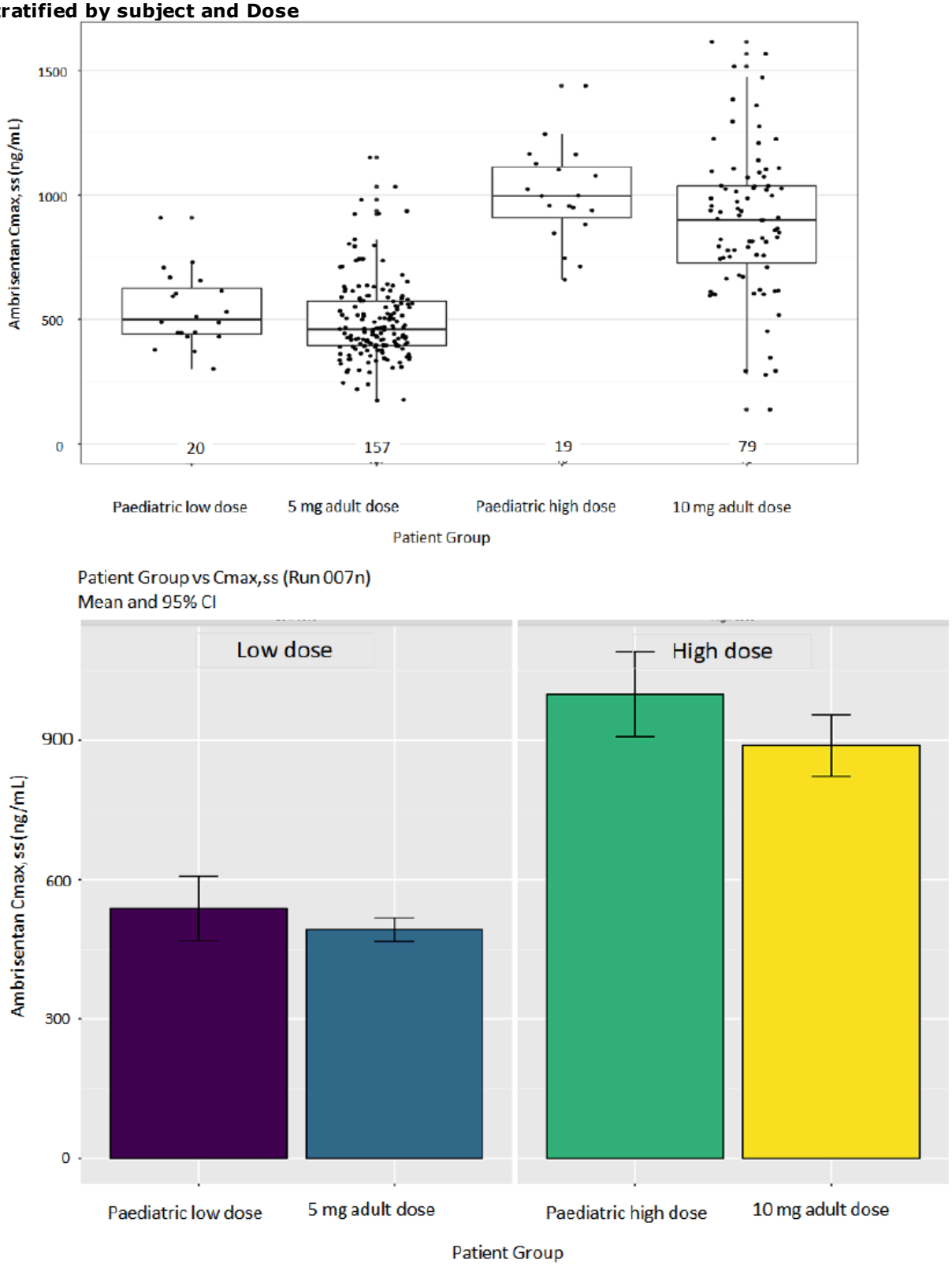


Figure 7 Comparison of Model-Derived Ambrisentan AUC ss Following Administration of Ambrisentan in Paediatric Population (8 to less than 18 years old) and Adult population, Stratified by patient, Dose and weight group

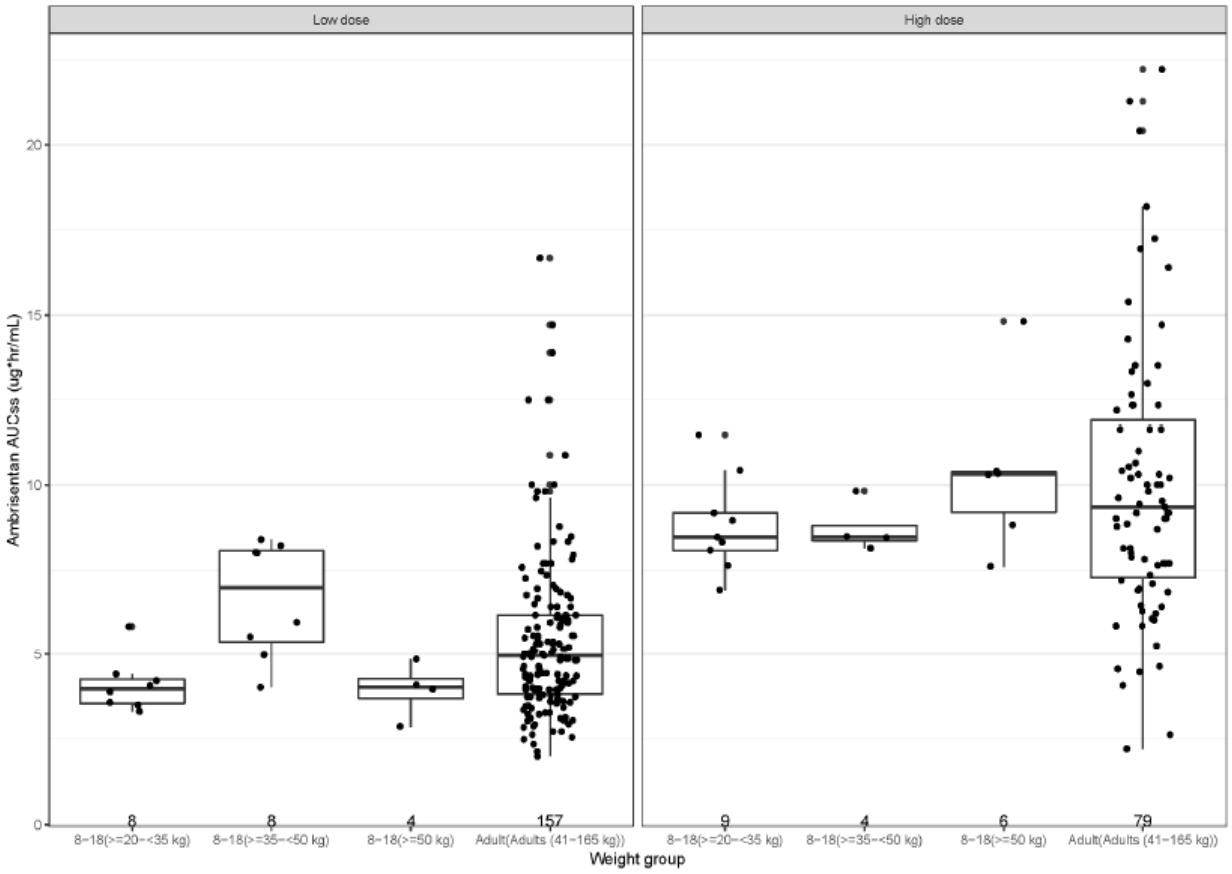
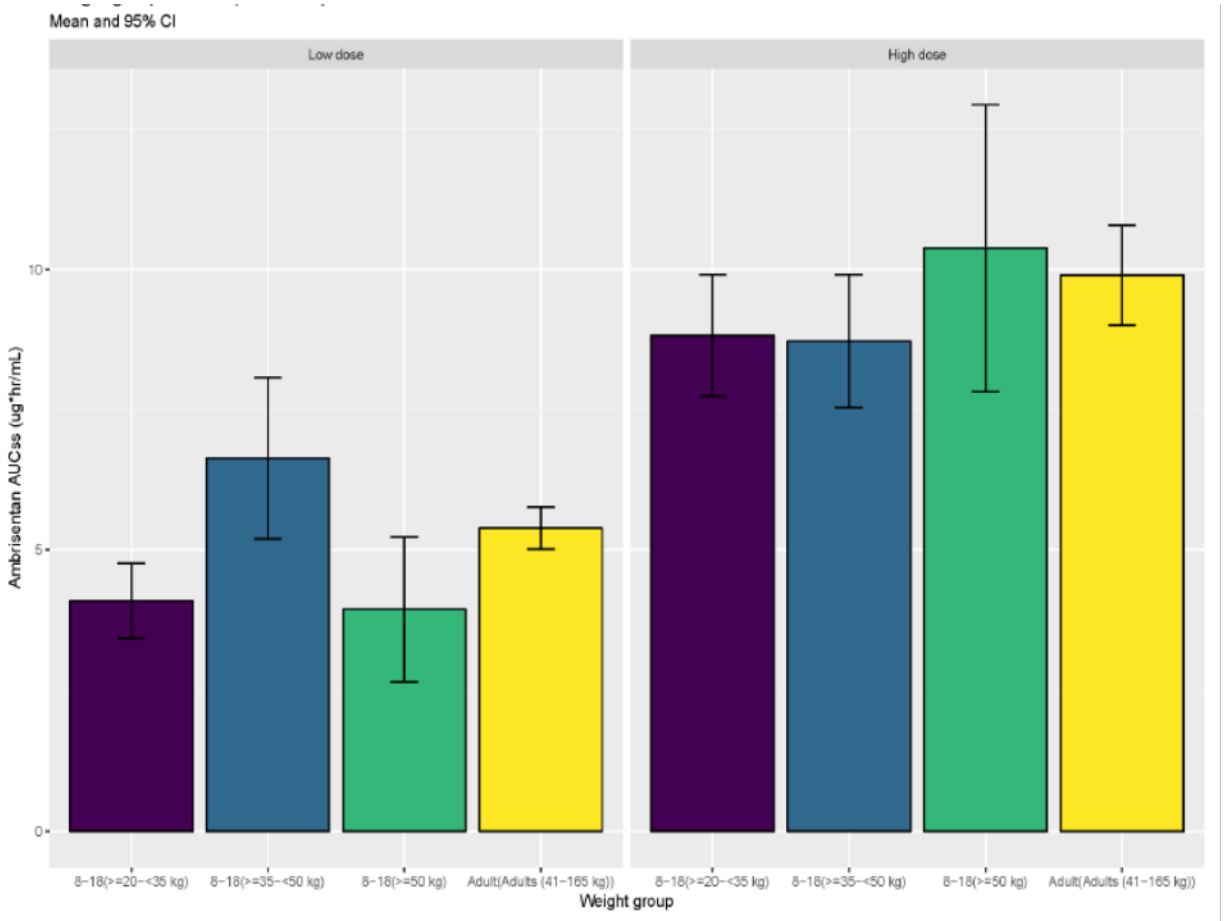
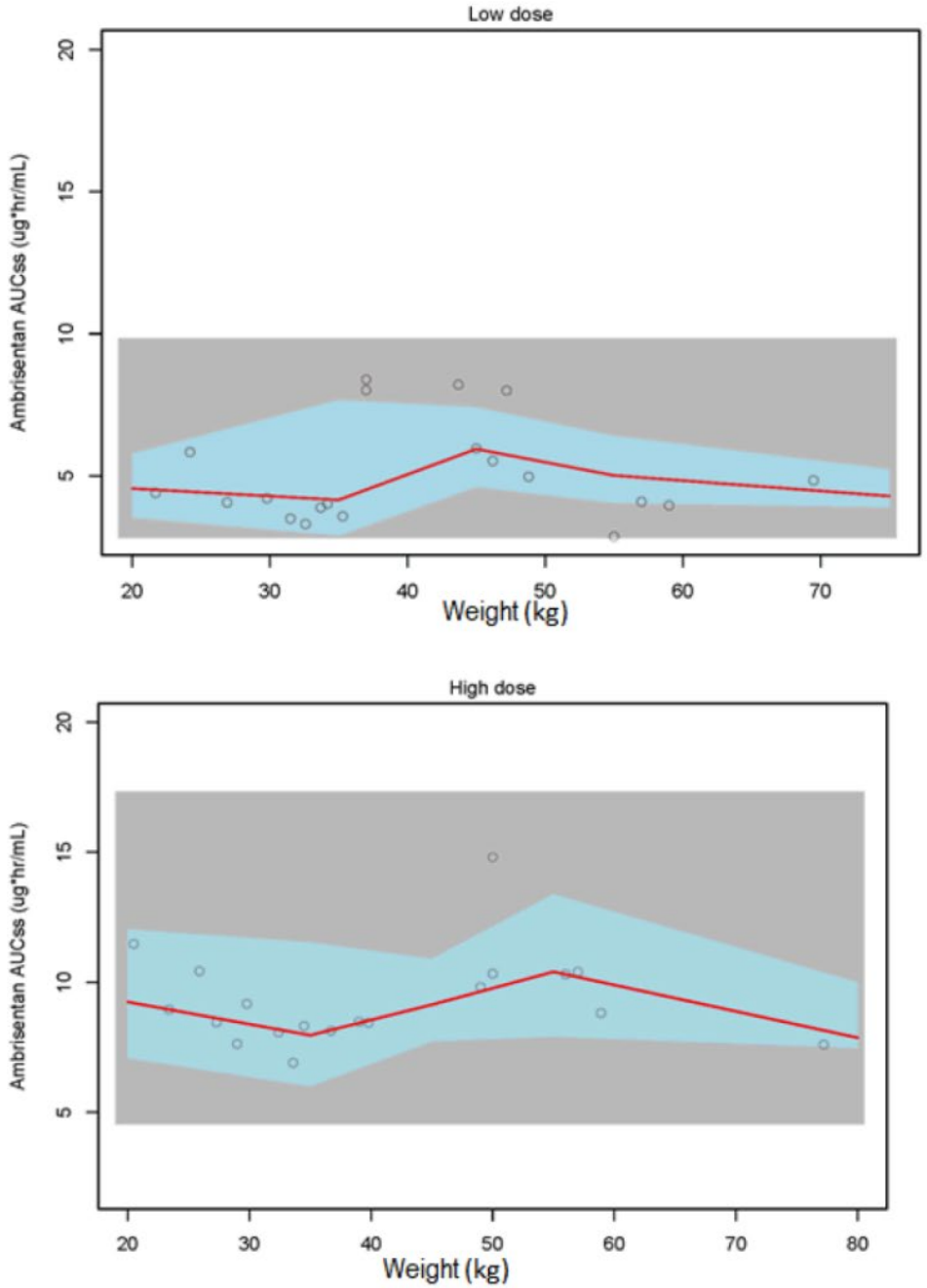

Low dose
High dose
Ambrisentan AUCss (ug*hr/mL)
0
5
10
15
20
8
8
4
157
9
4
6
79
8-18(>=20-<35 kg)
8-18(>=35-<50 kg)
8-18(>=50 kg)
Adult(Adults (41-165 kg))
Weight group

Figure 7 continued Comparison of Model-Derived Ambrisentan AUC ss Following Administration of Ambrisentan in Paediatric Population (8 to less than 18 years old) and Adult population, Stratified by patient, Dose and weight group



Data Source: Figure 7.6-2 from PK-PD report (GSK Document Number 2019N411467_00)
Black circles (paediatrics aged 8 to less than 18 years) are the final paediatric POP-PK model (Run 007n) derived AUC_{ss}; Black circles (adults) are the final adult POP-PK model (Run 411) derived AUC_{ss}. Number below each boxplot represent the number of subjects in the respective boxplot.

Figure 8 Model Derived and Paediatric AUC_{ss} versus Body Wright Using the Final Paediatric Population PK Model



Open circle: observed paediatric AUC; Solid Line: Median of predicated paediatric AUC; Blue shade: 90% PI for predicted paediatric AUC; Grey share: 5th and 95th percentiles for adult observed AUC at 10 mg dose
Data Source: Figure 7.6-3 from PK-PD report (GSK Document Number 2019N411467_00)
Open circle: Model-derived paediatric AUC_{ss}, Solid line=Median of the predicted paediatric AUC_{ss}, Blue shaded region= 90% PI for the predicted paediatric AUC_{ss}, Grey shaded region: 5th and 95th percentiles for adult model-derived AUCss at Low dose (5 mg) or High Dose (10 mg).

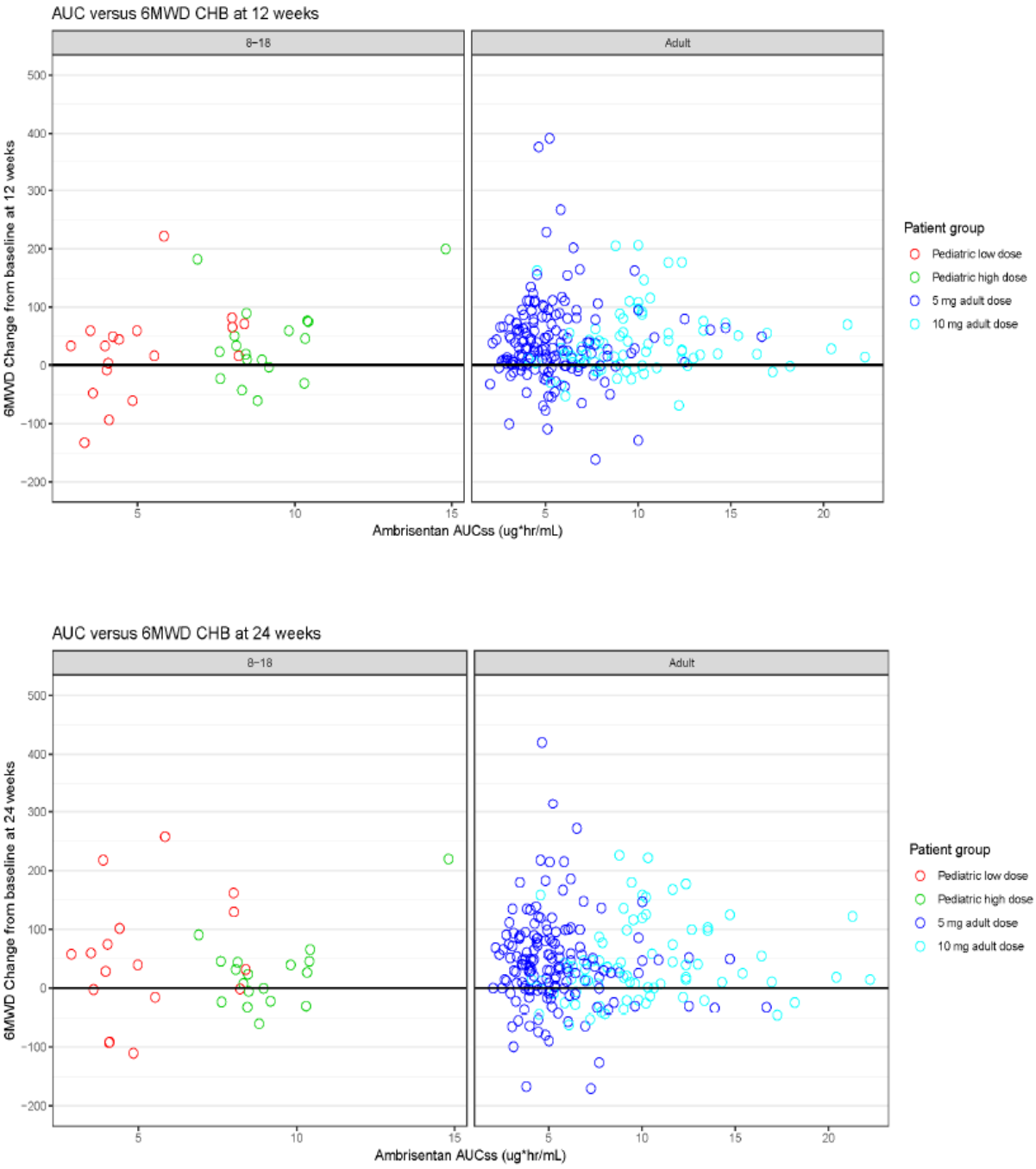
2.6.2.1. Pharmacodynamics

Exposure-efficacy relationship

The ambrisentan individual AUCs plotted against change from baseline in 6MWD at both Weeks 12 and 24 stratified by patient (adults versus paediatric population) and dose group presented in Figure 9 suggest no clear correlation between ambrisentan systemic exposure and the change from baseline in 6MWD in 8 up to 18-year-old subjects. Therefore, any formal exposure response (ER) assessment with the extent of PK-PD information available from this study is limited. Based on that, no further PK-PD modelling was considered.

These observations are consistent with those in adults in whom there were also no strong relationships between ambrisentan exposure and efficacy measures. The lack of a strong exposure-response relationship in both adults and paediatric subjects is expected given the relatively narrow range of evaluated active doses and large between-subject variability in response. A wider dose range including placebo data would allow to better discriminate between doses, however this type of study would not be practical given the context of a rare disease and the safety profile. Nevertheless, given that similar exposure, efficacy, and safety profiles have been demonstrated between the paediatric and adult populations, extrapolation of data is considered valid.

Figure 9 **Scatter Plot of Ambrisentan AUC_{ss} and Change from Baseline in 6MWD (metres) at 12 and 24 Weeks, Stratified by Patient and Dose Group**



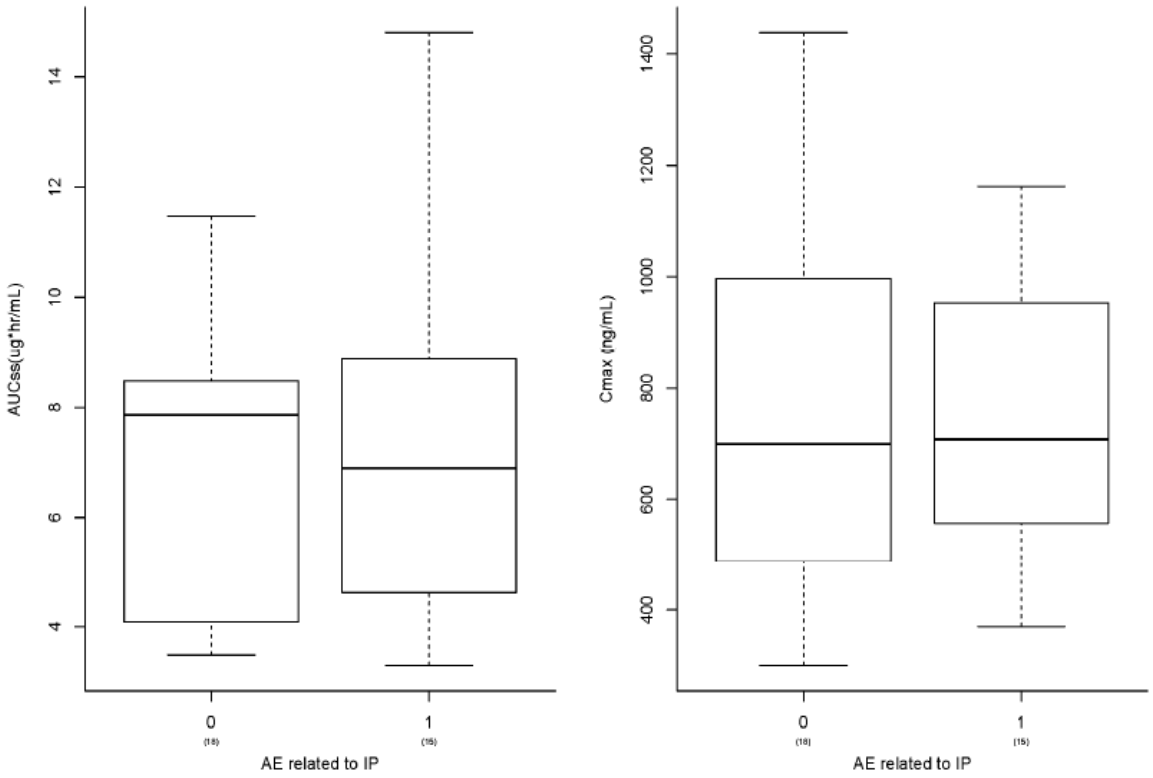
Data Source: Figure 8.1-1 from PK-PD report (GSK Document Number 2019N411467_00)
CHB: Change from baseline, Adult AUC and 6MWD CHB is taken from adult POP-PK report (GSK Document number HM2007/00511/00)

Exposure-safety relationship

The ambrisentan individual exposures (AUCss and Cmax,ss) plotted against incidence of any AE related to ambrisentan are presented in Figure 10. These plots suggest a lack of correlation between the ambrisentan exposure and the incidence of drug-related AEs.

The observations in the paediatric subjects are in concordance with those in the adult population where the reported incidence of AEs did not appear to be related to estimates of increased ambrisentan exposure. In adults, the analysis of the relationship between the predicted measures of ambrisentan exposure and the frequency and severity of AEs was consistent with the efficacy analysis that did not show a strong relationship.

Figure 10 Ambrisentan Predicted Exposures versus Incidence of Any Adverse Event Related to Ambrisentan



Data Source: Figure 8.3-1 from PK-PD report (GSK Document Number 2019N411467_00)
IP=Investigational product (Ambrisentan)
0=no ambrisentan related reported AE
1=ambrisentan related AE reported

2.6.3. Discussion on clinical pharmacology

Bioequivalence

The registration of additional strength of 2.5 mg is based on qualitative similarity with commercially available 5 mg and 10 mg strengths and bioequivalence study AMB-103 which demonstrated bioequivalence between the to be marketed strength and 2.5 mg strength used during clinical development. The new strength has the same qualitative composition and same manufacturing process as commercially available 5 mg and 10 mg strengths and similar dissolution profile.

The data to support additional strength of 2.5 mg are considered adequate.

Pharmacokinetics

The pharmacokinetics of ambrisentan in 39 paediatric patients from 8 to less than 18 years of age have been characterized based on 211 observations from Study AMB112529. Paediatric patients received two dose levels (5 or 10 mg) and both sub-groups of patients shared similar demographic characteristics. The number of data below the quantification limit is negligible (<3%).

A previously developed population PK model in the adult population was used to predict the exposure in paediatric patients from 8 to less than 18 years of age. The results suggested a model-misspecification at early (4-8 hours) and later (16-20 hours) time points. Therefore, the population PK model was refined to adequately characterize the ambrisentan exposure. The final population PK model in paediatric patients incorporated equal structural PK model as the adult population (two-compartment model with linear absorption and disposition), but allometric exponents to account for the different effects of weight on the disposition parameters clearly differed to the adult population PK model. Standard allometric exponents were considered in the paediatric population, which is endorsed. The model evaluation demonstrated the ability of the population PK model to characterize the observed behaviour.

