Division: Worldwide Development
Retention Category: GRS019
Information Type: Protocol Amendment

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

Compound Number: GSK1325760

Effective Date: 25-MAY-2021

Protocol Amendment Number: 04

This is an open label, long term extension to Study AMB112529. All subjects may remain in the extension study for a minimum of six months. Beyond the six month period, subjects may continue in the extension study until one of the following conditions is met:

- the subject turns 18 years of age (when the subject can receive marketed product) or the subject has reached pubertal maturity before 18 years of age and ambrisentan can be supplied through a named patient or expanded access program until the subject reaches 18 years of age
- the product is approved and available for use in the subject's age group,
- development for use in the paediatric population is discontinued.
- the subject decides he/she no longer wants to participate in the study,
- the investigator considers it is in the best interest of the subject to discontinue ambrisentan (e.g. for safety reasons).

The primary objective is the long-term safety and tolerability of ambrisentan in the paediatric PAH population. Secondary objectives are all cause mortality and change from baseline in Study AMB112529 on efficacy parameters.

Subject: Pulmonary Arterial Hypertension, Long Term Extension, Paediatrics

Author: PPD
PPD

Revision Chronology:

RM2010/00282/00	2010-AUG-17	Original
RM2010/00282/01	2010-OCT-26	Amendment No.: 01 Clarify that alkaline phosphatase is a clinical chemistry parameter that will be assessed every three months. Clarify that vital signs, body weight, and height will be assessed every three months. Clarify that for the duration of Study AMB112529, data from AMB114588 will be reviewed by the IDMC at the same times as data from AMB112529 are being reviewed. Clarify the definition of the analysis populations to reflect the fact that this is not a randomized trial.
RM2010/00282/02	2011-FEB-02	Amendment No.: 02 Created in error – never implemented
RM2010/00282/03	2011-FEB-08	Amendment No.: 02 Add oestrogen to the laboratory tests being performed on female subjects at all times that pubertal development assessments are performed. Remove testosterone from the laboratory tests being performed on female subjects at all times that the pubertal development assessments are performed. Change the storage requirements for the study medication to store below 30□C.
RM2010/00282/04	2020-JUN-10	Amendment No.: 03 Update the Medical Monitor, Sponsor Address and Sponsor Signatory

		Remove the requirement for monthly liver function tests unless clinically indicated or occurring at the time of a 3-month visit. Modify the requirement for monthly pregnancy tests to reflect that they may be performed by the subject at home using urine test kits provided by the site or occurring at the time of a 3-month visit Modify the requirement for 6MW testing at 6-month visits to make optional. Clarify the language in Section 5.7 that the 30-day follow-up described after the completion of treatment specifically refers to adverse events. Update Section 8.3.1, Section 8.3.5.1 and Section 8.3.5.2 to reflect that for analyses of the ITT population subjects will be considered as belonging to their treatment group at the time of entering the study, and that analyses using the Safety Population will consider subjects as belonging to the treatment group according to the highest dose received.
TMF-13359039	2021-MAY-25	Amendment No.: 04 Update to the Sponsor Signatory Updates to Summary page 1, Protocol summary, Section 2.1.1, Section 3.1, Section 5.7, Section 6.2.4 and Table 1 footnotes to include changes to when subjects can leave the study and the timing of the pubertal development assessment. New wording to account for the different end of study scenarios for any remaining subjects who are either still

		active or in follow-up in the study: Subjects who reached pubertal maturity before 18 years of age and ambrisentan can be supplied through a named patient or expanded access program until the subject reaches 18 years of age will complete their end of study visit at the investigator site. Subjects who have reached the age of 18 and who have reached pubertal maturity at a previous visit will complete their final study visits in the form of a telephone follow-up. Subjects who have reached the age of 18 and who have not reached pubertal maturity in previous visits will complete their final study visit at the investigator site to have their pubertal development assessed. Clarify that pubertal development assessments do not need to be repeated if pubertal maturity has been reached in a previous visit.

SPONSOR SIGNATORY:

Protocol 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

Protocol Number: AMB114588/Amendment 04

Compound Number or Name: GSK1325760

Kaivan Khavandi, MBChB, MRes, MBA, PhD, MCRP Future Disease Area Lead Clinical Sciences, Specialty	**Date**

The signed page is a separate document.

Medical Monitor Name and Contact Information will be provided separately

SPONSOR INFORMATION PAGE

Clinical Study Identifier: AMB114588

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In some countries, the clinical trial sponsor may be the local GlaxoSmithKline affiliate company (or designee). Where applicable, the details of the Sponsor and contact person will be provided to the relevant regulatory authority as part of the clinical trial submission.

Sponsor Medical Monitor and Serious Adverse Events (SAE) Contact Information:

PPD MD FACC

Clinical Sciences, Respiratory and Specialty
GlaxoSmithKline
Collegeville, Pennsylvania

Regulatory Agency Identifying Number(s): EudraCT 2010-021572-29

US IND 64,915

INVESTIGATOR AGREEMENT PAGE

For protocol AMB114588

I confirm agreement to conduct the study in compliance with the protocol, as amended by this protocol amendment.

I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described clinical study.

I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Investigator Name: _____

_____ _____

Investigator Signature Date

TABLE OF CONTENTS

PAGE

LIST OF ABBREVIATIONS

6MWD	6 minute walking distance test
ACE	Angiotensin-converting enzymes
AE	Adverse Event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BMI	Body mass index
BSA	Body surface area
BUN	Blood urea nitrogen
CCBs	Calcium Channel Blockers
cGMP	Cyclic guanosine monophosphate
CHD	Congenital heart defects
COPD	Congestive obstructive pulmonary disease
CPK	Creatine phosphokinase
CTD	Connective tissue disease
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ERA	Endothelin receptor antagonist
ET	endothelin
EU	European Union
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
GGT	gamma glutamyl transferase
GSK	GlaxoSmithKline
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
INR	International Normalized Ratio
IPAH	Idiopathic Pulmonary Arterial Hypertension
IRB	Institutional Review Board
ITT	Intent-to-Treat
IVRS	Central interactive voice recognition system
IVRS	Interactive Voice Response System
kg	kilogram
LDH	Lactate dehydrogenase
LEVDP	Left ventricular end diastolic pressure
LFT	Liver function test
LH	Luteinizing hormone
m	meter
MCH	mean corpuscular haemoglobin
MCHC	mean corpuscular haemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
mPAP	mean pulmonary arterial pressure
MSDS	Material Safety Data Sheet

NT-Pro BNP	N-Terminal pro-B-type Natriuretic Peptide
PAH	Pulmonary Arterial Hypertension
PAH-CTD	pulmonary arterial hypertension associated with connective tissue disease
PCWP	Pulmonary capillary wedge pressure
PDCO	EMA Paediatric Committee
PDE-5	Phosphodiesterase type 5
PGx	Pharmacogenetic
PIP	Paediatric Investigational Plan
Pk	pharmacokinetic
PVR	Pulmonary vascular resistance
RA	Right atrial
RHC	Right heart catheterisation
RV	Right ventricle
RVF	Right ventricular failure
SAE	Serious Adverse Event
SEM	Standard error of the mean
SHBG	Sex hormone binging globulin
SPC	Summary of Product Characteristics
SPM	Study Procedures Manual
TAPSE	Tricuspid annular plane systolic excursion
TRAX	Tracleer excellence database
TRJ	Tricuspid regurgitant jet
ULN	Upper limit of normal
V/Q	Ventilation/perfusion
WHO	World Health Organization

Trademark Information

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Thelin
Tracleer
Ventavis
Viagra

PROTOCOL SUMMARY

Rationale

Pulmonary arterial hypertension (PAH) is a rare, progressive, highly debilitating disease characterized by vascular obstruction and the variable presence of vasoconstriction, leading to increased pulmonary vascular resistance and right-sided heart failure [Moledina, 2010; Newman, 2004]. If left untreated, PAH ultimately leads to right ventricular failure and death; adult subjects have a median survival of 2.8 years without treatment [Krum, 2000]. Epidemiological estimates vary but prevalence in Europe is thought to be of the order of 15 cases per million [Humbert, 2006]. Large scale epidemiology studies of PAH in children have not been conducted and there is no or limited outcome data in paediatric PAH patients. A register in France (1995-1996) estimates the prevalence in children is as low as 3.7 cases per million [Fraisse, 2010]. In a national, comprehensive country wide survey of the epidemiology of idiopathic PAH (IPAH) management and survival in the United Kingdom (UK) the incidence was 0.48 cases per million children per year and the prevalence was 2.1 cases per million children [Moledina, 2010].

Ambrisentan (VOLIBRIS™ tablets) is an endothelin receptor antagonist (ERA) marketed in the European Union (EU) and some other countries by GlaxoSmithKline (GSK) and in the United States as Letairis by Gilead Sciences Inc. Ambrisentan is indicated for the treatment of adult patients with PAH to improve exercise capacity, decrease the symptoms of PAH, and delay clinical worsening.

The primary purpose of this long term paediatric study is to provide clinically relevant information on the long term safety of ambrisentan in children with the most common causes of PAH in this age group. This study is only open to patients who have participated in 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, and in whom continued treatment with ambrisentan is warranted.

This study is part of a Paediatric Investigational Plan (PIP; EMEA-000434-PIP01-08) agreed with the European Medicines Agency's Paediatric Committee (PDCO).

Objective(s)

The primary objective of this study is to evaluate the long term safety and tolerability of ambrisentan in the paediatric (aged 8 years up to 18 years) PAH population. The secondary objective is to obtain supportive efficacy data (change from baseline in efficacy parameters) on the paediatric use of ambrisentan in PAH. Because patient recruitment in Study AMB112529 was limited by the low prevalence of the disease in children, powered clinical hypotheses testing cannot be performed.

Study Design

This is an open label, long term extension to Study AMB112529. All subjects may remain in the extension study for a minimum of six months. Beyond the six month period, subjects may continue in the extension study until one of the following conditions is met:

- The subject turns 18 years of age (when the subject can receive marketed product) or the subject has reached pubertal maturity before 18 years of age and ambrisentan can be supplied through a named patient or expanded access program until the subject reaches 18 years of age
- The product is approved and available for use in the subject's age group;
- Development for use in the paediatric population is discontinued;
- The subject decides he/she no longer wants to participate in the study;
- The investigator considers it is in the best interest of the subject to discontinue ambrisentan (e.g. for safety reasons).

Study Endpoints/Assessments

Primary

The primary objective is the long-term safety and tolerability of ambrisentan in the paediatric PAH population (see Safety).

Safety

- Adverse Events;
- Serious Adverse Events;
- Clinical laboratory parameters;
- Physical examination (including height, weight, body mass index / body surface area, oxygen saturation, jugular venous pressure, liver size, and presence of peripheral oedema and/or ascites);
- Vital Signs;
- Pubertal development (change from Study AMB112529 baseline in endocrinology assessments every six months and at 20 years of age unless pubertal maturity has been reached in previous visits);
- The time to change in dose of ambrisentan or other targeted PAH therapeutic agents (prostanoids, PDE-5 inhibitors) due to tolerability issues (e.g. adverse events).

Secondary

Efficacy

- All cause mortality;
- The change from Study AMB112529 baseline in the 6 minute walking distance (6MWD) test evaluated every six months;
- The time to clinical worsening of PAH;
- The time to addition of another targeted PAH therapeutic agents (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 three months using the SF-10 health survey for children;
- The change from Study AMB112529 baseline in WHO functional class every six months;
- Change from Study AMB112529 baseline in N-terminal pro-B-type natriuretic peptide (NT-Pro BNP) concentration every six months.

