CLINICAL STUDY PROTOCOL

Study Title:	ABS-LT: A Phase 3, Long-Term, Open Label, Multicenter Safety Study of Ambrisentan in Subjects with Pulmonary Hypertension
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404
IND No.: **EudraCT Number**	
Indication:	Pulmonary Hypertension
Protocol ID:	GS-US-300-0124
Protocol Version/Date:	Version 2.0 Rest of World 12 June 2013 Amendment 1.0 ROW

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PROTOCOL SYNOPSIS

Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404

Study Title:	ABS-LT: A Phase 3, Long-Term, Open Label, Multicenter Safety Study of Ambrisentan in Subjects with Pulmonary Hypertension
IND Number:	64,915
EudraCT Number:	2008-001838-27
Study Centers Planned:	Up to 80 investigational sites worldwide
Objectives:	The objective of this study is to monitor the long-term safety of ambrisentan in subjects with pulmonary hypertension (PH).
Number of Subjects Planned:	Approximately 300 subjects
Target Population:	Men and women who are discontinuing a clinical study of ambrisentan in PH due to study closure by the Sponsor and for whom ambrisentan is not yet commercially available.
Duration of Treatment:	Long-term
Diagnosis and Main Eligibility Criteria:	Men and women with PH who are discontinuing a clinical study of ambrisentan due to study closure by the Sponsor. Eligible subjects are those participating in countries where ambrisentan is not yet commercially available. Subjects participating in countries where ambrisentan is commercially available may be eligible if they do not qualify for treatment per the current prescribing information of that country. Subjects who have discontinued an ambrisentan clinical study for any other reason than Sponsor-initiated study closure are not eligible.

Study Design/Procedures	This Phase 3, international, multicenter, open-label study will monitor the long-term safety of ambrisentan in subjects with PH. The available ambrisentan doses for this study are 5 or 10 mg once daily (qd); these are the approved doses in the United States, Canada, and the European Union. Investigators will be able to adjust ambrisentan dose as clinically indicated. A minimum of 4 weeks between dose adjustments is required. Subjects receiving other therapies for PH that are not contraindicated for concomitant use with ambrisentan are permitted to enroll in this study and continue to receive such therapies. Subjects enrolled in this study will receive treatment with ambrisentan until such time as the Investigator or subject chooses to stop ambrisentan treatment, ambrisentan becomes commercially available, or the Sponsor stops the study. Subjects will be followed by the Investigator according to clinical practice, with formal (per protocol) safety assessments conducted at the Screening/Enrollment Visit and at Clinic Visits every 24 weeks thereafter. These safety assessments will include adverse events (AEs), clinical laboratory tests, vital signs, and concomitant medications. In addition, serum liver function tests (LFTs) will be monitored at Laboratory Visits every 4 weeks throughout the study. These LFTs will be performed at a local phlebotomy laboratory or at the Investigator clinic. A central laboratory will not be used for this study. In animals, ambrisentan and other ERAs have been shown to be teratogenic. Therefore, female subjects of childbearing potential will undergo pregnancy testing every 4 weeks and will be required to use 2 reliable methods of contraception to reduce the risk of pregnancy during the course of the study and for at least 30 days following the last dose of ambrisentan. If a subject has undergone tubal sterilization or has had a Copper T 380A intrauterine device (IUD) inserted, no other contraception is needed. A Data Monitoring Committee (DMC) will monitor the safety and welfare of the study subjects. The DMC will meet at designated intervals to review the accumulated data.
Test Product, Dose, and Mode of Administration:	Ambrisentan tablets: 5 mg and 10 mg Doses: 5 mg and 10 mg qd Administration: oral tablet

Reference Therapy, Dose, and Mode of Administration:	None
Criteria for Evaluation:	
Safety:	The primary endpoint of this study is the incidence and severity of AEs associated with long-term exposure to ambrisentan in subjects with PH. Additional safety endpoints of interest include: • Shift from baseline (low/normal/high) over time in clinical laboratory values • Change from baseline over time in vital signs
Efficacy:	Efficacy will not be examined in this study.
Statistical Methods:	Interim analyses for this study will be performed periodically to generate safety data for regulatory submissions and for review by the DMC. Safety data will be summarized by treatment group and all subjects combined for cumulative 24-week intervals. Most continuous data will be summarized using the following descriptive statistics: number of observations, mean, standard deviation, standard error, median, minimum and maximum. Categorical data will be summarized using frequencies and percentages. Changes from baseline will be calculated as the later value minus the baseline value. Baseline will be defined for all endpoints as the time of enrollment into this study.

This study will be conducted in accordance with the guidelines of Good Clinical Practices (GCPs) including archiving of essential documents.

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

ADME	absorption, distribution, metabolism, and elimination
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
bid	twice daily
BDI	Borg dyspnea index
BMI	body mass index
BNP	B-type natriuretic peptide
BSEP	bile salt export pump
BUN	blood urea nitrogen
CCB	calcium channel blockers
Cmax	maximum plasma concentration
CONMED	concomitant medication
CRF	case report form
CRO	clinical research organization
CTD	connective tissue disease
CYP	cytochrome P450
DMC	Data Monitoring Committee
DSPH	Drug Safety and Public Health
E2	estradiol
ECE-1	endothelin converting enzyme
ECG	electrocardiogram
EEG	electroencephalogram
ERA	endothelin receptor antagonist
ET-1	endothelin-1
ETA	endothelin receptor type A
ETB	endothelin receptor type B
EU	European Union
FAS	full analysis set
FDA	Food and Drug Administration
FPAH	familial pulmonary arterial hypertension
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
hCG	human chorionic gonadotropin
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS (CONTINUED)

IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
INR	international normalized ratio
IPAH	idiopathic pulmonary arterial hypertension
IUD	intrauterine device
IVRS	Interactive Voice Response System
IRB	Institutional Review Board
iv	intravenous
LFT	liver function test
MedDRA	Medical Dictionary for Regulatory Activities
m	meter
mg	milligram
mmHg	millimeters mercury
mPAP	mean pulmonary artery pressure
MRP2	multidrug resistance-associated protein 2
NDA	New Drug Application
NO	nitric oxide
NTCP	sodium-taurocholate co-transporter protein
OATP	organic anion transporter polypeptide
PAH	pulmonary arterial hypertension
PAH-CTD	pulmonary arterial hypertension associated with connective tissue disease
PAP	pulmonary artery pressure
PCWP	pulmonary capillary wedge pressure
PDE-5	phosphodiesterase type 5
PGI_2	prostacyclin
P-gp	P-glycoprotein
PH	pulmonary hypertension
po	by mouth, orally
PT	prothrombin time
PVR	pulmonary vascular resistance
qd	once daily
RAP	right atrial pressure
ROW	Rest of World
SAE	serious adverse event
SOC	System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Reaction
tid	three times daily

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS (CONTINUED)

UGT	uridine glucuronosyltransferase
ULN	upper limit of normal
US	United States
WHO	World Health Organization
6MWD	6-minute walk distance

1. INTRODUCTION

1.1. Background

1.1.1. Pulmonary Hypertension

Pulmonary hypertension (PH) is a serious and life-threatening disease of the pulmonary vasculature, characterized by profound vasoconstriction and an abnormal proliferation of smooth muscle cells in the walls of the pulmonary arteries [1,2]. PH develops in response to various pathological conditions, which are categorized as: 1) pulmonary arterial hypertension (PAH); 2) PH associated with left heart disease; 3) PH associated with lung diseases and/or hypoxia; 4) PH due to chronic thrombolic and/or embolic disease and; 5) PH associated with miscellaneous pathologies affecting the pulmonary vasculature such as sarcoidosis, histiocytosis X, lymphangiomatosis, or the compression of pulmonary vessels by adenopathy, tumors or fibrosing mediastinitis [3].