Higher Vc/F and Vp/F were estimated for paediatrics compared to adults. No statistical differences were observed on ka and Vc/F and statistical but not clinically relevant differences were predicted on Vp/F. The previously developed population PK model in adults demonstrated an adequate agreement to describe the observed behaviour in paediatric patients, adequacy of the current population PK model in paediatrics. Therefore, model-predicted exposure metrics should be considered with caution, since several concerns have been raised regarding differences in the population PK model between paediatric patients from 8 to less than 18 years of age and adults.

A simulation-based analysis was performed using the population PK model developed in the paediatric population (8-18 years of age) to evaluate different dose levels in paediatric patients. Model predicted exposures in each sub-group of paediatric patients were compared across body weight ranges and ultimately, compared to the predicted exposure in adults. The previously developed adult population PK without allometric scaling effects has demonstrated a good ability to reproduce the paediatric data. This confirms that differences in PK model structures and parameter estimates were conducted to better reproduce the experimental evidence in paediatric patients.

Exposure-response analyses

No exposure-response (efficacy or safety) relationships were found in paediatric patients receiving 5 to 10 mg of ambrisentan. Similar results were observed when adult patients were considered in previous analysis. The lack of any exposure-efficacy or exposure-safety relationship could be influenced by the limited dose levels evaluated in clinical trials.

2.6.4. Conclusions on clinical pharmacology

Bioequivalence between the to be marketed strength and 2.5 mg strength used during clinical development was demonstrated in study AMB-103. The new strength also has similar qualitative characteristics with commercially available strengths.

The clinical pharmacology characteristics have been adequately addressed and no other concerns remain.

The evaluation of the exposure-efficacy or exposure-safety relationship in paediatric patients receiving 5 or 10 mg of ambrisentan demonstrated the lack of any significant relationship between the exposure metrics (AUC and Cmax) and response endpoints. Therefore, no exposure-response relationship could

be established so far in paediatric patients (8-18 years) due to the limited number of dose levels evaluated and the reduced number of patients recruited. The Applicant is encouraged to assess, when possible, any plausible exposure-response relationship in this and other sub-groups of paediatric patients during its clinical development.

2.6.5. Clinical efficacy

2.6.5.1. Dose response studies

See section 2.6.5.2. The main study in this application was a phase IIb study AMB112529 and its extension.

2.6.5.2. Main study(ies)

STUDY AMB112529

Study AMB112529, a randomized, open label study comparing safety and efficacy parameters for a high and a low dose of ambrisentan (adjusted for body weight) for the treatment of pulmonary arterial hypertension in paediatric patients aged 8 years up to 18 years

This was a 6-month (24-week), randomised, open-label evaluation of the safety, tolerability, and efficacy of 2 doses of ambrisentan (Low and High, adjusted for body weight) in paediatric subjects aged 8 years up to 18 years with PAH. The study included a Screening/Baseline Period (up to a maximum of 2 weeks), a Treatment Period, and a Follow-up assessment within 4 to 6 weeks of last investigational drug. The Treatment Period was 24 weeks or until the subject's clinical condition deteriorated to the point that alternative/additional treatment was necessary. Subjects who completed the study were eligible to enrol into a long-term follow-up study (AMB114588) and those subjects were not required to attend the Follow-up assessment in this study.

Methods

- **Study Participants**

Inclusion criteria:
Male or female subjects aged 8 up to 18 years of age at the time of randomisation were eligible. Key inclusion criteria required a current diagnosis of PAH (WHO Group 1) with WHO Class II or III symptoms in one of the following categories: idiopathic; heritable; secondary to connective tissue disease; or persistent PAH despite surgical repair. Subjects with right heart catheterisation also had to meet the following: mean pulmonary arterial pressure of ≥25 mmHg; pulmonary vascular resistance of ≥240 dyne sec/cm5; and left ventricular end diastolic pressure or pulmonary capillary wedge pressure of ≤15 mmHg. All subjects must have either been: treatment naïve; discontinued treatment with another endothelium receptor antagonist (ERA) at least 1 month previously because of elevated liver function tests (LFTs); or on a stable dose of drug therapy for PAH for at least 1 month prior to the Screening Visit. The baseline drug therapy for PAH, if any, was not permitted to change from the time of the Screening Visit until the end of all Treatment Period assessments, and subjects who discontinued ERA treatment due to elevated LFTs, must have had LFTs of <3 x Upper Limit of Normal (ULN).

Exclusion criteria:
Key reasons subjects were not eligible for the study included 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). A diagnosis of active hepatitis (hepatitis B surface antigen and hepatitis C

antibody), or clinically significant hepatic enzyme elevation at Screening was also excluded, as well as subjects with severe renal impairment, clinically significant fluid retention or anaemia.

- **Treatments**

Subjects were dosed orally (tablet swallowed whole) once daily for 24 weeks after randomisation to either a High dose or a Low dose group. For subjects randomised to the High dose group, in each body weight subgroup there was an initial lower dose that was increased at Week 2 to the final higher dose, if deemed appropriate by the investigator.

Table 12 Ambrisentan doses given in study AMB112529 by body weight and dose group.

Body Weight	**Low dose group**		**High dose group**	
	Starting dose dispensed at baseline	Dispensed at week 2 onwards	Starting dose dispensed at baseline	Dispensed at week 2 onwards
≥50 kg	5 mg	5 mg	5 mg	10 mg
≥35 kg and <50 Kg	5 mg	5 mg	5 mg	7.5 mg
≥20 kg and <35 Kg	2.5 mg	2.5 mg	2.5 mg	5 mg

- **Objectives**

The primary purpose of this paediatric study was to provide clinically relevant information on the safety and PK profile of ambrisentan in children with the most common causes of PAH in this age group. The design of the study was also intended to provide information to guide dose selection and supportive efficacy data.

- **Outcomes/endpoints**

Efficacy was a secondary objective in study AMB112529 (main objective was related to safety)

Summary of Efficacy endpoints in study AMB112529

- Primary:
- Change from Baseline in the 6-minute walking distance (6MWD) test evaluated after 24 weeks of therapy.
- Secondary:
- Mean changes from Baseline in the 6MWD test at Weeks 4, 8, 12, 16, and 20.
- Time to clinical worsening of PAH.
- Change from Baseline in Subject Global Assessment to Week 24 using the Short Form 10 (SF-10) health survey for children.
- Change from Baseline in World Health Organisation (WHO) functional class to Week 24.
- Change from Baseline in N-terminal pro-B-type natriuretic peptide (NT-ProBNP) concentration at Week 24.
- Exploratory objectives:
- Change from Baseline in major prognostic factors based on echocardiograms: pericardial effusion, right atrial (RA) pressure, tricuspid annular plane systolic excursion (TAPSE), eccentricity index (systolic and diastolic), and right ventricular (RV) pressure by tricuspid regurgitant jet (TRJ) velocity to Week 24.
- Change from Baseline in cardiopulmonary haemodynamics at Week 24 (a sub-study in subjects enrolled at centres where the collection of haemodynamic data was considered part of the standard of care).

An Independent Data Monitoring Committee (IDMC) was utilised to conduct external objective medical and/or statistical review of safety, exposure (ambrisentan plasma concentration), and/or efficacy issues.

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 both studies is provided in Table below.

Table 13 Efficacy Endpoints Utilized in Studies AMB112529 and AMB114588

Efficacy endpoint	Study AMB112529	Study AMB114588
Primary		
6MWD[a]	Week 24 (or early withdrawal)	--
All cause mortality	--	Collected as part of worsening of PAH
Secondary		
6MWDT	Weeks 4, 8, 12, 16, and 20	Every 6 months (or 4 to 6 weeks after discontinuing ambrisentan
Time to clinical worsening of PAH	As required	As required
Change from Baseline in WHO functional class	Monthly to Week 24	Every 6 months (or 4 to 6 weeks after discontinuing ambrisentan
Change from Baseline in plasma NT-proBNP concentration	Week 24	Every 6 months or early withdrawal
Health outcomes (SF-10 and school days missed)	Monthly to Week 24	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	Week 12 and Week 24	Every 6 months (or 4 to 6 weeks after discontinuing ambrisentan
Other		
Change from Baseline in cardiopulmonary haemodynamics[d]	Week 24 (taken only if part of subject's standard care)	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 haemodynamic data was considered part of the standard of care

6-Minute Walk Distance: 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 exposure-response (ER) model relating ambrisentan PK to change from baseline in 6MWD.

The 6MWD endpoint has been shown in the adult PAH population to correlate with long-term 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].

At a pre submission meeting the Rapporteur requested an additional assessment of subject response to therapy using a minimal clinically important difference (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 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;
- Hospitalisation 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 oedema, increase in liver size, ascites, increase in jugular venous pressure, pericardial effusion, increased dyspnoea).

Change in WHO Functional Class: The WHO classification of functional capacity, an adaptation of the New York Heart Association (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 below, is useful to monitor disease progression and response to treatment [McGoon, 2004].

Table 14 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 dyspnoea, 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 dyspnoea, 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 dyspnoea, 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. Dyspnoea 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.

An adhoc analysis was performed of the proportion of subjects who achieved an NT-proBNP level of less than 1200 ng/L by randomized group and overall at Week 12 and Week 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.

Prognostic Factors Based on Echocardiograms: Prognostic factors evaluated in both Study AMB112529 and Study AMB114588 included pericardial effusion, RA pressure, tricuspid annular plane systolic excursion (TAPSE), eccentricity index (systolic and diastolic), and RV pressure by tricuspid regurgitant jet (TRJ) velocity.

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

Haemodynamic assessments included:

- heart rate
- mean blood pressure (systolic, diastolic)
- mean pulmonary arterial pressure (PA; systolic, diastolic)
- mean RA pressure
- left ventricular end diastolic pressure (LVEDP) or
- pulmonary capillary wedge pressure (PCWP)
- cardiac output
- cardiac index (calculated value)
- arterial and mixed venous oxygen saturation (method used to calculate cardiac output measurement was recorded, if Fick's principle was used it was to be stated if oxygen consumption was measured or assumed).

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 only. 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 only. 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.

- **Sample size**

Sixty-six subjects (33 per dose group) were planned and 41 subjects were recruited prior to a nonclinical toxicology finding in juvenile rats that led to regulatory notification, discussions with investigators/competent authorities, and the study being placed on clinical hold for new enrolment. Following further nonclinical investigations and discussions with the EMA Paediatric Committee (PDCO), it was determined in February 2019 not to enrol further subjects and the study was terminated and reported with 41 subjects.

- **Randomisation**

All subjects who met the inclusion and exclusion criteria were randomised to one of 2 dose groups (Low dose or High dose, based on body weight) of ambrisentan according to a computer-generated randomisation schedule. To ensure balance with respect to the number of subjects assigned to each dose group, the allocation schedule was generated in blocks. Each subject was assigned to a pack number according to the predefined randomisation list. A central Interactive Voice Response System was used for treatment assignment.

Once a randomisation number had been assigned, the subject was considered as definitely included and the number was not re-assigned. Randomisation was stratified by the age groups 8 years up to 11 years and 12 years up to 18 years, and by aetiology of PAH as follows:

- Idiopathic.
- Heritable [familial].
- Secondary to connective tissue disease.
- Persistent despite surgical repair of atrial septal defects, ventricular septal defects, atrio-ventricular septal defects, and persistent patent ductus.

Subjects were assigned to study treatment in accordance with the randomisation schedule.

- **Blinding (masking)**

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 (see "Treatments" section above). The 2.5 mg, 5 mg, 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 randomised treatment was unblinded to the investigators to allow for informed dose adjustments and follow-up treatment as necessary.

- **Statistical methods**

All subjects from the ITT population were included in the analysis of efficacy data. The ITT population consisted of all randomised subjects who received at least 1 dose of study drug. Given the small sample size, all efficacy data were summarised descriptively and graphically. Data were summarised by dose group (Low and High) and overall. For key efficacy endpoints, data were also summarised by age strata (8 to 11 years and 12 to <18 years).

Time to clinical worsening was presented graphically by Kaplan-Meier curves. The 10 items of the SF-10 Health Survey were aggregated into 2 summary scores (Physical Health and Psychosocial) each containing 5 mutually exclusive elements from the 10-item survey. A higher value on each summary score indicated better functioning. The aggregate score was then standardised and transformed to a norm-based scoring metric in accordance with the developer's guidelines.

A summary analysis of the differences between Low and High dose groups was planned to be performed for efficacy endpoints. However, due to low subject numbers, this was removed from the final analysis plan. Data presentation of school days missed due to PAH was added to the final

Reporting and Analysis Plan (RAP). In addition, presentation of ambrisentan plasma concentration-time data was not specified and was
provided as additional output after finalisation of the RAP.

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 as updated in the RAP prior to the data cut off and reporting of data for this interim report.

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.

Subgroup Analysis: Selected demographic, safety and efficacy outputs were produced by age strata (8 to 11 years, and 12 up to 18 years) in Study AMB112529.

Interim Analyses: Study AMB112529 was placed on enrolment hold in 2013 following juvenile rat toxicology data findings of decreased brain weights, believed to be due to hypoxia related to apnoeic episodes. At this time, 41 paediatric subjects had been recruited into the study and in the interim between enrolment hold and the submission of additional nonclinical data to the CHMP, the enrolled subjects had either completed the study (37 subjects) or had withdrawn (4 subjects). An interim efficacy analysis was conducted in 2018 but since the study was subsequently terminated, this interim analysis became the final analysis for Study AMB112529.

There were no planned interim analyses for the extension study. However, an interim analysis was added post finalisation of the study protocol, in order to provide analyses in support of regulatory interactions. All data collected by a pre-determined clinical cut-off date of 23 August 2019 were analysed in accordance with the planned final analyses specified in the RAP utilised for this interim analysis report.

Adhoc Analyses of 6MWD and NT-proBNP from Study AMB112529 and Study AMB114588: At the VOLIBRIS Paediatric Pre-submission meeting in December 2019 the Spanish Rapporteur requested an assessment of subject response to therapy using a MCID criteria of ≥20 metres for the 6MWD and for NT-proBNP (criteria not specified) (m1.0 Rapporteur meeting minutes, 2020).

For the 6MWD, the proportion of subjects with a change from baseline in 6MWD of ≥20 metres 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.

The literature cites a target level of NT-proBNP of less than 1200 ng/L as desirable since patients achieving this level have better outcomes when compared to those who have higher levels [Ploegstra, 2015]. Consequently, an adhoc analysis was performed of the proportion of subjects who achieved an NT-proBNP level of less than 1200 ng/L by randomized group and overall at Week 12 and Week 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. In addition, the proportion of subjects with NT-proBNP levels above 1200 ng/L at baseline or any time during the study, proportion with levels between 500 to <1200 ng/L, and those with levels <500 ng/L were also calculated. For those subjects with baseline NT-proBNP values greater than 1200 ng/L, the proportion who remained high or had at least 1 value or the last value<1200 ng/L was calculated. Of those subjects with values between 500 to 1200 ng/L, how many remained between these levels or transitioned to higher (greater than 1200 ng/L) or lower values (<500 ng/L) was also calculated.

Similarly, of those subjects with baseline values <500 ng/L, the proportion who remained at this level or transitioned to higher values (between 500 to 1200 ng/L or greater than 1200 ng/L) was also calculated.

Results

- **Participant flow**

A total of 41 patients were randomized to the ambrisentan low dose group (n=21) or high dose group (n=20)
The majority of subjects in both dose groups completed the study (Table 15). The primary reasons for withdrawal were similar across the 2 dose groups. Both subjects withdrawn from the study due to an AE died as a result of the reported event.

In total, 38 subjects (93%) entered the long-term extension study AMB114588; 19 subjects from the Low dose group and 19 subjects from the High dose group.

Table 15 Summary of Subject Disposition (ITT Population)

	Ambrisentan Dose Group		
	Low Dose (N=21) n (%)	High Dose (N=20) n (%)	Total (N=41) n (%)
Status			
Completed	19 (90)	18 (90)	37 (90)
Withdrawn	2 (10)	2 (10)	4 (10)
Primary reason for study withdrawal [a]			
Adverse event	1 (5)	1 (5)	2 (5)
Lost to follow-up	0	1 (5)	1 (2)
Investigator discretion	1 (5)[b]	0	1 (2)

Source: Table 1.1
Low dose: 2.5 mg (body weight ≥20 kg and <35 kg); 5 mg (≥35 kg).
High dose: 5 mg (body weight ≥20 kg and <35 kg); 7.5 mg (≥35 kg and <50 kg); 10 mg (≥50 kg).
a. Percentages are based on the number of subjects in the dose group.
b. Investigator discretion reasons: SAE, lack of efficacy, poor tolerance of treatment, no rationale for continuation.

Recruitment

Subjects were randomised from 9 countries; 8 subjects from the Russian Federation, 7 from the United States, 6 from Argentina, 5 each from Hungary and Japan, 3 each from France and Germany, and 2 each from Italy and Spain.

In March 2013, a Dear Investigator Letter was sent by GSK to inform all investigators and responsible national competent authorities of a nonclinical finding of brain weight decrease in juvenile rats with low clinical margins for human paediatric dose exposures.

At that time, 41 subjects had been recruited to the study. Further to notification of the juvenile rat toxicology findings, questions were received from the EMA and the competent authorities in Germany, France, and Italy. Following consultation with the national agencies governing the trial in each country, existing subjects were permitted to remain on ambrisentan if the investigator, guardians, and subjects wished. A global clinical enrolment hold was imposed soon afterwards, subject to availability of further nonclinical data.

Further nonclinical investigations were conducted, and the findings submitted to CHMP in November 2017. These studies demonstrated that ambrisentan can cause apnoea and hypoxemia in juvenile rats. Investigations also concluded that decreases in brain weight were not associated with

neurobehavioural effects, brain microscopic or gene expression alterations. Although not fully understood, it is postulated that the juvenile rat brain weight decrease could be mediated by sustained hypoxemia during a period of rapid brain growth that was associated with mechanically-induced apnoea. Thus, improper interaction of rat laryngeal tissues, which are in close apposition during early postnatal stage, may constitute a sensitive period. This may be considered a potential risk for young children (0 to 3 years) since the human oropharynx orientation has similarities with the juvenile rat in early infancy and repositions with age.

All 41 enrolled subjects in this study had either withdrawn or completed the study during the period between clinical hold initiation and submission of nonclinical data to the CHMP. To further support clinical use in children aged 8 to 18 years, an unplanned interim analysis including all data collected up to January 2018 was conducted in which all safety, tolerability, population-PK, and efficacy data were reviewed, analysed and summarised. Taking into consideration the duration of time elapsed since the initiation of the clinical hold, shifts in clinical management for PAH during that period, challenges relating to re-initiation of recruitment, and the potential for confounding when pooling and interpreting data from 2 potentially distinct populations, the unplanned interim analysis based on the 41 subjects was deemed a reasonable sample size for submission for review by the PDCO, to inform a data-driven decision regarding the clinical and scientific merit of continuing the study.

Notification of the opinion of a proposed PIP modification submitted by GSK was received from the EMA PDCO in February 2019 (EMEA-000434-PIP01-08-M05). The study was agreed to be closed and a reduction in number of subjects from the planned 66 subjects (for 60 evaluable) to 40 was accepted. Therefore, recruitment was not re-initiated, the study was declared as terminated on 11 Feb 2019, and the unplanned interim analysis became the final analysis for this study (based on 41 subjects enrolled).

Conduct of the study

At the time of signature of the CSR, no major GCP noncompliance issues were identified by monitoring or audit.

Approximately one fifth of all subjects reported at least one important protocol deviation throughout the study (Table 16). Reasons for deviations were similar across dose groups.

Table 16 Summary of Important Protocol Deviations (ITT Population)

Protocol Deviation Category	Ambrisentan Dose Group		
	Low Dose (N=21) n (%)	High Dose (N=20) n (%)	Total (N=41) n (%)
Any important deviation	4 (19)	4 (20)	8 (20)
Eligibility criteria not met	1 (5)	2 (10)	3 (7)
Administer/dispense study medication	1 (5)	2 (10)	3 (7)
Study treatment supply procedures	1 (5)	1 (5)	2 (5)
Assessment procedures	1 (5)	0	1 (2)
Other	0	1 (5)	1 (2)

Source: Table 1.14
Low dose: 2.5 mg (body weight ≥20 kg and <35 kg); 5 mg (≥35 kg).
High dose: 5 mg (body weight ≥20 kg and <35 kg); 7.5 mg (≥35 kg and <50 kg); 10 mg (≥50 kg).
Note: 'Other' was due to 1 subject with poor treatment compliance between Weeks 12 and 16.

Baseline data

The study recruited 41 subjects. All of them were included in the Safety Population and the ITT Population.

The mean age (range) of subjects included in the study was 12.0 years (8 to 16 years), and a similar mean weight was observed across the 2 dose groups (38.76 kg and 40.12 kg for the Low dose and High dose group, respectively). There was a higher proportion of female subjects than males (27 females [66%] across all subjects). Most subjects were White/Caucasian/European heritage (30 subjects [73.2%]).

The majority of subjects (66%) had idiopathic aetiology at Baseline, with 80% of all subjects receiving ongoing PAH therapy at the start of the Treatment Period. The mean Baseline 6MWD test was similar across the 2 dose groups (442.23 and 407.32 metres for the Low and High dose groups, respectively).

All subjects met the protocol-defined diagnostic criteria of PAH (WHO Group 1) and WHO Class II or III symptoms, with over three-quarters of all subjects reported as Class II (indicating slight limitation of physical activity due to PAH as opposed to marked limitation for Class III symptoms). The female predominance observed across the 2 dose groups (66%) aligns with the known higher female prevalence in the wider paediatric/adult population, and implications in the literature of a link with endogenous sex hormones (particularly 17β oestradiol and its metabolites) in the development of the disease.

Table 17 Summary of demographic and baseline characteristics, ITT population (study AMB112529)

	Ambrisentan Dose Group		
	Low Dose (N=21)	High Dose (N=20)	Total (N=41)
Age (yrs)			
Mean (SD)	11.8 (2.70)	12.3 (2.85)	12.0 (2.75)
Median	13.0	12.0	13.0
Min to Max	8 to 16	8 to 16	8 to 16
Age category (yrs; n [%])			
8 to 11	7 (33)	7 (35)	14 (34)
12 to <18	14 (67)	13 (65)	27 (66)
Sex (n [%])			
Female	12 (57)	15 (75)	27 (66)
Male	9 (43)	5 (25)	14 (34)
Child bearing potential (females only; n [%])			
n	12	15	27
Pre-menarcheal	8 (67)	7 (47)	15 (56)
Potentially able to bear children	4 (33)	8 (53)	12 (44)
Ethnicity (n [%])			
Hispanic or Latino	5 (24)	8 (40)	13 (32)
Not Hispanic or Latino	16 (76)	12 (60)	28 (68)
Geographic ancestry (n [%])[a]			
African American/African Heritage	2 (10)	0	2 (5)
American Indian or Alaskan Native	1 (5)	0	1 (2)
Asian – Central/South Asian Heritage	1 (5)	0	1 (2)
Asian – East Asian Heritage	1 (5)	0	1 (2)
Asian – Japanese Heritage	5 (24)	0	5 (12)
Asian – South East Asian Heritage	0	1 (5)	1 (2)
White – White/Caucasian/European Heritage	11 (52)	19 (95)	30 (73)
Weight (kg)			
Mean (SD)	38.76 (12.042)	40.12 (14.990)	39.42 (13.406)
Median	36.00	38.05	36.10
Min to Max	20.9 to 67.0	20.1 to 77.0	20.1 to 77.0
Weight category (kg, n [%])			
20 to <35 kg	10 (48)	9 (45)	19 (46)
35 to <50 kg	7 (33)	5 (25)	12 (29)
≥50 kg	4 (19)	6 (30)	10 (24)

Aetiology of PAH randomised strata			
Idiopathic	13 (62)	14 (70)	27 (66)
Familial	0	2 (10)	2 (5)
Persistent PAH despite surgical repair	5 (24)	3 (15)	8 (20)
Secondary to connective tissue diseaase	3 (14)	1 (5)	4 (10)
Duration of PAH (days)			
n	20	20	40
Mean (SD)	1023.6 (1245.29)	1304.0 (1399.95)	1163.8 (1315.47)
Median	449.5	682.5	508.5
Min to Max	2 to 4189	0 to 4065	0 to 4189
PAH therapy use (n [%])			
Ongoing therapy at Baseline	18 (86)	15 (75)	33 (80)
Prior PAH therapy, not ongoing at Baseline	0	1 (5)	1 (2)
No PAH therapy recorded	3 (14)	4 (20)	7 (17)
WHO Functional Class (n [%])			
Class II	18 (86)	14 (70)	32 (78)
Class III	3 (14)	6 (30)	9 (22)
6 Minute Walk Distance (m)			
Mean (SD)	442.23 (108.152)	407.32 (118.420)	425.20 (113.233)
Median	453.00	420.00	425.50
Min to Max	168.0 to 600.0	160.0 to 592.8	160.0 to 600.0

Source: Table 1.5
Min=minimum; Max=maximum; PAH=pulmonary arterial hypertension; SD=standard deviation; WHO=World Health Organication.
Low dose: 2.5 mg (body weight ≥20 kg and <35 kg); 5 mg (≥35 kg).
High dose: 5 mg (body weight ≥20 kg and <35 kg); 7.5 mg (≥35 kg and <50 kg); 10 mg (≥50 kg).
a. A subject may be represented in more than one geographical ancestry group.

A total of 39 subjects aged 8-16 years from study AMB112529 were included in the population PK dataset. There was an almost equal number of subjects in the Low (20) and High (19) dose groups. The median (range) age across the 39 subjects was 13 (8-16) years, with approximately two-thirds of the population being females (67%) and one third being males (33%). The median (range) body weight at baseline was 36.1 (20.1-77.0) kg. The majority of the population was White (72%), with 15% being East Asian (East Asian heritage + Japanese heritage) and 13% Other (all remaining race groups). Of the East Asians, there were 5 Japanese subjects in the Low dose group.

Numbers analysed

All 41 subjects were included in the Safety Population and the ITT Population.

Outcomes and estimation

Six-minute walk distance (6MWD): Overall, the mean (SD) 6MWD was similar across the 2 dose groups at Baseline. Change from Baseline at Week 24 showed a mean improvement of approximately 55 metres and 26 metres in the Low dose and High dose groups, respectively.

Table 18 Change in 6MWD from baseline to week 24 (main efficacy endpoint), ITT population (study AMB112529)

Walking Distance (metres)	Ambrisentan Dose Group		
	Low Dose (N=21)	High Dose (N=20)	Total (N=41)
Baseline			
n	21	20	41
Mean (SD)	442.23 (108.152)	407.32 (118.420)	425.20 (113.233)
Median	453.00	420.00	425.50
Min to Max	168.0 to 600.0	160.0 to 592.8	160.0 to 600.0
Change from Baseline at Week 24			
n	18	18	36
Mean (SD)	55.14 (102.182)	26.25 (62.011)	40.69 (84.580)
Median	49.00	25.50	32.00
Min to Max	-110.0 to 258.0	-60.0 to 220.0	-110.0 to 258.0

Min=minimum; Max=maximum; SD=standard deviation.
Low dose: 2.5 mg (body weight ≥20 kg and <35 kg); 5 mg (≥35 kg).
High dose: 5 mg (body weight ≥20 kg and <35 kg); 7.5 mg (≥35 kg and <50 kg); 10 mg (≥50 kg).
Baseline is the last value recorded prior to start of study treatment
There were no subjects with post-last dose follow up visits.