Exploratory

- The change from Study AMB 112529 baseline in major prognostic factors based on echocardiogram: 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 every six months.

Other

- The change from Study AMB112529 baseline cardiopulmonary hemodynamic assessments data in subjects in whom hemodynamic data is considered part of the standard of care (see Appendix 1).

1. INTRODUCTION

Pulmonary arterial hypertension (PAH) is a group of diseases characterised by a progressive increase of pulmonary vascular resistance (PVR) leading to right ventricular failure (RVF) and premature death. A recent meta-analysis estimates survival for untreated idiopathic PAH (IPAH) in adults to be only 79% at 1 year and 66% at 2 years [McLaughlin, 2006]. In the UK, survival in treated children with IPAH at 1, 3 and 5 years was 89%, 84%, and 75% respectively; whilst transplant free survival was 89%, 76%, and 57% respectively [Moledina, 2010].

Detailed, consensus, evidence-based guidelines for the treatment of PAH have been published [Badesch, 2004; Galiè, 2009]. Pharmacological approaches are divided into those that are 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.

Diuretics and anticoagulants have been widely used in the management of PAH, yet response varies [Humbert, 2004]. Calcium channel blockers (CCBs) have shown improved survival in vasoreactive IPAH patients, yet the relatively low incidence of vasoreactivity make CCBs useful only in a minority of the population with PAH [Humbert, 2004; Rich, 1992].

The pathophysiologic mechanisms which underpin the disease spectrum of PAH involve pulmonary vascular dysfunction, which produces an imbalance in vasoactive substances as well as proliferation signals that lead to structural remodelling and pulmonary vasoconstriction. Although its role is not fully understood, endothelin (ET) is considered to be an important mediator of pathology in PAH. Almost all components of the endothelin system are upregulated in PAH [Giaid, 1993; Galiè, 2004]. There appears to be a significant correlation between serum endothelin 1 (ET-1) levels and disease severity, reflected by elevations in PVR, mean pulmonary artery pressure (mPAP) and right atrial pressure [Nootens, 1995]. Endothelin-1 (ET-1) receptor antagonists are a targeted pharmacological approach that limit both the vasoconstrictor and proliferative action of endothelin [Dingemanse, 2004], and in this way ameliorate the clinical manifestations of the disease.

Three signalling pathways involved in the pathogenesis of PAH have been targeted for therapeutic intervention [Humbert, 2004]: the cAMP-dependent prostacyclin (PGI_2) pathway, the cGMP-dependent nitric oxide (NO) pathway, and the phospholipase-C-dependent endothelin pathway. These pathways are targeted by the following classes of PAH medicines: prostanoids (FLOLAN™ [epoprostenol], Ventavis [iloprost] and Remodulin [terprostinil]); phosphodiesterase type-5 (PDE-5) inhibitors (Revatio [EU]/Viagra [sildenafil] and Adcirca [tadalafil])); and ERAs (VOLIBRIS [EU]/Letairis [US] (ambrisentan), Tracleer [bosentan] and Thelin [sitaxentan]).

There is evidence that prostanoid therapies are effective in children, but in common to their use in adults, the pharmacokinetic properties of these drugs and routes of administration (e.g., intravenous, subcutaneous injection, and multiple inhalations) present substantial challenges to their successful use in a paediatric population.

The clinical profile of ambrisentan (an ERA selective for the ETA receptor) 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. It is noted that data from the TRAX[1] database indicates that the risk of elevated aminotransferases with bosentan is lower in children than adults [Beghetti, 2008]. Nevertheless the liver safety profile of ambrisentan in adults has been favourable and if replicated in children would provide a clinically useful option. Children, like adults with PAH, commonly require many concomitant medications. The low risk of drug-drug interactions and convenient once a day dosing associated with ambrisentan may provide a therapeutic option that simplifies treatment in this complex disease.

1.1. Rationale

Pulmonary arterial hypertension (PAH) is a rare, progressive, highly debilitating disease characterized by vascular obstruction and the variable presence of vasoconstriction, leading to increased pulmonary vascular resistance and right-sided heart failure [Moledina, 2010; Newman, 2004]. If left untreated, PAH ultimately leads to right ventricular failure and death; adult subjects have a median survival of 2.8 years without treatment [Krum, 2000]. Epidemiological estimates vary but prevalence in Europe is thought to be of the order of 15 cases per million [Humbert, 2006]. Large scale epidemiology studies of PAH in children have not been conducted and there is no or limited outcome data in paediatric PAH patients. A register in France (1995-1996) estimates the prevalence in children is as low as 3.7 cases per million [Fraisse, 2010]. In a national, comprehensive country wide survey of the epidemiology of idiopathic PAH (IPAH) management and survival in the United Kingdom (UK) the incidence was 0.48 cases per million children per year and the prevalence was 2.1 cases per million children [Moledina, 2010].

Ambrisentan (VOLIBRIS tablets) is an endothelin receptor antagonist (ERA) marketed in the European Union (EU) and some other countries by GlaxoSmithKline (GSK) and in the United States as Letairis by Gilead Sciences Inc. Ambrisentan is indicated for the treatment of adult patients with PAH to improve exercise capacity, decrease the symptoms of PAH, and delay clinical worsening.

The primary purpose of this paediatric study is to provide clinically relevant information on the long term safety of ambrisentan in children with the most common causes of PAH in this age group. This study is only open to patients who have participated in 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, and in whom continued treatment with ambrisentan is warranted.

[1] TRAX - the Tracleer Excellence database is a non-interventional, prospective, internet-based surveillance system initiated by the manufacturer in cooperation with Regulatory agencies to collect potential safety signals associated with bosentan use including adverse events, elevations of liver aminotransferase levels, other abnormal laboratory values, deaths, and hospitalisation [Segal, 2005].

This study is part of a Paediatric Investigational Plan (PIP; EMEA-000434-PIP01-08) agreed with the European Medicines Agency's Paediatric Committee (PDCO).

2. OBJECTIVE(S)

The primary objective of this study is to evaluate the long term safety and tolerability of ambrisentan in the paediatric (aged 8 years up to 18 years) PAH population. The secondary objective is to obtain supportive efficacy data (change from baseline in efficacy parameters) on the paediatric use of ambrisentan in PAH. Because patient recruitment in Study AMB112529 was limited by the low prevalence of the disease in children, powered clinical hypotheses testing cannot be performed.

2.1. Primary

The primary objective is the long-term safety and tolerability of ambrisentan in the paediatric PAH population (see Safety).

2.1.1. Safety

- Adverse Events;
- Serious Adverse Events;
- Clinical laboratory parameters;
- Physical examination (including height, weight, body mass index / body surface area, oxygen saturation, jugular venous pressure, liver size, and presence of peripheral oedema and/or ascites);
- Vital Signs;
- Pubertal development (change from Study AMB112529 baseline in endocrinology assessments every six months and at 20 years of age unless pubertal maturity has been reached in previous visits);
- The time to change in dose of ambrisentan or other targeted PAH therapeutic agents (prostanoids, PDE-5 inhibitors) due to tolerability issues (e.g. adverse events).

2.2. Secondary

2.2.1. Efficacy

- All cause mortality;
- The change from Study AMB112529 baseline in the 6 minute walking distance (6MWD) test evaluated every six months;
- The time to clinical worsening of PAH (Section 6.3.3);
- The time to addition of another targeted PAH therapeutic agents (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 three months using the SF-10 health survey for children;
- The change from Study AMB112529 baseline in WHO functional class every six months;
- Change from Study AMB112529 baseline in N-terminal pro-B-type natriuretic peptide (NT-Pro BNP) concentration every six months.

2.2.2. Exploratory

- The change from Study AMB112529 baseline in major prognostic factors based on echocardiogram: 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 at every 6 months.

2.2.3. Other

- The change from Study AMB112529 baseline in cardiopulmonary hemodynamic assessments data in subjects in whom hemodynamic data is considered part of the standard of care (see Appendix 1).

3. INVESTIGATIONAL PLAN

3.1. Study Design

This is an open label, long term extension to Study AMB112529. All subjects may remain in the extension study for a minimum of six months. Beyond the six month period, subjects may continue in the extension study until one of the following conditions is met:

- The subject turns 18 years of age (when the subject can receive marketed product) or the subject has reached pubertal maturity before 18 years of age and ambrisentan can be supplied through a named patient or expanded access program until the subject reaches 18 years of age;
- The product is approved and available for use in the subject's age group;
- Development for use in the paediatric population is discontinued;
- The subject decides he/she no longer wants to participate in the study;

- The investigator considers it is in the best interest of the subject to discontinue ambrisentan (e.g. for safety reasons).

Protocol waivers or exemptions are not allowed. Therefore, adherence to the study design requirements, including those specified in the Time and Events Table, are essential.

Supplementary study conduct information not mandated to be present in this protocol is provided in the accompanying Study Procedures Manual (SPM). The SPM will provide the site personnel with administrative and detailed technical information that does not impact subject safety.

4. SUBJECT SELECTION AND WITHDRAWAL CRITERIA

4.1. Number of Subjects

As this study is only open to subjects who have participated in AMB112529, no more than 66 subjects will be enrolled into this extension study.

4.2. Inclusion Criteria

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on the GSK investigational product or other study treatment that may impact subject eligibility is provided in the Investigators Brochure and product label.

Deviations from inclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

Subjects eligible for enrolment in the study must meet all of the following criteria:

1. Have participated in and complied, to the best of their ability, with the protocol for AMB112529 and have met **one** of the following:
    a. Completed the Week 24 visit in AMB112529;
    b. Required additional targeted treatment for PAH due to inadequate response to the current treatment or worsening of their clinical condition prior to week 24 in AMB112529;
    c. Required reduction in dose of baseline targeted treatment for PAH after ambrisentan was added to the treatment regimen;
    d. In the opinion of the investigator, continued treatment with ambrisentan is warranted.
2. A female is eligible to participate in this study, as assessed by the investigator, if she is of:
    a. Non-childbearing potential (i.e., physiologically incapable of becoming pregnant); or,

b. Child-bearing potential - has a negative pregnancy test and is not lactating and, if sexually active, agrees to continue to use 2 reliable methods of contraception until study completion and for at least 30 days following the last dose of study drug (reliable methods of contraception are listed in Appendix 2).

3. Subject or subject's legal guardian is able and willing to give written informed consent. As part of the consent, female subjects of childbearing potential will be informed of the risk of teratogenicity and will need to be counselled in a developmentally appropriate manner on the importance of pregnancy prevention; and male subjects will need to be informed of potential risk of testicular tubular atrophy and aspermia.

French subjects: In France, a subject will be eligible for inclusion in this study only if either affiliated to or a beneficiary of a social security category.

4.3. Exclusion Criteria

Deviations from exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

Subjects meeting any of the following criteria must not be enrolled in the study:

1. Subjects who were **withdrawn from ambrisentan** in Study AMB112529;
2. Subjects who did not comply with the protocol in Study AMB112529;
3. Female subjects who are pregnant or breastfeeding;
4. Subjects with severe renal impairment (estimated creatinine clearance <30 mL/min assessed within the previous 45 days) at the point of transition from Study AMB112529 into this study;
5. Subject with clinically significant fluid retention in the opinion of the investigator;
6. Subject with clinically significant anaemia in the opinion of the investigator;
7. Subjects who are to enter another clinical trial or be treated with another investigational product after exiting Study AMB112529.

4.4. Withdrawal Criteria

The Independent Data Monitoring Committee (IDMC) may stop the study at any time if they consider that the potential risks outweigh the potential benefits (based on review of safety [adverse experiences] data (see Section 9.8).