PAH consists of a group of diseases characterized by a progressive increase of pulmonary vascular resistance (PVR) and pulmonary artery pressure (PAP). PAH includes idiopathic pulmonary arterial hypertension (IPAH), familial pulmonary arterial hypertension (FPAH), and PAH associated with various conditions such as connective tissue disease (CTD), congenital systemic-to-pulmonary shunts, portal hypertension, drug and toxin use, and human immunodeficiency virus (HIV) infection [4]. All of these disorders share similar proliferative and obstructive changes of the pulmonary microcirculation, including plexiform lesions [5].

The vascular damage that defines PAH is characterized by a mean pulmonary artery pressure (mPAP) ≥25 mmHg at rest or >30 mmHg with exertion and a pulmonary capillary wedge pressure (PCWP) ≤15 mmHg. Patients with PAH typically develop significant increases in PVR and sustained elevations in PAP, which ultimately lead to right ventricular failure and death [2,6]. Patients diagnosed with PAH have a poor prognosis and equally compromised quality of life, with a mean life expectancy of 2 to 5 years from the time of diagnosis if untreated [7]. Drugs that block or reduce the vasoconstriction and hypertrophy associated with the narrowing of the pulmonary arteries may ameliorate the cycle of constriction and improve pulmonary vascular blood flow.

1.1.2. Current Treatment Options

Diuretics and anticoagulants have been widely used in the management of PH, yet treatment response varies [8]. 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 [8,9].

Three signaling pathways involved in the pathogenesis of PAH have been targeted for therapeutic intervention: the cAMP-dependent prostacyclin (PGI_2) pathway [8], the cGMP-dependent nitric oxide (NO) pathway, and the phospholipase-C-dependent endothelin

pathway. These pathways are targeted by the following classes of drugs: PGI_2 derivatives, phosphodiesterase type-5 (PDE-5) inhibitors, and endothelin receptor antagonists (ERAs). The following summary is provided for illustration only, as not all treatments are available in all markets.

Intravenous (iv) epoprostenol (Flolan®), subcutaneous, iv, and inhaled treprostinil (Remodulin®), and inhaled iloprost (Ventavis®) are PGI_2 derivatives targeting the cAMP-dependent PGI_2 pathway. These medicinal products mimic the effects of PGI_2, an endogenous prostaglandin produced by the vascular endothelium, to stimulate cAMP-dependent vasodilation of the pulmonary arterial bed and inhibit platelet aggregation [10]. Epoprostenol, a potent vasodilator, is a treatment option for patients with IPAH and PAH associated with connective tissue disease (PAH-CTD). There are several adverse events (AEs) associated with the drug including jaw pain, headache, nausea, and vomiting. The continuous infusion of epoprostenol requires the use of cold packs and a battery-operated ambulatory pump for 24-hour uninterrupted iv infusion, thereby necessitating a substantial commitment from patients for successful administration [11,12]. Treprostinil was originally given marketing authorization for administration as a continuous, subcutaneous infusion; however, use of this chronic prostanoid therapy has been associated with pain at the site of administration [13], prompting the development of iv and inhaled formulations [14]. Inhaled iloprost was approved for the treatment of PAH based on demonstrated improvement compared to placebo in 6-minute walk distance (6MWD) and World Health Organization (WHO) functional class after 12 weeks of therapy. This drug has a half-life of 20-25 minutes that requires 6-9 nebulization sessions per day and often requires patients to wake from sleep to administer iloprost at night [15].

Sildenafil citrate (Revatio®), the first PDE-5 inhibitor approved for the treatment of PAH, targets the NO pathway. Through inhibition of PDE-5, sildenafil increases cytoplasmic cGMP concentrations and enhances NO-mediated vasodilation of the vasculature [16]. Sildenafil demonstrated significant exercise capacity benefit compared with placebo over 12 weeks of treatment [17]; however, the long-term effect of the approved dose of sildenafil (20 mg three times daily [tid]) as monotherapy has not been established.

The third targeted pathway is the phospholipase-C-dependent endothelin pathway. Endothelin-1 (ET-1) is the primary member of a family of potent vasoconstrictor peptides, which are known to play an essential role in mammalian cardiovascular physiology [18]. ET-1 is synthesized *de novo* and released from endothelial cells in response to a variety of factors, including angiotensin II, catecholamines, cytokines, hypoxia, and shear stress [19-22]. Two receptor subtypes, endothelin receptor type A (ET_A) and endothelin receptor type B (ET_B), mediate the effects of ET-1. In humans, the ET_A receptor is preferentially expressed in vascular smooth muscle cells and is primarily responsible for the vasoconstrictive and mitogenic effects of ET-1 [23,24]. In contrast, ET_B receptors are found mainly in the vascular endothelium, and their activation results in vasodilation via the production of NO and prostacyclin [25,26]. The ET_B receptor is also involved in the regulation of circulating concentrations of ET-1, through effects on endothelin converting enzyme (ECE-1) expression, and the synthesis and reuptake of ET-1 by endothelial cells [27,28].

ET-1 is rapidly cleared from the systemic circulation primarily by the lungs [29]. In healthy subjects, circulating plasma concentrations of ET-1 are normally quite low [30]; however, in patients with PAH, plasma ET-1 levels are elevated by as much as 10-fold [30,31]. Such elevations in plasma ET-1 also appear to correlate well with increased mean right atrial pressure (RAP) in this patient population [31]. ET_A and ET_B receptor mRNAs are abundantly expressed in human lung tissue [32]. Similarly, expression of ET-1 and ET-1 mRNA may be increased as much as 9-fold in the lung tissue of patients with PAH, primarily in the endothelium of pulmonary arteries [1]. Based on these findings, it has been suggested that ET-1 plays a critical role in the pathogenesis and progression of PAH.

Bosentan (Tracleer®), a non-selective, sulfonamide-class ERA, is approved globally for the treatment of PAH in patients with WHO functional class III or IV symptoms. Bosentan was demonstrated to increase exercise capacity in subjects with PAH, and reduce dyspnea during exercise [33-35].

1.2. Ambrisentan

Ambrisentan [(+)-(2S)-2-[(4,6-dimethylpyrimidin-2-yl)oxy]-3-methoxy-3,3-diphenylpropanoic acid] is an orally active ERA that is selective for the ET_A receptor. Ambrisentan (trade name: Letairis™) is approved by the United States (US) Food and Drug Administration (FDA) for the treatment of PAH (WHO Group 1) in patients with WHO class II or III symptoms to improve exercise capacity and delay clinical worsening. Ambrisentan has also been granted marketing authorization (under the tradename of Volibris™) by the European Commission and Health Canada for the treatment of patients with PAH classified as WHO functional class II and III. Additional marketing applications for ambrisentan have been filed or are planned in many countries world-wide.

1.2.1. Pharmacokinetics and Metabolism

Clinical studies in healthy volunteers have demonstrated that ambrisentan is rapidly absorbed, with maximum plasma concentrations (C_{max}) typically observed around 1.5 hours after oral dosing, under both fasted and fed conditions; therefore, absorption is unaffected by food. In subjects with PAH, ambrisentan was rapidly absorbed following oral administration with C_{max} typically occurring between 2 and 3 hours after dose. For both healthy volunteers and PAH patients, C_{max} and area under the plasma concentration-time curve (AUC) increased dose proportionally over the therapeutic dose range, and steady-state was generally achieved following 4 days of repeat dosing. Steady-state plasma elimination half-life ranged from 13.6 to 16.5 hours in healthy volunteers and from 12.9 to 17.9 hours in patients with PAH.

Ambrisentan plasma concentrations were consistently higher ($AUC_{ss,0-24}$ 2-3 fold) in subjects with PAH compared to healthy subjects. A similar difference was observed in bosentan clinical studies [36]. Reduction in the metabolic capacity of the liver as a consequence of PAH-related hepatic congestion or hypoperfusion may alter the systemic clearance of ambrisentan (as well as other ERAs) in patients with PAH.