Mean improvements in change from Baseline in 6MWD were also observed from Week 4 and at all visits to Week 20 in both dose groups.

Table 19 Summary of Change from Baseline in Six Minute Walking Distance (ITT Population)

Walking Distance (metres)[a]	Ambrisentan Dose Group		
	Low Dose (N=21)	High Dose (N=20)	Total (N=41)
Change from B/L at Week 4			
n	21	18	39
Mean (SD)	33.10 (66.979)	24.96 (71.254)	29.34 (68.187)
Median	35.00	-0.5	24.00
Min to Max	-68.0 to 228.0	-81.0 to 200.0	-81.0 to 228.0
Change from B/L at Week 8			
n	20	18	38
Mean (SD)	23.84 (65.154)	37.70 (74.339)	30.40 (69.052)
Median	18.75	26.00	24.75
Min to Max	-89.0 to 192.0	-104.0 to 212.9	-104.0 to 212.9
Change from B/L at Week 12			
n	19	18	37
Mean (SD)	29.51 (79.657)	40.29 (69.137)	34.75 (73.890)
Median	34.00	29.10	34.00
Min to Max	-132.0 to 222.0	-60.0 to 200.0	-132.0 to 222.0
Change from B/L at Week 16			
n	19	18	37
Mean (SD)	22.31 (88.832)	36.43 (78.220)	29.18 (82.982)
Median	20.00	16.00	20.00
Min to Max	-178.0 to 222.0	-60.0 to 260.0	-178.0 to 260.0
Change from B/L at Week 20			
n	19	18	37
Mean (SD)	48.49 (90.645)	31.19 (71.209)	40 08 (81.114)
Median	55.00	26.00	33.00
Min to Max	-97.0 to 238.0	-90.0 to 205.3	-97.0 to 238.0

Source: Table 2.2
B/L=Baseline; Min=minimum; Max=maximum; SD=standard deviation.
Low dose: 2.5 mg (body weight ≥20 kg and <35 kg); 5 mg (≥35 kg).
High dose: 5 mg (body weight ≥20 kg and <35 kg); 7.5 mg (≥35 kg and <50 kg); 10 mg (≥50 kg).
a. Data presented is for overall subjects, with and without oxygen use.

Subgroup analysis of 6MWD by age

Subjects in both age categories showed a similar pattern of mean improvement from Baseline in 6MWD at Week 24 to that observed in the overall population (Table 20). The change from baseline in 6MWD at Week 24 was similar between the dose groups in paediatric subjects in the 12-18 age category but was higher in the Low dose group compared with the high dose group in the 8-11 age category.

Table 20 Change from Baseline in Six-Minute Walking Distance at Week 24 by Age Category in Study AMB112529 (ITT Population)

Walking Distance (metres)	Ambrisentan Dose Group		
	Low Dose (N=21)	High Dose (N=20)	Total (N=41)
Age category 8-11 years			
Baseline[a]			
n	7	7	14
Mean (SD)	367.14 (105.225)	341.90 (110.310)	354.52 (104.393)
Median	410.00	370.00	374.85
Min to Max	168.0 to 486.0	160.0 to 498.0	160.0 to 498.0
Change from Baseline at Week 24[b]			
n	6	6	12
Mean (SD)	102.08 (113.922)	15.85 (31.419)	58.97 (91.520)
Median	116.00	12.00	48.95
Min to Max	-92.0 to 258.0	-21.8 to 65.9	-92.0 to 258.0
Age category 12-18 years			
Baseline[a]			
n	14	13	27
Mean (SD)	479.78 (91.272)	442.54 (110.811)	461.85 (100.956)
Median	495.50	450.00	471.00
Min to Max	298.0 to 600.0	219.2 to 592.8	219.2 to 600.0
Change from Baseline at Week 24[b]			
n	12	12	24
Mean (SD)	31.67 (91.837)	31.45 (73.522)	31.56 (81.357)
Median	30.50	33.50	30.50
Min to Max	-110.0 to 218.0	-60.0 to 220.0	-110.0 to 220.0

Source: Study AMB112529 CSR Table 2.1002, Table 2.2002, Table 2.1003, Table 2.2003
Min=minimum; Max=maximum; SD=standard deviation.
Low dose: 2.5 mg (body weight ≥20 kg and <35 kg); 5 mg (≥35 kg).
High dose: 5 mg (body weight ≥20 kg and <35 kg); 7.5 mg (≥35 kg and <50 kg); 10 mg (≥50 kg).
a. Baseline is the last value recorded prior to start of study treatment
b. There were no subjects with post-last dose follow up visits.

Subgroup analysis of responders to 6MWD by PAH aetiology in Study AMB112529

An ad hoc analysis showed that 24 subjects (59%) had an increase from baseline in 6MWD of ≥20 metres at Week 12 and Week 24 in Study AMB112529 and these were fairly evenly distributed across the idiopathic subgroup (15 of 27; 56%) and non-idiopathic subgroup (9 of 14; 64%).

Clinical worsening of PAH: Three subjects in each dose group experienced clinical worsening of PAH during the study. The reasons and mean time to clinical worsening of PAH were similar across the 2 dose groups, the most frequent being clinical signs or symptoms of right sided heart failure and hospitalisation due to worsening of PAH. One patient died in the low dose group due to worsening of PAH. The Kaplan-Meier analysis showed similar event-free survival probability across both dose groups.

Table 21 Summary of Clinical Worsening of Pulmonary Arterial Hypertension (ITT Population)

	Ambrisentan Dose Group		
	Low Dose (N=21)	High Dose (N=20)	Total (N=41)
Subjects with at least one criterion (n [%])	3 (14)	3 (15)	6 (15)
Death (all cause) or placement on active list for lung transplant	1 (5)	0	1 (2)
Hospitalisation for worsening of PAH	2 (10)	1 (5)	3 (7)
PAH related deterioration (n [%])	2 (10)	2 (10)	4 (10)
Increase from Baseline in WHO functional class	1 (50)	0	1 (25)
Clinical signs or symptoms of right sided heart failure	2 (100)	2 (100)	4 (100)
Time to Clinical Worsening			
n	3	3	6
Mean (SD)	77.3 (62.56)	71.7 (29.26)	74.5 (43.79)
Median	55.0	86.0	70.5
Min to Max	29 to 148	38 to 91	29 to 148

Source: Table 2.6, Table 2.7.
Min=minimum; Max=maximum; SD=standard deviation; PAH = pulmonary arterial hypertension; WHO = World Health Organisation.
Low dose: 2.5 mg (body weight ≥20 kg and <35 kg); 5 mg (≥35 kg).
High dose: 5 mg (body weight ≥20 kg and <35 kg); 7.5 mg (≥35 kg and <50 kg); 10 mg (≥50 kg).

World Health Organisation Functional Class
At all post-Baseline visits, the WHO functional class for all subjects ranged from class I to III for subjects in the Low dose group and from class I to IV in the High dose group.

Other than 1 subject in the Low dose group, all subjects had no change or an improvement in WHO functional class at Week 24 and no subject shifted from Baseline by more than 1 class category (Table 22). This pattern of change was similar across the 2 age strata at Week 24.

There was no clinically relevant mean change from Baseline in the WHO functional class for either dose group based on summary statistics.

Table 22 Summary of World Health Organisation Functional Class Change from Baseline Categorisation (ITT Population)

WHO Category[a]	Ambrisentan Dose Group		
	Low Dose (N=21) n (%)	High Dose (N=20) n (%)	Total (N=41) n (%)
Change from Baseline at Week 24			
n	19	18	37
Improved	6 (32)	4 (22)	10 (27)
No change	12 (63)	14 (78)	26 (70)
Deteriorated	1 (5)	0	1 (3)
Change categorisation[b]			
-1	6 (32)	4 (22)	10 (27)
0	12 (63)	14 (78)	26 (70)
+1	1 (5)	0	1 (3)

Source: Table 2.11.
WHO = World Health Organisation.
Low dose: 2.5 mg (body weight ≥20 kg and <35 kg); 5 mg (≥35 kg).
High dose: 5 mg (body weight ≥20 kg and <35 kg); 7.5 mg (≥35 kg and <50 kg); 10 mg (≥50 kg).
a. There are 4 WHO Functional Class grades based on severity of symptoms (Class I=none, Class IV=most severe). Grades mapped to numeric scale 1-4 (i.e., Class IV=4).
b. Change categorisation (based on -2, -1, 0, +1, +2); No Change (0), Improved (-1,-2), Deterioration (+1,+2).

ProBNP: The geometric mean change from Baseline showed a similar percentage decrease from Baseline in NT-ProBNP concentrations across both dose groups at Week 12 and Week 24. A mean (SD) percentage decrease of 29.63 (1.008) was observed at Week 24 for both dose groups combined.

Prognostic Factors Based on Echocardiograms
Exploratory echocardiogram readings showed that 80% of all subjects had no pericardial effusion at Baseline with a similar incidence observed for both dose groups. Mean (SD) values were also similar across dose groups for right atrial pressure (mmHg), tricuspid annular plane systolic excursion (cm), eccentricity index systolic, eccentricity index diastolic, and tricuspid regurgitant jet velocity (m/s); 9.7 (5.34), 1.79 (0.426), 1.640 (1.1377), 1.283 (0.3589) and 3.636 (1.5239), respectively.

The mean (SD) value for right ventricular pressure (mmHg) at Baseline was lower in the Low dose group compared with the High dose group.

At Week 24, there was no change from Baseline in status of pericardial effusion for most subjects (88% and 82% with no change from Baseline in the Low dose and High dose respectively), and mean changes from Baseline were small and similar in both dose groups for most other parameters. A mean (SD) decrease from Baseline in right ventricular pressure was observed in both dose groups.

Cardiopulmonary Haemodynamics
Additional cardiopulmonary haemodynamic data were collected for a small subgroup of subjects who underwent right heart catheterisation (5 subjects in the Low dose group and 2 subjects in the High dose group). Small numerical improvements in haemodynamic parameters were observed at Week 24 in the Low dose group including cardiac index, mPAP and PVR. No subjects had Week 24 assessments in the High dose group.

Quality of life: Mean values in the Physical Health and Psychosocial Summary scores remained stable across the Treatment Period for subjects in the Low dose group, as measured using the SF-10 health survey. A small numerical increase in mean score was observed from Week 12 to Week 24 in the Physical Health Summary for subjects in the High dose group.

Missing school days: At Week 24, change from Baseline in number of missed school days within the past month due to PAH ranged from a 19-day improvement to a 10-day worsening in the Low dose group, and a 6-day improvement to no worsening in the High dose group (median of 0 days for both dose groups). Correspondingly, change in proportion of days missed within the past month due to PAH ranged from a 95.45% improvement to a 41.18% deterioration in the Low dose group and a 23.49% improvement to no deterioration in the High dose group. Other than 1 subject in the Low dose group, all subjects had no change or an improvement in WHO functional class at Week 24.

Extension Study AMB114588

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.

Investigator(s): Multi-centre study.

Study centre(s): There were 22 centres in 9 countries who enrolled subjects; 3 in Argentina, 3 in France, 2 in Germany, 1 in Hungary, 2 in Italy, 3 in Japan, 3 in the Russian Federation, 1 in Spain, and 4 in the US. All of these investigational sites were the same as those which had participated in Study AMB112529.

Publication(s): None at the time of the interim study report (dated on 3rd April 2020) submitted within this variation application.

Study Period: 21 Jun 2011 (date of first subject roll-over from Study AMB112529) – 12 Nov 2013 (last subject rolled over to this long-term extension study).

Data cut-off date for this interim report: 23 Aug 2019.

Phase of Development: IIb

Objectives:

Primary: The primary objective was the long-term safety and tolerability of ambrisentan in the paediatric pulmonary arterial hypertension (PAH) population.

Secondary; *Efficacy*:
- All-cause mortality;
- The change from Study AMB112529 Baseline in the 6-minute walking distance (6MWD) test evaluated every 6 months;
- The time to clinical worsening of PAH;
- The time to addition of another targeted PAH therapeutic agent(s) (prostanoids, PDE-5 inhibitors) due to the following reasons:
- Deterioration of clinical condition
- Lack of beneficial effect with previous therapy (not reaching set treatment goals);
- The time to change in dose of ambrisentan or other targeted PAH therapeutic agents (prostanoids, PDE-5 inhibitors) due to deterioration of clinical condition;
- The change from Study AMB112529 baseline in Subject Global Assessment every 3 months using the Short Form – 10 item (SF-10) health survey for children;
- The change from Study AMB112529 baseline in World Health Organisation functional class (WHO FC) every 6 months;
- Change from Study AMB112529 baseline in N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentration every 6 months.

Methodology:
This was an open-label, long-term extension to Study AMB112529. All subjects could remain in the extension study for a minimum of 6 months. Beyond the 6-month period, subjects could continue in the extension study until one of the following conditions was met:
- The subject turned 18 years of age (when the subject could receive marketed product);
- The product was approved and available for use in the subject's age group;
- Development for use in the paediatric population was discontinued;
- The subject decided he/she no longer wanted to participate in the study;
- The investigator considered it in the best interest of the subject to discontinue ambrisentan (e.g., for safety reasons).

Subjects entered Study AMB114588 at an individually tailored dose based on the investigator's best judgement and consideration of body weight, change in clinical condition, tolerability issues, and any other relevant clinical consideration. The dose could be maintained at the same level, adjusted downward in 2.5 mg increments to not less than 2.5 mg per day, or adjusted upward in 2.5 mg increments to not more than the lesser of 10 mg per day or 0.25 mg/kg per day. On completion of one of the specified study continuation conditions, the subjects were treated according to best standard of care available to the investigator. Subjects had monthly, 3-monthly, and/or 6-monthly assessments as required for each parameter of interest, and were followed for 30 days post their last dose of study medication. In addition, subjects were asked to return for a pubertal development assessment at 20 years of age.

Number of subjects:
In total, 38 of the 41 subjects who entered the initial 24-week study (Study AMB112529) continued into this long-term extension study.

Diagnosis and main criteria for inclusion:
Subjects were eligible for enrolment in the study if they had participated and complied with the protocol for Study AMB112529 and had completed the Week 24 Visit of Study AMB112529, OR if the Week 24 Visit had not been completed, at least one of the following was applicable: the subject required additional targeted treatment for PAH due to inadequate response or worsening of their clinical condition prior to Week 24 in Study AMB112529; the subject 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 not eligible for this long-term extension study if they were withdrawn from ambrisentan in Study AMB112529, were unable to comply with Study AMB112529 protocol requirements, had severe renal impairment (estimated creatinine clearance <30 mL/min as assessed within the previous 45 days of transition from Study AMB112529 into this study), or had clinically significant fluid retention or anaemia.

Treatment administration:
The sponsor provided commercially available ambrisentan 5 mg (batch numbers: CBVNT, CFNC, DHHX, HHGW, TZNN), and 10 mg tablets (batch numbers: CBHKS, CFND, DHHV, HHHB, VBKM), as well as 2.5 mg tablets of equivalent quality (batch numbers CDSH, GHVY, KHWV, KWKH, NFGB, YCMK). For centres in Japan, one or more 2.5 mg tablets were used to achieve the appropriate dose. Subjects were dosed orally (tablet swallowed whole) once daily. Subjects could receive 2.5, 5, 7.5, or 10 mg of ambrisentan per day, as long as the dose did not exceed 0.25 mg/kg/day.

Statistical methods:

*Sample size calculation**:*** Sample size was based on the number of subjects who entered and completed Study AMB112529. No sample size calculations were performed.

Analysis Populations: The Intention-to-Treat (ITT) Population consisted of all subjects who received at least 1 dose of study drug, which was used in all efficacy summaries. For the ITT population, the protocol had specified that subjects would be considered as belonging to their dose group at the time of the visit/event, which was re-specified in the final Reporting and Analysis Plan to be their treatment group at the time of entry to this study.
The Safety Population was defined as all subjects who received at least 1 dose of study drug and was used in all safety summaries. Subjects were considered as belonging to the dose group according to the highest dose received in the study.

Analysis Methods: All efficacy data were summarised descriptively and graphically, with presentations by dose group and overall. The number of school days missed due to PAH was also specified under efficacy endpoints in the protocol in addition to SF-10 assessments.
Time to event parameters (clinical worsening, addition of other targeted PAH therapeutic agents, and change in dose of ambrisentan or other targeted PAH therapeutic agents) were presented graphically by Kaplan-Meier curves.

Summary:

Disposition and Demographics: Of the 41 subjects who entered the initial 24-week study (Study AMB112529), a total of 38 subjects were enrolled into this long-term extension study. Approximately half had completed the study at the time of the data cut-off for this interim report, with a higher proportion completing the study for each increment in dose group. Of the remaining 20 subjects, 16 had been withdrawn and 4 were continuing on treatment. In total, 7 females and 3 males returned for their 20-year old pubertal assessment.

The most frequently reported primary reason for withdrawal was investigator discretion, followed by AE. Of the 5 subjects withdrawn due to an AE, all were due to fatal events not regarded as related to ambrisentan treatment. One further subject who died had an AE that initiated during the study, but then completed the study treatment period prior to the final AE outcome of death (and therefore is not counted among those withdrawn).

Table 23 Patients' disposition in extension study AMB114588 (after initial 24-week study AMB112529)

	Ambrisentan Dose Group[a]				
	2.5 mg (N=9) n (%)	5 mg (N=19) n (%)	7.5 mg (N=5) n (%)	10 mg (N=5) n (%)	Total (N=38) n (%)
Status					
Completed[b]	3 (33)	7 (37)	3 (60)	5 (100)	18 (47)
Withdrawn	4 (44)	10 (53)	2 (40)	0	16 (42)
Ongoing	2 (22)	2 (11)	0	0	4 (11)
Primary reason for study withdrawal[c]					
Adverse event	0	4 (21)	1 (20)	0	5 (13)
Lost to follow-up	0	2 (11)	0	0	2 (5)
Investigator discretion[d]	3 (33)	3 (16)	1 (20)	0	7 (18)
Withdrew consent	1 (11)	1 (5)	0	0	2 (5)

a. Subjects were considered as belonging to their treatment group at the start of Study AMB114588.
b. Subjects continued in the study until they reached 18 years of age.
c. Percentages were based on the number of subjects in the dose group.
d. Investigator discretion reasons: Enrolment to another study, precautionary due to toxicity concern (alert note relating to preclinical studies) – 2 subjects, to strengthen treatment, subject/parent did not wish to continue, subject/family situation interfering with ability to continue participation, and investigator decision (no further information reported).

The majority of subjects were female (66%) and the mean age of subjects in this study increased with each dose increment (9.7, 11.9, 12.6, and 15.2 years for subjects from the 2.5, 5, 7.5, and 10 mg dose groups, respectively). Most subjects were White/Caucasian/European heritage (27 subjects [71%]) or of Japanese origin (5 subjects [13%]). Approximately one third (32%) of subjects were of Hispanic/Latino ethnicity.

The majority of subjects entering this study (63%) had idiopathic aetiology at Study AMB112529 Baseline, with approximately 80% of all subjects receiving ongoing PAH therapy at start of ambrisentan treatment.

All subjects entered into this study were initially classified as WHO functional Class (FC) II or III at Study AMB112529 Baseline in accordance with the protocol requirements. At entry to this long-term extension study, approximately one-quarter (24%) of subjects were classified as WHO FC I (least severe status). The remainders of subjects were FC II or III at the Entry Visit with the exception of 1 subject with FC IV. Overall, the mean Baseline 6MWD test was 434.42 metres at Study AMB112529 Baseline and 479.70 metres at entry to this long-term extension study.

Exposure and compliance:
There were 4 subjects who remained ongoing in this long-term extension study at the time of the data cut-off date for the interim report; exposure data for these subjects is not yet complete and were not included in summaries of exposure for this report. The remaining 34 subjects, who had completed or withdrawn from the study at the time of the data cut-off, received at least 14 weeks of investigational product, with the longest duration of exposure among these 34 subjects being greater than 6 years. Efficacy and/or safety assessments were reported at or beyond Month 72 (6 years) and all were attributable to the 4 ongoing subjects, with 1 subject continuing to be assessed at 96 months (8 years). The overall percentage of visits at which a subject was compliant with investigational product was 97.8%.

Efficacy:
There were 5 subjects who had a clinical worsening resulting in death during this study, and the mean time to death (all-cause mortality) was over 3 years from the start of treatment in Study AMB112529. One additional subject who died was inadvertently not entered onto the electronic Case Report Form (eCRF) as a clinical worsening prior to site closure (as intended in accordance with Protocol, Section

6.3.3). Therefore, this subject was not included in the efficacy analysis of time to death but was included in safety summaries of fatal TEAEs.

For subjects who entered this long-term extension study, the mean (SD) 6MWD was lowest at Study AMB112529 Baseline for subjects from the 2.5 and 5 mg dose groups. At the Entry Visit to this study, a mean improvement from Baseline had been observed across all dose groups, with the largest improvement observed for subjects in the 2.5 mg group. Change from Baseline at the End of Study Visit showed a mean improvement for all dose groups. There were 4 subjects with assessments at 6 years (Month 72), decreasing to 2 subjects at 6.5 years and 1 subject at 8 years. However, substantial positive improvements from Baseline continued to be observed for these subjects whilst they remained in the study, with increased walking distance ranging from 130.0 to 235.5 metres (equating to a 26.75% to 56.00% improvement from Baseline).

Table 24 Results of 6MWD in extension study AMB114588 from baseline (start of 24-week study AMB112529) to entry visit (start of extension study AMB114588) and end of study (end of study AMB114588)

Walking Distance (m)	Ambrisentan Dose Group[h]				
	2.5 mg (N=9)	5 mg (N=19)	7.5 mg (N=5)	10 mg (N=5)	Total (N=38)
Baseline[i]					
n	9	19	5	5	38
Mean (SD)	393.32 (99.393)	433.96 (123.120)	484.56 (89.889)	460.0 (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
Change from Baseline to:					
Entry Visit[j]					
n	9	18	5	5	37
Mean (SD)	92.06 (106.229)	22.78 (67.095)	53.48 (98.387)	5.80 (48.200)	41.49 (83.536)
Median	75.00	26.50	40.00	27.00	32.00
Min to Max	-92.0 to 258.0	-110.0 to 162.0	-32.0 to 220.0	-60.0 to 46.0	-110.0 to 258.0
End of Study					
n	7	10	4	5	26
Mean (SD)	71.47 (117.363)	48.15 (53.344)	3.05 (94.659)	34.24 (72.135)	44.82 (82.115)
Median	55.50	54.50	-36.90	27.00	53.05
Min to Max	-81.6 to 282.0	-41.0 to 121.0	-58.0 to 144.0	-40.0 to 123.0	-81.6 to 282.0

Max=maximum; Min=minimum; n=number of subjects with data available; SD=standard deviation.
h. Subjects were considered as belonging to their treatment group at the start of Study AMB114588.
i. Baseline was the last value recorded prior to start of study treatment in Study AMB112529.
j. Entry Visit was value at entry to Study AMB114588.

Subgroup analysis of 6MWD by PAH aetiology in extension Study AMB114588

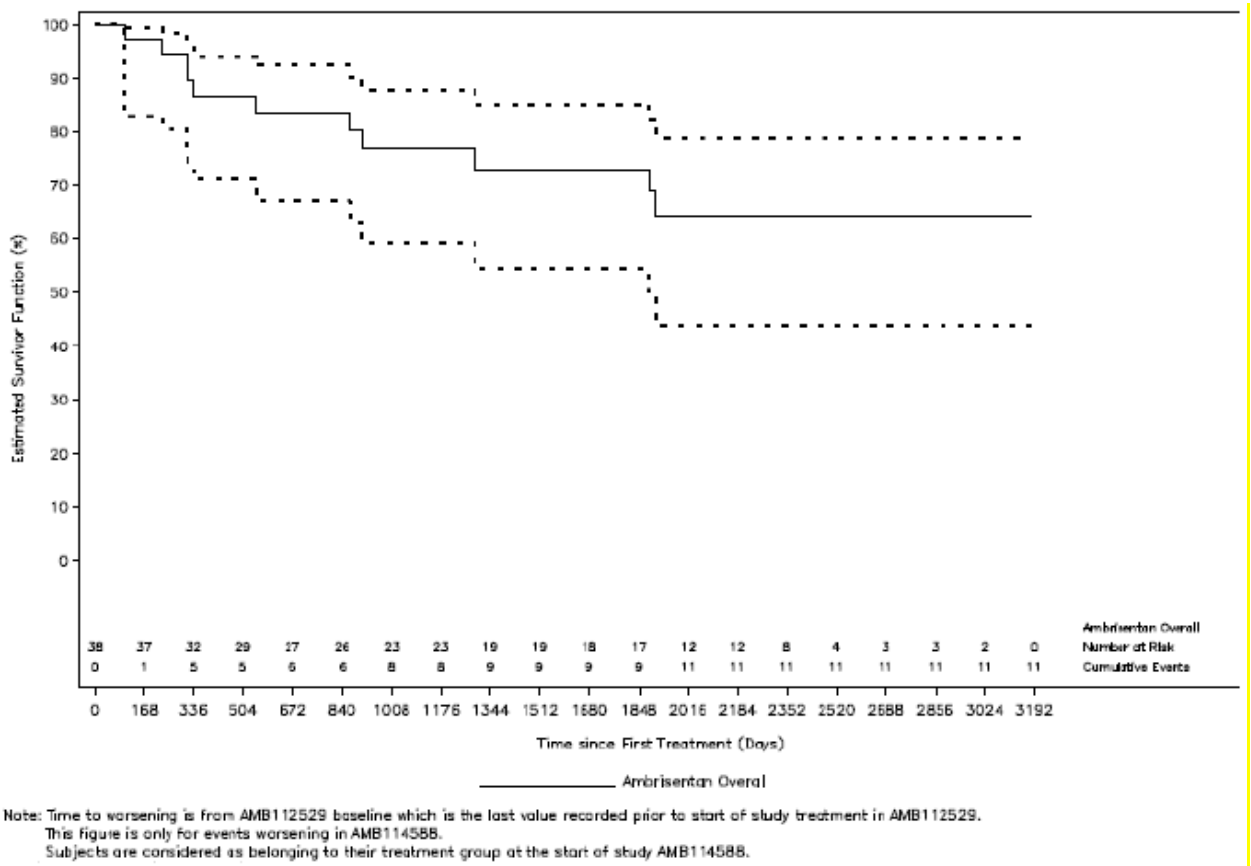
An ad-hoc analysis showed that more than half of subjects had an increase from baseline in 6MWD of ≥20 metres at Month 12 and at the last observation in Study AMB114588. Around half of the 24 subjects with idiopathic PAH had an increase from baseline in 6MWD of ≥20 metres at Month 12 and at the last observation, respectively. Of the 14 subjects with PAH aetiology other than idiopathic, more than half had an increase from baseline of ≥20 metres at Month 12 and at the last observation in Study AMB114588.