A subject may also be discontinued from the study for the following reasons:

- Liver chemistry values exceeding the threshold criteria (as outlined in Section 6.2.7);
- Adverse event which in the opinion of the investigator requires withdrawal;
- Pregnancy;

- Consent withdrawn;
- Lost to follow-up;
- Protocol violation;
- Termination of study by sponsor;
- Investigator's discretion (document reason in eCRF).

5. STUDY TREATMENTS

5.1. Investigational Product and Other Study Treatment

The sponsor will provide commercially available ambrisentan 5 mg, and 10 mg tablets, as well as 2.5 mg tablets of equivalent quality. For centres in Japan, one or more 2.5 mg tablets will be used to achieve the appropriate dose. Subjects will be dosed orally (tablet must be swallowed whole) once daily. Subjects may receive 2.5, 5, 7.5, or 10 mg of ambrisentan per day, as long as the dose does not exceed 0.25 mg/kg/day.

The contents of the label will be in accordance with all applicable regulatory requirements.

Under normal conditions of handling and administration, investigational product is not expected to pose significant safety risks to site staff. A Material Safety Data Sheet (MSDS) describing the occupational hazards and recommended handling precautions will be provided to site staff if required by local laws or will otherwise be available from GSK upon request.

Investigational product must be stored in a secure area under the appropriate physical conditions for the product. The Investigator, the hospital pharmacist, or other personnel allowed to store and dispense the investigational products will be responsible for ensuring that the investigational product used in the study will be securely maintained as specified by the Sponsor and in accordance with applicable regulatory requirements.

Study medication will be stored in secure (locked) areas at a temperature below 30°C and dispensed according to the protocol under the supervision of the Investigator or his/her designee. Investigational product must be dispensed or administered only to subjects enrolled in the study and in accordance with the protocol. Subjects will be instructed to keep dispensed treatment in a secure place, out of reach of children, and at room temperature.

Subjects will be instructed to return unused medication to the Investigator. Any unused product will be returned by the Investigator to GSK or destroyed at the site based on local regulations.

5.2. Treatment Assignment

This is an open label study. All subjects will receive ambrisentan at a dose individually tailored for each subject. At the time the subject exits Study AMB112529, the investigator will be told the dose of ambrisentan that the subject was receiving. Based on the investigator's best judgement, the subject may continue on the same dose, the dose may be adjusted downward in 2.5 mg increments to not less than 2.5 mg per day or the dose may be 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. Whenever the dose of ambrisentan is changed, one of the following reasons for the change will be recorded:

- Change in body weight;
- Deterioration of clinical condition;
- Tolerability issues (e.g. adverse events);
- Other.

5.3. Blinding

This is an open label study.

5.4. Product Accountability

In accordance with local regulatory requirements, the investigator, designated site staff, or head of the medical institution (where applicable) must document the amount of investigational product dispensed and/or administered to study subjects, the amount returned by study subjects, and the amount received from and returned to GSK, when applicable. Product accountability records must be maintained throughout the course of the study.

5.5. Treatment Compliance

Compliance will be assessed by the investigator or designee every three months and recorded in the eCRF. Compliance is calculated based on the number of tablets dispensed and the number of tablets returned, and the days between the date dispensed and the date returned. Compliance should be assessed for each child resistant blister pack to ensure an accurate assessment. The range of compliance at the appropriate visits will be recorded on the eCRF.

5.6. Concomitant Medications and Non-Drug Therapies

5.6.1. Permitted Medications and Non-Drug Therapies

Standard medical treatment(s), other than those that are explicitly excluded below, that are required by the subject may be added or changed at any time. All prescribed treatments and changes in doses will be recorded in the eCRF. Whenever the dose of other targeted PAH therapeutic agents (e.g. prostanoid or PDE-5 inhibitor) is changed, one of the following reasons will be recorded:

- Change in body weight;
- Deterioration of clinical condition;
- Tolerability issues (e.g. adverse events);
- Other.

Subjects may begin oral contraceptive therapy as per the prescribing information.

5.6.2. Addition of Other Targeted PAH Therapeutic Agents

Other targeted PAH therapeutic agents (e.g., prostanoid or PDE-5 inhibitor) may be added at the discretion of the investigator. Whenever a new treatment is added, one of the following reasons will be recorded:

- Deterioration of clinical condition;
- Lack of beneficial effect with previous therapy (not reaching set treatment goals);
- Electively (preset treatment strategy independent of effects with previous therapies).

5.6.3. Prohibited Medications and Non-Drug Therapies

During the study, patients may not receive:

- Endothelin receptor antagonists other than ambrisentan (e.g., bosentan, sitaxentan);
- Cyclosporine A.

5.7. Treatment after the End of the Study

Subjects can remain in this study until one of the following conditions is met:

- The subject turns 18 years of age (when the subject can receive marketed product) or the subject has reached pubertal maturity before 18 years of age and ambrisentan can be supplied through a named patient or expanded access program until the subject reaches 18 years of age;
- The product is approved and available for use in the subject's age group;
- Development for use in the paediatric population is discontinued;
- The subject decides he/she no longer wants to participate in the study;

- The investigator considers it is in the best interest of the subject to discontinue ambrisentan (e.g. for safety reasons).

The Investigator should then treat the subjects according to best standard of care available to the investigator. Subjects will be followed for 30 days post their last dose of study medication for monitoring of AEs/SAEs.

Subjects will only be asked to return for a pubertal development assessment following their 18th birthday if pubertal maturity had not been reached in a previous visit.

All subjects who reached pubertal maturity before 18 years of age and ambrisentan can be supplied through a named patient or expanded access program until the subject reaches 18 years of age will complete their end of study visit at the investigator site for their end of study assessments as outlined in Table 1. As these subjects had already reached pubertal maturity, no further pubertal development assessments are required.

All subjects who have reached the age of 18 and who have reached pubertal maturity at a previous visit will complete their final study visits in the form of a telephone follow-up. This is to notify the subjects of the end of the study and that no further study visits and assessments will take place.

All subjects who have reached the age of 18 and who have not reached pubertal maturity in previous visits will complete their final study visit at the investigator site to have their pubertal development assessed. These patients may return at any point and do not need to wait until 20 years of age to have their pubertal maturity evaluated.

GSK will continue to provide post-study medication only to subjects in territories where the medication is not available through normal distribution channels.

The investigator is responsible for ensuring that consideration has been given to the post-study care of the patient's medical condition whether or not GSK is providing specific post study treatment.

5.8. Treatment of Study Treatment Overdose

There is no experience in PAH patients of ambrisentan at daily doses greater than 10 mg. In healthy volunteers, single doses of 50 mg and 100 mg (5 to 10 times the maximum recommended dose) were associated with headache, flushing, dizziness, nausea, and nasal congestion.

Due to the mechanism of action, an overdose of ambrisentan could potentially result in hypotension. In case of pronounced hypotension, active cardiac support may be required. No specific antidote is available.

6. STUDY ASSESSMENTS AND PROCEDURES

The following measurements and evaluations will be conducted during the trial. Please refer to the Time and Events Table (Table 1) for additional details on the timing of the assessments. Every effort must be made to adhere to the protocol defined visit schedule.

The data collection tool for this study will be GSK defined eCRFs. In all cases, subject initials will not be collected nor transmitted to GSK. Subject data necessary for analysis and reporting will be entered/transmitted into a validated database or data system. Clinical data management will be performed in accordance with applicable GSK standards and data cleaning procedures.

Table 1 Time and Events Table

Procedure	At Entry into the Study[1]	Monthly[2]	Every Three Months	Every Six Months	End of Study	Follow-up[3]	At 20 years of age[14]
Written informed consent and assent	X						
Inclusion/Exclusion Criteria	X						
Adverse Events	X		X		X	X	
Serious Adverse Events	X		X		X	X	
Liver Function Tests[4]	X	X			X	X	
Clinical Chemistry[5]			X		X		
Haematology[6]			X		X		
Physical Examination				X	X	X	
Vital Signs[7]			X		X	X	
12-lead ECG				X	X	X	
Concomitant Medication			X		X	X	
6 Minute Walk Distance[8]				X	X	X	
WHO Functional Class				X	X	X	
Health Outcome Assessments[9]			X		X	X	
Echocardiogram				X	X	X	
Plasma NT-Pro BNP concentration				X	X	X	
Hemodynamic assessment[10]							
Pregnancy Test[11]	X	X			X	X	
Pubertal Development Assessment[12]				X	X	X	X
Dispense Investigational Product[13]	X		X				
Assess Investigational Product Compliance			X		X		

Table 1 Time and Events Table (Continued)

1. These are transcribed from the End of Therapy (Week 24) visit in Study AMB112529
2. For months that do not correspond to the every three month visits LFTs need not be performed unless clinically indicated, and, these assessments may be performed by the subject's local physician and laboratory. From the time of Amendment 03, urine pregnancy tests may be performed at the subject's home using kits supplied by the site.
3. Only assessed in patients who are withdrawn from ambrisentan; assessment should be conducted within 4 to 6 weeks after last dose of ambrisentan.
4. Includes ALT (SGPT), AST (SGOT), GGT, and total bilirubin
5. Includes sodium, magnesium, potassium, calcium, glucose, chloride, bicarbonate (CO2,) phosphorus-inorganic, creatinine, total protein, albumin, LDH, creatine phosphokinase (CPK), blood urea nitrogen (BUN), uric acid, and alkaline phosphatase
6. Includes platelet count, RBC count, reticulocyte count, hematocrit, hemoglobin, RBC indices (mean corpuscular volume [MCV], mean corpuscular haemoglobin [MCH], and mean corpuscular haemoglobin concentration [MCHC]), WBC count, automated WBC differential (neutrophils-total, lymphocytes, monocytes, eosinophils, basophils)
7. Includes height, weight, supine blood pressure, and heart rate
8. From the time of Amendment 03, this test is optional at the every six month visits. Subjects with a 20% decrease in 6MWD will need to return in 1 week to repeat the test, to confirm PAH deterioration.
9. SF 10 and a record of school days scheduled and missed. A diary card will be given to the subject at each 3-monthly visit on which to record the number of school days scheduled, the number missed for any reason, and the number missed because of symptoms of PAH. The diary cards will be returned at the next visit. Data from all diary cards will be transcribed into the eCRF.
10. Collected only if the assessment is being done as part of the subject's standard care. This is not scheduled per protocol, but if the assessment is being done at any time during the study, the following data will be transcribed into the eCRF: Heart rate, mean blood pressure (systolic, diastolic), mean pulmonary artery (PA) pressure (systolic, diastolic), mean right atrium (RA) pressure, left ventricular end diastolic pressure (LEVDP) or pulmonary capillary wedge pressure (PCWP), cardiac output, cardiac index (calculated value), arterial oxygen saturation and mixed venous oxygen saturation. Record method used to calculate cardiac output measurement (if Fick's principle was used it must be stated if oxygen consumptions is measured or assumed).
11. Either Urine or blood monthly pregnancy tests for females of childbearing potential for the duration of the study: From the time of Amendment 03, urine pregnancy tests may be performed at the subject's home using kits supplied by the site.
12. Pubertal development in male and female subjects will be assessed using Tanner criteria. In male subjects, testicular volume will be assessed using Prader's orchidometer, and blood samples will be obtained to measure follicle-stimulating hormone (FSH), luteinizing hormone (LH), testosterone, sex hormone binding globulin (SHBG) and inhibin B levels. In female subjects, blood samples will be obtained to measure FSH, LH, oestrogen, SHBG and inhibin B levels.
13. Doses may be adjusted upward or downward by 2.5 mg increments. The minimum dose may not be less than 2.5 mg, and the maximum dose may not be greater than the lower of 10 mg per day or 0.25 mg/kg/day.
14. In subjects where pubertal maturity has been reached prior to 20 years of age, the 20-year pubertal development assessment will not be required. All subjects who are over the age of 18 and who have not reached pubertal maturity in previous visits will complete their final study visit at the investigator site and will have their pubertal development assessed. These patients may return at any point and do not need to wait until 20 years of age to have their pubertal maturity evaluated.