Ambrisentan is highly plasma protein bound, and the distribution of ambrisentan into red blood cells is low. Ambrisentan is primarily metabolized in the liver by glucuronidation and to a lesser extent by oxidative metabolism. Ambrisentan is glucuronidated by several uridine glucuronosyltransferase (UGT) enzymes (UGT1A9S, UGT2B7S and UGT1A3S) to form ambrisentan glucuronide. Ambrisentan glucuronide is rapidly excreted into the bile and partially converted back to ambrisentan by deconjugation in the gut. Ambrisentan undergoes oxidative metabolism to form 4-hydroxymethyl ambrisentan; however, the AUC of this metabolite is approximately 4% of parent ambrisentan in plasma, which indicates that it is a minor metabolite. The 4-hydroxymethyl metabolite is generated primarily by cytochrome P450 (CYP) 3A4 and to a lesser extent by CYP3A5 and CYP2C19. The hydroxylated metabolite is further glucuronidated to 4-hydroxymethyl ambrisentan glucuronide. The binding affinity of 4-hydroxymethyl ambrisentan for the human ET_A receptor is at least 100-fold less than that of ambrisentan. Therefore at concentrations observed in the plasma (~4%), 4-hydroxymethyl ambrisentan is not expected to contribute to pharmacological activity of ambrisentan.

Ambrisentan and its metabolites are primarily excreted in the bile following hepatic and/or extra-hepatic metabolism and eliminated in the feces (65%). Approximately 22% of the administered dose is recovered in the urine following oral administration, with 3.3% being unchanged ambrisentan.

Additional details regarding the pharmacokinetic and ADME (absorption, distribution, metabolism, and excretion) properties of ambrisentan, as determined in the ambrisentan nonclinical and clinical studies, are provided in the Investigator's Brochure (IB) [37].

1.2.2. Preclinical Pharmacology and Toxicology

The nonclinical pharmacology of ambrisentan has been studied in vitro and in vivo. In vitro nonclinical studies with ambrisentan have demonstrated that it is a potent and selective inhibitor of the ET_A receptor. In studies using endogenously expressed, native ET_A and ET_B receptors obtained from human ventricular myocardial membranes, ambrisentan demonstrated a K_i (dissociation constant for the inhibitor) of approximately 0.011 nM for the ET_A receptor and a K_i of 40.9 nM for the ET_B receptor, resulting in a >4000-fold selectivity for the ET_A versus the ET_B receptor.

The vasodilatory and antiproliferative effects of endothelin receptor antagonism with ambrisentan have been established in several in vivo studies. Ambrisentan has a depressor action in the systemic circulation of rats and dogs and a vascular antiproliferative effect in the injured coronary artery of the pig. Numerous studies have also been conducted in animals to evaluate the safety of ambrisentan on the nervous, cardiovascular, respiratory, gastrointestinal, musculoskeletal, and genitourinary systems. Ambrisentan elicited only minor effects in most of these assays, even at high concentrations or doses.

The toxicological profile of ambrisentan has been evaluated in single dose, repeat dose, carcinogenicity, and reproductive/developmental studies in mice, rats, rabbits and dogs, and

in genotoxicity studies in vitro (mammalian and bacterial cells) and in vivo (rats). In single and repeat dose toxicity studies in mice, rats, and dogs, few significant systemic or organ toxicities were observed. The target organs identified in mice, rats, and dogs with chronic ambrisentan administration were the gastrointestinal tract, kidneys, heart, nasal cavity, and testes. In rats only, chronic dosing of ambrisentan was also associated with an increase in osseous hyperplasia of the nasal cavities, which in turn led to suffocation and premature death in a portion of these obligate nose breathers.

Teratogenicity is a class effect of ERAs, and exposure of animals to ERAs has been shown to cause a specific and potentially lethal combination of embryonic defects including craniofacial, cardiac, and thyroid abnormalities. Oral administration of ambrisentan to pregnant rats or rabbits on gestation days 6 to 17 resulted in abnormalities of the lower jaw, tongue, and/or palate at all doses evaluated. For humans, this means that the potential teratogenic effect of ambrisentan could occur before a patient knows she is pregnant.

The development of testicular tubular atrophy and impaired fertility has been linked to the chronic administration of ERAs, although the potential for human injury has not been determined. Ambrisentan administration was associated with the development of testicular lesions in rats, but there was no consistent effect of these lesions on fertility and/or sperm morphology or motility. In clinical studies, the analysis of male fertility hormones in combination with the limited number of subjects providing serial semen samples did not suggest that long-term ambrisentan treatment was associated with an adverse effect on male reproductive potential.

The genotoxicity of ambrisentan was assessed in a comprehensive battery of in vitro and in vivo studies. Ambrisentan was clastogenic (structural chromosome damage) when tested at high concentrations in mammalian cells in vitro. Ambrisentan was not mutagenic to bacteria, and produced minimal evidence of carcinogenic potential in two 104-week rodent studies.

1.2.3. Potential for Drug-Drug Interactions

The management of PH often requires multi-drug regimens; therefore, the risk of adverse drug-drug interactions should be carefully considered. Concomitant medications for the treatment of PAH include anticoagulants, diuretics, CCBs, and digoxin. Subjects may also require concomitant therapy for co-morbidities, such as immunosuppressants for CTD and protease inhibitors for HIV infection. In addition, the strategy of administering more than one PAH medication to target different pathological mechanisms is increasingly being implemented.

Ambrisentan parent is the predominant ambrisentan-related species circulating in the plasma, and the minor ambrisentan metabolism that occurs is mediated by a variety of CYP and UGT enzymes, rather than by one predominant enzyme (Section 1.2.1). Therefore, the pharmacokinetics of ambrisentan are unlikely to be affected by coadministered drugs that induce or inhibit specific phase I or phase II enzymes.

Likewise, in vivo and in vitro studies have demonstrated that ambrisentan does not inhibit (Section 1.2.3.1) or induce (Section 1.2.3.2) CYP or UGT metabolic pathways at clinically relevant doses or concentrations. Therefore, administration of ambrisentan is unlikely to alter the pharmacokinetics of other drugs that may be metabolized by these pathways.

In vitro studies using rat and human hepatocyte cultures have demonstrated that ambrisentan does not inhibit the organic anion transporter polypeptide (OATP), sodium-taurocholate co-transporter protein (NTCP), multidrug resistance-associated protein 2 (MRP2), or the bile salt export pump (BSEP). Rat hepatocyte assays have demonstrated that ambrisentan does not induce protein levels of BSEP and P-glycoprotein (P-gp). Ambrisentan is a possible substrate for the hepatic influx transporter OATP and for the efflux transporter P-gp, but not for the hepatic influx or efflux transporters NTCP or BSEP, respectively.

Cyclosporine A is a strong inhibitor of P-gp; therefore, caution should be used when ambrisentan is coadministered with cyclosporine A [38].

1.2.3.1. In Vitro Enzyme Inhibition Studies

The ability of ambrisentan to inhibit hepatic phase I and II metabolizing enzymes has been evaluated in microsomes prepared from a human lymphoblastoid cell line or baculovirus-infected insect cells. Inhibition did not exceed 50% for any enzyme at the highest concentration (300 μM) of ambrisentan tested. These results suggest a low potential for ambrisentan to inhibit hepatic phase I and phase II metabolism at clinically relevant concentrations.

1.2.3.2. In Vitro Enzyme Induction Studies

The activity of ambrisentan as a modulator of hepatic phase I and II enzyme induction was examined in rats and dogs. No induction of CYP, glutathione-S-transferase (GST), or uridine diphospho-glucuronosyltransferase (UDP-GT) enzyme concentrations or activities were observed at clinically relevant doses. Enzyme induction that was observed in these studies generally occurred at the highest doses, corresponding to an equivalent human pharmacokinetic exposure that is 50- to 200-fold higher than that determined in clinical development. Results suggest that ambrisentan should not possess clinically significant hepatic phase I or II metabolizing enzyme induction potential.