Clinical worsening: Overall, 11 of 38 subjects experienced clinical worsening according to at least one criterion with the most frequently reported reasons being death (5 subjects [13%]) and PAH-related

deterioration (4 subjects [11%]). 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 (315.5, 896.2, 1122.0, and 228.0 days, in the 2.5 mg, 5 mg, 7.5 mg, and 10 mg dose groups, respectively).

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 below).

Figure 11 Kaplan-Meier Survival Curves with 95% Confidence Bands of Time to First Clinical Worsening of PAH in Study AMB114588 (ITT Population)



Note: Time to worsening is from AMB112529 baseline which is the last value recorded prior to start of study treatment in AMB112529.
This figure is only for events worsening in AMB114588.
Subjects are considered as belonging to their treatment group at the start of study AMB114588.

Source: AMB114588 CSR Figure 2.4

Rescue with addition of other targeted PAH therapies: in total, approximately 45% of subjects had another targeted PAH therapeutic agent added to their treatment regimen during the study, of which 6 subjects were due to deterioration of their clinical condition, and 3 subjects were due to lack of beneficial effect with previous PAH therapy. The time to change in dose in ambrisentan or another targeted PAH therapeutic agent due to deterioration of clinical condition ranged from approximately 12 weeks to over 5 years.

Change in WHO FC: At the Entry Visit to this study, the majority of subjects had reported either the same WHO FC category or a shift that indicated improvement from Study AMB112529 Baseline, with 2 subjects reporting a worsening (one from a WHO FC category of II to III, the other from II to IV). At the End of Study Visit, all subjects reported no change or an improvement from Study AMB112529 Baseline in WHO FC with 1 subject shifted from Baseline by more than 1 category.

For the subjects who entered this long-term extension study, the geometric mean NT-proBNP concentration at Study AMB112529 Baseline was variable across subjects and dose groups which was also evident at the Entry Visit to this study. The geometric change from Baseline showed a mean

percentage decrease from Baseline across the lower dose groups (2.5 mg and 5 mg) at the End of Study Visit (65.66% and 35.5% decrease, respectively with corresponding percentage increases of 59.06% and 101.96% for the 7.5 mg and 10 mg groups, respectively).

Psychosocial summary scores: For subjects entering this long-term extension study, mean psychosocial summary scores at Study AMB112529 Baseline were similar across all dose groups with a numerically higher mean Study AMB112529 Baseline Physical Health score for subjects in the 2.5 mg dose group compared with all higher dose groups. Mean scores in the 2 domains remained stable at the Entry Visit and across this long-term extension study.

School days missed: summary statistics showed stability or improvement across all dose groups with regards to change from Study AMB112529 Baseline in school days missed which ranged from a 21-day improvement to no change (median value of 6 days reduction) at the End of Study Visit. Correspondingly, change in proportion of days missed due to PAH at End of Study ranged from a 100% improvement to no change.

Summary of main study

The following tables summarise the efficacy results from the main study supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 25 Summary of Efficacy for trial AMB112529

Title: A randomized, open label study comparing safety and efficacy parameters for a high and a low dose of ambrisentan (adjusted for body weight) for the treatment of pulmonary arterial hypertension in paediatric patients aged 8 years up to 18 years.			
Study identifier	AMB112529		
Design	Phase IIb. Open label, two dose groups, not comparative, not controlled with placebo or active treatment.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		24 weeks Not applicable ≈72 months (Study AMB114588; ongoing; Interim report Aug 2019)
Hypothesis	Exploratory: dose-finding for 6MWD and extrapolation exercise from adults.		
Treatments groups	Ambrisentan low dose		First week: 5 mg/d. Week 2 onwards: 5 mg for children of ≥35 kg, and 2.5 mg for children between ≥20 kg and <35 Kg.
	Ambrisentan high dose		First week: 5 mg/d. Week 2 onwards: 10 mg in children ≥50 kg, 7.5 mg in children between ≥35 kg and <50 Kg, and 5 mg in children between ≥20 kg and <35 Kg.
Endpoints and definitions	Primary efficacy endpoint	6MWD	Chance in 6MWD from baseline to week 24, ITT population
	Secondary efficacy endpoint	Clinical worsening	Subjetct with at least one criterion among: a) All-cause death or active list for lung transplant b) Hospitalisation for worsening of PAH c) PAH related deterioration: defined as increase from baseline in WHO functional class and/or clinical signs or symptoms of right sided heart failure
Database lock	Not available		
Results and Analysis			
Analysis description	**Primary Analysis**		

Analysis population and time point description	Intent to treat				
Descriptive statistics and estimate variability	Primary endpoint: Change in 6MWD from baseline to week 24	Comparison groups	Low dose N=18	High dose N = 18	Total N = 36
		Mean (SD)	55.14 (102.18)	26.25 (62.01)	40.69 (84.58)
		Median	49	25.5	32
		Min to Max	-110 to 258	-60 to 220	-110 to 258
	Secondary endpoint: Clinical worsening	Comparison groups	Low dose	High dose	Total
		N (%)	3 (14%)	3 (15%)	6 (15%)
Effect estimate per comparison	Exploratory, descriptive study. No effect estimate per comparison was planned.				

Analysis performed across trials (pooled analyses and meta-analysis)

The MAH has followed a request by the PDCO concerning a post-hoc extrapolation study in order to evaluate the efficacy in paediatric patients (8-18 years old) based on the variable change from baseline in 6MWD.

The MAH proposed the following analyses:

1) A frequentist analysis has been conducted to assess the appropriateness to treat all dosed patients from AMB112529 as a single combined dose group. The results are compared between the adult AMB112565 study and the paediatric AMB112529 study to ensure that the efficacy data is consistent between both trials. First, an ANCOVA analysis is performed on the primary endpoint where the missing data is imputed as 6MWD=0. Also, a MMRM was fitted to the paediatric study with an unstructured covariance structure. In addition, due to the imbalance in WHO FC score across the two doses in the paediatric data, two frequentist analyses were presented, one assuming balances classes in the population and the other assuming classes in the population proportional to the observed data.

2) A pooled analysis combines the results of 4 adult studies (AMB112565, AMB-220, AMB-320 and AMD-321) for the change from baseline in 6MWD with the assumption that the effect of ambrisentan on adults with PAH follows the same distribution between studies

3) For the primary bayesian analysis of the change in the 6MWD variable are considered two prior distribution; an informative prior with a full borrowing (weight = 1) from the adult study AMB112565 and a non-informative prior (weight = 0). Also, the MAH proposes a bayesian "dynamic borrowing" approach (Schmidli, 2014) and a tipping point analysis are shown in order to justify post-hoc how much weight should be chosen for the prior distribution according to the data observed from the paediatric and adult studies.

4) Lastly, as sensitivity analysis, a similar analysis for 3) performed using this time the 4 adult studies.

The results are strongly limited, and a statistical conclusion cannot be drawn from these analysis. Overall, the methods are endorsed as sensitivity analysis and no statistical conclusions should be made to justify the results since they are very limited, mainly for the small sample size, multiple dosing groups or lack of control arm.

For the analysis proposed in 1) and 2) the MAH suggests that there is no significant difference between the two dose groups due to the overlapping of both sets, but from a regulatory point of view, that suggestion cannot be shared considering the weak data analysed. The overlapping of the CI could be

product of the high variability of the data (among other reasons) due to the limitations explained above and no conclusions should be drawn.

With respect to 3) and 4) the MAH states that the results from the Bayesian analyses provide evidence of a significant increase in 6MWD in paediatric subjects after the PDCO requested an extrapolation study. The selection of the amount of data used for the prior distribution is essential and simulations of the operating characteristics showing adequate power with overall adequate type I error control must be provide beforehand to justify the weight selected. In this case, multiple weights have been tested *a posteriori* once the data is available to assess the minimal amount of data necessary to have a positive outcome (weight of 25%). Due to the numerous limitations, no statistical conclusions should be made on the consistency between the paediatric and adult data. This analysis can only be seen as exploratory and could be useful for future studies.

Clinical studies in special populations

N/A.

Supportive study(ies)

N/A.

2.6.6. Discussion on clinical efficacy

Design and conduct of clinical studies

This paediatric indication is based on the pivotal phase IIb Study AMB112529, which was a 6-month (24-week), randomised, open-label evaluation of the safety, tolerability, and efficacy of 2 doses of ambrisentan (Low and High, adjusted for body weight) in paediatric subjects aged 8 years up to 18 years with PAH. The dossier also includes the open-label extension study AMB114588, including 38 of the 41 children completing study AMB112529.

All children received a fixed dose of 5 mg during the first week of treatment in study AMB112529. At week 2 onwards, the ambrisentan low dose was defined as 5 mg for children of ≥35 kg, and 2.5 mg for children between ≥20 kg and <35 Kg. The ambrisentan high dose was defined as 10 mg in children ≥50 kg, 7.5 mg in children between ≥35 kg and <50 Kg, and 5 mg in children between ≥20 kg and <35 Kg. The sponsor provided commercially available ambrisentan 5 mg tablets, and 10 mg tablets as well as manufactured 2.5 mg tablets of equivalent quality.

The primary comparison stated in the AMB112529 protocol was to evaluate the safety and tolerability of the 2 ambrisentan dose groups (Low versus High) in the paediatric PAH population. The secondary comparison was change from Baseline in the efficacy parameters between the 2 dose groups. Because subject recruitment was limited by the low prevalence of the disease in children, powered clinical hypothesis tests were not planned. Sixty-six subjects constituted the selected sample size based on the predicted recruitment rate from historic data so that the study could be completed in a reasonable time frame (2 years) for it to be useful and informative to the medical community. A 10% drop out rate was anticipated to leave 60 evaluable subjects.

The study was stopped in March 2013 after 41 children (out of 60 planned) were recruited due to a nonclinical finding of brain weight decrease in juvenile rats with low clinical margins for human paediatric dose exposures. Further nonclinical investigations were conducted, and the findings submitted to CHMP in November 2017. Notification of the opinion of a proposed PIP modification submitted by the applicant was received from the EMA PDCO in February 2019 (EMEA-000434-PIP01-08-M05). The study was agreed to be closed and a reduction in number of subjects from the planned 66 subjects (for 60 evaluable) to 40 was accepted. Therefore, recruitment was not re-initiated, the

study was declared as terminated on 11 Feb 2019, and the unplanned interim analysis became the final analysis for this study (based on 41 subjects enrolled).

The study AMB114588 and its open-label extension (study AMB114588) lacked a control group and therefore the results are difficult to put into clinical context. A placebo comparison is unfeasible in children with PAH, and an active comparator is also challenging because of the need for a high sample size to allow for demonstration of superiority or non-inferiority in a clinical context in which combination therapy is currently the standard practice.

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. The analysis used imputed data for the primary endpoint, where the worst-case scenario was imputed as 6MWD=0 for missing data following death or hospitalization, and the traditional LOCF imputation was used in all other scenarios.

In addition, a separate Bayesian analysis of data from the 6MWD from Study AMB112529 was performed. A meta-analysis to check consistency between the effects on 6MWD in adults and children was conducted. 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 exposure-response (ER) model relating ambrisentan PK to change from baseline in 6MWD.

Efficacy data and additional analyses

In pivotal phase IIb study AMB112529, in 41 children aged 8 to 17 years, Over the 24-week Treatment Period there was evidence of an improvement in exercise capacity (6MWD), but there was no dose trend in the effect of ambrisentan on this endpoint. The mean change from baseline at Week 24 in 6MWD for patients in the low and high dose groups was +55.14 metres and +26.25 metres, respectively. In subgroup analyses, the change from baseline in 6MWD at Week 24 was similar between the dose groups in paediatric subjects in the 12-18 age category but was higher in the Low dose group compared with the high dose group in the 8-11 age category. An ad hoc analysis showed that 24 subjects (59%) had an increase from baseline in 6MWD of ≥20 metres at Week 12 and Week 24 in Study AMB112529 and these were fairly evenly distributed across the idiopathic subgroup (15 of 27; 56%) and non-idiopathic subgroup (9 of 14; 64%).

Regarding secondary endpoints, there were also positive shifts in WHO functional class. At Week 24, 95% and 100% of patients in the low and high dose groups, respectively, remained stable (no change or improved functional class). The number of paediatric subjects with clinical worsening of PAH was small in both dose groups (3 in each dose group). One patient died in the low dose group due to worsening of PAH. The Kaplan-Meier event-free survivor estimate for worsening of PAH (death [all cause], lung transplantation, or hospitalisation for PAH worsening or PAH-related deterioration) at 24 weeks was 86% and 85% in the low- and high dose groups, respectively. Haemodynamics were measured in 5 patients (low dose group). There were also positive effects in haemodynamics: mean increase from baseline in cardiac index was +0.94 L/min/m^2, the mean decrease in mean pulmonary arterial pressure was -2.2 mmHg, and the mean decrease in PVR was -3.46 mmHg/L/min. In addition, these efficacy findings were also supported by a small mean decrease in NT-proBNP over the 24-week Treatment Period. Geometric mean decrease from baseline in NT-pro-BNP was 31% in the low dose group (2.5 and 5 mg) and 28% in the high dose group (5, 7.5, and 10 mg). Change from Baseline in Physical and Psychosocial summary scores, as measured by the SF-10 health survey, remained generally stable across the 24-week Treatment Period in this study.

Volibris is currently approved for treatment idiopathic PAH (IPAH) and PAH associated with connective tissue disease in adults only. The indication proposed by the Applicant in this application contains above that indications of familial PAH and corrected congenital PAH in paediatric population. A discussion regarding the addition of these two latter PAH aetiologies in the indications was provided by

the applicant. The Applicant also provided a discussion regarding extrapolation of ambrisentan efficacy from approved adults indications IPAH and PAH associated in connective tissue disease. A similar exposure was demonstrated between children > 8yrs and adults and a similar PK/PD. In addition, a similar shallow PK-PD relationship was confirmed between adults and paediatric subjects >8yrs with PAH, which is consistent with the expected similarity in PAH disease progression between these two populations. Therefore, the extrapolation from the adult indication for IPAH and PAH associated with connective tissue disease is accepted.

The applicant provided further effectiveness and safety data in children with familial PAH and corrected congenital PAH from literature and a Japanese post-marketing study (study 114782) in 119 children with PAH. These data were deemed sufficient to conclude that ambrisentan may be used in the range of PAH aetiologies included in the proposed paediatric indication.

The applicant also provided a subgroup analyses study AMB112529 for the primary endpoint in order to explore the consistency of the treatment effect in important patients subsets mentioned in the indication: single treatment vs. combination treatment; idiopathic PAH vs. other aetiologies; functional class II versus class III-IV; age < 12 vs. ≥ 12 years. The results were consistent in most subgroups analysed.

The applicant did not plan a statistical comparison of the change in 6MWD at week 24 versus baseline values. As a result, it was difficult to interpret whether the 55.14 m improvement in the low dose group or the 40.69 metres improvement in the overall population after 24 weeks is statistically significant compared to baseline values. The applicant provided the results on 6MWD (improvement versus baseline) by dose group and as well for the total study population, in terms of mean and median metres of change in 6MWD with 95%CI. These data have been included in section 5.1 of the SmPC.

A comparison versus putative placebo was requested from the applicant. From the limited studies that do have placebo information for change from Baseline in 6MWD (SERAPHIN study in adults), there is consistent evidence of a mean/median reduction in 6MWD across a 6-month period (with approximate magnitude of 8 to 15 metres) compared with an increased 6MWD for active treatments. Data from the most closely matching study in the literature (SERAPHIN study) has allowed the applicant to provide an overall estimated treatment effect of 50.09 m (95% CI: 15.43, 84.75) for study AMB112529, which suggests superiority in favour of ambrisentan treatment.

In addition, the applicant conducted a bibliographic search to discuss published studies with ambrisentan in children, and compared these results to those obtained in the study AMB112529 and its extension, in terms of studied populations (i.e.: age ranges, PAH aetiology, FC, concomitant PAH therapies) and results (i.e.: change in 6MWD, clinical worsening, change in FC). These bibliographic references are supportive of the effectiveness of ambrisentan in various PAH aetiologies. A Japanese PMS study did include 7 subjects identified as having a familial aetiology. In the said PMS study, the majority had an aetiology of CHD (68.6%). Although 6MWD were not available in this subset, there was a notable improvement in WHO Functional Class in this subset, as well as evidence of improvement in biomarkers (NTproBNP) and in haemodynamics (mPAP, PAWP and CO).

There appears not to be a dose-response relationship in 6MWD and other secondary efficacy endpoints. In fact, most clinical outcomes, with few exceptions, show a better effect for the low-dosing regime compared with the high-dose regime. The applicant was invited to discuss about the lack of dose-response. The Company answered that adult systemic exposure was found to be predictive of exposures in paediatric subjects from 8 to less than 18 years of age in Study AMB112529 thereby supporting bridging of dose/exposure-dependent pharmacology between the two populations. Based on the extrapolation of exposure and response from adults to paediatric subjects with PAH, the proposed dose recommendation for paediatric subjects is primarily based on providing systemic exposure in the same range to adults with PAH, and consistent with the current dose recommendation for titration in adult subjects with PAH adjusted for body weight. The explanation was considered acceptable and therefore, the recommendation included in section 4.2 regarding uptitration according to clinical response and tolerability can be maintained.

Looking at baseline NT-ProBNP concentrations it seems that randomisation was not successful, with more children in the high dose groups having characteristics of a more severe disease and/or a better background treatment indicating less room for improvement compared with the low dose group. For example, more children in the high dose group were on FCIII compared to the low dose group (6 vs. 3) and patients in the high dose group had higher mean NT-ProBNP levels than those randomised to the low ambrisentan dose, indicating a worse cardiac function in patients randomised to the high ambrisentan dose. In addition, there was also a significant imbalance in the number of non-white, non-European subjects, with more of these subjects been enrolled in the low-dose group compared to the high-dose group (10 vs. 1), and therefore the better outcome in the low dose group could be related to a suboptimal background therapy in non-European subjects (10 of 11 non-white non-European children fall in the low dose group). These baseline imbalances could explain to some extent the lack of dose-response in efficacy. Whether these imbalances may have led to the lack of demonstration of a dose-response (i.e.: no better results on 6MWD with the high dose compared to the low dose) cannot be confirmed or ruled out. In addition, few patients received rescue medications or change in concomitant cardiovascular medications. This information was provided by the applicant. The introduction of rescue medications or change in concomitant cardiovascular medications does not appear to have influenced the assessment of the main outcome of 6MWD.

Finally, study AMB112529 was stopped in 2013 due to nonclinical findings. The applicant was requested to discuss whether the study results are representative of current management of PAH in 2020. The applicant submitted the results of a consultation with PAH experts and a literature review to support the external validity of study AMB112529, as this pivotal study for the application was stopped in 2013 and PAH treatment approach has changed overtime. The consensus comments provided by the experts consulted were the following: a) Regarding demographics, the ambrisentan paediatric study AMB112529 can be considered representative. The demographics of paediatric PAH have not changed in a way that would affect generalizability of the ambrisentan paediatric data over the past decade; b) The majority of subjects in AMB112529 were of IPAH aetiology, and familial PAH is usually analysed with the IPAH group. The CHD population is representative as a percentage compared to what is reported in paediatric and adult studies. It is notable that having 4 CTD patients is quite a high percentage in this study compared to the rarity of this condition as reported in ongoing paediatric registries; c) Combination therapy is commonly used in current practice for paediatric PAH patients, and the fact that 2/3rds of the population in the ambrisentan trials were on combination therapy only increases the generalizability of the data. Newer agents like selexipag and orenitram are rarely used outside of ongoing studies (although being used more frequently off-label) and therefore do not impact the external validity of the ambrisentan data.

In addition, a literature review conducted by the applicant, including 10 references of contemporary PAH studies, also supports the representative nature of the AMB112529 data to the current management of paediatric subjects with PAH. As noted in the comments made by the IDMC and Expert Consultants, the use of targeted PAH medications in the majority of subjects in the trial is an important factor in defining the relevance of the study results to current practice.

A total of 38 of 41 patients recruited in study AMB112529 entered the long-term extension study AMB114588. There was no further improvement in exercise capacity from start of study AMB112529 to end of study. In the overall patients the improvement was of only 3 metres (from 41.49 metres at the entry visit to 44.82 metres at end of study). These data can be interpreted as that the improvement observed during the 24-week study was maintained during the extension study. However, about half of the study population (45%) needed the addition of other PAH therapies due to deterioration or insufficient response. Anyway, extension data are difficult to interpret due to important methodological limitations like small sample size, multiple dosing subgroups (2.5 mg, 5 mg, 7.5 mg and 10 mg for a total of only 38 children), lack of control group and heterogeneous follow up (between 3 months to over 5 years). No data of end of study visit were provided (mean follow-up for these 6MWD values were not provided). In addition, from entry visit in the extension study to end of study visit there was a deterioration of 6MWD in some dosing groups (2.5 mg: from 92.06 at entry visit to 71.47 metres at end of study; i.e.: 21 m deterioration; 7.5 mg: from 53.48 m at entry visit to 3.05 m at end of study; i.e.: 50 m deterioration). The interpretation of these results is hampered by the low number of subjects by dosing group (i.e.: 9 children in the 2.5 mg subgroup and 5 children in the 7.5 mg

subgroup). Overall, 11 of 38 subjects (29%) experienced clinical worsening during the extension study AMB114588 according to at least one criterion with the most frequently reported reasons being death (5 subjects [13%]) and PAH-related deterioration (4 subjects [11%]). The Kaplan-Meier analysis showed most events occurred within 3 years of Study AMB112529 Baseline. All deaths reported in Study AMB114588 were due to events associated with the natural progression profile and known characteristics of children with PAH disease, with a mean time to death of over 3 years from treatment initiation. None of the deaths were considered related to ambrisentan. The time to first clinical worsening of PAH was variable across subjects and dose groups and ranged from approximately 100 days to over 5 years. NT-proBNP values were variable across the duration of the long-term extension Study AMB114588 there was evidence of a small mean decrease from Study AMB112529 Baseline at the End of Study Visit. Change from Baseline in Physical and Psychosocial summary scores, as measured by the SF-10 health survey, remained generally stable across the duration of long-term Study AMB114588. In summary, the extension study AMB114588 showed that 71% of children remained clinically stable on treatment without deterioration, while about 29% of children had deterioration despite the addition of other target PAH therapeutic agents. In the absence of a control group no firm conclusions can be made, but anyway the results are consistent with the natural progression of the PAH disease.

A Bayesian extrapolation analysis conducted by the applicant suggest that the increases in 6MWD by 26.25 m to 55.14 metres from baseline to week 24 in the high and low dose groups in children is consistent to those reported with ambrisentan in placebo-controlled trials in adults. However, the extrapolation has a number of major limitations. First of all, all the results are strongly limited, and a statistical conclusion cannot be drawn from these analysis. Overall, the methods are endorsed as sensitivity analysis and no statistical conclusions should be made to justify the results since they are very limited, mainly for the small sample size, multiple dosing groups or lack of control arm. The MAH suggests that there is no significant difference between the two ambrisentan dose groups due to the overlapping of both sets, but from a regulatory point of view, that suggestion cannot be shared considering the weak data analysed. The overlapping of the CI could be product of the high variability of the data (among other reasons) due to the limitations explained above and no conclusions should be drawn. The MAH also states that the results from the Bayesian analyses provide evidence of a significant increase in 6MWD in paediatric subjects after the PDCO requested an extrapolation study. The selection of the amount of data used for the prior distribution is essential and simulations of the operating characteristics showing adequate power with overall adequate type I error control were to be provided beforehand to justify the weight selected. In this case, multiple weights have been tested *a posteriori* once the data is available to assess the minimal amount of data necessary to have a positive outcome (weight of 25%). Due to the numerous limitations, it only should be seen as exploratory and it could be useful for future studies. The CHMP requested additional clarification of aspects of the meta-analysis and Bayesian analysis. In this respect, the Applicant was asked to thoroughly justify why meta-analysis was not performed also for dose 5 mg. The most important adult study AMB112565 from the Applicant's point of view includes only dose 10 mg for ambrisentan. Thus, comparison to paediatric study AMB112529 can be performed only with respect to dose 10 mg. Moreover, both studies have the same treatment period of 24 weeks. Thus, information from study AMB112565 for comparison with study AMB112529 with respect to endpoint 6-minute walk distance is the most relevant. This was considered acceptable.

Considering only pooled data, (data both from dose 5 mg and dose 10 mg) for Bayesian sensitivity analysis can be problematic. In this case, information about individual doses is lost. The Applicant was asked to discuss bias of results in comparison to Bayesian sensitivity analysis which would be performed separately for dose 5 mg and separately for dose 10 mg. The Applicant clarified that they performed meta-analysis based on studies including data for dose 5 mg and data for dose 10 mg, respectively. Studies using dose 5 mg (AMB-220, AMB-320 and AMB-321) gave summary effect for mean change from baseline in 6-minute walk distance (6MWD) 37.2 metres with standard error (SE) 6.13 metres. This result can be related to change from baseline to week 12 as all studies investigate 12-week treatment period. Studies using dose 10 mg (AMB112565, AMB-220 and AMB-320) gave summary effect for mean change from baseline in 6MWD 30.2 metres with SE 4.43 metres. This result cannot be clearly related to change from baseline in 6MWD to any fixed time point as study

AMB112565 investigates 24-week treatment period and studies AMB-220, AMB-320 investigate 12-week treatment period. If both doses are combined, then mean change from baseline in 6MWD is 32.6 metres with SE 3.59 metres. This is comparable with results for dose 10 mg alone due to statistical insignificance with combined dose. Thus, combined dose was used for Bayesian sensitivity analysis. The Applicant further justified combination of doses by comparison of mean change from baseline in 6MWD in 3 adult studies with dose 5 mg with mean change from baseline in 6MWD in 3 adult studies with dose 10 mg. Resulting 95% confidence interval for difference in mean change from baseline in 6MWD between dose 5 mg and dose 10 mg is (-7.82, 21.82) metres. This is a biased comparison as length of treatment periods differ for dose 10 mg and comparison with dose 5 mg is disputable. Overall, the primary Bayesian analysis led to an acceptable result. In this case, both adult study AMB112565 and paediatric study AMB112529 had 24-week treatment period. Further, not so much prior weight was given to data from adult study (weight 0.25) in mixture of prior distribution for adult data with prior distribution for paediatric data to conclude statistically significant increase in 6MWD in paediatric patients treated with ambrisentan. The issue was considered as resolved.

Additional expert consultation

N/A.

2.6.1. Conclusions on the clinical efficacy

Efficacy data supporting this paediatric indication for ambrisentan is mainly composed by study AMB112529, which was a 6-month (24-week), randomised, phase IIb, open-label evaluation of the safety, tolerability, and efficacy of 2 doses of ambrisentan (Low and High, adjusted for body weight) in paediatric subjects aged 8 years up to 18 years with PAH.