6.1. Critical Baseline Assessments

The subject's clinical response in study AMB112529 will be assessed upon exiting Study AMB112529. Only those subjects for whom, in the opinion of the investigator, continued treatment with ambrisentan is in the best interest of the subject will continue into this study.

6.2. Safety

6.2.1. Physical examination

Physical examinations will be performed every six months while the subject is in the study, at the time he subject exits the study, and 4 to 6 weeks after discontinuing ambrisentan for those subjects who do not remain on ambrisentan (including height, weight, body mass index [BMI] / body surface area [BSA], oxygen saturation, jugular venous pressure, liver size, and presence of peripheral oedema and/or ascites) and pubertal development (see Section 6.2.4).

Note: BMI and BSA to be calculated centrally using height and weight collected in the eCRF.

6.2.2. Electrocardiogram / Echocardiogram

A 12-lead ECG will be performed every six months while the subject is in the study, at the time the subject exits the study, and 4 to 6 weeks after discontinuing ambrisentan for those subjects who do not remain on ambrisentan. Any changes since Baseline felt to be significant in the medical and scientific judgement of the investigator are to be recorded as AEs or SAEs in the eCRF.

An echocardiogram will be performed every six months while the subject is in the study, at the time the subject exits the study, and 4 to 6 weeks after discontinuing ambrisentan for those subjects who do not remain on ambrisentan.

6.2.3. Vital Signs, Body Weight and Height

Vital signs (including heart rate and supine blood pressure), height, and weight will be collected every three months.

All measures of blood pressure will be performed using standard sphygmomanometry. If possible, the same sphygmomanometer and arm should be used. Procedural details are provided in the study procedures manual.

6.2.4. Pubertal Development Assessment

Pubertal development in male and female subjects will be assessed every six months while the subject is in the study, at the time the subject exits the study, 4 to 6 weeks after discontinuing ambrisentan for those subjects who do not remain on ambrisentan, and at 20 years of age, unless pubertal maturity has been reached in previous visits. using the Tanner criteria [Marshall, 1969; Marshall, 1970; Cameron, 2004]. In male subjects, testicular volume will be assessed by Prader's orchidometer. These assessments will be performed by a paediatric endocrinologist or another individual with comparable experience employing the Tanner criteria and Prader's orchidometer. Preferably, the same assessor will evaluate an individual subject at each assessment time.

In addition, follicle-stimulating hormone (FSH), luteinizing hormone (LH), testosterone (in male subjects only), oestrogen (in female subjects only), sex hormone binding globulin (SHBG), and inhibin B levels will be assessed every six months while the subject is in the study, at the time the subject exits the study, and 4 to 6 weeks after discontinuing ambrisentan for those subjects who do not remain on ambrisentan.

6.2.5. Time to Change in Dose

The time to change in dose of ambrisentan or other targeted PAH therapeutic agents (prostanoids, PDE-5 inhibitors) is defined as the time from randomization to the first occurrence of a tolerability issue (e.g. adverse events).

6.2.6. Clinical Laboratory Tests

A central laboratory (Quest Diagnostics) will be used for the three and six monthly laboratory assessments. Results from local laboratories can be used for the monthly assessments that do not correspond with a three- or six-month clinic visit. If local laboratories are used, the results will be forwarded to the study site, where they will be entered into the eCRF.

6.2.6.1. Safety Tests

The following tests are required at the time the subject exits the study, four to six weeks after discontinuing ambrisentan for those subjects who do not remain on ambrisentan and at intervals listed below.

- **Liver Function:** serum alanine aminotransferase (ALT/SGPT), aspartate aminotransferase (AST/SGOT), gamma glutamyl transferase (GGT), and total bilirubin at the site visits that take place every 3 months, and otherwise as clinically indicated.
- **Chemistry:** alkaline phosphatase, lactate dehydrogenase (LDH), creatine phosphokinase (CPK), creatinine, sodium, magnesium, potassium, chloride, bicarbonate (CO2), phosphorus-inorganic, calcium, blood urea nitrogen (BUN), uric acid, glucose, total protein, and albumin every three months.

- **Haematology:** haemoglobin, hematocrit, red cell count, red cell indices (mean corpuscular volume [MCV], mean corpuscular haemoglobin [MCH], and mean corpuscular haemoglobin concentration [MCHC]), white blood cell count (total and differential), reticulocyte count, and platelet count every three months.
- **Pregnancy:** Either urine or blood pregnancy tests for female subjects of child bearing potential at the site visits that take place every 3 months. At the intervening monthly intervals, a urine pregnancy test will be performed by the subject at home using a test kit supplied by the site.

6.2.6.2. NT-Pro BNP

- Blood samples for NT-Pro BNP concentration will be collected every six months while the subject is in the study, at the time the subject exits the study, and 4 to 6 weeks after discontinuing ambrisentan for those subjects who do not remain on ambrisentan. Assays for plasma concentrations will be performed in the central laboratory.

Collection, processing, labelling, and shipping of the NT-pro BNP samples to central laboratory are detailed in the SPM.

6.2.7. Liver chemistry stopping and follow up criteria

Phase II liver chemistry stopping and follow up criteria have been designed to assure subject safety and evaluate liver event aetiology.

Phase II liver chemistry stopping criteria 1-5 are defined below:

1. ALT ≥ 3xULN and bilirubin ≥ 2xULN (>35% direct bilirubin) (or ALT ≥ 3xULN and International Normalized Ratio [INR]>1.5, if INR measured).

NOTE: if serum bilirubin fractionation is not immediately available, study drug should be discontinued if ALT ≥ 3xULN **and** bilirubin ≥ 2xULN. Serum bilirubin fractionation should be performed if testing is available. If testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.

2. ALT ≥ 5xULN.
3. ALT ≥ 3xULN if associated with the appearance or worsening of symptoms of hepatitis or hypersensitivity such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash or eosinophilia.
4. ALT ≥ 3xULN persists for ≥4 weeks.
5. ALT ≥ 3xULN and cannot be monitored weekly for 4 weeks.

When any of the liver chemistry stopping criteria 1-5 is met, do the following:

- **Immediately** withdraw investigational product **.**
- Report the event to GSK **within 24 hours** of learning its occurrence.

- Complete the liver event CRF and SAE data collection tool if the event also meets the criteria for an SAE. All events of ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin) (or ALT ≥ 3xULN **and** INR>1.5, if INR measured; INR measurement is not required and the threshold value stated will not apply to patients receiving anticoagulants), termed 'Hy's Law', **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**.

NOTE: if serum bilirubin fractionation is not immediately available, study drug should be discontinued if ALT ≥ 3xULN **and** bilirubin ≥ 2xULN. Serum bilirubin fractionation should be performed if testing is available. If testing is unavailable, **record presence of detectable urinary bilirubin on dipstick,** indicating direct bilirubin elevations and suggesting liver injury.

- Complete the liver imaging and/or liver biopsy CRFs if these tests are performed.
- Perform liver event follow up assessments, and monitor the subject until liver chemistries resolve, stabilize, or return to baseline values as described below.
- Withdraw the subject from the **study** (unless further safety follow up is required) after completion of the liver chemistry monitoring as described below.
- Do not re-challenge with investigational product.

In addition, for criterion 1:

- Make every reasonable attempt to have subjects return to clinic within **24 hours** for repeat liver chemistries, liver event follow up assessments (see below), and close monitoring.
- A specialist or hepatology consultation is recommended.
- Monitor subjects twice weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values.

For criteria 2, 3, 4, and 5:

- Make every reasonable attempt to have subjects return to clinic **within 24-72 hrs** for repeat liver chemistries and liver event follow up assessments (see below)
- Monitor subjects weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values; criterion 5 subjects should be monitored as frequently as possible.

Subjects with ALT ≥3xULN **but** <5xULN **and** bilirubin <2xULN, without hepatitis symptoms or rash, and who can be monitored weekly for 4 weeks

- Notify the GSK medical monitor within 24 hours of learning of the abnormality to discuss subject safety.
- Can continue investigational product [this can be deleted for single-dose studies]
- Must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilize or return to within baseline

- If at any time these subjects meet the liver chemistry stopping criteria, proceed as described above
- If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor subjects twice monthly until liver chemistries normalize or return to within baseline values.

For criteria 1-5, make every attempt to carry out the **liver event follow up assessments** described below:

- Viral hepatitis serology including:
  - Hepatitis A IgM antibody;
  - Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM);
  - Hepatitis C RNA;
  - Cytomegalovirus IgM antibody;
  - Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing);
  - Hepatitis E IgM antibody (if subject resides outside the US or Canada, or has travelled outside US or Canada in past 3 months);
- Blood sample for pharmacokinetic (PK) analysis, obtained within 24 hours of last dose. Record the date/time of the PK blood sample draw and the date/time of the last dose of investigational product prior to blood sample draw on the eCRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SPM.
- Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
- Fractionate bilirubin, if total bilirubin≥2xULN.
- Obtain complete blood count with differential to assess eosinophilia.
- Record the appearance or worsening of clinical symptoms of hepatitis, or hypersensitivity, such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever rash or eosinophilia as relevant on the AE report form.
- Record use of concomitant medications, acetaminophen, herbal remedies, other over the counter medications, or putative hepatotoxins, on the concomitant medications report form.
- Record alcohol use on the liver event alcohol intake case report form

The following are required for subjects with ALT ≥3xULN and bilirubin ≥2xULN (>35% direct) but are optional for other abnormal liver chemistries:

- Anti-nuclear antibody, anti-smooth muscle antibody, and Type 1 anti-liver kidney microsomal antibodies.

- Liver imaging (ultrasound, magnetic resonance, or computerized tomography) to evaluate liver disease.

6.2.8. Adverse Events

The investigator or site staff will be responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

6.2.8.1. Definition of an AE

Any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Note: An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e., lack of efficacy), abuse or misuse.

Events meeting the definition of an AE include:

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition
- New conditions detected or diagnosed after investigational product administration even though it may have been present prior to the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected interaction
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either investigational product or a concomitant medication (overdose per se will not be reported as an AE/SAE).

“Lack of efficacy” or “failure of expected pharmacological action” per se will not be reported as an AE or SAE. However, the signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfil the definition of an AE or SAE.

Events that **do not** meet the definition of an AE include:

- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject’s condition.

6.2.8.2. Definition of a SAE

A serious adverse event is any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

   NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires hospitalization or prolongation of existing hospitalization

   NOTE: In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

   Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in disability/incapacity, or

   NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Medical or scientific judgement should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

g. All events of possible drug-induced liver injury with hyperbilirubinaemia defined as ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct) (or ALT ≥ 3xULN and INR>1.5, if INR measured) termed 'Hy's Law' events (INR measurement is not required and the threshold value stated will not apply to patients receiving anticoagulants).

NOTE: bilirubin fractionation is performed if testing is available. If testing is unavailable, record the presence of detectable urinary bilirubin on dipstick indicating direct bilirubin elevations and suggesting liver injury. If testing is unavailable and a subject meets the criterion of total bilirubin ≥ 2xULN, then the event is still reported as an SAE. If INR is obtained, include values on the SAE form. INR elevations >1.5 suggest severe liver injury.