1.2.3.3. Clinical Drug-Drug Interaction Studies

Several clinical studies have been conducted with ambrisentan to examine the potential for adverse drug-drug interactions. In EE-002, daily dosing of ambrisentan (5, 7.5, or 10 mg by mouth [po] once daily [qd]) did not increase 6β-hydroxycortisol excretion, indicating a lack of CYP3A4 induction.

In healthy subjects receiving a single dose of sildenafil (20 mg), daily doses of ambrisentan (10 mg qd) did not have a clinically relevant effect on the pharmacokinetics of sildenafil (a CYP3A4 and CYP2C9 substrate) or the active metabolite, n-desmethyl sildenafil. Similarly,

daily doses of sildenafil (20 mg tid) did not have a clinically relevant effect on the pharmacokinetics of a single-dose of ambrisentan (10 mg). Therefore, no dose-adjustments of sildenafil or ambrisentan are required when co-administered.

Ambrisentan (10 mg qd) did not have a clinically relevant effect on the pharmacokinetics of S-warfarin (CYP2C9 substrate) or R-warfarin (CYP3A4 substrate) in healthy subjects receiving a single 25 mg dose of racemic warfarin. Similarly, warfarin had no clinically significant effects on the pharmacokinetics of ambrisentan. In addition, daily doses of ambrisentan (10 mg qd) did not have a clinically significant effect on prothrombin time (PT) or International Normalized Ratio (INR). Consistent with this result, no clinically relevant changes in PT, INR or warfarin-type anticoagulant dose were observed with ambrisentan treatment in the clinical studies of patients with PAH. Therefore, no dose adjustments for warfarin or ambrisentan are required when co-administered.

The effect of daily doses of ambrisentan (10 mg qd) on the pharmacokinetics of a single 0.5 mg dose of digoxin, a substrate for P-gp, was evaluated in healthy subjects. Slight increases in the plasma concentrations of digoxin were observed in the presence of daily ambrisentan dosing, however, these increases were not considered to be clinically relevant. Based on the results of this study, no dose adjustment of digoxin is recommended with ambrisentan co-administration.

Finally, the effects of ketoconazole, a potent CYP3A4 inhibitor, on the pharmacokinetics of ambrisentan were also assessed in healthy subjects. Daily doses of ketoconazole (400 mg qd) did not have a clinically relevant effect on the single-dose pharmacokinetics of ambrisentan. Therefore, no ambrisentan dose adjustment is recommended when co-administered with ketoconazole.

These clinical data are consistent with the in vitro and in vivo nonclinical studies and support the conclusion that ambrisentan has a low risk of adverse drug-drug interactions.

1.2.4. Clinical Studies

The safety, tolerability, pharmacokinetics, and pharmacodynamics of ambrisentan have been evaluated in ten Phase 1 studies in healthy subjects: EE-001 (single ascending dose study), EE-002 (multiple ascending dose study), AMB-103 (bioequivalence study), AMB-104 (thorough QTc prolongation study), AMB-105 (sildenafil drug-drug interaction study), AMB-106 (warfarin drug-drug interaction study), AMB-107 (ADME/mass balance study), AMB-108 (metabolite/chirality study), ABS-109 (digoxin drug-drug interaction) and ABS-1010 (ketoconazole drug-drug interaction study).

In subjects with PAH, ambrisentan (2.5, 5, and 10 mg qd) has been evaluated in two pivotal randomized, placebo-controlled Phase 3 studies (AMB-320 and AMB-321), two Phase 2 studies (AMB-220 and AMB-222), and two long-term safety and efficacy studies (AMB-220-E and AMB-320/321-E). Furthermore, ambrisentan is currently being evaluated in a Phase 3 open-label study in subjects with pulmonary hypertension of various etiologies (AMB-323).

Further information on all clinical studies of ambrisentan in healthy volunteers and subjects with PAH is provided in the IB [37].

1.2.4.1. Clinical Efficacy

In two Phase 3, placebo-controlled studies (AMB-320 [ARIES-1] and AMB-321 [ARIES-2]), ambrisentan demonstrated statistically significant improvement in 6MWD. An increase in 6MWD was observed after 4 weeks of treatment with ambrisentan, with a dose-response observed after 12 weeks of treatment. Results from AMB-321 demonstrated that 5 mg and 2.5 mg po qd of ambrisentan improved the placebo-corrected 6MWD by 59.4 meters ($p < 0.001$) and 32.3 meters ($p = 0.022$), respectively. Similarly, results from AMB-320 demonstrated that 10 mg and 5 mg po qd of ambrisentan improved the placebo-corrected 6MWD by 51.4 meters ($p < 0.001$) and 30.6 meters ($p = 0.008$), respectively.

Time to clinical worsening, an indicator of disease progression, was a key secondary endpoint in the two Phase 3, placebo-controlled studies. The individual studies were not statistically powered to examine secondary endpoints such as time to clinical worsening; therefore, to increase the power to observe a treatment effect, a combined analysis of the two Phase 3 studies was prespecified to examine secondary endpoints. The log-rank test for the comparison of the combined ambrisentan group versus placebo demonstrated that a significant delay in the time to clinical worsening of PAH was observed for subjects receiving ambrisentan ($p < 0.001$). Furthermore, the hazard ratio was 0.29 (95% CI: 0.14 to 0.59), indicating a 71% reduction in the probability of clinical worsening over the 12-week treatment period for subjects receiving ambrisentan compared to placebo.

The conclusions of the combined analysis were supported by similar trends in the individual studies. In AMB-320, a 2-fold increase in the number of subjects with an event of clinical worsening was observed in the placebo group compared to each of the ambrisentan dose groups; however, the log-rank comparison of the combined ambrisentan group versus placebo did not demonstrate a statistically significant difference in the time to clinical worsening of PAH ($p = 0.214$). In AMB-321, a 4-fold increase in the number of subjects with an event of clinical worsening was observed in the placebo group compared to each of the ambrisentan dose groups. The log-rank test demonstrated a significant delay in time to clinical worsening of PAH for the comparison of the combined ambrisentan group versus placebo ($p < 0.001$). The adjudication and analysis of clinical worsening events in the Phase 3 placebo-controlled studies were prespecified; however, during the FDA review of the New Drug Application (NDA), the agency performed a separate analysis of time to clinical worsening that included re-adjudication of some clinical worsening events. Per this analysis, both studies demonstrated a significant improvement in time to clinical worsening for the combined ambrisentan group compared to placebo (AMB-320, $p = 0.030$; AMB-321, $p = 0.005$), which is consistent with the results of the prespecified integrated analysis of the 2 studies. Therefore, ambrisentan has been indicated in the US to delay clinical worsening in patients with PAH.

Clinically relevant or statistically significant improvements were observed in the individual studies for the secondary endpoints of WHO functional class, the SF-36™ health survey, and Borg dyspnea index (BDI). In the prespecified combined analysis, all secondary endpoints were statistically significant.

In addition, statistically significant improvements from baseline with ambrisentan treatment were observed for several hemodynamics parameters (cardiac index, mPAP, and PVR) in a Phase 2 dose-controlled study (AMB-220), consistent with an overall improvement in disease state.

Plasma B-type natriuretic peptide (BNP), a hormone secreted primarily from the cardiac ventricles, has been proposed as a prognostic factor of mortality in patients with PAH [39-41]. Reductions in BNP have been shown to parallel improvements in hemodynamics, 6MWD, and WHO functional class in patients with PAH [42]. Substantial ($p < 0.05$) and clinically relevant decreases (29% to 45%) in BNP compared to placebo were observed in the Phase 3 pivotal studies, and decreases in BNP correlated with and were predictive of improvements in 6MWD.