The study planned to include 60 subjects but was stopped in March 2013, after 41 children were recruited, due to a nonclinical finding of brain weight decrease in juvenile rats with low clinical margins for human paediatric dose exposures. Further nonclinical investigations were conducted, and the findings submitted to CHMP in November 2017.

All children received a fixed dose of 5 mg during the first week of treatment. At week 2 onwards, the ambrisentan low dose was defined as 5 mg for children of ≥ 35 kg, and 2.5 mg for children between ≥ 20 kg and <35 Kg. The ambrisentan high dose was defined as 10 mg in children ≥50 kg, 7.5 mg in children between ≥35 kg and <50 Kg, and 5 mg in children between ≥20 kg and <35 Kg. The sponsor provided commercially available ambrisentan 5 mg tablets, and 10 mg tablets as well as manufactured 2.5 mg tablets of equivalent quality.

The study showed an improvement in exercise capacity in children treated with ambrisentan at 24 weeks compared with baseline values and some positive shifts in FC and haemodynamic secondary endpoints. The sponsor did not plan a statistical comparison of the change in 6MWD at week 24 versus baseline values, which is unfortunate. As a result, it was difficult to interpret whether the 55.14 m improvement observed in the low dose group or the 40.69 metres improvement reported in the overall population after 24 weeks is statistically significant compared to baseline values. The applicant provided the results on 6MWD (improvement versus baseline) by dose group and well as for the total study population, in terms of mean and median metres of change in 6MWD with 95%CI. These data have been included in section 5.1 of the SmPC.

The number of paediatric subjects with clinical worsening of PAH was small in both dose groups (3 in each dose group). In the absence of a control group no firm conclusions can be made, but anyway the results are consistent with the natural progression of the PAH disease.

A total of 38 of 41 patients recruited in study AMB112529 entered the long-term extension study AMB114588. There was no further improvement in exercise capacity from start of study AMB112529 to end of study. In the overall patients the improvement was of only 3 metres (from 41.49 metres at the

entry visit to 44.82 metres at end of study). These data can be interpreted as that the improvement observed during the 24-week study was maintained during the extension study. However, about half of the study population needed the addition of other PAH therapies due to deterioration or insufficient response.

A Bayesian extrapolation analysis conducted by the applicant suggest that the increases in 6MWD by 26.25 m to 55.14 metres from baseline to week 24 in the high and low dose groups in children is consistent to those reported with ambrisentan in placebo-controlled trials in adults.

Despite limitations of studies presented, ambrisentan is expected to provide benefit in treating children also with PAH associated with CHD and familial PAH. It is acknowledged that due to rare nature of the disease, the data regarding the familial and corrected congenital PAH are limited. From data presented the main support of the broader indication comes from the subgroup analysis of study AMB112529, which are supported by additional data provided from literature reference and a post-marketing authorization study in Japan in children with PAH of various PAH aetiologies (n=119). A description of the types of "corrected congenital" heart defects reported in the 11 children with CHD in the AMB112529 study are included in the SmPC, in order to better describe target population with corrected congenital PAH**.**

2.6.2. Clinical safety

Patient exposure

In the present application all clinical studies contributing to support the safety information from children and adolescents aged 8 to less than 18 years were study AMB112529 and its extension study AMB114588.

Overall Extent of Exposure

The ITT efficacy population was the same than the Safety population. Please see Efficacy section.

Study AMB112529

Exposure to ambrisentan ranged from 53 to 184 days, with a median duration of 169 days (24.1 weeks) in the low dose group (n=21). Exposure to ambrisentan ranged from 17 to 190 days, with a median duration of 171 days (24.4 weeks) in the high dose group (n=20).

At least 94% of subjects in each dose group were treatment-compliant (defined as receiving ≥80% and ≤120% of planned study treatment) at all visits. The overall percentage of visits at which a subject was compliant was 98.5%.

All 41 subjects received at least 2 weeks of ambrisentan and 37 subjects (90%) completed the planned treatment period of 24 weeks.

Extension study AMB114588

Overall, exposure to ambrisentan ranged from 100 to 2,346 days (14.3 to 335.1 weeks), with a median duration of 1,263 days (176.6 weeks) (Table 26). The median duration of exposure to ambrisentan was comparable across dose groups. More than half of the subjects received ambrisentan treatment for at least 3 years and the longest cumulative* duration of treatment was greater than 6.6 years.

(*Note: this represents combined exposure to ambrisentan for Study AMB112529 and the extension study.)

At the time of data cut-off date (23 August 2019) for the interim analysis, 4 ongoing subjects in the extension study were excluded from analysis of the exposure data since the data were not yet complete. Therefore, the exposure data presented in this section are for 34 subjects. With the exception of exposure data, all 4 ongoing subjects were included in the safety analysis.

Table 26 Summary of Exposure to Ambrisentan, Study AMB114588 (Safety Population)

	Ambrisentan[1]				
Exposure Days	2.5 mg N=4	5 mg N=16	7.5 mg N=6	10 mg N=12	Total N=38
n	3	15	6	10	34
Mean±SD	1177.3±734.13	1170.5±747.67	1278.2± 674.77	1335.1±589.72	1238.5±662.73
Median	1291.0	1260.0	1321.0	1256.5	1263.0
Min to max	393 to 1848	100 to 2346	476 to 2106	440 to 2230	100 to 2346

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

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. 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%).

Demographic Characteristics

For further details, please see efficacy section.

PAH History

Patients who entered at study AMB114588 were diagnosed with IPAH (24/38 subjects [63%]), persistent PAH despite surgical repair (8/38 subjects [21%]), connective PAH (4/38 subjects [11%]) or familial PAH (2/38 subjects [5%]).

Ongoing Background PAH Therapy

Overall, 68% of subjects (26/) from study AMB114588 had at least one ongoing background PAH medication at entry to the extension study: use of a PDE-5 inhibitor as monotherapy (mainly sildenafil) was recorded in 17 subjects (45%); the PDE-5 inhibitor in combination with a prostanoid were used in 8 subjects (21%) and all were in the lower dose groups (2.5 mg and 5 mg).

Adverse events

Adverse events (AEs) from study AMB112529 and its ongoing long-term extension study AMB114588 were categorized by treatment period based on time of occurrence.

Treatment-emergent AEs were defined in the study AMB112529 as events that started on or after first dose date of study treatment, whereas in the study AMB114588 they were defined as either events starting in the extension study or events starting in study AMB112529 and continuing into the extension study. As the number of subjects in each dose group of study AMB114588 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.

Baseline values (collected prior to the first dose of ambrisentan) recorded in study AMB112529 were also the baseline values for the extension study.

Treatment-Emergent Common AEs

Study AMB112529

The majority of subjects reported at least 1 treatment-emergent AE and the majority were mild (22%) or moderate (49%) in intensity. The incidence observed was similar in both dose groups (81% in the low dose group and 80% in the high dose group) (Table 27).

The most frequently reported treatment-emergent AE in both dose groups was headache (6 subjects [30%] in the high dose group and 4 subjects [19%] in the low dose group).

The overall incidence of AEs during the first 2 weeks of treatment was 57% in the low dose group and 35% in the high dose group. The most common AEs during the first 2 weeks of treatment were headache for both dose groups (4, 19% of subjects in the low dose group and 5, 25% in the high dose group). The first occurrence of treatment-emergent AEs for all subjects were within 8 weeks of starting ambrisentan treatment in the low dose group and within 16 weeks in the high dose group.

SOCs with the highest incidence of treatment-emergent AEs were those relating gastrointestinal (GI) disorders and infections and infestations for both dose groups.

Table 27 Treatment-Emergent AEs Occurring in >1 Subject in any Dose Group, Study AMB112529 (Safety Population)

	Ambrisentan		
Preferred Term, n (%)	Low Dose N=21	High Dose N=20	Total N=41
Any event	17 (81)	16 (80)	33 (80)
Headache	4 (19)	6 (30)	10 (24)
Nausea	4 (19)	3 (15)	7 (17)
Abdominal pain	4 (19)	1 (5)	5 (12)
Abdominal pain upper	3 (14)	2 (10)	5 (12)
Nasopharyngitis	3 (14)	2 (10)	5 (12)
Pneumonia	3 (14)	0	3 (7)
Upper respiratory tract infection	3 (14)	1 (5)	4 (10)
Diarrhoea	2 (10)	0	2 (5)
Gastroenteritis	2 (10)	1 (5)	3 (7)
Nasal congestion	2 (10)	2 (10)	4 (10)
Oedema peripheral	2 (10)	1 (5)	3 (7)
Pain in extremity	2 (10)	1 (5)	3 (7)
Pharyngitis	2 (10)	1 (5)	3 (7)
Pyrexia	2 (10)	1 (5)	3 (7)
Vomiting	2 (10)	0	2 (5)
Back pain	1 (5)	2 (10)	3 (7)
Erythema	1 (5)	2 (10)	3 (7)
Face oedema	1 (5)	2 (10)	3 (7)
Laryngitis	0	2 (10)	2 (5)

Low dose: 2.5 mg (body weight ≥20 kg and <35 kg); 5 mg (≥35 kg).
High dose: 5 mg (body weight ≥20 kg and <35 kg); 7.5 mg (≥35 kg and <50 kg); 10 mg (≥50 kg).

Extension study AMB114588

Overall, 89% of subjects reported at least 1 treatment-emergent AE and the majority were mild (21%) or moderate (37%) in intensity. The lowest incidence (81%) was observed in the 5 mg group (Table 28).

The most frequently reported treatment-emergent AE for overall subjects was upper respiratory tract infection (10 subjects, 26%) followed by nasopharyngitis (9 subjects, 24%).

The overall incidences of first occurrence AEs were reported in 23 subjects (61%) for the first year of the study, 76% of subjects (29) for year 2, 82% of subjects (31) for year 3, and 87%-89% of subjects (33-34) from year 4 through year 8. The most common AE during the first year of the study was headache (5 subjects, 13%).

SOCs with the highest incidence of treatment-emergent AEs were those relating Infections and Infestations (61%) for all dose groups.

Table 28 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)	3 (50)	2 (17)	10 (26)
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)

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 Relationship to Ambrisentan

A drug-related AE was an event recorded by the investigator as having a reasonable possibility of being caused by the treatment with ambrisentan.

Study AMB112529

The overall incidence of drug-related AEs was 38% in the low dose group and 35% in the high dose group (Table 29). Headache was the most frequently reported drug-related AE for both dose groups (3 each). The drug-related AEs reported in more than 1 subject were nasal congestion and oedema peripheral in the low dose group and nausea in the high dose group.

Table 29 Drug-Related Treatment-Emergent AEs, Study AMB112529 (Safety Population)

Preferred Term, n (%)	Ambrisentan		
	Low Dose N=21	High Dose N=20	Total N=41
Any event	8 (38)	7 (35)	15 (37)
Headache	3 (14)	3 (15)	6 (15)
Nasal congestion	2 (10)	1 (5)	3 (%)
Oedema peripheral	2 (10)	0	2 (5)
Angioedema	1 (5)	0	1 (2)
Cardiac failure congestive	1 (5)	0	1 (2)
Dyspnoea exertional	1 (5)	0	1 (2)
Eosinophilia	1 (5)	0	1 (2)
Exercise tolerance decreased	1 (5)	0	1 (2)
Faeces pale	1 (5)	0	1 (2)
Face oedema	1 (5)	1 (5)	2 (5)
Fatigue	1 (5)	1 (5)	2 (5)
General physical health deterioration	1 (5)	0	1 (2)
Hot flush	1 (5)	0	1 (2)
Hypotension	1 (5)	0	1 (2)
Iron deficiency	1 (5)	0	1 (2)
Palpitations	1 (5)	1 (5)	2 (5)
Pericardial effusion	1 (5)	0	1 (2)
Stress	1 (5)	0	1 (2)
Vomiting	1 (5)	0	1 (2)
Abdominal pain upper	0	1 (5)	1 (2)
Back pain	0	1 (5)	1 (2)
Dry mouth	0	1 (5)	1 (2)
Erythema	0	1 (5)	1 (2)
International normalised ratio increased	0	1 (5)	1 (2)
Lymphopenia	0	1 (5)	1 (2)
Nausea	0	2 (10)	2 (5)

Low dose: 2.5 mg (body weight ≥20 kg and <35 kg); 5 mg (≥35 kg).
High dose: 5 mg (body weight ≥20 kg and <35 kg); 7.5 mg (≥35 kg and <50 kg); 10 mg (≥50 kg).

Extension study AMB114588

The overall incidence of drug-related AEs was 39% (Table 30. Drug-related AEs which occurred in more than 1 subject were headache (3), anaemia, and gastroenteritis (2 each).

Table 30 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)
Nasopharyngitis0	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)

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.

Other Significant Adverse Events

The events of anaemia, hepatoxicity, hypersensitivity, hypotension, male infertility, and oedema/fluid retention were specified as Adverse Events of Special Interest (AESIs) for both studies.

Study AMB112529

Treatment-emergent AESIs were reported in 6 subjects (with 8 events) in the low dose group and in 3 subjects (with 3 events) in the high dese group (Table 31). With the exceptions of anaemia and hypotension (1 each in the low dose group), all events were oedema-related events. Regardless of dose groups, AESIs reported in more than 1 subject were oedema peripheral and face oedema (3 each), which occurred within the first 16 weeks and first 8 weeks, respectively.

Six AESIs were considered by the investigator to be related to ambrisentan treatment: 4 events (oedema peripheral, face oedema, angioedema, hypotension) in the low dose group; 2 events (oedema peripheral and face oedema) in the high dose group.

No AESIs led to permanent discontinuation of ambrisentan treatment or withdrawal from the study.

Table 31 Treatment-Emergent Adverse Events of Special Interest, Study AMB112529 (Safety Population)

	Ambrisentan		
Preferred Term, n (%)	Low Dose N=21	High Dose N=20	Total N=41
Any event	6 (29)	3 (15)	9 (22)
Oedema peripheral[1]	2 (10)	1 (5)	3 (7)
Anaemia	1 (5)	0	1 (2)
Angioedema[2]	1 (5)	0	1 (2)
Eyelid oedema	1 (5)	0	1 (2)
Face oedema[1]	1 (5)	2 (10)	3 (7)
Hypotension[2]	1 (5)	0	1 (2)
Periorbital oedema	1 (5)	0	1 (2)

1. Two drug-related events (1 in each dose group).
2. A subject had drug-related events of angioedema and hypotension.
Low dose: 2.5 mg (body weight ≥20 kg and <35 kg); 5 mg (≥35 kg).
High dose: 5 mg (body weight ≥20 kg and <35 kg); 7.5 mg (≥35 kg and <50 kg); 10 mg (≥50 kg).

Extension 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 32).

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.

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 8 events. One subject had events of localised oedema, ascites, and angioedema. Events of 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. One subject had an SAE of ALT increased 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

A severe AE of hepatomegaly was reported, 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.

The majority of AESIs were resolved. There was no correlation between the time on treatment and the first occurrence of an AESI.

Table 32 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)

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 Age in Study AMB112529

A total of 14 subjects aged 8-11 years (7 in each dose group) and 27 subjects aged 12 to <18 years (14 in the low dose group and 13 in the high dose group) were enrolled in Study AMB112529. Treatment-emergent AEs that occurred in those subjects were analysed by age.

- *Treatment-Emergent Common AEs*

In the 8-11 years age stratum, the majority of subjects reported at least 1 treatment-emergent AE: 71% of subjects (5) in the low dose group and 57% of subjects (4) in the high dose group. AEs that occurred in more than 1 subject were abdominal pain, pharyngitis, and vomiting (2 subjects each) in the low dose group and none were reported in the high dose group.

In the 12 to <18 years age stratum, treatment-emergent AEs were reported in 86% of subjects in the low dose group and 92% of subjects in the high dose group.

Abdominal pain upper, headache, and nausea were the most frequently reported AEs in the low dose group (3 subjects each). Headache was the most frequently reported AE in the high dose group (6 subjects).

- *Treatment-Emergent AEs by Relationship to Ambrisentan*

In the 8-11 years age stratum, 3 treatment-emergent AEs (eosinophilia, vomiting, and headache) in 2 subjects in the low dose group and an AE of lymphopenia in 1 subject in the high dose group were considered by the investigator to be related to ambrisentan treatment.

In the 12-18 years age stratum, treatment-emergent AEs that were considered by the investigator to be related to ambrisentan treatment were reported in 6 subjects in each dose group. Drug-related AEs of oedema peripheral, headache, and nasal congestion were reported in 2 subjects each in the low dose group. Headache was the most frequently reported drug-related AE in the high dose group (3 subjects).

- *SAEs*

In the 8-11 years age stratum, treatment-emergent SAEs were reported in 3 low dose subjects (device breakage, pharyngitis, and syncope) and in 2 high dose subjects with 3 events (acute cardiac failure, right ventricular failure, and device related infection).

In the 12 to <18 years stratum, 3 subjects in the low dose group reported treatment-emergent SAEs of general physical health deterioration, pneumonia, and pulmonary hypertension. No SAE was reported in the high dose group.

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

One subject (12 to <18 years year-old) in the low dose group had an SAE of pneumonia that led to withdrawal from the study. The subject died due to pneumonia.

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. Numbers of subjects in each dose group in the 8-11 years age stratum in the Safety Population were 4, 7, and 3 in the 2.5 mg, 5 mg, and 10 mg groups*, respectively. Numbers of subjects in each dose group in the 12 to <18 years age stratum in the Safety Population were 9, 6, and 9 in the 5 mg, 7.5 mg, and 10 mg groups**, respectively. Treatment-emergent AEs that occurred in those subjects were analysed by age.

(*Note: No subject was in the 7.5 mg group in the 8-11 years age stratum.

**Note: No subject was in the 2.5 mg group in the 12-18 years age stratum.)

- *Treatment-Emergent Common AEs*

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).

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 7 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).

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).

In the 8-11 years age stratum, treatment-emergent SAEs were reported in 9 subjects (64%). An SAE that occurred in more than 1 subject was cardiac failure acute (2, all in the 5 mg group).

In the 12 to <18 years age stratum, treatment-emergent SAEs were reported in 12 subjects (50%). SAEs that occurred in more than 1 subject were anaemia pneumonia, and pulmonary arterial hypertension (2 each).

- *AEs/SAEs 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 or SAE: 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.

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.

Serious adverse events and deaths

Study AMB112529

A total of 9 treatment-emergent Serious Adverse Events (SAEs) were reported in 8 subjects: 6 SAEs in 6 subjects in the low dose group and 3 SAEs in 2 subjects in the high dose group (Table 33). None of these SAEs occurred in more than 1 subject. With the exception of the fatal event of pneumonia, all events were resolved and all subjects continued their ambrisentan treatment. With the exception of general physical health deterioration, none of these SAEs were considered by the investigator to be related to ambrisentan treatment.

Table 33 Treatment-Emergent SAEs, Study AMB112529 (Safety Population)

	Ambrisentan		
Preferred Term, n (%)	Low Dose N=21	High Dose N=20	Total N=41
Any event	6 (29%)	2 (10%)	8 (20%)
Device breakage	1 (5%)	0	1 (2%)
General physical health deterioration	1 (5%)[1]	0	1 (2%)
Pulmonary hypertension	1 (5%)	0	1 (2%)
Pharyngitis	1 (5%)	0	1 (2%)
Pneumonia	1 (5%)	0	1 (2%)
Syncope	1 (5%)	0	1 (2%)
Cardiac failure acute	0	1 (5%)	1 (2%)
Device related infection	0	1 (5%)	1 (2%)
Right ventricular failure	0	1 (5%)	1 (2%)

1. The event was assessed by the investigator to be related to ambrisentan treatment.
Low dose: 2.5 mg (body weight ≥20 kg and <35 kg); 5 mg (≥35 kg).
High dose: 5 mg (body weight ≥20 kg and <35 kg); 7.5 mg (≥35 kg and <50 kg); 10 mg (≥50 kg).

Extension study AMB114588

A total of 38 treatment-emergent SAEs were reported in 21 subjects (55%) (Table 34). 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.

SAEs with a fatal outcome were reported in 6 subjects.

None of the SAEs were considered by the investigator to be related to ambrisentan treatment.

Table 34 Treatment-Emergent SAEs, Study AMB114588 (Safety Population)

	Ambrisentan[1]				
Preferred Term	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)
Malaise	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)

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

Study AMB112529

One 12 to <18 years -old subject in the low dose group died due to an SAE of pneumonia. The event of pneumonia was considered by the investigator to be unrelated to ambrisentan treatment.

Extension study AMB114588

As the data cut-off date for the interim analysis, 6 subjects had died due to an SAE and are tabulated in Table 35. For these 6 deaths, 3 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, and failure to thrive in 1 subject. Treatment with ambrisentan was recorded as discontinued in 2 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.

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.

Table 35 Deaths, Study AMB114588 (Safety Population)

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
Cardiac failure acute[2]	Y	N	Not applicable	Y
Acute right ventricular failure	Y	N	Not applicable	Y
Ambrisentan 7.5 mg Group[1]				
Failure to thrive[3]	Y	N	Y	Y
Ambrisentan 10 mg Group[1]				
Pulmonary arterial hypertension[4]	Y	N	Not applicable	N
Pulmonary arterial hypertension	Y	N	Not applicable	Y

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 she 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.

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 she 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.

Laboratory and clinical findings

Haematology

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). Haematology were assessed at baseline and at every 4-week clinical visits over 24 weeks treatment in study AMB112529, whereas they were assessed every 3-month throughout the study and at the end of study visit in study AMB114588.

- *Haematology Values Over Time*

Study AMB112529

There were no clinically relevant changes in blood haematology parameters over time other than a small mean reduction from baseline in haemoglobin, haematocrit, and platelet count for both dose groups, which was consistently evident by Week 4 and remained stable thereafter. The mean change from baseline at Week 24 across both dose groups was -12.1 g/L, -0.0378, and -26.0 GI/L for haemoglobin, haematocrit, and platelet count, respectively.

Extension study AMB114588

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.
There were also small mean reductions in red blood cell indices, as well as lymphocytes.

- *Haematology Abnormalities of Potential Clinical Concern*

Study AMB112529

Few subjects (≤2 in a specific lab parameter) in each dose group had haematology (haemoglobin, haematocrit, and platelet count) values of potential clinical concern (PCC) and there was no increase in incidence over time in the study.

Laboratory abnormalities were reported as AEs in 3 subjects with 4 events (neutropenia, anaemia, eosinophilia [drug-related], and leukopenia) in the low dose group and in 1 subject with 3 events (neutropenia, heparin-induced thrombocytopenia, and lymphopenia [drug-related]) in the high dose group.

Extension study AMB114588

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.

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.

Clinical Chemistry and Liver Function Tests
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). Clinical chemistry was assessed at baseline and at every 4-week clinical visits over 24 weeks treatment in study AMB112529, whereas they were assessed every 3-month throughout the study and at the end of study visit in study AMB114588.
Liver function tests (LFTs) included ALT, AST, gamma-glutamyl transferase (GGT), and total bilirubin.

Study AMB112529

There were no clinically relevant changes in clinical chemistry parameters during the study.

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

No subject had liver function test values that met protocol defined liver chemistry monitoring and stopping criteria. There was no liver event reported during the study.
One subject (9-11 year group) in the low dose group had elevated total bilirubin values at baseline and intermittent elevations at most post-baseline visits (ranged 30-46 µmol/L; normal reference range [NR] =0-22 µmol/L).

Extension study AMB114588

Clinical Chemistry Values Over Time and Changes 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 exceptions of ALP and creatinine.

Clinical Chemistry Abnormalities of Potential Clinical Concern

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 >34.2 µmol/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.
There were no subjects with values of potential clinical concern for creatinine and all other protocol-specified clinical chemistry parameters.

Liver Function Laboratory Abnormalities Reported as AEs and AEs of Hepatobiliary Disorders

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.

Liver Function Laboratory Values of Potential Clinical Concern

Liver function laboratory values of potential clinical concern at any post-baseline visits with no associated AE reported were observed in 4 subjects: 3 had bilirubin values of PCC (2 had an abnormal bilirubin value at study AMB112529 baseline) and 1 had a GGT value of PCC (also had GGT values outside reference range at AMB112529 baseline, at the entry visit to the extension study, and at most of post-baseline visits).

Vital signs, physical findings, and other observations related to safety

- *Physical Examination Study AMB112529*

Overall, 89% of subjects (34/38) had normal liver size on physical examination and 82% 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%.

- *Vital Signs*

Study AMB112529

Overall, there was a small mean/median decrease in heart rate observed at most visits beyond Week 2 for both dose groups. At Week 24, the mean/median decrease was 4.0/6.0 beats/min and was similar across dose groups.
There were no other clinically relevant changes from baseline in vital signs and the proportion of subjects with vital sign values of potential clinical concern was low and similar across the 2 dose groups.

Extension study AMB114588

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 7.0/5.5 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.
Few subjects had systolic blood pressure, diastolic blood pressure, or heart rate value of clinical concern at any post-baseline visit (≤6 subjects for each measure).

- *Pubertal Development*

Pubertal development in male and female subjects was 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 (SHBG) and inhibin B levels.

Study AMB112529
All enrolled subjects (27 female and 14 male) had pubertal assessments.

Female Subjects: There was no clear pattern of change from baseline in endocrinology parameters at the post-baseline visits (Table 36).