6.2.9. Laboratory and Other Safety Assessment Abnormalities Reported as AEs and SAEs

Any abnormal laboratory test results (haematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgement of the investigator are to be recorded as AEs or SAEs.

However, any clinically significant safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition, are **not** to be reported as AEs or SAEs.

6.2.10. Pregnancy

Subjects who become pregnant during the study must discontinue study drug immediately. The Investigator should counsel the subject regarding the possible effects of prior study drug exposure on the foetus (See SmPC and USPI) and the need to inform the study site of the outcome of the pregnancy. Subjects should be instructed to notify the Investigator if they become pregnant at any time during the study, or if they become pregnant within 30 days of last study drug dose.

Any pregnancy that occurs during study participation must be reported using a clinical trial pregnancy form. To ensure subject safety, each pregnancy must be reported to GSK within 2 weeks of learning of its occurrence. The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE.

Any SAE occurring in association with a pregnancy brought to the investigator's attention after the subject has completed the study and considered by the investigator as possibly related to the investigational product, must be promptly reported to GSK.

6.2.11. Time Period and Frequency of Detecting AEs and SAEs

The investigator or site staff is responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

AEs will be collected from the start of investigational product and until 30 days after the last dose of investigational product.

SAEs will be collected over the same time period as stated above for AEs. However, any SAEs assessed **as related** to study participation (e.g., investigational product, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK concomitant medication, will be recorded from the time a subject consents to participate in the study up to and including any follow up contact. All SAEs will be reported to GSK within 24 hours, as indicated in Section 6.2.12.

6.2.12. Prompt Reporting of Serious Adverse Events and Other Events to GSK

SAEs, pregnancies, and liver function abnormalities meeting pre-defined criteria will be reported promptly by the investigator to GSK as described in the following table once the investigator determines that the event meets the protocol definition for that event.

	Initial Reports		Follow-up Information on a Previous Report	
Type of Event	**Time Frame**	**Documents**	**Time Frame**	**Documents**
All SAEs	24 hours	"SAE" data collection tool	24 hours	Updated "SAE" data collection tool
Pregnancy	2 Weeks	Pregnancy Notification Form	2 Weeks	Pregnancy Follow up Form
Liver chemistry abnormalities Phase II:				
ALT≥3xULN **and** Bilirubin≥2xULN (>35% direct) (or ALT≥3xULN **and** INR>1.5, if INR measured)***	24 hours*	SAE data collection tool. **Liver Event Case Report Form (CRF) and liver imaging and/or biopsy CRFs if applicable	24 hours	Updated SAE data collection tool. **Updated Liver Event CRF
ALT≥5xULN; ALT≥3xULN with hepatitis or rash **or** 3xULN ≥4 weeks	24 hours*	**Liver Event CRF	24 hours	**Updated Liver Event CRF
ALT≥3xULN and <5xULN and biliribin <2xULN	24 hours*	**Liver Event CRF does not need completing unless elevations persist for 4 weeks or subject cannot be monitored weekly for 4 weeks		

*GSK to be notified at onset of liver chemistry elevations to discuss subject safety.
** Liver event documents should be completed as soon as possible.
*** INR measurement is not required; if measured, the threshold value stated will not apply to patients receiving anticoagulants.

The method of detecting, recording, evaluating and follow-up of AEs and SAEs plus procedures for completing and transmitting SAE reports to GSK are provided in the SPM. Procedures for post-study AEs/SAEs are provided in the SPM.

Procedures for documenting, transmitting and follow-up of medical device incidents along with the regulatory reporting requirements for medical devices are provided in the SPM.

6.2.12.1. Regulatory reporting requirements for SAEs

Prompt notification of SAEs by the investigator to GSK is essential so that legal obligations and ethical responsibilities towards the safety of subjects are met.

GSK has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. GSK will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and investigators.

Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and GSK policy and are forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from GSK will file it with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

6.3. Efficacy

6.3.1. All cause mortality

All-cause mortality will be assessed.

6.3.2. Change from Study AMB112529 baseline in the 6 minute walking distance (6MWD) test.

The 6MWD will be assessed every six months while the subject is in the study but will be considered optional to perform at visits that take place after the approval of Protocol Amendment 03. The 6MWD will also be assessed at the time the subject exits the study, and 4 to 6 weeks after discontinuing ambrisentan for those subjects who do not remain on ambrisentan. Subjects with a 20% decrease in 6MWD will need to return in 1 week to repeat the test, to confirm PAH deterioration.

6.3.3. Time to worsening of PAH

Time to clinical worsening of PAH is defined as the time from randomization to the first occurrence of:

- Death (all cause), placed on active list for lung transplant, and/or atrial septostomy;
- Hospitalisation due to PAH deterioration;
- Addition of another targeted PAH therapeutic agents (prostanoids, PDE-5 inhibitors) due to deterioration of clinical condition;
- Change in dose of ambrisentan or other targeted PAH therapeutic agents (prostanoids, PDE-5 inhibitors) due to deterioration of clinical condition;

- PAH related deterioration identified by:
  - Increase in WHO functional class;
  - Deterioration in exercise testing (i.e., 20% decrease in 6MWD on two consecutive tests - 1 week apart);
  - Clinical signs or symptoms of right sided heart failure (i.e., new peripheral edema, increase in liver size, ascites, increase in jugular venous pressure, pericardial effusion, increased dyspnea).

6.3.4. Time to Addition of Other Targeted PAH Therapeutic Agents

Time to addition of another targeted PAH therapeutics agents are defined as the time from randomization to the first occurrence of:

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

6.3.5. Time to Change in Dose

Time to change in dose of ambrisentan or other targeted PAH therapeutic agents (prostanoids, PDE-5 inhibitors) is defined as the time from randomization to the first occurrence of a dose change due to deterioration of clinical condition.

6.3.6. Change from Study AMB112529 baseline in Subject Global Assessment.

Global assessments will be performed every three months while the subject is in the study, at the time the subject exits the study, and 4 to 6 weeks after discontinuing ambrisentan for those subjects who do not remain on ambrisentan.

6.3.7. Change from Study AMB112529 baseline in WHO functional class.

WHO functional class will be determined every six months while the subject is in the study, at the time the subject exits the study, and 4 to 6 weeks after discontinuing ambrisentan for those subjects who do not remain on ambrisentan.

6.3.8. Change from Study AMB112529 baseline plasma N-terminal pro-B type natriuretic peptide (NT-Pro BNP).

Blood samples for determination of N-Terminal pro-B-type Natriuretic Peptide plasma concentrations will be determined every six months or early withdrawal. A central lab (Quest Diagnostics) will analyze all samples.

6.3.9. Change from Study AMB112529 baseline in major prognostic factors.

Echocardiograms will be performed every six months while the subject is in the study, at the time the subject exits the study, and 4 to 6 weeks after discontinuing ambrisentan for those subjects who do not remain on ambrisentan.

Prognostic factors included pericardial effusion, RA pressure, tricuspid annular plane systolic excursion (TAPSE), eccentricity index (systolic and diastolic), and right ventricular (RV) pressure by tricuspid regurgitant jet (TRJ) velocity. These evaluations were considered exploratory in this study.

6.3.10. Change from Study AMB112529 baseline in cardiopulmonary hemodynamics.

Cardiopulmonary hemodynamic assessments data will be collected in subjects in whom hemodynamic data is considered part of the standard of care (see Appendix 1).

6.4. Health Outcomes

Patient global assessments will be performed every three months while the subject is in the study, at the time the subject exits the study, and 4 to 6 weeks after discontinuing ambrisentan for those subjects who do not remain on ambrisentan. Health outcomes will be recorded using the parent-completed Short Form 10 (SF-10) Health Survey for children.

The short-form 10 (SF-10) Health Survey for Children is a 10-item, 4-week recall, parent-completed health assessment that measures physical and psychosocial functioning for children ages five and over. Specific domains include Physical Functioning (2 items), Role/Social Emotional-Behavioral (1 item), Role/Social Physical (1 item), Bodily Pain (1 item), General Behavior (1 item), Mental Health (1 item), Self Esteem (2 items), and General Health Perceptions (1 item). This instrument provides a brief, reliable, and scientifically valid health status measurement that is easy to administer and interpret.

In addition to the SF-10, specific questions will be asked regarding school days as follows:

1. CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.
2.
3.

Subjects will record the days of school scheduled and missed on a patient diary card, which will be returned to the clinic at the scheduled visits.

7. DATA MANAGEMENT

For this study, subject data will be entered into GSK defined electronic case report forms (eCRFs), transmitted electronically to GSK, and combined with data provided from other sources in a validated data system.

Management of clinical data will be performed in accordance with applicable GSK standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data. Adverse events and concomitant medications terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), and an internal validated medication dictionary, GSKDrug. eCRFs (including queries and audit trails) will be retained by GSK, and copies will be sent to the investigator to maintain as the investigator copy. In all cases, subject initials will not be collected or transmitted to GSK according to GSK policy.

8. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

8.1. Hypotheses

No formal hypothesis testing is planned for the study

8.2. Study Design Considerations

Study design considerations are described below.

8.2.1. Sample Size Assumptions

Sample size is based on feasibility. Due to low prevalence of the disease, no more than 66 will be enrolled in the study.

8.2.2. Sample Size Sensitivity

No sample size sensitivity calculations were performed.

8.2.3. Sample Size Re-estimation

No sample size re-estimation is planned

8.3. Data Analysis Considerations

8.3.1. Analysis Populations

The Intention-to-Treat (ITT) Population will consist of all subjects who received at least 1 dose of study drug. For the ITT population, subjects were considered as belonging to their treatment group corresponding to the dose being received at the time the subject

transitioned into the study from Protocol AMB112529. . The ITT population will be used in all population and efficacy summaries.

The Safety Population is defined as all subjects who received at least 1 dose of study drug. Subjects were considered as belonging to the treatment group according to the highest dose received. The safety population will be used in all safety summaries.

8.3.2. Analysis Data Sets

Analysis datasets will consist of all data collected in the study and evaluated according to the populations described in Section 8.3.1.

8.3.3. Treatment Comparisons

8.3.3.1. Primary Comparisons of Interest

There are no formal comparisons planned for this study. Doses of Ambrisentan will be summarized descriptively based on available data for:

- Adverse Events;
- Serious Adverse Events;
- Clinical laboratory parameters;
- Physical examination (Including height, weight, body mass index / body surface area, oxygen saturation, jugular venous pressure, liver size, and presence of peripheral oedema and/or ascites);
- Vital Signs;
- Pubertal development (change from Study AMB112529 baseline in endocrinology assessments every six months);
- The time to change in dose of ambrisentan or other targeted PAH therapeutic agents (prostanoids, PDE-5 inhibitors) due to tolerability issues (e.g. adverse events).

8.3.3.2. Other Comparisons of Interest

The following data will also be presented descriptively and graphically by dose levels:

- All cause mortality;
- The change from Study AMB112529 baseline in the 6 minute walking distance (6MWD) test evaluated every six months;
- The time to clinical worsening of PAH;
- The time to addition of another targeted PAH therapeutic agents (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 three months using the SF-10 health survey for children;
- The change from Study AMB112529 baseline in WHO functional class every six months;
- Change from Study AMB112529 baseline in N-terminal pro-B-type natriuretic peptide (NT-Pro BNP) concentration every six months;
- The change from Study AMB112529 baseline in major prognostic factors based on echocardiogram: 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 at every 6 months;
- Change from Study AMB112529 baseline in cardiopulmonary hemodynamic assessments data in subjects in whom hemodynamic data is considered part of the standard of care (see Appendix 1).