The long-term follow-up of the subjects who were treated with ambrisentan in the Phase 3, placebo-controlled studies and their open-label extension (N = 383) shows a 95% probability of survival at 1 year (Kaplan-Meyer analysis) and of those with 48 weeks of data, 94% were still receiving monotherapy. The improvements in 6MWD, WHO functional class, and BDI were maintained for at least 48 weeks with ambrisentan treatment in the Phase 3 studies and were generally maintained for up to 3 years in the Phase 2 study (AMB-220-E).

1.2.4.2. Clinical Adverse Event Profile

Safety data for ambrisentan were obtained from the two Phase 3, placebo-controlled studies and four non-placebo-controlled studies in a total of 483 patients with PAH who were treated with doses of 1, 2.5, 5, or 10 mg qd. As of 30 November 2006, the mean exposure to ambrisentan was 79.5 ± 50.28 weeks (1.5 years) with a range of 1 day to 4 years. The majority of these subjects had drug exposures of at least 6 months (418, 86.5%). More than two-thirds of subjects had drug exposure of at least 1 year (343, 71.0%), approximately one-fourth for 2 or more years (120, 24.8%), and 42 (8.7%) subjects had drug exposures of 3 or more years.

In AMB-320 and AMB-321, a total of 261 subjects received ambrisentan at doses of 2.5, 5, or 10 mg qd and 132 subjects received placebo. Given that PAH is a serious and life-threatening condition, certain types of AEs are expected. In the combined analysis of the Phase 3, placebo-controlled studies, the most frequent AEs experienced by the placebo group were headache (14%), right ventricular failure (12%), peripheral edema (11%), dizziness (10%), and nausea (9%). The most notable AEs that occurred more often in the subjects receiving placebo compared to ambrisentan were right ventricular failure and nausea.

To evaluate the effects of ambrisentan beyond the disease process that defined the study population, placebo-adjusted incidences were calculated for the common AEs from the

combined analysis of the pivotal studies by subtracting the placebo incidence from the ambrisentan incidence (Table 1-1).

Table 1-1. Adverse Events in >3% of Ambrisentan-Treated Subjects and More Frequent than Placebo (AMB-320/321 Population: Safety)

Adverse Event	Placebo (N = 132)	Combined ambrisentan (N = 261)	
	n (%)	n (%)	Placebo-adjusted (%)
Peripheral edema	14 (11)	45 (17)	6
Nasal congestion	2 (2)	15 (6)	4
Sinusitis	0 (0)	8 (3)	3
Flushing	1 (1)	10 (4)	3
Palpitations	3 (2)	12 (5)	3
Nasopharyngitis	1 (1)	9 (3)	2
Abdominal pain	1 (1)	8 (3)	2
Constipation	2 (2)	10 (4)	2
Dyspnea	4 (3)	11 (4)	1
Headache	18 (14)	38 (15)	1

Note: This table includes all AEs >3% incidence in combined ambrisentan treatment group and greater than in the placebo group with a difference of ≥1% between the ambrisentan and placebo groups.

Peripheral edema is a known class effect of ERAs, and is also a clinical consequence of PAH and worsening PAH [43,44]. In the placebo-controlled studies, there was an increased incidence of peripheral edema in subjects treated with doses of 5 or 10 mg ambrisentan compared to placebo (Table 1-1). Most edema was mild to moderate in severity. Peripheral edema was similar in younger patients (<65 years) receiving ambrisentan (14%; 29/205) or placebo (13%; 13/104), and was greater in elderly patients (>65 years) receiving ambrisentan (29%; 16/56) compared to placebo (4%; 1/28).

Of the AEs shown in Table 1-1, only nasal congestion consistently displayed trends of increasing frequency with higher dose. However, the majority of these events were mild, and none were considered severe, serious, or led to premature discontinuation from the study.

AE profiles following long-term ambrisentan therapy continued to be consistent with that observed in the 12-week, placebo-controlled studies. In general, ambrisentan is well-tolerated and associated with a manageable safety profile in subjects with PAH.

To date, postmarketing surveillance of commercial ambrisentan (Letairis) safety has shown that the nature and severity of AEs observed with commercial therapy were generally consistent with the known safety of ambrisentan, or were attributable to concurrent disease

processes or other concomitant medications. Of note, postmarketing reports of fluid retention occurring within weeks after starting Letairis have been received and, in some cases, have required intervention with a diuretic or hospitalization for fluid management.

AEs that have been associated with ERA administration include headache, nasopharyngitis, flushing, peripheral edema, and nasal congestion [43,44]. Other safety signals associated with ERAs include dose-dependent abnormalities in liver function tests (LFTs, Section 1.2.4.2.1) [44-46], the potential adverse effects to fetal development (Section1.2.4.2.3), the potential for adverse effects on male fertility (Section 1.2.4.2.2), and decreases in hemoglobin and hematocrit (Section 1.2.4.2.4) [33,35,43,47].

1.2.4.2.1. Elevations in Liver Function Tests

Previous clinical studies with ERAs for the treatment of PAH have demonstrated dose-dependent increases in serum aminotransferase concentrations, specifically alanine aminotransferase (ALT) and aspartate aminotransferase (AST), which may be associated with liver injury. The incidence of serum aminotransferases >3x upper limit of normal (ULN) in the pivotal studies of bosentan was 12% and 14% for 125 mg and 250 mg twice daily (bid) bosentan, respectively [44]. LFT abnormalities have led to dose reduction and discontinuation of bosentan therapy in a significant number of patients.

Sitaxsentan has also been associated with dose-dependent LFT abnormalities, including 1 fatal case of acute hepatitis and 1 case of acute hepatitis requiring subsequent liver transplantation [48,49]. In the Phase 3 PAH study (STRIDE-1), the incidence of serum aminotransferases >3xULN was 0% and 10% after 100 mg and 300 mg qd po dosing of sitaxsentan, respectively [43]. When results were combined with an extension study with a median exposure of 26 weeks, the incidence increased to 5% and 21% for the 100 mg and 300 mg groups, respectively. This phase of the study was terminated prematurely due to concerns regarding the risk of possible liver injury [46]. STRIDE-2 was an 18-week, placebo-controlled study of PAH patients treated with placebo, sitaxsentan (50 mg or 100 mg qd), or bosentan (125 mg bid). In this study, the incidence of serum aminotransferases >3xULN was 6% for placebo, 5% for 50 mg sitaxsentan, 3% for 100 mg sitaxsentan, and 11% for bosentan [50]. Sitaxsentan was withdrawn from the worldwide market in December 2010 due to two cases of fatal liver injury causally related to the drug [51].

LFTs were closely monitored in all clinical studies with ambrisentan. In the 12-week placebo-controlled studies, the incidence of serum aminotransferase elevations >3xULN was 0% for subjects receiving ambrisentan (N = 261), compared to 2.3% for subjects receiving placebo (N = 132). For all ambrisentan-treated subjects (N = 483), the 12-week incidence of aminotransferases >3xULN was 0.8% and >8xULN was 0.2%. The 1-year rate of aminotransferase elevations >3xULN with ambrisentan was 2.8% and >8xULN was 0.5%. Most aminotransferase events were generally mild (<5xULN), transient, and did not require any action. Only 1 case of aminotransferase elevations >3xULN has been accompanied by bilirubin elevations >2xULN. The subject had these elevations while being hospitalized due to acute pneumonia. These LFT abnormalities resolved shortly after resolution of the

pneumonia, and the subject received 10 mg ambrisentan for an additional 177 days without incidence. The subject subsequently died due to a new event of viral pneumonia and acute respiratory failure.

Given the literature on aminotransferase abnormalities in subjects with PAH who received placebo in controlled studies, the accumulated clinical experience with ambrisentan suggests that the incidence of aminotransferase abnormalities was not greater than the background incidence expected in subjects with PAH [35,43].