Table 36 Endocrinology Data (Females Only), Study AMB112529 (Safety Population)

Parameters	Ambrisentan			
	Low Dose N=21		High Dose N=20	
Estriol (nmol/L)	n		n	
Baseline mean±SD	10	0.150±0	11	0.150±0
Week 12, mean±SD	10	0.150±0	10	0.150±0
Mean change from baseline±SD	8	0	8	0
Week 24, mean±SD	8	0.150±0	10	0.150±0
Mean change from baseline±SD	6	0	8	0
Estrone (pmol/L)				
Baseline mean±SD	10	98.40±106.046	11	153.23±127.852
Week 12, mean±SD	10	94.60±83.699	10	204.55±227.900
Mean change from baseline±SD	8	6.88±88.030	8	41.75±255.552
Week 24, mean±SD	10	67.50±60.248	10	163.15±173.394
Mean change from baseline±SD	6	21.50±50.545	8	16.38±211.492
Estradiol (pmol/L)				
Baseline, mean±SD	9	133.28±169.959	11	202.41±271.316
Week 12, mean±SD	9	127.61±163.965	10	296.20±411.918
Mean change from baseline±SD	7	22.57±182.249	8	65.81±568.752
Week 24, mean±SD	7	46.21±43.101	10	244.10±360.103
Mean change from baseline±SD	5	-31.30±71.487	8	52.13±481.237
Follicle Stimulating Hormone (IU/L)				
Baseline mean±SD	12	3.908±3.3258	15	5.560±3.1052
Week 12, mean±SD	11	3.868±2.8674	13	5.431±3.3370
Mean change from baseline±SD	11	0.586± 1.4121	13	-0.023±2.1048
Week 24, mean±SD	10	2.990±2.6015	12	6.933±3.9672
Mean change from baseline±SD	10	0.010±1.3900	12	1.542±2.5185
Inhibin B (ng/L)				
Baseline, mean±SD	10	28.5±39.38	8	47.4±36.71
Week 12, mean±SD	10	35.3±40.04	10	52.4±38.74
Mean change from baseline±SD	9	4.9±10.03	7	1.7± 33.70
Week 24, mean±SD	10	27.6±26.99	11	62.2±46.84
Mean change from baseline±SD	9	-5.2±36.44	7	16.0±37.96
Luteinizing Hormone (IU/L)				
Baseline, mean±SD	12	3.46±4.516	15	6.42±6.596
Week 12, mean±SD	11	3.43±4.309	13	6.19±5.530
Mean change from baseline±SD	11	0.39±3.117	13	-0.28±6.881
Week 24, mean±SD	11	2.47±3.552	13	7.63±9.062
Mean change from baseline±SD	11	-0.56±1.192	13	1.15±6.806
Sex Hormone Binding Globulin (nmol/L)				
Baseline, mean±SD	11	65.2±28.59	11	58.2±17.85
Week 12, mean±SD	10	66.8±33.41	11	63.2±29.73
Mean change from baseline±SD	10	1.3±9.55	9	7.4±18.91
Week 24, mean±SD	10	56.7±23.12	11	60.5±23.74
Mean change from baseline±SD	10	-9.2±13.62	8	3.1±14.21

At baseline, 7 female subjects (58%) in the low dose group were pre-adolescent with regards to breast development compared with 4 subjects (27%) in the high dose group. One subject (8%) in the low dose group had pubic hair development of adult type compared with 4 subjects (40%) in the high dose group. Pubertal development assessments remained similar at Week 24 other than 2 subjects (18%) in the low dose group had shifted status from pre-adolescent to next stage breast development.

Male Subjects: For 10 and 12 male subjects with right and left testicular volume measurements, respectively, median volume was 6.5 ml (ranged 1 to 25 ml) at study AMB112529 baseline for both measures. Corresponding values at the entry visit to the extension study were 11.5 ml and 8.0 ml (ranged 1 to 25 ml for both) across 12 and 13 subjects, respectively. Overall, 38% of subjects (5/13) remained pre-adolescent at baseline and at entry visit with regards to genital and pubic hair development. At the end of study visit, median change in right and left testicular volumes were 5.0 ml (ranged 0 to 20 ml) and 12.0 ml (ranged 0 to 20 ml), respectively, and 4 of the 5 subjects with genital and pubic hair development assessments had progressed to the last 2 development stages. Overall, of the 3 male subjects with pubertal change assessment at 20 years of age, all showed increased volume in both right and left testicular volumes (range: 8 to 10 ml and 8 to 17 ml, respectively) and all had progressed to final maturity in genital/pubic hair development.

Overall: No clinically relevant change from baseline was observed at the end of study visit in female/male plasma endocrine parameters.

Extension study AMB114588

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 10 subjects (7 females and 3 males) had their 20-year old pubertal assessment.

Female Subjects: There was no clear pattern of change from baseline in endocrinology parameters at the post-baseline visits (Table 37).

Table 37 Endocrinology Data (Females Only), Study AMB114588 (Safety Population)

Parameters	Ambrisentan[1] N=38	
Estriol (nmol/L)	n	
Baseline[2] mean±SD	19	0.150±0
Entry Visit[3], mean±SD	15	0.150±0
Mean change from baseline±SD	11	0
End of Study, mean±SD	14	0.164±0.0535
Mean change from baseline±SD	11	0
Estrone (pmol/L)		
Baseline[2] mean±SD	19	121.45±122.888
Entry Visit[3], mean±SD	15	131.47±151.344
Mean change from baseline±SD	11	14.95±178.202
End of Study, mean±SD	16	166.38±113.184
Mean change from baseline±SD	13	-0.08±140.684
Estradiol (pmol/L)		
Baseline[2] mean±SD	18	168.28±240.674
Entry Visit[3], mean±SD	15	178.63±305.338
Mean change from baseline±SD	11	25.23±407.553
End of Study, mean±SD	16	227.81±232.786
Mean change from baseline±SD	12	-50.58±257.744
Follicle Stimulating Hormone (IU/L)		
Baseline[2] mean±SD	25	4.420±3.0112
Entry Visit[3], mean±SD	21	5.743±4.0267
Mean change from baseline±SD	21	1.052±2.0619
End of Study, mean±SD	18	5.981±3.5208
Mean change from baseline±SD	18	0.786±3.6903
Inhibin B (ng/L)		
Baseline[2] mean±SD	17	37.3±39.47
Entry Visit[3], mean±SD	17	47.0±44.37
Mean change from baseline±SD	12	13.7±31.62
End of Study, mean±SD	15	44.8±44.48
Mean change from baseline±SD	10	-4.6±52.45
Luteinizing Hormone (IU/L)		
Baseline[2] mean±SD	25	4.7±5.886
Entry Visit[3], mean±SD	20	4.28±5.167
Mean change from baseline±SD	20	-0.30±3.685
End of Study, mean±SD	18	8.56±8.037
Mean change from baseline±SD	18	2.20±8.686
Sex Hormone Binding Globulin (nmol/L)		
Baseline[2] mean±SD	21	62.1±24.01
Entry Visit[3], mean±SD	16	56.8±21.18
Mean change from baseline±SD	13	-5.2±13.89
End of Study, mean±SD	16	68.4±28.52
Mean change from baseline±SD	13	8.1±17.40

1. Subjects were considered as belonging to the treatment group according to highest dose received.
2. Baseline was the last value recorded prior to start of study treatment from AMB112529.
3. Entry Visit was at entry to the extension study.

At the entry visit to the extension study, pubertal development assessments remained similar with some shift within lower dose groups to more mature development status. By the end of study visit, all subjects had shifted status from pre-adolescent status to later development stages with the exception of 2 subjects (1 each in the 2.5 mg and 5 mg dose groups) who remained as pre-adolescent status for breast and pubic hair development. Of the 7 females who returned for a pubertal assessment at 20 years of age, all were assessed to meet the final 2 stages of breast and pubic hair development.

Male Subjects: Right and left testicular volume values at the entry visit to the extension study were 11.5 ml and 8.0 ml (ranged 1 to 25 ml for both) across 12 and 13 subjects, respectively. Overall, 38% of subjects (5/13) remained pre-adolescent at baseline and at entry visit with regards to genital and pubic hair development. At the end of study visit, median change in right and left testicular volumes were 5.0 ml (ranged 0 to 20 ml) and 12.0 ml (ranged 0 to 20 ml), respectively, and 4 of the 5 subjects with genital and pubic hair development assessments had progressed to the last 2 development stages. Overall, of the 3 male subjects with pubertal change assessment at 20 years of age, all showed increased volume in both right and left testicular volumes (range: 8 to 10 ml and 8 to 17 ml, respectively) and all had progressed to final maturity in genital/pubic hair development.

Overall: No clinically relevant change from baseline was observed at the end of study visit in female/male plasma endocrine parameters.

- *12-lead electrocardiogram (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 details on ECG findings are available.

Study AMB112529

ECGs were performed at baseline and at Weeks 12 and 24 (or early withdrawal), and at the follow-up visit.

The majority of subjects in both dose groups had abnormal but not clinically significant ECG findings at baseline and at post-baseline visits.

Mild AEs of bundle branch block right and tachycardia (1 subject each) were reported during the study. Both events were resolved within 2 days and none were considered by the investigator to be related to ambrisentan treatment. No QT prolongation-related AE was reported during the study.

Extension study AMB114588

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%, 76%, and 79% of subjects, respectively). A total of 6 subjects had a clinically significant abnormal ECG at any post-baseline visit. Of these, 1 subject had clinically significant ECGs at Week 12 visit and at early withdrawal visit in study AMB112529, and at entry visit to the extension study.

Three subjects had SAEs of atrioventricular block complete, atrioventricular block first degree, and supraventricular tachycardia during the study. All events were resolved. The event of atrioventricular block complete led to ambrisentan treatment temporarily interrupted. None of SAEs were considered by the investigator to be related to ambrisentan treatment. No QT prolongation-related AE was reported during the study.

- *Echocardiogram*

In both studies, data from ECHO examinations were collected to ensure full safety assessment of a subject in the case when PAH had deteriorated. It was also regarded as an exploratory efficacy endpoint to evaluate if potential prognostic factors could be identified as associated with clinical worsening of PAH.
Study AMB112529

In brief, the majority of subjects in both dose groups had no pericardial effusion at baseline (81% in the low dose group and 79% in the high dose group) and remained in the same status at Week 24.

Mean baseline values of right atrial pressure, tricuspid annular plane systolic excursion, eccentricity index systolic, eccentricity index diastolic, and tricuspid regurgitant jet velocity were comparable between dose groups.

With the exception of mean right ventricular pressure, no or small mean changes from baseline to Week 24 in all ECHO parameters. A mean decrease in right ventricular pressure was observed at Week

12 in the high dose group (-0.3 mmHg) and at Week 24 in both dose groups (-1.9 mmHg in the low dose group and -4.5 mmHg in the high dose group.

Extension study AMB114588

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.

At the Entry Visit to the extension study, 31/36 subjects (86%) had no change in pericardial effusion with 3 subjects showing an improvement (1 subject each in the 2.5 mg, 5 mg, and 10 mg groups) and 2 subjects showing a worsening (1 subject each in the 2.5 mg and 7.5 mg groups).

At the End of Study Visit, 21/24 subjects (88%) had no change in pericardial effusion with 3 subjects (2 in the 2.5 mg group and 1 in the 5 mg group) showing an improvement.

Among the 13 subjects who had 1 or more ECHO report of pericardial effusion either in Study AMB112529, the extension study, or both, the majority of readings were of effusions that were trace or small, and the majority of fluctuations were between absent and trace or small. Three subjects had reports of a moderate effusion (including 1 reported at AMB112529 baseline with fluctuation noted throughout their participation in the studies). No subject had a reading of a large pericardial effusion; there were no AE reports of cardiac tamponade and only 1 AE of worsening pericardial effusion. All 3 subjects with reports of a moderate pericardial effusion died. One subject who died in study AMB112529 of pneumonia after 138 days had a trace effusion at baseline reported as moderate at Week 12. The other 2 subjects (including the 1 whose moderate effusion was present at baseline) died in the extension study from events consistent with PAH worsening. Therefore, a moderate effusion might be considered a negative prognostic indicator in this population.

At the end of study, with the exception of right ventricular pressure, mean changes from baseline in all parameters were variable without apparent dose relationship. With the exception of the 5 mg dose group, a mean reduction in right ventricular pressure was observed across all dose groups.

Safety in special populations

Elderly

There were no reports of adults (including elderly) during the ambrisentan paediatric studies AMB112529 and AMB114588.

Pregnancy and Lactation

Ambrisentan is contraindicated during pregnancy and breastfeeding. Treatment must not be initiated when planning to become pregnant.

No pregnancies were reported during these studies AMB112529 and AMB114588.

Immunological events
Not applicable.

Safety related to drug-drug interactions and other interactions

No formal drug interaction studies have been conducted with ambrisentan in paediatric PAH subjects.

Discontinuation due to AES

Study AMB112529

The reason for withdrawal this study was due to an AE in 2 of a total of 4 patients.

One subject was withdrawn from the study due to a fatal event of pneumonia.

In addition, 1 subject had an early withdrawal visit due to an SAE of cardiac failure acute after had been enrolled in the extension study. The subject subsequently died from the ongoing SAE in the extension study.

No treatment-emergent AEs led to drug interruption or dose reduction.
Extension study AMB114588

The reason for withdrawal this interim analysis was mainly due to investigator discretion (including 5 deaths). These 5 subjects were recorded as withdrawn due to an SAE (cardiac failure acute [2 subjects]) and acute right ventricular failure (1), failure to thrive (1), and pulmonary arterial hypertension (1). All 5 events led to a fatal outcome and none were considered by the investigator to be related to ambrisentan.

AEs/SAEs led to an interruption in ambrisentan treatment in 1 subject with 4 events in the 2.5 mg dose group. 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 in the 10 mg dose group.

Post marketing experience

Ambrisentan was first approved in the US on 15 June 2007 under the trade name Letairis and is currently approved in all European Economic Area countries, and Japan as well as over 20 further countries under the trade name Volibris. GSK submitted an initial MAA EMEA/H/C/000839 under Article 8.3 of Directive 2001/83/EC as a full dossier in adults for the treatment of indication treatment of PAH. The application was approved in the EU on 21 April 2008.

Volibris is indicated for treatment of PAH in adult patients of WHO Functional Class II to III, including use in combination treatment.

Routine Pharmacovigilance

Reports of the use of ambrisentan outside of this indication or in non-approved populations (including paediatric use) are maintained in the global safety database by Gilead and are reported in Periodic Benefit Risk Evaluation Reports (PBRERs) periodically as agreed with central and local regulatory agencies. The last PBRER submitted to EMA was in 2017; following assessment the EMA recommended that ambrisentan should be moved to a 3 yearly cycle and therefore the next EU PBRER will be submitted in 2020. There have been 2 yearly PBRERs created in 2018 and 2019 for local regulatory submission. The off-label use in children and adolescents detailed in the most recent two non-EU PBRERs is summarized below:

- Non-EU PBRER Reporting Period from 15 June 2017 to 14 June 2018

  From the global safety database (5,640 cases), a total of 159 spontaneous or solicited (non-clinical) cases have reported the use of ambrisentan in patients younger than 18 years were analysed. The majority of the 159 cases were reported in patients at or over the age of 2 years. Specifically, there were 100 reports (63%) for children aged 2 to under 12 years, and 51 reports (32%) in adolescents (12 to 18 years). For the 94 cases for which an indication for use was provided, all were pulmonary hypertension or other cardiac disorder.

  During the reporting period a total of 191 serious events and 71 non-serious events were received. The most common SAE was pneumonia (n=11), followed by cardiac failure (n=8). The most common non-serious events were off label use (27) and drug administered to patient of inappropriate age (24). Fourteen cases reported a fatal outcome involving 8 females and 6 males, ages 32 months to 17 years. The indication for treatment was unknown (n=6), PAH

(n=3), essential hypertension (n=1), pulmonary hypertension (PH) with sickle cell disease (n=1), PAH with connective tissue disorder and congenital heart disease (n=1), PAH with congenital heart disease (n=1) and PAH with respiratory failure (n=1). The causes of death were reported in 4 cases as follows: 1) congestive cardiac failure in a 8-11 year old patient with a history of neuroblastoma, approximately 28 days after initiation of ambrisentan; 2) cardiac failure secondary to pulmonary artery dissection in an 12 to <18 years -old year old patient with PH 2 days after initiation of ambrisentan; 3) right heart failure in a 12 to <18 years year old patient with worsening of idiopathic pulmonary hypertension and history of sickle cell disease and 4) respiratory/cardiac failure in a 12 to <18 years year-old patient who received ambrisentan treatment for PAH. Cause of death was not provided in 10 cases.

- Non-EU PBRER Reporting Period from 15 June 2018 to 14 June 2019

  From the global safety database (5,640 cases), a total of 192 spontaneous or solicited (non-clinical study) cases reporting use of ambrisentan in patients younger than 18 years were received. The majority of the 192 cases were reported in patients at or over the age of 2 years. Specifically, there were 126 reports (66%) for children aged 2 to under 12 years, and 59 reports (31%) in adolescents (12 to 18 years). For the 110 cases for which an indication for use was provided, all were pulmonary hypertension or other cardiac disorder.

  A total of 244 serious events and 71 non-serious events were received. The most common SAEs reported were death (n=12) and pneumonia (n=11). The most common non-serious events were off label use (n=31) and product use issue (n=21).

  Eighteen cases overall reported a fatal outcome including 7 females and 11 males, ages 34 months to 16 years. The indication for treatment was unknown (n=9), PAH (n=4), PH group 1, 3 (n=1), pulmonary hypertension (n=3), cor pulmonale chronic (n=1). The cause of death was reported in 6 cases as follows: Cardiac arrest in 2 male patients (young child and adolescent) receiving ambrisentan for PAH; suspected worsening of pulmonary hypertensive disease in an 8-11 year old male receiving ambrisentan for pulmonary hypertension; complications of respiratory syncytial virus in a 5-7 year old male who received ambrisentan for an unknown indication; and end-stage cardiopulmonary disease in a 8-11 year old female who received ambrisentan for PH group 1, 3. Cause of death was not provided in 12 cases.

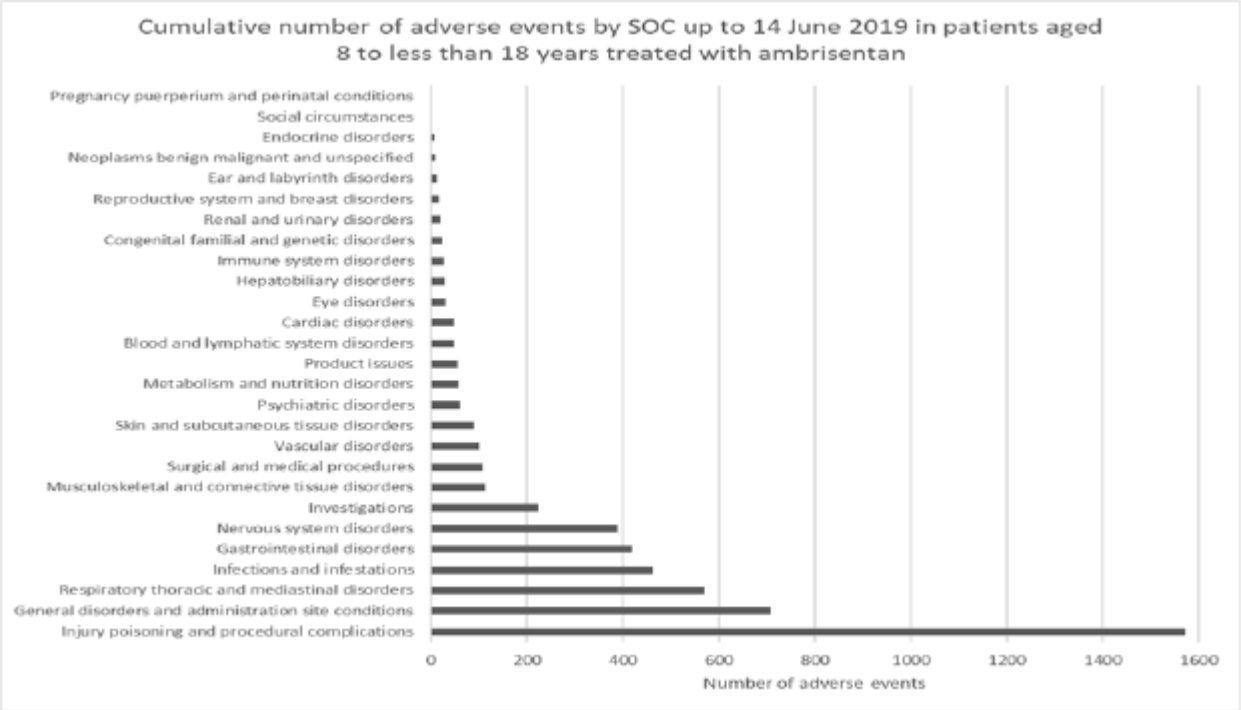
The conclusion from review of these off-label use reports, was that no new safety issues associated with ambrisentan in paediatric population had been identified.

To further investigate off label use in paediatric patients, cumulative data from the International birth date (IBD) to 14 June 2019 was obtained from Gilead. Gilead's ARGUS, the Pharmacovigilance and Epidemiology (PVE) safety database was searched for all cases reported up to 14 June 2019 where ambrisentan had been administered to a child aged 8 to less than 18 years. Since ambrisentan is not indicated for use in children and adolescents, all of the cases were considered off label use.

A total of 1,934 cases, where patients aged 8 to less than 18 years old have received ambrisentan, have been reported to Gilead since launch until 14 June 2019. These cases have reported a total of 5,279 events, with some cases reporting more than one event.

Figure 12 shows the total number of adverse events by SOC since launch in the 8 to less than 18 years population, with the injury, poisoning and procedural complications SOC receiving the majority of AEs. This is expected as the adverse event of "off label use" is included in this SOC (1,348 cases) and although ambrisentan is not licensed for paediatric population, it is recognised that this product is given off label.

Figure 12 Cumulative Number of AEs by SOC in Paediatric Patients (Aged 8 to <18 Years) Treated with Ambrisentan (up to 14 June 2019)



With the exception of off label use, the general distribution of events by SOC is similar to the safety profile seen in adult patients with the most frequently reported AEs being in the context of either listed adverse reactions noted in the SmPC for the adult population or by the underlying disease for which the patient was receiving ambrisentan. There were also a number of events reported that were not related to use of ambrisentan, for example injection/infusion/application site or device related conditions, as ambrisentan is given orally.

The most commonly reported adverse events, after off label use, were headache (194), dyspnoea (111), vomiting (86) and diarrhoea (85) all of which are listed in the EU SmPC with a frequency of very common or common. Other frequently reported adverse events included nasal congestion, nasopharyngitis, sinusitis and fatigue, all of which are also listed events for ambrisentan and have a frequency of very common or common. Table 38 summarises the 10 most frequently reported adverse events in the 8 to less than 18 years old population.

Table 38 The Most Frequently Reported AEs in Paediatric Patients (Aged 8 to <18 Years)

Adverse event	Cumulative number of reports (includes serious and non-serious)
Off label use	1384
Headache	194
Dyspnoea	111
Vomiting	86
Diarrhoea	85
Pneumonia	76
Cough	73
Fatigue	69
Chest pain / Nausea	63 each
Nasopharyngitis / Dizziness	54 each

It is noted that a number of events of pneumonia (76) have been reported in the 8 to less than 18 years population. As this population has a higher incidence of infections and this, based on a background of their underlying condition which makes the patient more susceptible to pneumonia, is thought to be the reason for this reporting. Cases of pneumonia have been documented in previous

safety update reports for ambrisentan, in the adult registration studies and in the clinical studies in paediatric patients.

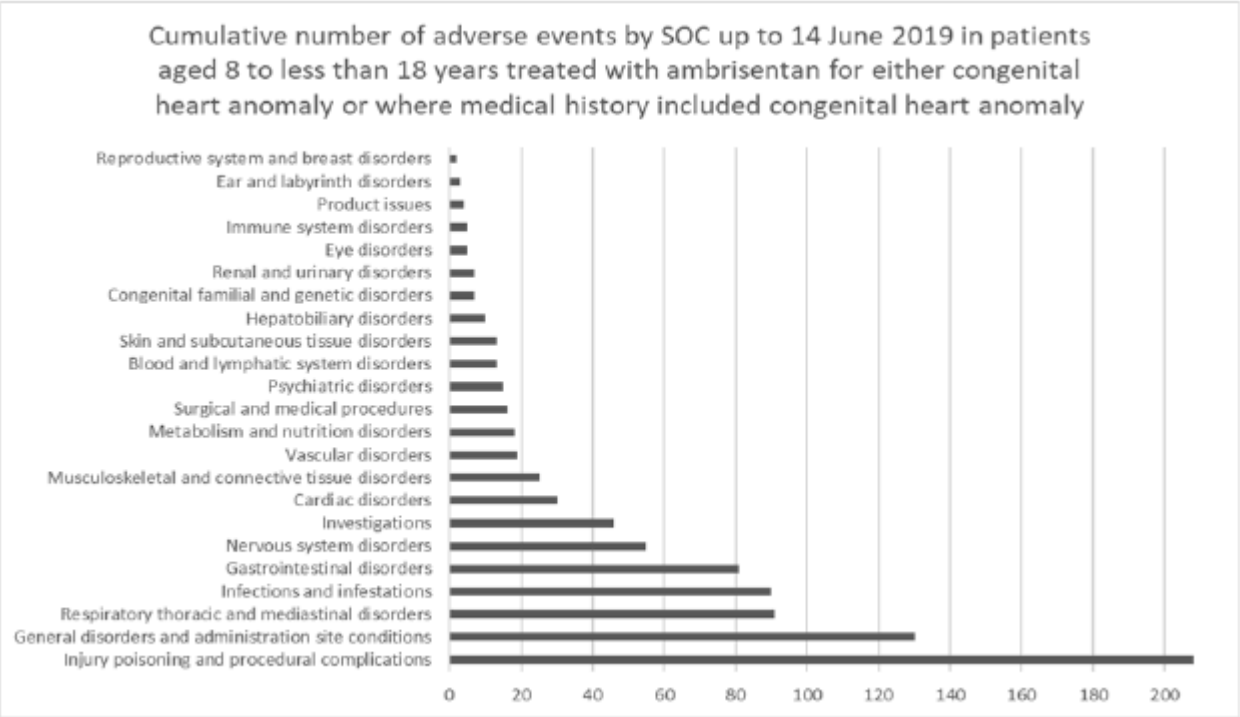
Review of the paediatric data in patients aged 8 to less than 18 years shows a similar safety profile to that of the adult population with the adverse reactions reported being consistent with those seen in adults, with headache occurring most frequently. No new patterns or trends were seen, and no new safety information has been highlighted from this review.

Sub-Set of Congenital Heart Disease

A sub-set of cases from the 8 to less than 18 years old population was retrieved, in which the patients had either received ambrisentan for a congenital heart related anomaly, or where the patient reported a current or past medical history of congenital heart anomaly. The safety profile of this sub-set was then compared to the cumulative paediatric data in patients aged 8 to less than 18 years old.

A total of 261 cases were retrieved that reported 893 events. The spread of these events by SOC is shown in Figure 13.

Figure 13 Cumulative Number of AEs by SOC in Paediatric Patients (Aged 8 to <18 Years) Treated with Ambrisentan for Congenital Heart Anomaly (up to 14 June 2019)



The distribution of cases by SOC for this sub-set of cases is comparable to that of the paediatric population as a whole. It is noted that the proportion of events in the cardiac SOC is higher than in the overall population, but this is expected from a sub-set which is specifically highlighting cases with a focus on congenital heart anomalies.

The most commonly reported adverse events after off label use (179 cases), were headache (32) and dyspnoea (16), again, both of which are listed events in the Product Information for ambrisentan. The most frequently reported AEs were in the context of either listed adverse reactions noted in the SmPC for the adult population or by the underlying disease for which the patient was receiving ambrisentan.

Table 39 tabulates the cumulative number of serious and non-serious events by SOC up to 14 June 2019 in patients aged 8 to less than 18 years treated with ambrisentan for or with history of congenital heart anomaly. The majority of events were considered non-serious in nature.