8.3.4. Interim Analysis

No interim analysis have been planned for the study

8.3.5. Key Elements of Analysis Plan

8.3.5.1. Safety Analyses

All subjects who received at least one dose of study medication will be assessed for clinical safety and tolerability and will be denoted as the Safety population.

Clinical interpretation will be based upon review of displays of adverse events, laboratory values, vital signs, physical examination, and pubertal development. Principal considerations in this evaluation of adverse events will be time to onset and investigator-reported relationship of either adverse events or laboratory abnormalities to study medication. For each laboratory test, the number and percentage of subjects with values above the reference range will be displayed for each treatment group and overall. Appropriate monitoring of safety data will be conducted throughout the conduct of the study.

No formal statistical analysis is planned for safety parameters. All data will be presented descriptively or graphically, by treatment group according to the highest dose received **and overall**. Where data are available, it will be summarised by visit.

8.3.5.2. Efficacy Analyses

All subjects from the ITT population will be included in the analysis of efficacy data. Given the small sample size, all efficacy data will be summarized descriptively (including 95% CI) and graphically. Data will be summarized by treatment group corresponding to the dose being received at the time the subject transitioned into the study from Protocol AMB112529, and overall.

The summary analysis will include:

- All cause mortality;
- Mean change from Study AMB112529 baseline in the 6MWD at every 6 months;
- Mean time to clinical worsening of PAH;
- Mean time to addition of another targeted PAH therapeutic agents (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);
- Mean time to change in dose of ambrisentan or other targeted PAH therapeutic agents (prostanoids, PDE-5 inhibitors) due to deterioration of clinical condition;
- Change from Study AMB112529 baseline in Subject Global Assessment at every 3 months;
- Change from Study AMB112529 baseline in WHO functional class at every 6 months;
- Change from Study AMB112529 baseline in NT-Pro BNP concentration at every 6 months;
- The change from Study AMB112529 baseline in major prognostic factors based on echocardiogram: 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 at every 6 months;
- The change from Study AMB112529 baseline in cardiopulmonary hemodynamic assessments data in subjects in whom hemodynamic data is considered part of the standard of care (see Appendix 1).

Time to clinical worsening will be also presented graphically by Kaplan-Meier curve.

More details of the statistical analysis will be presented in the Research and Analysis Plan (RAP).

8.3.5.3. Health Outcomes Analyses

Two sets of summary scores will be calculated based on responses to each item on the SF-10 Health Survey for Children (see Section 6.4):

- Physical Health Summary (PHS-10); and
- Psychosocial Summary (PSS-10).

The mean change from Study AMB112529 baseline in SF-10 scores will be calculated every three months.

8.3.5.4. Pharmacodynamic Analyses

Not planned

8.3.5.5. Pharmacokinetic/Pharmacodynamic Analyses

Not planned

9. STUDY CONDUCT CONSIDERATIONS

9.1. Posting of Information on Clinicaltrials.gov

Study information from this protocol will be posted on clinicaltrials.gov before enrolment of subjects begins.

9.2. Regulatory and Ethical Considerations, Including the Informed Consent Process

Prior to initiation of a study site, GSK will obtain approval from the appropriate regulatory agency to conduct the study in accordance with applicable country-specific regulatory requirements, including those required under a US IND.

The study will be conducted in accordance with all applicable regulatory requirements.

The study will be conducted in accordance with Good Clinical Practice (GCP), all applicable subject privacy requirements, and the ethical principles that are outlined in the Declaration of Helsinki 2008, including, but not limited to:

- Institutional Review Board (IRB)/Independent Ethics Committee (IEC) review and approval of study protocol and any subsequent amendments;
- Subject informed consent;
- Investigator reporting requirements.

GSK will provide full details of the above procedures, either verbally, in writing, or both.

Written informed consent must be obtained from each subject prior to participation in the study.

9.3. Quality Control (Study Monitoring)

In accordance with applicable regulations, GCP, and GSK procedures, GSK monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and GSK requirements. When reviewing data collection procedures, the discussion will include identification, agreement and documentation of data items for which the CRF will serve as the source document.

GSK will monitor the study to ensure that the:

- Data are authentic, accurate, and complete;
- Safety and rights of subjects are being protected;
- Study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents.

9.4. Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, GSK may conduct a quality assurance audit of the site records, and the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study. In the event of an audit or inspection, the investigator (and institution) must agree to grant the auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss any findings/relevant issues.

9.5. Study and Site Closure

Upon completion or termination of the study, the GSK monitor will conduct site closure activities with the investigator or site staff (as appropriate), in accordance with applicable regulations, GCP, and GSK Standard Operating Procedures.

GSK reserves the right to temporarily suspend or terminate the study at any time for reasons including (but not limited to) safety issues, ethical issues, or severe non-compliance. If GSK determines that such action is required, GSK will discuss the reasons for taking such action with the investigator or head of the medical institution (where applicable). When feasible, GSK will provide advance notice to the investigator or head of the medical institution of the impending action.

If a study is suspended or terminated for **safety reasons**, GSK will promptly inform all investigators, heads of the medical institutions (where applicable),and/or institutions conducting the study. GSK will also promptly inform the relevant regulatory authorities

of the suspension/termination along with the reasons for such action. Where required by applicable regulations, the investigator or head of the medical institution must inform the IRB/IEC promptly and provide the reason(s) for the suspension/termination.

9.6. Records Retention

Following closure of the study, the investigator or head of the medical institution (where applicable) must maintain all site study records (except for those required by local regulations to be maintained elsewhere) in a safe and secure location. The records must be easily accessible when needed (e.g., for a GSK audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.

Where permitted by local laws/regulations or institutional policy, some or all of the records may be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution must be exercised before such action is taken. The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original. In addition, they must meet accessibility and retrieval standards, including regeneration of a hard copy, if required. The investigator must also ensure that an acceptable back-up of the reproductions exists and that there is an acceptable quality control procedure in place for creating the reproductions.

GSK will inform the investigator of the time period for retaining the site records in order to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to a particular site, as dictated by local laws/regulations, GSK standard operating procedures, and/or institutional requirements.

The investigator must notify GSK of any changes in the archival arrangements, including, but not limited to archival of records at an off-site facility or transfer of ownership of the records in the event that the investigator is no longer associated with the site.

9.7. Provision of Study Results to Investigators, Posting to the Clinical Trials Register and Publication

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

GSK will provide the investigator with the randomization codes for their site only after completion of the full statistical analysis.

The results summary will be posted to the Clinical Study Register no later than 12 months after the last subject's last visit (LSLV) or sooner if required by legal agreement, local law or regulation. In addition, a manuscript will be submitted to a peer-reviewed journal for publication within 18 months of LSLV. When manuscript publication in a peer-reviewed journal is not feasible, further study information will be posted to the GSK Clinical Study Register to supplement the results summary.

9.8. Independent Data Monitoring Committee (IDMC)

The IDMC from Study AMB112529 will be utilized in this study to ensure external objective medical and/or statistical review of safety and/or efficacy issues in order to protect the ethical and safety interests of subjects and to protect the scientific validity of the study. For the duration of Study AMB112529, the IDMC will review the data from AMB114588 at the same time the IDMC reviews the data from AMB112529. The schedule of any planned interim analysis and the analysis plan for IDMC review is described in the charter, which is available upon request.

10. REFERENCES

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11. APPENDICES

11.1. Appendix 1: Cardiopulmonary Hemodynamic Sub-study

Hemodynamic assessments are neither scheduled nor required as a part of this study; however, any time that hemodynamic data are being collected as a part of the standard of care for a subject enrolled in this study, the following data will be transcribed to the eCRF:

Hemodynamic assessments will include:

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

11.2. Appendix 2: List of Highly Effective Methods for Avoidance of Pregnancy in Women of Childbearing Potential

The following is the all inclusive list of the highly effective methods for avoiding pregnancy (i.e., have a failure rate of less than 1% per year):

- Abstinence [Hatcher, 2004];
- Combination Oral Contraceptive [Hatcher, 2004];
- Injectable progestogen [Hatcher, 2004];
- Implants of levonorgestrel [Hatcher, 2004];
- Estrogenic vaginal ring [Hatcher, 2004];
- Percutaneous contraceptive patches [Hatcher, 2004];
- Intrauterine device (IUD) or intrauterine system (IUS) that meets the SOP effectiveness criteria as stated in the product label [Hatcher, 2004];
- Male partner sterilization (vasectomy with documentation of azoospermia) prior to the **female subject's entry** into the study, and this male is the sole partner for that subject [Hatcher, 2004]. For this definition, "documented" refers to the outcome of the investigator's/designee's medical examination of the subject or review of the subject's medical history for study eligibility, as obtained via a verbal interview with the subject or from the subject's medical records;
- Double barrier method: condom and an occlusive cap (diaphragm or cervical/vault caps) with a vaginal spermicidal agent (foam/gel/film/cream/suppository) [Trussell, 2003].

  Nonoxynol-9 is the critical component in most spermicides, and is regarded as an acceptable spermicidal agent. Concern has been raised that nonoxynol-9 damages the epithelial lining of the vagina, and exposure may facilitate transmission of viruses, particularly human immunodeficiency virus (HIV). The World Health Organization (WHO) conducted a technical consultation in October 2001 and concluded that the increased risk for such transmission was low to minimal [Trussell, 2003].

References

Hatcher RA, Trussell J, Stewart F, Nelson AL, Cates W, Guest F, Kowal DD, editors. Contraceptive Technology. New York: Ardent Media, 2004: 226. Table 9-2, "% of Women Experiencing an Unintended Pregnancy During the First Year of Typical Use and the First Year of Perfect Use of Contraception and the Percentage Continuing Use at the End of the First Year. United States", column entitled, "% of Women Experiencing an Unintended Pregnancy Within the First Year of Use. Perfect Use".

Trussell J. Personal communication WHO/CONRAD Technical consultation on nonoxynol-9. WHO, Geneva, 9-10 October 2001. Summary Report. World Health Organization, 2003

11.3. Appendix 3: Country Specific Requirements

Not Applicable.

11.4. Appendix 4: Protocol Amendment 01

Statement of Intent

The intents of this amendment are to clarify procedural issues to insure a better global understanding of intent of the protocol and to correctly categorize alkaline phosphatase as a clinical chemistry parameter rather than a liver function test..

Amended Sections of the Protocol

Deletions are noted in *Italics*

Insertions are noted in **bold face**.

Sponsor Information Page

Was

Sponsor Medical Monitor Contact Information:

PPD FRCS
Clinical Development Physician
MDC Clinical Metabolic EU
GlaxoSminthKline
Stockley Park

Sponsor Serious Adverse Events (SAE) Contact Information:

PPD *MD*
PPD *Safety Evaluation & Risk Management*
GCSP Cardio & Metabolic SERM
GlaxoSmithKline
1250 South Collegeville Road
Collegeville, PA 19426-2990
United States

Is

Sponsor Medical Monitor **and Serious Adverse Events (SAE)** Contact Information:

PPD FRCS
Clinical Development Physician
MDC Clinical Metabolic EU
GlaxoSminthKline
Stockley Park

Section 4.3 Withdrawal Criteria

Was

The Independent Data Monitoring Committee (IDMC) may stop the study at any time if they consider that the potential risks outweigh the potential benefits (based on review of safety [adverse experiences] data *every three months*.