In an uncontrolled, open label study, 36 subjects with PAH who had previously discontinued either bosentan, sitaxsentan, or both due to aminotransferase elevations >3xULN were treated with ambrisentan (AMB-222). Prior elevations were predominantly moderate, with 64%. of the ALT elevations <5xULN; however, 9 subjects had ALT or AST elevations >8xULN. Eight subjects had been rechallenged with bosentan and/or sitaxsentan and all eight had a recurrence of aminotransferase abnormalities that required discontinuation of ERA therapy. All subjects had to have normal aminotransferase levels on entry to this ambrisentan study. Twenty five of the 36 subjects were also receiving prostanoid and/or PDE-5 inhibitor therapy. Two subjects discontinued early (including one of the subjects with a prior 8xULN elevation) for reasons other than elevated aminotransferase levels. Of the remaining 34 subjects, one subject experienced a mild aminotransferase elevation at 12 weeks on ambrisentan 5 mg that resolved with decreased dosage to 2.5 mg, and that did not recur with later dose escalations to 10 mg. With a median follow up of 13 months and with 50% of subjects increasing the dose of ambrisentan to 10 mg, no subjects were discontinued for aminotransferase elevations.

1.2.4.2.2. Potential Risk of Testicular Injury

It is not known if the testicular lesions seen in animals (Section 1.2.2) correspond to any measurable effect in humans. Data from the literature indicates that endothelin receptors are localized to different cell types in the rat and human testes [52-54], suggesting the potential for a different response in man. In the Phase 2 and Phase 3 studies of ambrisentan, male subjects underwent semen and male fertility hormone analyses to assess fertility before and after treatment with ambrisentan. These analyses did not suggest that long-term ambrisentan treatment is associated with a substantial adverse effect on male reproductive potential.

This clinical study includes clear informed consent regarding the potential development of testicular injury and infertility. The ambrisentan IB should be reviewed for additional information.

1.2.4.2.3. Potential Risk to Fetal Development

Teratogenicity is a class effect of ERAs (Section 1.2.2). There are no data on the use of ambrisentan in pregnant women.

Ambrisentan is contraindicated in women who are or may become pregnant while taking this drug. Pregnant women will be excluded from participation in the current study, and female

subjects of childbearing potential will be required to use at least 2 reliable methods of contraception throughout their participation in the study and 30 days after discontinuation of study drug unless the subject has undergone tubal sterilization or has had a Copper T 380A intrauterine device (IUD) or LNg 20 IUD inserted, in which case no other contraception is needed. In addition, monthly pregnancy tests will be required for subjects of childbearing potential.

1.2.4.2.4. Hematological Changes

The development of drug-related reductions in hemoglobin concentration and hematocrit have been associated with ERA administration in subjects with PAH, including ambrisentan, and there have been cases where this has resulted in anemia [33,35,38,43,47]. Reversible hemodilution has been proposed as the mechanism of action for this ERA class effect [34].

In the placebo-controlled ambrisentan studies, the mean decrease in hemoglobin concentration was 0.8 g/dL [38], which was comparable to the decrease observed with bosentan treatment (0.9 g/dL) [44]. Mean hemoglobin concentration decreased over the first 4 weeks for subjects receiving ambrisentan but stabilized by 4–12 weeks of treatment. There appeared to be no clear relationship between the decrease in hemoglobin and ambrisentan dose. Similar findings were observed for mean hematocrit.

In the placebo-controlled studies, marked decreases in hemoglobin (≥15% decrease resulting in a value below the lower limit of normal) were observed in 7% of subjects receiving ambrisentan compared to 4% of subjects receiving placebo.

No other notable hematology findings were observed with ambrisentan treatment. The cause of the decrease in hemoglobin is unknown, but it does not appear to result from hemorrhage or hemolysis.

1.3. Rationale for the Current Study

Ambrisentan was approved in the US on 15 June 2007 and was made commercially available to US patients soon thereafter. Ambrisentan also received marketing authorization from Health Canada on 20 March 2008 and the European Commission on 21 April 2008. Additional marketing applications have been filed or are planned in many countries world-wide. Subjects who participated in the pivotal studies supporting the marketing applications for ambrisentan in PH are currently receiving long-term therapy in several open-label extension studies. The objectives of these original extension studies have been met and the studies are being closed by the Sponsor as patients transition to commercial ambrisentan therapy. The purpose of this protocol is to provide continuous, uninterrupted access to ambrisentan therapy to subjects who are discontinuing an ambrisentan PH study due to study closure by the Sponsor and for whom ambrisentan is not yet commercially available.

For subjects participating in the ongoing clinical studies of ambrisentan, commercial availability does not guarantee immediate access to ambrisentan treatment. For example, ambrisentan may be commercially available, but the subject may not qualify for treatment if

their diagnosis is not consistent with the current approved indication. To ensure uninterrupted, continued access to ambrisentan, subjects meeting these criteria in countries where ambrisentan is commercially available are eligible for enrollment in this study.

This study provides a mechanism for collecting ongoing safety data to supplement the existing ambrisentan safety database. The safety of subjects receiving long-term ambrisentan treatment will be monitored with monthly (every 4 weeks) LFT assessments and bi-annual (every 24 weeks) Clinic Visits. The Screening/Enrollment visit for this study will coincide with the final study visit of the previous ambrisentan study. Baseline will be defined as the time of enrollment into this study.

Elevations in serum aminotransferase (ALT and/or AST) values may be detected at the Screening/Enrollment visit. Per the treatment guidelines for the review and management of elevated serum aminotransferases, which are included in all ambrisentan clinical protocols (see Section 6.2 of this protocol), subjects with an increase in ALT or AST concentrations >8xULN must immediately stop ambrisentan treatment. These subjects may not re-initiate ambrisentan even after serum aminotransferase concentrations have decreased below 3xULN and therefore will not be allowed to enroll in this study. Subjects with ALT/or AST concentrations >3xULN but ≤8xULN will be allowed to enroll, and must treated and monitored per the guidelines provided in Section 6.2.

2. OBJECTIVES

The objective of this study is to monitor the long-term safety of ambrisentan in subjects with PH.

3. STUDY DESIGN

3.1. Treatment Plan and Regimen

This Phase 3, international, multicenter, open-label study will monitor the long-term safety of ambrisentan in subjects with PH. The available ambrisentan doses for this study are 5 or 10 mg qd; these are the approved doses in US, Canada, and EU.

Investigators will be able to adjust ambrisentan dose as clinically indicated. A minimum of 4 weeks between dose adjustments is required. Subjects receiving other therapies for PH that are not contraindicated for concomitant use with ambrisentan are permitted to enroll in this study and continue to receive such therapies.