Table 39 Cumulative Number of AEs by SOC in Paediatric Patients (Aged 8 to <18 Years) in the Sub-Set of Cases (up to 14 June 2019)

SOC	Serious	Non-serious	Total
Injury poisoning and procedural complications	11	197	208
General disorders and administration site conditions	32	98	130
Respiratory thoracic and mediastinal disorders	36	55	91
Infections and infestations	46	44	90
Gastrointestinal disorders	28	53	81
Nervous system disorders	13	42	55
Investigations	21	25	46
Cardiac disorders	28	2	30
Musculoskeletal and connective tissue disorders	2	23	25
Vascular disorders	7	12	19
Metabolism and nutrition disorders	8	10	18
Surgical and medical procedures	14	2	16
Psychiatric disorders	1	14	15
Blood and lymphatic system disorders	0	13	13
Skin and subcutaneous tissue disorders	1	12	13
Hepatobiliary disorders	4	6	10
Congenital familial and genetic disorders	6	1	7
Renal and urinary disorders	4	3	7
Eye disorders	0	5	5
Immune system disorders	2	3	5
Product issues	0	4	4
Ear and labyrinth disorders	1	2	3
Reproductive system and breast disorders	0	2	2
Total	**265**	**628**	**893**

The numbers and types of events reported in this subset were generally proportional to that of the 8 to less than 18 years age group and therefore, similar to the known adult safety profile.

Review of Off Label Data and Increasing Use Over Time

Off label use in this population has increased year on year since June 2007, as demonstrated in Table 40.

Table 40 Off Label Use by Year

Year	Paediatrics (0-11 years)	Adolescents (12-17 years)	Total number of cases
15 June 2007 to 14 June 2008	1	4	5
15 June 2008 to 14 June 2009	3 + 1 x unknown 0-11	13	17
15 June 2009 to 14 June 2010	6 + 1 x unknown 0-11	10	17
15 June 2010 to 14 June 2011	14 (includes 5-month-old)	27	41
15 June 2011 to 14 June 2012	50 (includes 9-month-old)	63	113
15 June 2012 to 14 June 2013	70 + 9 x unknown 0-11	109	188
15 June 2013 to 14 June 2014	100 + 3 x unknown 0-11 (includes 4, 6, 8, 12-month olds)	92 + 1 x unknown 12-17	196
15 June 2014 to 14 June 2015	181 + 5 x unknown 0-11 (includes 17 day, 3, 4, 8, 10, 11-month olds)	145 + 2 x unknown12-17	333
15 June 2015 to 14 June 2016	229 + 10 x unknown 0-11 (includes neonate, 1, 5, 7, 8, 11, 12-month olds)	191 + 2 x unknown12-17	432
15 June 2016 to 14 June 2017	226 + 4 x unknown 0-11 (includes 10 day old, 4, 5, 7, 8, 9-month olds)	154	384
15 June 2017 to 14 June 2018	296 + 8 x unknown 0-11 (includes 20 day old, 7, 8, 9, 10, 11-month olds)	186	490
15 June 2018 to 14 June 2019	403 + 4 x unknown 0-11 (includes 5, 11 weeks old and 5-month olds)	216	623

The cumulative paediatric data set for patients aged 8 to less than 18 years has been evaluated and the safety profile determined to be similar to that of adults.

2.6.3. Discussion on clinical safety

The safety database supporting this application is composed by only 41 children included in study AMB112529 and 38 children included in its extension study AMB11458. Despite the safety profile seems similar to that reported in adults in qualitative terms (i.e.: headache, gastrointestinal adverse events, oedema, etc.), the small safety database and the absence of a comparator group does not allow for a precise estimate of adverse events in children. In addition, the number of children and adolescents in other conditions apart from IPAH was very scarce to draw any meaningful conclusion: 8 patients with persistent PAH despite surgical repair, 4 patients in connective PAH and 2 patients with familial PAH. In line with the objection raised for efficacy, the applicant was requested to conduct a systematic bibliographic search and to discuss published studies with ambrisentan in paediatric population, as well as to compare these results to those obtained in the study AMB112529 and its extension, in terms of adverse events.

The applicant commented on the difficulties encountered with the clinical studies enrolment that leads the submission of a limited safety database (41 children included in study AMB112529 and 38 children included in its extension study AMB11458) to support this application. The Applicant has also provided a more detailed adverse events evidence by including a nominally off-label dataset of children and adolescents in the age range of 8 to <18 years receiving ambrisentan for the treatment of PAH. This

dataset was composed by data obtained from the paediatric subgroup (119 patients) of an unpublished Japan Post Marketing Surveillance study (Study 114782) as well as reports of off-label use of ambrisentan in this population from the Global Safety Database between 15 June 2018 and 14 June 2019 period. Paediatric patients included in submitted dataset were comparable to those included in the study AMB112529 and its extension AMB114588. Moreover, it seems acceptable to inform on the qualitative similarity of the adult and paediatric safety profile. It is considered that broadening the safety database submitted in the application has improved the safety paediatric profile of this product, despite it does not allow for a precise estimate of adverse events in paediatric population. The company also presented safety paediatric data including different PAH aetiologies retrieved from divergent sources after a systematic bibliographic search, which appeared to be comparable to those seen in performed clinical trials. Based on them no observation of new safety risks associated with ambrisentan administration was made. Similarly, no divergency in the safety profile compared to the adult population was seen. Despite of the observed limitations it can be concluded that the summarized outcomes obtained from several sources do not show any differences across aetiology subgroups.

In study AMB112429 all patients received a fixed dose of 5 mg during the first week of treatment in study AMB112529. At week 2 onwards, the ambrisentan low dose (n=21) was defined as 5 mg for patients of ≥35 kg, and 2.5 mg for children between ≥20 kg and <35 Kg. The ambrisentan high dose (n=20) was defined as 10 mg in patients ≥50 kg, 7.5 mg in patients between ≥35 kg and <50 Kg, and 5 mg in patients between ≥20 kg and <35 Kg. In extension study AMB11458, patients received ambrisentan at the dose of 2.5 mg (n=4), 5 mg (n=16), 7.5 mg (n=6) or 10 mg (n=12).

Cumulative exposure to ambrisentan in study AMB112529 and the extension study ranged from 14.3 to 335.1 weeks, with a median duration of 176.6 weeks. More than half of the subjects received ambrisentan treatment for at least 3 years and the longest cumulative duration of treatment was greater than 6.6 years.

The majority of subjects used a background PAH medication(s) in both studies, mainly a PDE-5 inhibitor as monotherapy or in combination with a prostanoid. Adverse events by concomitant medications should be provided. The applicant provided adverse events data (Treatment-Emergent Adverse Events, Serious Treatment-Emergent Adverse Events, Non-Serious Treatment-Emergent Adverse Events and Common[>=5%] Treatment-Emergent Adverse Events) by concomitant PAH therapy (None, Any, PDE-5 inhibitor Only, Prostanoid Only and Both PDE5i and prostanoid) during study AMB112529. As concluded by the applicant, there appears to be a trend where subjects taking 1 or more PAH concomitant medication experience more non-serious events compared with those taking no other medication to treat PAH, but this trend is not seen when reviewing the serious adverse event data.

The majority of subjects in both studies reported at least 1 treatment-emergent AE and the majority were mild or moderate in intensity. The most frequently reported treatment-emergent AE was headache in study AMB112529 and upper respiratory tract infection in the extension study. The most common drug-related AE was headache for both studies. Other ambrisentan-related TEAEs included anaemia and gastroenteritis. Details about two cases of unlisted gastroenteritis (drug-related) cases were provided. In both cases the confounding factor as concomitant medication may have contributed to the events. Therefore, no new safety concern was identified.

A total of 7 deaths were reported, 1 was in study AMB112529 due to an SAE of pneumonia and 6 were in the extension study. These 6 deaths were considered related to the subjects' underlying PAH condition, with a mean time to death of more than 3 years from treatment initiation. SAEs were reported in 8 subjects (20%) with 9 events in study AMB112529 and none of SAEs occurred in more than 1 subject. With the exception of the fatal event of pneumonia, all events were resolved, and all subjects continued ambrisentan treatment. With the exception of general physical health deterioration, none of these SAEs were considered by the investigator to be related to ambrisentan treatment and occurred only in one patient. In the extension study, 38 SAEs were reported in 21 subjects (55%). SAEs which occurred in more than 2 subjects each were: PAH (3), anaemia, cardiac failure acute, and pneumonia (2 each). Two SAEs (cardiac failure acute and failure to thrive) which led to discontinuation

of ambrisentan treatment. Three SAEs (ALT increased, atrioventricular block complete, and hypotension) in 1 subject led to ambrisentan treatment being temporarily interrupted. None of SAEs were considered by the investigator to be related to ambrisentan treatment.

AESIs were reported in 9 subjects (with 11 events) in study AMB112529. With the exceptions of anaemia and hypotension (1 each), all events were related to oedema. Six AESIs were considered by the investigator to be related to ambrisentan treatment: oedema peripheral (2), face oedema (2), angioedema (1), and hypotension (1). No AESIs led to permanent discontinuation of ambrisentan treatment or withdrawal from the study. In the extension study, AESIs were reported in 20 subjects (53%). Anaemia was the most frequently reported AESI, 11 events in 6 subjects. Oedema-related events were reported in 6 subjects with 8 events. Five events of liver laboratory abnormalities were reported as AEs in 2 subjects. SAEs were reported as follows: anaemia (2), ALT increased, and hypotension (1 each). The events were considered by the investigator to be related to ambrisentan treatment as follows: anaemia (3), angioedema, swelling face, AST increased, blood bilirubin increased, syncope, and presyncope (1 each). No AESIs led to permanent discontinuation of ambrisentan treatment or withdrawal from the study. The Applicant proposes to add a new paragraph to section 4.8 dealing with paediatric safety profile. Although reported AEs are mostly in line with the known ambrisentan safety profile, the Rapporteurs are on the opinion of adjusting the currently suggested wording in order to specifically reflect the results (drug-related events) reported in two submitted clinical studies. Moreover, although the currently approved SmPC includes a warning on the fluid retention events in section 4.4 and corresponding PTs are listed in the Section 4.8, information on higher occurrence of fluid retention events also in paediatric population should be supplemented to the SmPC as regards of several other individual cases reported in both submitted studies. The Applicant has updated the paragraph related to the available safety data collected from clinical studies enrolling paediatric population. Regarding to the events related to the fluid retention, the Applicant specifically elaborated on all events reported in paediatric and adult patients. The consistency in the overall incidence and severity of the cases comparing both populations is claimed, which is agreed. The updated paragraph in Section 4.8 does not contain any information on this matter as only two events of peripheral oedema attributed to the study treatment were seen within paediatric development. The previously listed information in Section 4.4 corresponds with the provided paediatric data and thus can be considered sufficient.

Details about unlisted non-serious eosinophilia and lymphopenia (drug-related) cases were provided. In both cases the confounding factors including underlying conditions and concomitant medications may have contributed to the events. Therefore, no new safety concern was identified. No other laboratory abnormalities coded as ambrisentan-related AEs were reported by the Investigator and no PCC has been identified in the study AMB114588.

Adverse events were analysed by age stratum. In Study AMB112529, a total of 14 subjects aged 8-11 years (7 in each dose group) and 27 subjects aged 12 to <18 years (14 in the low dose group and 13 in the high dose group) were enrolled. In the extension study AMB114588 a total of 14 subjects aged 8-11 years and 24 subjects aged 12 to <18 years were enrolled. Numbers of subjects in each dose group in the 8-11 years age stratum in the Safety Population were 4, 7, and 3 in the 2.5 mg, 5 mg, and 10 mg groups, respectively. Adverse event profile was consistent by age stratum.

There was a lack of dose-response regarding adverse events, with more adverse events reported with the ambrisentan low dose. The applicant attempted to analyse different causes that could lead to the observed lack of dose-response regarding adverse events in study AMB112529, with more adverse events reported with the ambrisentan low dose. As stated by the Applicant, it is considered that there is no pattern or trend in adverse event reporting between dose groups, being the differences seen between the two dose groups probably to due to variability in such a small size population.
In line with expected pubertal development in this population, no clinically relevant change in male testicular volume from baseline was observed in both studies. No clinically relevant change in female/male endocrinology or plasma endocrine parameters were seen for both studies.

There were no liver events reported during the study AMB112529. One liver event, both ALT and AST ≥3X ULN, was reported in the extension study. No QT prolongation-related AE, as well as AEs of ventricular arrhythmias, were reported during both studies although there was 1 report of QT

prolongation in association with an event of atrioventricular block first degree that resolved with continued treatment and was not considered related to ambrisentan treatment. A small mean reduction from baseline in haemoglobin, haematocrit, and platelet count was observed in both study AMB112529 and the extension study. Small mean increases in creatinine were observed at entry to the extension study, which continued to be observed to a larger magnitude at subsequent visits. Corresponding small mean decreases in eGFR were observed at the end of study visit with no remarkable changes in other kidney function parameters. No clinical relevance is attributed to this finding.

The company has also provided data of off-label use in paediatric patients using the Gilead's ARGUS [the Pharmacovigilance and Epidemiology (PVE) safety database of Gilead]. A total of 1,934 cases, where patients aged 8 to less than 18 years old have received ambrisentan, have been reported to Gilead since launch until 14 June 2019. These cases have reported a total of 5,279 events, with some cases reporting more than one event. The most commonly reported adverse events, after off label use, were headache (194), dyspnoea (111), vomiting (86) and diarrhoea (85) all of which are listed in the EU SmPC with a frequency of very common or common. It is noted that a number of events of pneumonia (76 cases) have been reported in the 8 to less than 18 years population. As this population has a higher incidence of infections and this, based on a background of their underlying condition which makes the patient more susceptible to pneumonia, is thought to be the reason for this reporting. Cases of pneumonia have been documented in previous safety update reports for ambrisentan, in the adult registration studies and in the clinical studies in paediatric patients. The applicant was requested to discuss whether children and adolescents may be at a particular higher risk of pneumonia than adults and to propose strategies to minimise that risk if appropriate. The Applicant provided a review of pneumonia in paediatric patients aged 8 to less than 18 years receiving ambrisentan for the treatment of PAH. Safety data were obtained from clinical trials (AMB112529 and AMB114588, and Japan Post-marketing surveillance study [Study 114782]) as well as reports of off-label use in paediatric patients from the Global Safety Database. Evidence reviewed does not support a causal relationship between pneumonia in children aged 8 to less than 18 years and ambrisentan, exhibiting a relationship predominantly associated with the patients' underlying conditions. A comparison of the risk of pneumonia in adults and children, considering both a safety review of pneumonia in adult clinical trials and post-marketing data in the overall population (paediatric and adult), was also provided by the Applicant. On review of the data, there is no evidence to support a causal association between pneumonia and the use of ambrisentan in either paediatric or adult patients and cases of pneumonia do not appear to be more prevalent in children compared to adults. Therefore, there is no need for inclusion of a warning in the product information or other risk minimisation measures. Other frequently reported adverse events included nasal congestion, nasopharyngitis, sinusitis and fatigue, all of which are also listed events for ambrisentan and have a frequency of very common or common. The different data source used and time of assessment for events rates of headache and nasal congestion was specified in section 4.8 of the SmPC.

2.6.4. Conclusions on the clinical safety

The safety database supporting this application is composed by 41 children included in study AMB112529 and 38 children included in its extension study AMB11458. Cumulative exposure to ambrisentan in Study AMB112529 and the extension study ranged from 14.3 to 335.1 weeks, with a median duration of 176.6 weeks. More than half of the subjects received ambrisentan treatment for at least 3 years and the longest cumulative duration of treatment was greater than 6.6 years.

The safety profile of ambrisentan in the 41 children aged 8 to less than 18 years included in study AMB112529 and 38 children included in its extension study AMB11458 is consistent with adults from the Phase III PAH studies submitted with the initial MAA. However, the small safety database and the absence of a comparator group does not allow for a precise estimate of adverse events in children. No new clinically relevant safety concerns were identified including from physical examination and pubertal development assessments in paediatric subjects from 8 to less than 18 years of age following administration of ambrisentan oral doses adjusted for body weight.

The majority of subjects used a background PAH medication(s) in both studies, mainly a PDE-5 inhibitor as monotherapy or in combination with a prostanoid. Adverse events did not show a different pattern depending on the use of concomitant medications.

The number of children in other conditions apart from IPAH in the pivotal trial was very scarce to draw any meaningful conclusion: 8 children with persistent PAH despite surgical repair, 4 children in connective PAH and 2 children with familial PAH. The applicant was requested to conduct a systematic bibliographic search and to discuss published studies with ambrisentan in children, as well as to compare these results to those obtained in the study AMB112529 and its extension, in terms of adverse events. The additional paediatric safety data including different PAH aetiologies retrieved from divergent sources appeared to be comparable to those seen in performed clinical trials. Based on them no observation of new safety risks associated with ambrisentan administration was made. Similarly, no divergency in the safety profile compared to the adult population was seen. Despite of the observed limitations it can be concluded that the summarized outcomes obtained from several sources do not show any differences across aetiology subgroups.

There was a lack of dose-response regarding adverse events, with more adverse events reported with the ambrisentan low dose. The applicant attempted to analyse different causes that could lead to the observed lack of dose-response regarding adverse events in study AMB112529, with more adverse events reported with the ambrisentan low dose. As stated by the Applicant, it is considered that there is no pattern or trend in adverse event reporting between dose groups, being the differences seen between the two dose groups probably to due to variability in such a small size population.
The number of cases of off-label use reported in children from Gilead's ARGUS database (n=1,934 cases) is much higher than the number of children included in the pivotal study AMB112529 (n=41). The applicant states that the review of the off-label paediatric data in children aged 8 to less than 18 years shows a similar safety profile to that of the adult population with the adverse reactions reported being consistent with those seen in adults, with headache, dyspnoea, vomiting and diarrhoea occurring most frequently. While, qualitatively, the adverse events reported in off-label use in children are within expected for adults, no conclusions can be made with respect to compare incidence rates versus adults. The 76 pneumonia cases reported in off-label use were further discussed by the applicant and no particular concerns are raised in children.

In the context of the rare nature of pulmonary arterial hypertension, review of the clinical trial data in children along with the off label use data in this population, the additional data provided from the paediatric subgroup of the Japanese PMS study and the extensive post-marketing safety database in adults, it is reasonable to conclude that the safety profile in children is similar and consistent with that seen in the adult population.

2.7. Risk Management Plan

2.7.1. Safety concerns

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	Teratogenicity Decreased haemoglobin/haematocrit, anaemia, including anaemia requiring transfusion Hepatotoxicity
Important potential risks	Testicular tubular atrophy/ Male infertility

Summary of safety concerns	
Missing information	None

2.7.2. Pharmacovigilance plan

No new additional pharmacovigilance activities have been proposed on the basis of the new proposed indication. Therefore, only routine pharmacovigilance activities are proposed to address all the safety concerns.

2.7.3. Risk minimisation measures

Safety concern	Risk minimisation measures
Teratogenicity	**Routine risk minimisation measures** Text within Sections 4.2, 4.3, 4.4, 4.6 and 5.3 of the EU SmPC PL section 2 Limited package supply Restricted medical prescription **Additional risk minimisation measures** Patient Reminder Card
Decreased haemoglobin/haematocrit, anaemia, including anaemia requiring transfusion	**Routine risk minimisation measures** Text within Sections 4.4, 4.8 and 5.1 of the EU SmPC PL sections 2 and 4 Limited package supply Restricted medical prescription **Additional risk minimisation measures** None
Hepatotoxicity	**Routine risk minimisation**

	measures Text within Sections 4.2, 4.3, 4.4, 4.8, 5.1 and 5.2 of the EU SmPC PL Sections 2 and 4 Limited package supply Restricted medical prescription **Additional risk minimisation** **measures** Patient Reminder Card
Testicular tubular atrophy/ Male infertility	**Routine risk minimisation** **measures** Text within Sections 4.6 and 5.3 of the EU SmPC PL Section 2 Limited package supply Restricted medical prescription **Additional risk minimisation** **measures** None

2.7.4. Conclusion

The CHMP considered that the risk management plan version 9.0 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the MAH fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.9. Product information

2.9.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Volibris 5mg and Volibris 10 mg film coated tablets. The bridging report submitted by the MAH has been found acceptable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Pulmonary arterial hypertension (PAH) is a rare, progressive, highly debilitating disease characterised by vascular obstruction and the variable presence of vasoconstriction, leading to increased pulmonary vascular resistance (PVR) and right-sided heart failure [Moledina, 2010; Newman, 2004]. If left untreated, PAH ultimately leads to right ventricular failure and death [Krum, 2000].

Paediatric PAH is a rare and complex condition associated with diverse cardiac, pulmonary, and systemic diseases, with significant morbidity and mortality. It shares some similarities with adult PAH, but there are important known differences in vascular function, foetal origins of disease, growth and development, genetics, natural history, underlying disease, responses of the right ventricle, responsiveness to PAH-specific therapies, and gaps in knowledge, particularly in the youngest age groups [Abman et al. Circulation. 2015; 132: 2037–99].

Because of the limitations in conducting paediatric studies, therapeutic strategies used for adult PAH have not been studied sufficiently in children to allow the definition of potential toxicities or optimal dosing. Hence, the lack of randomized clinical trials in paediatrics makes it difficult to deliver strong guidelines [Ollivier et al. J Am Heart Assoc. 2019; 8: e01130].

Common hurdles for testing PAH therapies in children include: a) the rarity of the paediatric PAH; b) the many associated conditions that fragment the classification of paediatric PAH (e.g., idiopathic PAH [IPAH], familial PAH, corrected congenital PAH, PAH associated with connective tissue disease, pulmonary hypertension of the newborn [PPHN]) which leaves only a relatively small number of patients with PAH at each center; c) competing number of medicinal products for such a small population; d) The lack of suitable clinical end points in children: the 6-Minute Walking Distance (6MWD) Test cannot be used in all paediatric age subsets (ie.: not reliable in children <7 years), while there is a lack of consensus about the use of right sided heart catheterization to obtain hemodynamic end points in paediatric clinical trials [Ollivier et al, 2019].

This situation has resulted in a lack of equipoise after marketing authorization for new investigational drugs in adults, making it even more difficult to enroll children, and contributes to off-label use, which can increase the risk of inadequate dosing and results in lack of paediatric safety data. The main points of tension are related to finding the adequate balance between early access and sufficient exposure of children during paediatric trials for safety and adequate dosing. Methodological tools, such as extrapolation, could optimize obtaining information about children involved in clinical studies by predicting how a medicine may work in children and adolescents on the basis of studies conducted in adults [Ollivier et al, 2019], but dedicated studies in children are needed.

3.1.2. Available therapies and unmet medical need

Detailed, consensus, evidence-based guidelines for the treatment of PAH have been published [Galiè, 2015]. Because the underlying pathophysiology of PAH in children and adolescents is generally similar to that in adults, treatment guidelines for PAH in the paediatric population are similar to those in adults, although the majority of treatments are currently not approved for use in children and adolescents, and the level of evidence supporting the available treatments in the paediatric population is limited.

Treatment approaches are divided into those regarded as supportive or background treatment (aimed at alleviating vasoconstriction, breathlessness, and thromboembolic complications) and those (such as endothelial receptor antagonists [ERAs]) that target the underlying pathophysiology.

Supportive/background treatments
It is recommended that patients who show vasoreactivity (pulmonary vascular response to acute vasodilator challenge) are given a calcium channel blocker (CCB), however the majority of patients do not demonstrate significant vasoreactivity and in those that do the impact of this therapy is modest [Sitbon, 2005]. A small proportion of children who are 'responders' to acute vasodilator testing can be managed satisfactorily with oral CCB therapy although like adults, the great majority of children are non-responders. Oxygen relieves breathlessness in those who are hypoxic but does not affect the underlying pathophysiological processes. For patients with more severe disease, digoxin and other positive inotropes are sometimes used for the amelioration of symptoms. Oedema resulting from progressive right ventricular dysfunction is treated with diuretics. Anticoagulants are an important adjunctive therapy in some patients (especially those with IPAH), but do not affect the vasoconstrictive and remodelling aspects of the disease.

Targeted therapies
Three signalling pathways (nitric oxide, prostacyclin-thromboxane and endothelin-1) involved in the pathogenesis of PAH have been targeted for therapeutic intervention by the following classes of PAH medicines [Humbert, 2004; Frank, 2018]:

- prostanoids: FLOLAN (epoprostenol), Ventavis (iloprost), beraprost, and Remodulin (treprostinil);
- phosphodiesterase type 5 (PDE-5) inhibitors: Revatio [Europe (EU)]/Viagra (sildenafil), Adcirca (tadalafil);
- soluble guanylate cyclase stimulators: Adempas (riociguat); and
- ERAs: VOLIBRIS [EU]/Letaris [United States of America (US)] (ambrisentan), Tracleer (bosentan), and Opsumit (macitentan).

Only bosentan (Food and Drug Administration [FDA] and European Medicine Agency [EMA]) and sildenafil (EMA) have been approved for use in paediatric subjects [Farhat, 2019]. However, there are challenges to their successful use in a paediatric population. Bosentan is subject to clinically significant drug-drug interactions with several important concomitant medications and is also associated with potential hepatotoxicity [Hansmann, 2016]. Sildenafil is associated with a significantly increased risk of mortality at higher doses in children and adolescents [Hansmann, 2016]. Although not approved for use in the paediatric population, there is evidence that prostanoid therapies are effective in children and adolescents [Frank, 2018]. However, in common with their use in adults, the pharmacokinetic (PK) properties of these drugs and routes of administration (e.g., intravenous [IV]), present substantial challenges to their successful use in a paediatric population. There is an unmet need for an approved treatment that provides clear clinical benefit without the complexities associated with managing potential issues.

Ambrisentan, an ERA, is approved for the treatment of adults with PAH. Treatment with ambrisentan has been shown to improve exercise capacity, decrease the symptoms of PAH, and delay clinical worsening. The clinical profile of ambrisentan in adults is that it has an efficacy profile broadly comparable with other targeted oral treatments, but that it has potentially important advantages. Ambrisentan has been associated with a favourable liver safety profile and a low risk of drug-drug interactions, which may provide a better therapeutic option in a paediatric population that commonly require many concomitant medications.

3.1.3. Main clinical studies

This paediatric indication is based on the pivotal phase IIb Study AMB112529, which was a 6-month (24-week), randomised, open-label evaluation of the safety, tolerability, and efficacy of 2 doses of ambrisentan (Low and High, adjusted for body weight) in paediatric subjects aged 8 years up to 18 years with PAH. The dossier also includes the open-label extension study AMB114588, including 38 of the 41 children completing study AMB112529.

All children received a fixed dose of 5 mg during the first week of treatment in study AMB112529. At week 2 onwards, the ambrisentan low dose was defined as 5 mg for children of ≥35 kg, and 2.5 mg for children between ≥20 kg and <35 Kg. The ambrisentan high dose was defined as 10 mg in children ≥50 kg, 7.5 mg in children between ≥35 kg and <50 Kg, and 5 mg in children between ≥20 kg and <35 Kg. The sponsor provided commercially available ambrisentan 5 mg tablets, and 10 mg tablets as well as manufactured 2.5 mg tablets of equivalent quality.