Is

The Independent Data Monitoring Committee (IDMC) may stop the study at any time if they consider that the potential risks outweigh the potential benefits (based on review of safety [adverse experiences] data **(see Section 9.8).**

Rationale

Depending on the patient accrual rate in study AMB112529 and the rate of occurrence of serious adverse experiences, the IDMC review may be sooner or later than every three months.

Table 1 footnote 3

Was

3. Only *for* patients who are withdrawn from ambrisentan; within 4 to 6 weeks after last dose *of investigational drug*

Is

3. Only **assessed in** patients who are withdrawn from ambrisentan; **assessment should be conducted** within 4 to 6 weeks after last dose of **ambrisentan**

Rationale

To make the statement more clear.

Section 6.2.3 Vital Signs, Body Weight and Height

Was

Vital signs (including heart rate and supine blood pressure), height, and weight will be collected at *each study visit*.

Is

Vital signs (including heart rate and supine blood pressure), height, and weight will be collected **every three months.**

Rationale

The original intent was that the study visits would be every three months and liver function tests and pregnancy tests (where applicable) would be conducted locally (*i.e.,* outside of a scheduled “study visit”); however, for some patients, the liver function tests

and pregnancy tests will be conducted at the study centre. This makes the term "at each study visit" ambiguous.

Section 6.2.6.1 Safety Tests

Was

The following tests are required at the time the subject exits the study, four to six weeks after discontinuing ambrisentan for those subjects who do not remain on ambrisentan and at intervals listed below.

- **Liver Function:** serum alanine aminotransferase (ALT/SGPT), aspartate aminotransferase (AST/SGOT), *alkaline phosphatase*, gamma glutamyl transferase (GGT), and total bilirubin monthly.
- **Chemistry:** lactate dehydrogenase (LDH), creatine phosphokinase (CPK), creatinine, sodium, magnesium, potassium, chloride, bicarbonate (CO2), phosphorus-inorganic, calcium, blood urea nitrogen (BUN), uric acid, glucose, total protein, and albumin every three months.

Is

The following tests are required at the time the subject exits the study, four to six weeks after discontinuing ambrisentan for those subjects who do not remain on ambrisentan and at intervals listed below.

- **Liver Function:** serum alanine aminotransferase (ALT/SGPT), aspartate aminotransferase (AST/SGOT), gamma glutamyl transferase (GGT), and total bilirubin monthly.
- **Chemistry: alkaline phosphatase**, lactate dehydrogenase (LDH), creatine phosphokinase (CPK), creatinine, sodium, magnesium, potassium, chloride, bicarbonate (CO2), phosphorus-inorganic, calcium, blood urea nitrogen (BUN), uric acid, glucose, total protein, and albumin every three months.

Rationale

To correct a mistake in the original protocol. The time and events table of the original protocol correctly listed alkaline phosphatase under chemistry, but the text incorrectly listed alkaline phosphatase as a liver function test.

Section 8.3.1 Analysis Populations

Was

The Intention-to-Treat (ITT) Population will consist of all *randomized* subjects who received at least 1 dose of study drug. For the ITT population, subjects were considered as belonging to their *randomized* treatment group, regardless of the *actual* dose of ambrisentan *received*. The ITT population will be used in all efficacy summaries.

The Safety Population is defined as all *randomized* subjects who received at least 1 dose of study drug. Subjects were considered as belonging to the treatment group according to highest dose received. The safety population will be used in all safety summaries.

Is

The Intention-to-Treat (ITT) Population will consist of all subjects who received at least 1 dose of study drug. For the ITT population, subjects were considered as belonging to their treatment group **at the time of the visit/event**, regardless of the **baseline** dose of ambrisentan. The ITT population will be used in all efficacy summaries.

The Safety Population is defined as all subjects who received at least 1 dose of study drug. Subjects were considered as belonging to the treatment group according to **the** highest dose received. The safety population will be used in all safety summaries.

Rationale

From the time a patient enters AMB114388, doses may be adjusted based on the clinical judgment of the investigator; thus, the randomization that existed in AMB112529 is no longer applicable.

Section 9.8 Independent Data Monitoring Committee (IDMC)

Was

An IDMC will be utilized in this study to ensure external objective medical and/or statistical review of safety and/or efficacy issues in order to protect the ethical and safety interests of subjects and to protect the scientific validity of the study. The schedule of any planned interim analysis and the analysis plan for IDMC review is described in the charter, which is available upon request.

Is

The IDMC **from Study AMB112529** will be utilized in this study to ensure external objective medical and/or statistical review of safety and/or efficacy issues in order to protect the ethical and safety interests of subjects and to protect the scientific validity of the study. **For the duration of Study AMB112529, the IDMC will review the data from AMB114588 at the same time the IDMC reviews the data from AMB112529.** The schedule of any planned interim analysis and the analysis plan for IDMC review is described in the charter, which is available upon request.

Rationale

To clarify that the data from the two studies that are being conducted in the same patient population will be reviewed together.

11.5. Appendix 5: Protocol Amendment 02

Statement of Intent

The intents of this amendment are to add oestrogen and remove testosterone from laboratory assessments being conducted on female subjects and to align the storage conditions requirements in the protocol with those that are printed on the study medication package.

Amended Sections of the Protocol

Deletions are noted in *Italics*

Insertions are noted in **bold face**.

In Section 5.1 Investigational Product and Reference Therapy

Was:

Study medication will be stored in secure (locked) areas at a temperature *between 15° and* 30°C and dispensed according to the protocol under the supervision of the Investigator or his/her designee.

Is:

Study medication will be stored in secure (locked) areas at a temperature **below** 30°C and dispensed according to the protocol under the supervision of the Investigator or his/her designee.

Table 1 – Time and Events Table

Footnote 12

Was:

12. Pubertal development in male and female subjects will be assessed using Tanner criteria. In male subjects, testicular volume will be assessed using Prader's orchidometer. *In addition,* blood samples will be obtained to measure follicle-stimulating hormone (FSH), luteinizing hormone (LH), testosterone, sex hormone binding globulin (*SBGH*) and inhibin B levels.

Is:

12. Pubertal development in male and female subjects will be assessed using Tanner criteria. In male subjects, testicular volume will be assessed using Prader's orchidometer, **and** blood samples will be obtained to measure follicle-stimulating hormone (FSH), luteinizing hormone (LH), testosterone, sex hormone binding globulin (**SHBG**) and inhibin B levels. **In female subjects, blood samples will be obtained to measure FSH, LH, oestrogen, SHBG and inhibin B levels.**

In Section 6.2.4 Pubertal Development Assessment

Was:

In addition, follicle-stimulating hormone (FSH), luteinizing hormone (LH), testosterone, sex hormone binding globulin (SHBG), and inhibin B levels will be assessed every six months while the subject is in the study, at the time the subject exits the study, and 4 to 6 weeks after discontinuing ambrisentan for those subjects who do not remain on ambrisentan.

Is:

In addition, follicle-stimulating hormone (FSH), luteinizing hormone (LH), testosterone **(in male subjects only), oestrogen (in female subjects only)**, sex hormone binding globulin (SHBG), and inhibin B levels will be assessed every six months while the subject is in the study, at the time the subject exits the study, and 4 to 6 weeks after discontinuing ambrisentan for those subjects who do not remain on ambrisentan.

11.6. Appendix 6: Protocol Amendment 03

Statement of Intent

The intents of this amendment are primarily to modify the testing schedule for liver functions tests and to modify the locale for performing monthly pregnancy tests that do not occur at the quarterly visits, in light of the COVID-19 pandemic to minimize the subjects need to travel to the site while maintaining appropriate monitoring to ensure subject safety. In addition, the amendment seeks to clarify protocol language on the 30-day follow-up and on the dose groups to which the subjects will be considered to belong for the analysis displays, as well as updating the Medical Monitor and Sponsor Signatory.

Amended Sections of the Protocol

Deletions are noted in *Italics*

Insertions are noted in **bold face**.

Sponsor Signatory Page

Was

Rose G. Snipes, M.D.
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Metabolic Pathways and Cardiovascular Therapy Area Unit

Is

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Sponsor Information Page

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Was

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Is

PPD **MD FACC**
Clinical Sciences, Respiratory and Specialty
GlaxoSmithKline
Collegeville, Pennsylvania

In Section 5.7 Treatment after the End of the Study

Was

The Investigator should then treat the subjects according to best standard of care available to the investigator. Subjects will be followed for 30 days post their last dose of study medication. In addition, subjects will be asked to return for a pubertal development assessment at 20 years of age.

Is

The Investigator should then treat the subjects according to best standard of care available to the investigator. Subjects will be followed for 30 days post their last dose of study medication **for monitoring of AEs/SAEs**. In addition, subjects will be asked to return for a pubertal development assessment at 20 years of age.

Rationale

To make the section wording clearer as to the intent of the 30-day follow-up.

In Section 6 Study Assessments and Procedures

Table 1 Footnote 2

Was

2. For months that do not correspond to the every three month visits, these assessments may be performed by the subject's local physician and laboratory.

Is

2. For months that do not correspond to the every three month visits, **LFTs need not be performed unless clinically indicated, and** these assessments may be performed by the subject's local physician and laboratory. **From the time of Amendment 03, urine pregnancy tests may be performed at the subject's home using kits supplied by the site.**

Table 1 Footnote 8

Was

8. Subjects with a 20% decrease in 6MWD will need to return in 1 week to repeat the test, to confirm PAH deterioration.

Is

8. **From the time of Amendment 03, this test is optional at the every six month visits**. Subjects with a 20% decrease in 6MWD will need to return in 1 week to repeat the test, to confirm PAH deterioration.

Table 1 Footnote 11

Was

11. Either Urine or blood monthly pregnancy tests for females of childbearing potential for the duration of the study

Is

11. Either Urine or blood monthly pregnancy tests for females of childbearing potential for the duration of the study. **From the time of Amendment 03, urine pregnancy tests may be performed at the subject's home using kits supplied by the site.**

Rationale

To align the Time and Events table (Table 1) with the intended modification to the study procedures in light of travel restrictions due to the COVID-19 pandemic,

In Section 6.2.6.1 Safety Tests

Was

- **Liver Function:** serum alanine aminotransferase (ALT/SGPT), aspartate aminotransferase (AST/SGOT), gamma glutamyl transferase (GGT), and total bilirubin *monthly*.
- **Pregnancy:** Either urine or blood *monthly* pregnancy tests for female subjects of child bearing potential.

Is

- **Liver Function:** serum alanine aminotransferase (ALT/SGPT), aspartate aminotransferase (AST/SGOT), gamma glutamyl transferase (GGT), and total bilirubin **at the site visits that take place every 3 months, and otherwise as clinically indicated**.
- **Pregnancy:** Either urine or blood pregnancy tests for female subjects of child bearing potential **at the site visits that take place every 3 months. At the intervening monthly intervals, a urine pregnancy test will be performed by the subject at home using a test kit supplied by the site.**

Rationale

To simplify the required procedures for the remainder of the protocol in light of travel risks associated with the COVID-10 pandemic.

In Section 6.3.2 Change from Study AMB112529 baseline in the 6 minute walking distance (6MWD) test.

Was

The 6MWD will be assessed every six months while the subject is in the study, at the time he subject exits the study, and 4 to 6 weeks after discontinuing ambrisentan for those subjects who do not remain on ambrisentan. Subjects with a 20% decrease in 6MWD will need to return in 1 week to repeat the test, to confirm PAH deterioration.

Is

The 6MWD will be assessed every six months while the subject is in the study **but will be considered optional to perform at visits that take place after the approval of Protocol Amendment 03**. **The 6MWD will also be assessed** at the time **t**he subject exits the study, and 4 to 6 weeks after discontinuing ambrisentan for those subjects who do not remain on ambrisentan. Subjects with a 20% decrease in 6MWD will need to return in 1 week to repeat the test, to confirm PAH deterioration.