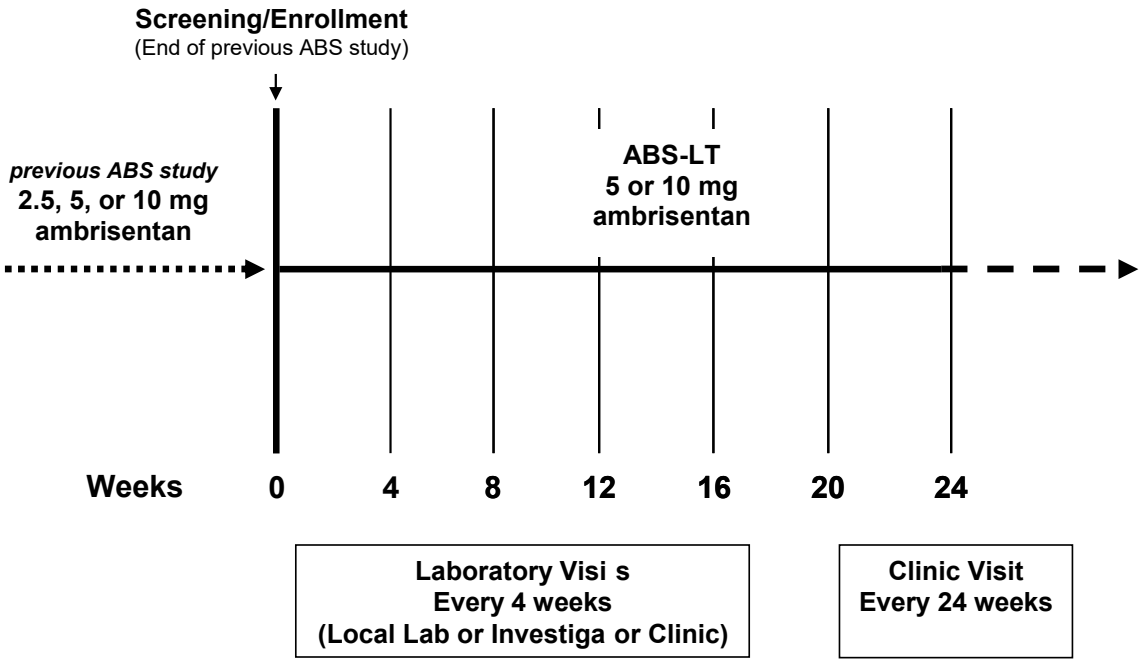
Subjects enrolled in this study will receive treatment with ambrisentan until such time as the Investigator or subject chooses to stop ambrisentan treatment, ambrisentan becomes commercially available, or the Sponsor stops the study.

Subjects will be followed by the Investigator according to clinical practice, with formal (per protocol) safety assessments conducted at the Screening/Enrollment Visit and at Clinic Visits every 24 weeks thereafter. These safety assessments will include AEs, clinical laboratory tests, vital signs, and concomitant medications. In addition, serum LFTs will be monitored at Laboratory Visits every 4 weeks throughout the study. These LFTs will be performed at a local phlebotomy laboratory or at the Investigator clinic. A central laboratory will not be used for this study.

In animals, ambrisentan and other ERAs have been shown to be teratogenic. Therefore, female subjects of childbearing potential will undergo pregnancy testing every 4 weeks and will be required to use 2 reliable methods of contraception to reduce the risk of pregnancy during the course of the study and for at least 30 days following the last dose of ambrisentan. If a subject has undergone tubal sterilization or has had a Copper T 380A IUD or LNg 20 IUD inserted, no other contraception is needed.

An internal Data Monitoring Committee (DMC) will monitor the safety and welfare of the study subjects. The ABS-LT study is an open label study, thus the data monitoring committee consists of internal employees of the Sponsor rather than external members. The committee chair is a physician with extensive pulmonary hypertension experience. The remaining committee members include a second physician, a clinical scientist, and a biostatistician. The internal DMC will meet at designated intervals to review the accumulated data.

3.2. Study Schematic



4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

This study is designed to provide continuous, uninterrupted access to ambrisentan therapy to subjects who are discontinuing an ambrisentan PH study due to study closure by the Sponsor and for whom ambrisentan is not yet currently available. It is estimated that approximately 300 subjects will be eligible for this study at the time of its inception. This number will vary as subjects discontinue this study, or as additional clinical studies of ambrisentan in PH are completed and subjects participating in these studies become eligible per the inclusion and exclusion criteria specified in Sections 4.2 and 4.3.

4.2. Inclusion Criteria

Subjects must meet *all* of the following inclusion criteria to be eligible for participation in this study.

1. Subject must be discontinuing a clinical study of ambrisentan in PH due to study closure by the Sponsor.
2. Subject must be discontinuing a clinical study of ambrisentan in PH in a country where:
    a. Ambrisentan is not yet commercially available; or
    b. Ambrisentan is commercially available, but the subject does not qualify for commercial therapy per the current prescribing information of that country
3. Subject must have completed study assessments and procedures for the previous ambrisentan study to the best of their ability.
4. Female subject of childbearing potential must have a negative serum or urine pregnancy test at the Screening/Enrollment Visit. A female subject of childbearing potential is defined in Section 8.7.
5. Female subject of childbearing potential must agree to use 2 reliable methods of contraception until study completion and for at least 30 days following the last dose of ambrisentan (reliable methods of contraception are described in Section 8.7).
6. Subject must agree not to participate in a clinical study involving another investigational drug or device for PH throughout this study (does not include registry or observational studies)
7. Subject must be competent to understand the information given in the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) approved Informed Consent Form (ICF) and must sign the form prior to the initiation of any study procedures.

4.3. Exclusion Criteria

Subjects who meet *any* of the following exclusion criteria are not to be enrolled in this study.

1. Subject who is discontinuing a clinical study of ambrisentan for any other reason than Sponsor-initiated study closure.
2. Subject who has a confirmed serum ALT and/or AST lab value >8xULN.
3. Female subject who is pregnant or breastfeeding.
4. Subject who has demonstrated noncompliance with previous medical regimens.
5. Subject who has a recent history of abusing alcohol or illicit drugs.
6. Subject who is receiving bosentan (Tracleer®), sitaxsentan (Thelin®), or any investigational drug for PH.
7. Subject with a known hypersensitivity to ambrisentan, the metabolites, or formulation excipients.

4.4. Study Specific Tolerance for Inclusion/Exclusion Criteria

Subjects with deviations to inclusion and exclusion criteria will not be permitted to enroll.

5. STUDY DRUGS

5.1. Randomization and Blinding

This is a non-randomized, open-label study.

5.2. Description and Handling of Ambrisentan

5.2.1. Formulation

Gilead will provide study drug in the form of film-coated, immediate-release tablets, containing either 5 mg or 10 mg ambrisentan.

5.2.2. Packaging and Labeling

All study drug will be packaged in containers with 30 study drug tablets. The study drug distributor will send the initial shipment of study drug to sites as soon as Gilead or a specified designee approves the site. Study drug resupply will occur as needed.

5.2.3. Storage and Handling

Gilead will provide ambrisentan. Upon initial receipt of study drug, the Investigator and/or site staff will acknowledge receipt of the material, indicating shipment content and condition. The study site must maintain a dated inventory record of all study drug received and dispensed to subjects along with all study drug returned. A copy of the inventory log for study drug will be sent to Gilead or a specified designee after the study is complete.

Store at controlled room temperature (25^{o} C or 77^{o} F). Brief excursions are permitted between 15^{o} C and 30^{o} C (59-86^{o} F). Excursions outside of this range or those lasting longer than 3 days must be reported to Gilead or designee.

5.3. Dosage and Administration of Ambrisentan

Ambrisentan is provided in oral tablets. Subjects are instructed to take ambrisentan with or without food once daily in the morning throughout the course of the study. Investigators will be able to adjust the ambrisentan dose as clinically indicated (available doses are 5 or 10 mg ambrisentan qd). A minimum of 4 weeks between dose adjustments is required.

5.4. Concomitant and Prohibited Medications

Standard medical treatment(s) being taken by the subject upon study entry may be maintained throughout the study. Subjects receiving other approved therapies for PH that are not contraindicated for concomitant use with ambrisentan are permitted to enroll in this study and continue to receive such therapies.

Drugs prohibited prior to the study and throughout the treatment period are:

- Bosentan (Tracleer®)
- Sitaxsentan (Thelin®)
- Any other investigational drug for PH.

6. STUDY PROCEDURES

6.1. General Instructions

- Ambrisentan should be taken with or without food once daily in the morning throughout the study unless otherwise instructed.
- Subjects should be instructed to bring their used and unused ambrisentan containers with them to every Clinic Visit to assess compliance and drug accountability.
- All study visits will be determined from the date of first dose of ambrisentan in this study, and all study visit windows are ± 4 days.
- Study compliance will be assessed via a telephone call on the day (± 2 days) of a Laboratory Visit

6.2. Monitoring of Liver Function Test Abnormalities

All subjects will have blood drawn every 4 weeks for LFTs. LFTs include serum ALT, AST, alkaline phosphatase, gamma glutamyl transferase (GGT), and total bilirubin concentrations. In order to ensure the safety of all subjects, the results of these tests must be reviewed by the Investigator immediately upon receipt. An increase in serum ALT or AST concentration >3xULN must be confirmed by a second test (>3xULN) that is collected no more than 7 days after receipt of the initial lab report. All events of ALT/AST (confirmed and unconfirmed) will be included in the assessment of aminotransferase abnormalities >3xULN; however, confirmed serum ALT or AST concentration >3xULN must also be immediately reported as a serious adverse event (SAE).