The primary comparison stated in the AMB112529 protocol was to evaluate the safety and tolerability of the 2 ambrisentan dose groups (Low versus High) in the paediatric PAH population. The secondary comparison was change from Baseline in the efficacy parameters between the 2 dose groups. Because subject recruitment was limited by the low prevalence of the disease in children, powered clinical hypothesis tests were not planned. Sixty-six subjects constituted the selected sample size based on the predicted recruitment rate from historic data so that the study could be completed in a reasonable time frame (2 years) for it to be useful and informative to the medical community. A 10% drop out rate was anticipated to leave 60 evaluable subjects.

The study was stopped in March 2013 after 41 children (out of 60 planned) were recruited due to a nonclinical finding of brain weight decrease in juvenile rats with low clinical margins for human paediatric dose exposures. Further nonclinical investigations were conducted, and the findings submitted to CHMP in November 2017. Notification of the opinion of a proposed PIP modification submitted by GSK was received from the EMA PDCO in February 2019 (EMEA-000434-PIP01-08-M05). The study was agreed to be closed and a reduction in number of subjects from the planned 66 subjects (for 60 evaluable) to 40 was accepted. Therefore, recruitment was not re-initiated, the study was declared as terminated on 11 Feb 2019, and the unplanned interim analysis became the final analysis for this study (based on 41 subjects enrolled).

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. The analysis used imputed data for the primary endpoint, where the worst-case scenario was imputed as 6MWD=0 for missing data following death or hospitalization, and the traditional LOCF imputation was used in all other scenarios.

In addition, a separate Bayesian analysis of data from the 6MWD from Study AMB112529 was performed. A meta-analysis to check consistency between the effects on 6MWD in adults and children was conducted. 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 exposure-response (ER) model relating ambrisentan PK to change from baseline in 6MWD.

3.2. Favourable effects

In pivotal phase IIb study AMB112529, in 41 children aged 8 to 17 years, over the 24-week Treatment Period there was evidence of an improvement in exercise capacity (6MWD), but there was no dose trend in the effect of ambrisentan on this endpoint. The mean change from baseline at Week 24 in 6MWD for patients in the low and high dose groups was +55.14 metres and +26.25 metres, respectively. In subgroup analyses, the change from baseline in 6MWD at Week 24 was similar between the dose groups in paediatric subjects in the 12-18 age category but was higher in the Low dose group compared with the high dose group in the 8-11 age category. An adhoc analysis showed that 24 subjects (59%) had an increase from baseline in 6MWD of ≥20 metres at Week 12 and Week 24 in Study AMB112529 and these were fairly evenly distributed across the idiopathic subgroup (15 of 27; 56%) and non-idiopathic subgroup (9 of 14; 64%).

A Bayesian extrapolation analysis conducted by the applicant suggest that the increases in 6MWD by 26.25 m to 55.14 metres from baseline to week 24 in the high and low dose groups in children is consistent to those reported with ambrisentan in placebo-controlled trials in adults. The extrapolation has a number of major limitations and has to be viewed as an exploratory exercise.

Regarding secondary endpoints, there were also positive shifts in WHO functional class. At Week 24, 95% and 100% of patients in the low and high dose groups, respectively, remained stable (no change or improved functional class). The number of paediatric subjects with clinical worsening of PAH was small in both dose groups (3 in each dose group). One patient died in the low dose group due to worsening of PAH. The Kaplan-Meier event-free survivor estimate for worsening of PAH (death [all cause], lung transplantation, or hospitalisation for PAH worsening or PAH-related deterioration) at 24 weeks was 86% and 85% in the low- and high dose groups, respectively. Haemodynamics were measured in 5 patients (low dose group). There were also positive effects in haemodynamics: mean increase from baseline in cardiac index was +0.94 L/min/m2, the mean decrease in mean pulmonary arterial pressure was -2.2 mmHg, and the mean decrease in PVR was -3.46 mmHg/L/min. In addition, these efficacy findings were also supported by a small mean decrease in NT-proBNP over the 24-week Treatment Period. Geometric mean decrease from baseline in NT-pro-BNP was 31% in the low dose group (2.5 and 5 mg) and 28% in the high dose group (5, 7.5, and 10 mg). Change from Baseline in Physical and Psychosocial summary scores, as measured by the SF-10 health survey, remained generally stable across the 24-week Treatment Period in this study.

A total of 38 of 41 patients recruited in study AMB112529 entered the long-term extension study AMB114588. There was no further improvement in exercise capacity from start of study AMB112529 to end of study. In the overall patients the improvement was of only 3 metres (from 41.49 metres at the entry visit to 44.82 metres at end of study). These data can be interpreted such that the improvement observed during the 24-week study was maintained during the extension study. However, about half of the study population (45%) needed the addition of other PAH therapies due to deterioration or insufficient response. The extension data are difficult to interpret due to important methodological limitations like small sample size, multiple dosing subgroups (2.5 mg, 5 mg, 7.5 mg and 10 mg for a total of only 38 children), lack of control group and heterogeneous follow up (between 3 months to over 5 years). No data of end of study visit were provided (mean follow-up for these 6MWD values were not provided). In addition, from entry visit in the extension study to end of study visit there was a deterioration of 6MWD in some dosing groups (2.5 mg: from 92.06 at entry visit to 71.47 metres at end of study; i.e.: 21 m deterioration; 7.5 mg: from 53.48 m at entry visit to 3.05 m at end of study; i.e.: 50 m deterioration). The interpretation of these results is hampered by the low number of subjects by dosing group (i.e.: 9 children in the 2.5 mg subgroup and 5 children in the 7.5 mg subgroup). Overall, 11 of 38 subjects (29%) experienced clinical worsening during the extension study AMB114588 according to at least one criterion with the most frequently reported reasons being death (5 subjects [13%]) and PAH-related deterioration (4 subjects [11%]). The Kaplan-Meier analysis showed most events occurred within 3 years of Study AMB112529 Baseline. All deaths reported in Study AMB114588 were due to events associated with the natural progression profile and known characteristics of children with PAH disease, with a mean time to death of over 3 years from treatment initiation. None of the deaths were considered related to ambrisentan. The time to first clinical worsening of PAH was variable across subjects and dose groups and ranged from approximately 100

days to over 5 years. NT-proBNP values were variable across the duration of the long-term extension Study AMB114588 there was evidence of a small mean decrease from Study AMB112529 Baseline at the End of Study Visit. Change from Baseline in Physical and Psychosocial summary scores, as measured by the SF-10 health survey, remained generally stable across the duration of long-term Study AMB114588. In summary, the extension study AMB114588 showed that 71% of children remained clinically stable on treatment without deterioration, while about 29% of children had deterioration despite the addition of other target PAH therapeutic agents. In the absence of a control group no firm conclusions can be made, but anyway the results are consistent with the natural progression of the PAH disease.

3.3. Uncertainties and limitations about favourable effects

Volibris is currently approved for treatment idiopathic PAH (IPAH) and PAH associated with connective tissue disease in adults only. The indication proposed by the Applicant in this application also contains indications of familial PAH and corrected congenital PAH in paediatric population. Further discussion was therefore provided by the Applicant regarding extrapolation of ambrisentan efficacy from approved adults indications IPAH and PAH associated in connective tissue disease to newly proposed indications familial PAH and corrected congenital PAH in paediatric population taking into account different aetiology and concomitant PAH therapies. The extrapolation from adults, coupled with the provision of additional effectiveness data from published studies and a Japanese PMS, was deemed acceptable.

The study AMB112529 has several limitations, mainly related to the small sample size and lack of dose-response in efficacy. The number of children is insufficient to allow for conclusion in several patient subsets mentioned in the proposed indication. As such subgroup analyses were carried out in order to explore the consistency of the treatment effect in important patient subsets mentioned in the indication. The effect was consistent in most subgroups analysed. A bibliographic search identified several published studies with ambrisentan in children, with the populations and results being consistent with the data provided by the study AMB112529 and its extension.

There appears not to be a dose-response relationship in 6MWD and other secondary efficacy endpoints. In fact, most clinical outcomes, with few exceptions, show a better effect for the low-dosing regime compared with the high-dose regime. Further discussion of the lack of dose-response was provided by the applicant. Adult systemic exposure was found to be predictive of exposures in paediatric subjects from 8 to less than 18 years of age in Study AMB112529 thereby supporting bridging of dose/exposure-dependent pharmacology between the two populations. Based on the extrapolation of exposure and response from adults to paediatric subjects with PAH, the proposed dose recommendation for paediatric subjects is primarily based on providing systemic exposure in the same range to adults with PAH, and consistent with the current dose recommendation for titration in adult subjects with PAH adjusted for body weight. The explanation was considered acceptable and therefore, the recommendation included in section 4.2 regarding uptitration according to clinical response and tolerability can be maintained.

The applicant did not plan a statistical comparison of the change in 6MWD at week 24 versus baseline values, which is unfortunate. As a result, it was difficult to interpret whether the 55.14 m improvement in the low dose group or the 40.69 metres improvement in the overall population after 24 weeks is statistically significant compared to baseline values. The applicant provided the results on 6MWD (improvement versus baseline) by dose group and well as for the total study population, in terms of mean and median metres of change in 6MWD with 95%CI. These data have been included in section 5.1 of the SmPC. A comparison versus putative placebo was requested from the applicant. From the limited studies that do have placebo information for change from Baseline in 6MWD (SERAPHIN study in adults), there is consistent evidence of a mean/median reduction in 6MWD across a 6-month period (with approximate magnitude of 8 to 15 metres) compared with an increased 6MWD for active treatments. Data from the most closely matching study in the literature (SERAPHIN study) has allowed the Company to provide an overall estimated treatment effect of 50.09 m (95% CI: 15.43, 84.75) for study AMB112529, which suggests superiority in favour of ambrisentan treatment.

Looking at baseline NT-ProBNP concentrations it seems that randomisation was not successful, with more children in the high dose groups having characteristics of a more severe disease and/or a better background treatment indicating less room for improvement compared with the low dose group. For example, more children in the high dose group were on FCIII compared to the low dose group (6 vs. 3) and patients in the high dose group had higher mean NT-ProBNP levels than those randomised to the low ambrisentan dose, indicating a worse cardiac function in patients randomised to the high ambrisentan dose. In addition, there was also a significant imbalance in the number of non-white, non-European subjects, with more of these subjects been enrolled in the low-dose group compared to the high-dose group (10 vs. 1), and therefore the better outcome in the low dose group could be related to a suboptimal background therapy in non-European subjects (10 of 11 non-white non-European children fall in the low dose group). These baseline imbalances could explain to some extent the lack of dose-response in efficacy. The applicant was invited to elaborate and discuss on this issue. These baseline imbalances could explain to some extent the lack of dose-response in efficacy. Whether these imbalances may have led to the lack of demonstration of a dose-response (i.e.: no better results on 6MWD with the high dose compared to the low dose) cannot be confirmed or ruled out.

It is unclear whether the 24-week improvement in 6MWD reflects ambrisentan treatment effect or to the use of rescue PAH medications or increase in dose of concomitant medications in the low dose group. The applicant was requested to analyse separately patients that continued with unchanged PAH medications doses for the 24 weeks and patients that had some dose-increase or received additional PAH medications introduced during that period. Few patients received rescue medications or change in concomitant cardiovascular medications. This information was provided by the applicant. The introduction of rescue medications or change in concomitant cardiovascular medications does not appear to have influenced the assessment of the main outcome of 6MWD.

Finally, study AMB112529 was stopped in 2013 due to nonclinical findings. The applicant was invited to discuss whether the study results are representative of current management of PAH in 2020. The applicant submitted the results of a consultation with 8 PAH experts [members of the Independent Data Monitoring Committee (IDMC) and other expert consultants] and a literature review to support the external validity of study AMB112529. These data support the representative nature of the AMB112529 data to the current management of paediatric subjects with PAH.

3.4. Unfavourable effects

The safety database supporting this application is composed by 41 children included in study AMB112529 and 38 children included in its extension study AMB11458. Cumulative exposure to ambrisentan in Study AMB112529 and the extension study ranged from 14.3 to 335.1 weeks, with a median duration of 176.6 weeks. More than half of the subjects received ambrisentan treatment for at least 3 years and the longest cumulative duration of treatment was greater than 6.6 years.

The majority of subjects in both studies reported at least 1 treatment-emergent AE and the majority were mild or moderate in intensity. The most frequently reported treatment-emergent AE was headache in Study AMB112529 and upper respiratory tract infection in the extension study. The most common drug-related AE was headache for both studies. A total of 7 deaths were reported, 1 was in Study AMB112529 due to an SAE of pneumonia and 6 were in the extension study. These 6 deaths were considered related to the subjects' underlying PAH condition, with a mean time to death of more than 3 years from treatment initiation. SAEs were reported in 8 subjects (20%) with 9 events in Study AMB112529 and none of SAEs occurred in more than 1 subject.

AESIs were reported in 9 subjects (with 11 events) in Study AMB112529. With the exceptions of anaemia and hypotension (1 each), all events were related to oedema. Six AESIs were considered by the investigator to be related to ambrisentan treatment: oedema peripheral (2), face oedema (2), angioedema (1), and hypotension (1). No AESIs led to permanent discontinuation of ambrisentan treatment or withdrawal from the study. In the extension study, AESIs were reported in 20 subjects

(53%). Anaemia was the most frequently reported AESI, 11 events in 6 subjects. Oedema-related events were reported in 6 subjects with 8 events. Five events of liver laboratory abnormalities were reported as AEs in 2 subjects.

Adverse events were analysed by age stratum. In Study AMB112529, a total of 14 subjects aged 8-11 years (7 in each dose group) and 27 subjects aged 12 to <18 years (14 in the low dose group and 13 in the high dose group) were enrolled. In the extension study AMB114588 a total of 14 subjects aged 8-11 years and 24 subjects aged 12 to <18 years were enrolled. Adverse event profile was consistent by age stratum.

In line with expected pubertal development in this population, no clinically relevant change in male testicular volume from baseline was observed in both studies. No clinically relevant change in female/male endocrinology or plasma endocrine parameters were seen for both studies.

There were no liver events reported during the Study AMB112529. One liver event, both ALT and AST ≥3X ULN, was reported in the extension study. No QT prolongation-related AE, as well as AEs of ventricular arrhythmias, were reported during both studies although there was 1 report of QT prolongation in association with an event of atrioventricular block first degree that resolved with continued treatment and was not considered related to ambrisentan treatment. A small mean reduction from baseline in haemoglobin, haematocrit, and platelet count was observed in both Study AMB112529 and the extension study.

The company has also provided data of off-label use in children using the Gilead's ARGUS [the Pharmacovigilance and Epidemiology (PVE) safety database of Gilead]. A total of 1,934 cases, where children aged 8 to less than 18 years old have received ambrisentan, have been reported to Gilead since launch until 14 June 2019. These cases have reported a total of 5,279 events, with some cases reporting more than one event. The most commonly reported adverse events, after off label use, were headache (194), dyspnoea (111), vomiting (86) and diarrhoea (85) all of which are listed in the EU SmPC with a frequency of very common or common. It is noted that a number of events of pneumonia (76 cases) have been reported in the 8 to less than 18 years population.

3.5. Uncertainties and limitations about unfavourable effects

The safety database supporting this application is very limited composed by 41 children included in study AMB112529 and 38 children included in its extension study AMB11458. Despite the safety profile seems similar to that reported in adults in qualitative terms (*i.e.*: headache, gastrointestinal adverse events, oedema, etc.), the small safety database and the absence of a comparator group does not allow for a precise estimate of adverse events in children. The applicant properly commented on the difficulties encountered with the clinical studies enrolment that leads the submission of a limited safety database (41 children included in study AMB112529 and 38 children included in its extension study AMB11458) to support this application. The Applicant has also provided a more detailed adverse events evidence by including a nominally off-label dataset of children and adolescents in the age range of 8 to <18 years receiving ambrisentan for the treatment of PAH. This dataset was composed by data obtained from the paediatric subgroup (119 patients) of an unpublished Japan Post Marketing Surveillance study (Study 114782) as well as reports of off-label use of ambrisentan in this population from the Global Safety Database between 15 June 2018 and 14 June 2019 period. Paediatric patients included in submitted dataset were comparable to those included in the study AMB112529 and its extension AMB114588. Moreover, it seems acceptable to inform on the qualitative similarity of the adult and paediatric safety profile. It is considered that broadening the safety database submitted in the application has improved the safety paediatric profile of this product, despite it does not allow for a

precise estimate of adverse events in paediatric population. The company also presented safety paediatric data including different PAH aetiologies retrieved from divergent sources after a systematic bibliographic search, which appeared to be comparable to those seen in performed clinical trials. Based on them no observation of new safety risks associated with ambrisentan administration was made. Similarly, no divergence in the safety profile compared to the adult population was seen. Despite of the observed limitations it can be concluded that the summarized outcomes obtained from several sources do not show any differences across aetiology subgroups.

Some reported adverse reactions in children were unlisted. Details about unlisted non-serious eosinophilia and lymphopenia (drug-related) cases were provided. In both cases the confounding factors including underlying conditions and concomitant medications may have contributed to the events. Therefore, no new safety concern was identified. No other laboratory abnormalities coded as ambrisentan-related AEs were reported by the Investigator and no PCC has been identified in the study AMB114588.

The majority of subjects used a background PAH medication(s) in both studies, mainly a PDE-5 inhibitor as monotherapy or in combination with a prostanoid. Adverse events by concomitant medications were provided and a similar pattern was observed regardless of concomitant medications used.

The number of children in other conditions apart from IPAH was very scarce to draw any meaningful conclusion about safety in these conditions: 8 children with persistent PAH despite surgical repair, 4 children in connective PAH and 2 children with familial PAH. The applicant was requested to conduct a systematic bibliographic search and to discuss published studies with ambrisentan in children, as well as to compare these results to those obtained in the study AMB112529 and its extension, in terms of adverse events. The additional paediatric safety data including different PAH aetiologies retrieved from divergent sources appeared to be comparable to those seen in performed clinical trials. Based on them no observation of new safety risks associated with ambrisentan administration was made. Similarly, no divergence in the safety profile compared to the adult population was seen. Despite of the observed limitations it can be concluded that the summarized outcomes obtained from several sources do not show any differences across aetiology subgroups.

There was a lack of dose-response regarding adverse events, with more adverse events reported with the ambrisentan low dose. The applicant attempted to analyse different causes that could lead to the observed lack of dose-response regarding adverse events in study AMB112529, with more adverse events reported with the ambrisentan low dose. As stated by the Applicant, it is considered that there is no pattern or trend in adverse event reporting between dose groups, being the differences seen between the two dose groups probably to due to variability in such a small size population.

The number of cases of off-label use reported in children from Gilead's ARGUS database (n=1,934 cases) is much higher than the number of children included in the pivotal study AMB112529 (n=41). The applicant states that the review of the off-label paediatric data in children aged 8 to less than 18 years shows a similar safety profile to that of the adult population with the adverse reactions reported being consistent with those seen in adults, with headache, dyspnoea, vomiting and diarrhoea occurring most frequently. While, qualitatively, the adverse events reported in off-label use in children are within expected for adults, no conclusions can be made with respect to compare incidence rates versus adults. In addition, the 76 pneumonia cases reported in off-label use were further discussed in the applicant and no particular concerns are raised in children.

The Applicant proposed to add new paragraph to the section 4.8 dealing with paediatric safety profile. Although the reported TEAEs are mostly in line with the known ambrisentan safety profile, the currently suggested wording does not specifically reflect the results (drug-related events) reported in two submitted clinical studies and that should be adjusted. In addition, the warning on the fluid

retention events is stated in the Section 4.4 and corresponding PTs are listed in the Section 4.8. The Applicant has also updated the paragraph related to the available safety data collected from clinical studies enrolling paediatric population. Regarding to the events related to the fluid retention, the Applicant specifically elaborated on all events reported in paediatric and adult patients. The consistency in the overall incidence and severity of the cases comparing both populations is claimed, which is agreed. The updated paragraph in Section 4.8 does not contain any information on this matter as only two events of peripheral oedema attributed to the study treatment were seen within paediatric development. The previously listed information in Section 4.4 corresponds with the provided paediatric data and thus can be considered sufficient.

3.6. Effects Table

Table 41 Effects Table for ambrisentan in children with PAH aged 8-17 years (study AMB112529)

Effect	Short description	Unit	Low dose*	High dose†	Uncertainties / Strength of evidence	References
Favourable Effects						
Exercise capacity	Change in 6MWD from baseline to week 24	Metres. Mean (SD)	55.14 (102.18)	26.25 (62.01)	No statistical comparison planned. High variability. No dose response.	Table 18
		Days. Median	49	25.5		
		Days. Min to Max	-110 to 258	-60 to 220		
Clinical worsening	Subject with one or more among: a) All-cause death or active list for lung transplant; b) Hospitalisation for worsening of PAH; c) PAH related deterioration	N (%)	3 (14%)	3 (15%)	No statistical comparison planned. No dose response.	Table 21 of clinical assessment report
Time to clinical worsening	Time to first event among: a) All-cause death or active list for lung transplant; b) Hospitalisation for worsening of PAH; c) PAH related deterioration	Days. Mean (SD)	77.3 (62.56)	71.7 (29.26)	No statistical comparison planned. High variability. No dose response.	Table 21 of clinical assessment report
		Days. Median	55	86		
		Days. Min to Max	29 to 148	38 to 91		
Unfavourable Effects						
All AEs	Adverse events	n (%)	17 (81%)	16 (80%)	Qualitatively similar to those reported in adults (e.g.: headache, nausea, abdominal pain, oedema, etc.). No statistical comparison planned. No dose response.	Table 27
SAEs	Serious adverse	n (%)	6 (29%)	2 (10%)	No statistical	Table 28

Effect	Short description	Unit	Low dose*	High dose†	Uncertainties / Strength of evidence	References
	events				comparison planned. No dose response.	
Deaths	Serious adverse event with a fatal outcome	n (%)	1 (5%)	0 (0%)	Very few events. No dose response.	AMB112529 Clinical study report

*Low dose was defined as: First week: 5 mg/d; Week 2 onwards: 5 mg for children of ≥35 kg, and 2.5 mg for children between ≥20 kg and <35 Kg.
†High dose was defined as: First week: 5 mg/d.

Week 2 onwards: 10 mg in children ≥50 kg, 7.5 mg in children between ≥35 kg and <50 Kg, and 5 mg in children between ≥20 kg and <35 Kg.

Abbreviations: 6MWD = six-minute walk distance; AEs = adverse events; PAH = pulmonary arterial hypertension; SAEs = serious adverse events; SD = standard deviation;

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

In the pivotal trial there was suggestion of an improvement in exercise capacity (6MWD). The 6MWD endpoint has been shown in the adult PAH population to correlate with long term clinical outcome and is generally used to follow exercise tolerance in paediatric PAH patients of appropriate age, being a reliable test in children ≥ 7 years. Interventional clinical trials in adults with PAH have commonly used the 6MWD test to demonstrate efficacy for drug approval [Ollivier, et al. J Am Heart Assoc. 2019;8:e011306]. In absolute terms, the increase in 6MWD was surprisingly more pronounced with the low ambrisentan dose compared to the high dose (55 m vs 26 m), and in the overall population was of 40.69 metres. The MCID for 6MWD reported in the literature is about 33 m [Mathai, et al. Am J Respir Crit Care Med. 2012; 186: 428-33]. Therefore, the favourable trend observed in exercise capacity can be considered of clinical relevance. The main analysis was supported by an ad-hoc analysis of responders, in which 59% of children improved by at least 20 metres at week 24 compared with baseline values. The 40.69 metres observed in children (55 m for the low ambrisentan dose) are consistent with the 44.6 metres (placebo-adjusted mean improvement) reported in a combined analysis of the Phase 3 studies (ARIES-C) conducted in adults for the 5 mg dose, and the 52.5 m improvement observed in adults with 10 mg dose. These comparisons are however fraught with risk because in adults, the improvement correspond to placebo-corrected improvement and in children correspond to improvement versus baseline. In IPAH, exercise capacity correlates with right atrial (RA) pressure, pulmonary arterial pressure (PAP), and cardiac index (CI). These were secondary endpoints in the paediatric trial and some improvements were found at 24 weeks compared to baseline, being consistent with the positive effects seen on exercise capacity.

The risks observed in the paediatric population were similar to those found in adults, with headache and oedema occurring very commonly. These events are usually mild to moderate and manageable in standard practice.

3.7.2. Balance of benefits and risks

The benefits observed in exercise capacity in children were consistent with those found in adults. The risks observed in the paediatric population were also similar to those found in adults, with headache

and oedema occurring very commonly. The applicant has demonstrated similar PK/PD relationship in children and adults, and therefore extrapolation from adults is accepted. In addition, the Company submitted further supportive information from literature and post-marketing studies in children. These data support the effectiveness and safety of ambrisentan in children with various PAH aetiologies. Therefore, the balance between benefits and risks observed in children could be regarded as similarly positive as in adults.

3.8. Conclusions

The overall benefit/risk balance of Volibris in the treatment of PAH in adolescents and children (aged 8 to less than 18 years) is positive.

Similarity with authorised orphan medicinal products

The CHMP is of the opinion that Volibris is not similar to Opsumit (macitentan) or Adempas (riociguat) within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000. See appendix on similarity.

4. Recommendations

Outcome

Based on the CHMP review of data on quality safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of, Volibris 2.5 mg <new pharmaceutical form in the following indication(s):

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

The CHMP therefore recommends the extension(s) of the marketing authorisation for Volibris subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The Marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.
- **Additional risk minimisation measures**

Prior to use of Volibris in each Member State the Marketing Authorisation Holder (MAH) must agree the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority. The MAH shall ensure that in each Member State where Volibris is marketed, all patients who are expected to use Volibris are provided with the following educational material:
• Patient reminder card
Patient reminder card should include the following key elements:
– That Volibris is teratogenic in animals;
– That pregnant women must not take Volibris;
– That women of reproductive potential must use effective contraception;
– The need for monthly pregnancy tests;
– The need for regular monitoring of liver function because Volibris may cause liver injury.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan EMEA-000434-PIP01-08-M06 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

In addition, CHMP recommends the variation(s) to the terms of the marketing authorisation concerning the following change(s):

Variations requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, IIIA and IIIB
A.7	A.7 - Administrative change - Deletion of manufacturing sites	Type IA	II and IIIB
X.02.III	Annex I_2.(c) Change or addition of a new strength/potency	Line Extension	I, IIIA, IIIB and A

Extension application to introduce a new strength (2.5 mg film-coated tablet), for use in paediatric patients from 8-18 years old to treat Pulmonary Arterial Hypertension (PAH).

Extension of indication to include treatment of Pulmonary Arterial Hypertension (PAH) in

adolescents and children (aged 8 to less than 18 years) of WHO Functional Class (FC) II to III including use in combination treatment. The Annex II, labelling and Package Leaflet are updated in accordance. Version 9.0 of the RMP has been submitted
Type IA category A.7, to delete the following manufacturing sites:
"Aspen Bad Oldesloe GmbH, Industriestrasse 32-36, 23843 Bad Oldesloe, Germany" as a site responsible for batch release of the finished product and "Patheon, Inc., Burlington Century Operations, 977 Century Drive, Burlington, ON L7L5J8 Canada" as a quality control release testing site of the finished product.