Rationale

To simplify the required procedures for the remainder of the protocol in light of travel risks associated with the COVID-10 pandemic.

In Section 8.3.1 Analysis Populations

Was

The Intention-to-Treat (ITT) Population will consist of all subjects who received at least 1 dose of study drug. For the ITT population, subjects were considered as belonging to their treatment group a*t the time of the visit/event, regardless of the baseline dose of ambrisentan*. The ITT population will be used in all efficacy summaries.

Is

The Intention-to-Treat (ITT) Population will consist of all subjects who received at least 1 dose of study drug. For the ITT population, subjects were considered as belonging to their treatment group **corresponding to the dose being received at the time the subject transitioned into the study from Protocol AMB112529**. The ITT population will be used in all **population and** efficacy summaries.

Rationale

The previous wording carried the risk that the analysis results could be difficult to interpret if a subject had multiple dose changes throughout the study.

In Section 8.3.5.1 Safety Analyses

Was

No formal statistical analysis is planned for safety parameters. All data will be presented descriptively or graphically, by treatment group ***at the time of the visit/event*** **and overall**. Where data are available, it will be summarised by visit.

Is

No formal statistical analysis is planned for safety parameters. All data will be presented descriptively or graphically, by treatment group **according to the highest dose received and overall**. Where data are available, it will be summarised by visit.

Rationale

To correct a mistake in the protocol and make this section consistent with the wording in Section 8.3.1.

In Section 8.3.5.2 Efficacy Analyses

Was

All subjects from the ITT population will be included in the analysis of efficacy data. Given the small sample size, all efficacy data will be summarized descriptively (including 95% CI) and graphically. Data will be summarized by treatment group ***at the time of the visit***, and overall.

Is

All subjects from the ITT population will be included in the analysis of efficacy data. Given the small sample size, all efficacy data will be summarized descriptively (including 95% CI) and graphically. Data will be summarized by treatment group **corresponding to the dose being received at the time the subject transitioned into the study from Protocol AMB112529**, and overall.

Rationale

The previous wording carried the risk that the analysis results could be difficult to interpret if a subject had multiple dose changes throughout the study.

11.7. Appendix 7: Protocol Amendment 04

Statement of Intent

The primary intent of this amendment is to include changes to when subjects can leave the study and the timing of the pubertal development assessment. Specifically, the amendment seeks to clarify that any subjects who reached pubertal maturity before 18 years of age and ambrisentan can be supplied through a named patient or expanded access program until the subject reaches 18 years of age will complete their end of study visit at the investigator site. No further pubertal development assessments will be required for these subjects. All subjects who have reached the age of 18 and who have reached pubertal maturity at a previous visit will complete their final study visit in the form of a telephone follow-up in order to notify the subjects of the end of the study and that no further study visits and assessments will take place. All subjects who have reached the age of 18 and who have not reached pubertal maturity in previous visits will complete their final study visit at the investigator site and will have their pubertal development assessed. These patients may return at any point and do not need to wait until 20 years of age to have their pubertal maturity evaluated.

Amended Sections of the Protocol

Deletions are noted in *Italics*

Insertions are noted in **bold face**.

Sponsor Signatory Page

Was

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Is

Kaivan Khavandi, MBChB, MRes, MBA, PhD, MCRP
Future Disease Area Lead
Clinical Sciences, Specialty

Rationale

Updated to sponsor signatory page

In Section – Page 1 Summary Page

Was

This is an open label, long term extension to Study AMB112529. All subjects may remain in the extension study for a minimum of six months. Beyond the six month period, subjects may continue in the extension study until one of the following conditions is met:

- the subject turns 18 years of age (when the subject can receive marketed product)

Is

This is an open label, long term extension to Study AMB112529. All subjects may remain in the extension study for a minimum of six months. Beyond the six month period, subjects may continue in the extension study until one of the following conditions is met:

- the subject turns 18 years of age (when the subject can receive marketed product) **or the subject has reached pubertal maturity before 18 years of age and ambrisentan can be supplied through a named patient or expanded access program until the subject reaches 18 years of age**

Rationale

Updated wording to allow mature under 18 year old subjects to leave the study and continue drug supply through a named patient or expanded access program until the subject reaches 18 years of age when the marketed product will become available.

In Section – Protocol Summary – Study Design

Was

This is an open label, long term extension to Study AMB112529. All subjects may remain in the extension study for a minimum of six months. Beyond the six month period, subjects may continue in the extension study until one of the following conditions is met:

- The subject turns 18 years of age (when the subject can receive marketed product)

Is

This is an open label, long term extension to Study AMB112529. All subjects may remain in the extension study for a minimum of six months. Beyond the six month

period, subjects may continue in the extension study until one of the following conditions is met:

- The subject turns 18 years of age (when the subject can receive marketed product) **or the subject has reached pubertal maturity before 18 years of age and ambrisentan can be supplied through a named patient or expanded access program until the subject reaches 18 years of age**

Rationale

Updated wording to allow mature under 18 year old subjects to leave the study and continue drug supply through a named patient or expanded access program until the subject reaches 18 years of age when the marketed product will become available.

In Section – Protocol Summary – Study Endpoints/Assessments - Safety

Was

- Pubertal development (change from Study AMB112529 baseline in endocrinology assessments every six months and at 20 years of age);

Is

- Pubertal development (change from Study AMB112529 baseline in endocrinology assessments every six months and at 20 years of **age unless pubertal maturity has been reached in previous visits**);

Rationale

Updated wording to clarify that pubertal development assessments do not need to be repeated if pubertal maturity has been reached in a previous visit.

In Section – 2.1.1 Safety

Was

- Pubertal development (change from Study AMB112529 baseline in endocrinology assessments every six months and at 20 years of age);

Is

- Pubertal development (change from Study AMB112529 baseline in endocrinology assessments every six months and at 20 years of age **unless pubertal maturity has been reached in previous visits**);

Rationale

Updated wording to clarify that pubertal development assessments do not need to be repeated if pubertal maturity has been reached in a previous visit.

In Section – 3.1 Study Design

Was

This is an open label, long term extension to Study AMB112529. All subjects may remain in the extension study for a minimum of six months. Beyond the six month period, subjects may continue in the extension study until one of the following conditions is met:

- The subject turns 18 years of age (when the subject can receive marketed product)

Is

This is an open label, long term extension to Study AMB112529. All subjects may remain in the extension study for a minimum of six months. Beyond the six month period, subjects may continue in the extension study until one of the following conditions is met:

- The subject turns 18 years of age (when the subject can receive marketed product) **or the subject has reached pubertal maturity before 18 years of age and ambrisentan can be supplied through a named patient or expanded access program until the subject reaches 18 years of age**;

Rationale

Updated wording to allow mature under 18 year old subjects to leave the study and continue drug supply through a named patient or expanded access program until the subject reaches 18 years of age when the marketed product will become available.

In Section – 5.7 Treatment after the end of the study

Was

Subjects can remain in this study until one of the following conditions is met:

- The subject turns 18 years of age (when the subject can receive marketed product);
- The product is approved and available for use in the subject's age group;
- Development for use in the paediatric population is discontinued;
- The subject decides he/she no longer wants to participate in the study;
- The investigator considers it is in the best interest of the subject to discontinue ambrisentan (e.g. for safety reasons).

The Investigator should then treat the subjects according to best standard of care available to the investigator. Subjects will be followed for 30 days post their last dose of study medication for monitoring of AEs/SAEs.

In addition, subjects will be asked to return for a pubertal development assessment at 20 years of age.

Is

Subjects can remain in this study until one of the following conditions is met:

- The subject turns 18 years of age (when the subject can receive marketed product) or **the subject has reached pubertal maturity before 18 years of age and ambrisentan can be supplied through a named patient or expanded access program until the subject reaches 18 years of age**;
- The product is approved and available for use in the subject's age group;
- Development for use in the paediatric population is discontinued;
- The subject decides he/she no longer wants to participate in the study;
- The investigator considers it is in the best interest of the subject to discontinue ambrisentan (e.g. for safety reasons).

The Investigator should then treat the subjects according to best standard of care available to the investigator. Subjects will be followed for 30 days post their last dose of study medication for monitoring of AEs/SAEs.

In addition, subjects will be asked to return for a pubertal development assessment at 20 years of age.

Subjects will only be asked to return for a pubertal development assessment following their 18th birthday if pubertal maturity had not been reached in a previous visit.

All subjects who reached pubertal maturity before 18 years of age and ambrisentan can be supplied through a named patient or expanded access program until the subject reaches 18 years of age will complete their end of study visit at the investigator site for their end of study assessments as outlined in Table 1. As these subjects had already reached pubertal maturity, no further pubertal development assessments are required.

All subjects who have reached the age of 18 and who have reached pubertal maturity at a previous visit will complete their final study visits in the form of a telephone follow-up. This is to notify the subjects of the end of the study and that no further study visits and assessments will take place.

All subjects who have reached the age of 18 and who have not reached pubertal maturity in previous visits will complete their final study visit at the investigator site and will have their pubertal development assessed. These patients may return at any point and do not need to wait until 20 years of age to have their pubertal maturity evaluated.

Rationale

Added new wording to account for the different end of study scenarios for any remaining subjects who are either still active or in follow-up in the study. Updated wording to clarify that pubertal development assessments do not need to be repeated if pubertal maturity has been reached in a previous visit.

In Section – Table 1 – Footnote 14

Was

- Footnote 14 did not exist

Is

14. In subjects where pubertal maturity has been reached prior to 20 years of age, the 20-year pubertal development assessment will not be required. All subjects who are over the age of 18 and who have not reached pubertal maturity in previous visits will complete their final study visit at the investigator site and will have their pubertal development assessed. These patients may return at any point and do not need to wait until 20 years of age to have their pubertal maturity evaluated.

Rationale

Added new footnote 14 to clarify that the 20 year pubertal development assessments do not need to be repeated if pubertal maturity has been reached in a previous visit. In

addition, added additional wording to clarify that immature over 18 year olds can have their pubertal development assessed at any time after their 18th birthday and do not need to wait until they are 20 years of age.

In Section – 6.2.4 Pubertal Development Assessment

Was

Pubertal development in male and female subjects will be assessed every six months while the subject is in the study, at the time the subject exits the study, 4 to 6 weeks after discontinuing ambrisentan for those subjects who do not remain on ambrisentan, and at 20 years of age. using the Tanner criteria [Marshall, 1969; Marshall, 1970; Cameron, 2004]. In male subjects, testicular volume will be assessed by Prader's orchidometer. These assessments will be performed by a paediatric endocrinologist or another individual with comparable experience employing the Tanner criteria and Prader's orchidometer. Preferably, the same assessor will evaluate an individual subject at each assessment time.

Is

Pubertal development in male and female subjects will be assessed every six months while the subject is in the study, at the time the subject exits the study, 4 to 6 weeks after discontinuing ambrisentan for those subjects who do not remain on ambrisentan, and at 20 years of age, **unless pubertal maturity has been reached in previous visits**. using the Tanner criteria [Marshall, 1969; Marshall, 1970; Cameron, 2004]. In male subjects, testicular volume will be assessed by Prader's orchidometer. These assessments will be performed by a paediatric endocrinologist or another individual with comparable experience employing the Tanner criteria and Prader's orchidometer. Preferably, the same assessor will evaluate an individual subject at each assessment time.

Rationale

Updated wording to clarify that pubertal development assessments do not need to be repeated if pubertal maturity has been reached in a previous visit.