The requirements presented in Table 6-1 must be applied to the review and management of elevated serum aminotransferases in subjects throughout the study:

Table 6-1. Dose Adjustment and Monitoring of Subjects Experiencing Serum Aminotransferase Elevations

ALT/AST Concentrations	Treatment and Monitoring Requirements
>3x and ≤5xULN	Notify Gilead or specified designee immediately. Confirm by another serum aminotransferase test within 7 days. If confirmed, report as a SAE and consider dose reduction or discontinuation of ambrisentan. Continue to monitor serum aminotransferase concentrations every 2 weeks or more frequently if clinically indicated. If the serum aminotransferase concentrations decrease below 3xULN, continue at the reduced dose or reintroduce ambrisentan at a reduced dose as appropriate.
>5x and ≤8xULN	Stop ambrisentan treatment immediately and notify Gilead or specified designee. Confirm by another serum aminotransferase test within 7 days. If confirmed, report as a SAE. Continue to monitor serum aminotransferase concentrations every 2 weeks, or more frequently if clinically indicated. If the serum aminotransferase concentrations decrease below 3xULN, reintroduction of ambrisentan treatment requires consultation and approval from Gilead or a specified designee.
>8xULN	Stop ambrisentan treatment immediately and notify Gilead or specified designee. Confirm by another serum aminotransferase test within 7 days. If confirmed, report as a SAE. After discontinuation of ambrisentan, continue to monitor serum aminotransferase concentrations every 2 weeks, or more frequently if clinically indicated. The subject should be followed until the serum aminotransferase concentrations decrease below 3xULN. Ambrisentan may not be reintroduced.

If ambrisentan is reintroduced, serum aminotransferase concentrations should be checked within 3 days and then every 2 weeks or more frequently if clinically indicated. If the serum aminotransferase elevations are accompanied by clinical symptoms of liver injury (such as nausea, vomiting, fever, abdominal pain, jaundice, or unusual lethargy or fatigue) or increases in total bilirubin ≥2xULN, treatment should be stopped. Continue to monitor serum aminotransferase concentrations at least every 2 weeks, or more frequently if clinically indicated.

6.3. Schedule of Assessments

	Screening/Enrollment Visit	Laboratory Visits[a]	Clinic Visits[b]
Week	**0**	**Every 4 Weeks**	**Every 24 Weeks**
Assessments			
Informed consent	X		
Medical history	X		
Vital signs/body weight	X		X
Clinical laboratory tests[c]	X[d]	X[c,e]	X[d]
Serum or urine pregnancy test[f]	X	X	X
CONMED assessment	X		X
Adverse events	X		X
Return unused ambrisentan	X		X
Dispense study drug[g]	X		X

[a] Laboratory Visits will be required every 4 weeks and will be completed at a local phlebotomy lab or at the Investigator clinic.
[b] Clinic Visits will be required every 24 weeks.
[c] Completion of the Laboratory Visit will be documented via telephone contact (within ± 2 days) if the Laboratory Visit occurs at a local phlebotomy lab.
[d] Clinical laboratory tests at the Screening/Enrollment Visit and Clinic Visits will include chemistry (including LFTs), hematology, and coagulation. Coagulation labs (PT, PTT, and INR) will only be completed for subjects who are receiving warfarin or any other warfarin-like anticoagulants.
[e] Clinical laboratory tests at the Laboratory Visits will be limited to LFTs, specifically ALT, AST, alkaline phosphatase, GGT, and total bilirubin. Please refer to Section 6.2 for specific guidance on dose adjustment and monitoring of subjects who develop aminotransferase elevations.
[f] Pregnancy testing required for women of childbearing potential.
[g] As necessary, a 3-month supply of study drug will be dispensed.

6.4. Study Procedures By Time Point

6.4.1. Screening/Enrollment Visit (Week 0)

Subjects will complete the Screening/Enrollment Visit for this study (GS-US-300-0124) on the same day as their final visit for the previous ambrisentan study.

The following procedures will be completed as part of the final visit for the previous ambrisentan study, and will be used for the Screening/Enrollment Visit of this study (GS-US-300-0124):

- Record vital signs, including sitting blood pressure and heart rate, and body weight (Section 7.3)
- Collect chemistry, hematology, and coagulation (Section 7.4)
- Collect serum or urine pregnancy test for female subjects of childbearing potential (Section 7.4)
- Record all concomitant medications (CONMEDS, Section 7.2)
- Record all AEs since last visit

The following procedures will be completed for enrollment in this study:

- Obtain written informed consent
- Review all inclusion/exclusion criteria (See Sections 4.2 and 4.3)
- Assess medical history (Section 7.1)
- Complete the Interactive Voice Response System (IVRS) Screening Module
- Dispense study drug and instruct the subject to return all used and unused ambrisentan containers at the next Clinical Visit
- Instruct the subject to call the clinic or return promptly should an AE occur

6.4.2. Laboratory Visits (Every 4 Weeks)

Subjects will be required to provide blood samples for LFTs every 4 weeks at Laboratory Visits. Females of childbearing potential will also provide a blood or urine sample for pregnancy testing at these visits. The Laboratory Visits will be completed at a local phlebotomy laboratory or at the Investigator clinic. Completion of the Laboratory Visit will be documented via telephone contact (within ± 2 days) if the Laboratory Visit occurs at a local phlebotomy lab. Any local phlebotomy laboratory utilized for Laboratory Visits must

be added to Section 4 of the FDA Form 1572. Applicable lab certifications and normal ranges must be collected.

The following procedures will be completed at each Laboratory Visit:

- Collect LFTs (Section 7.4)
- Collect serum or urine pregnancy test for female subjects of childbearing potential (Section 7.4)
- Assess study compliance via a telephone call on the day (±2 days) of a Laboratory Visit
- If the next visit is a Clinic Visit, remind the subject to return all used and unused ambrisentan containers with them at the Clinic Visit

6.4.3. Clinic Visits (Every 24 Weeks)

Subjects will be required to visit the Investigator Clinic every 24 weeks to be evaluated for safety.

The following procedures will be completed at each Clinic Visit:

- Record vital signs (including sitting blood pressure and heart rate) and body weight (Section 7.3)
- Collect chemistry, hematology, and coagulation (Section 7.4)
- Collect serum or urine pregnancy test for female subjects of childbearing potential (Section 7.4)
- Record all concomitant medications (CONMEDS, Section 7.2)
- Record all AEs
- Collect all used and unused ambrisentan drug containers
- Complete the IVRS Subject Subsequent Assignment Module to receive the new ambrisentan container number
- Dispense study drug and instruct the subject to return all used and unused ambrisentan containers with them at the next Clinic Visit

6.5. Premature Discontinuation/End of Study

All subjects have the right to withdraw formal consent without prejudice at any time during the study. If a subject withdraws formal consent, the Investigator should make a reasonable effort to determine the cause for withdrawal of consent.

If, for whatever reason, a subject discontinues study participation prematurely, the following procedures should be completed:

- Record vital signs (including sitting blood pressure and heart rate) and body weight (Section 7.3)
- Collect chemistry, hematology, and coagulation (Section 7.4)
- Collect serum or urine pregnancy test for female subjects of childbearing potential (Section 7.4)
- Record all concomitant medications (CONMEDS, Section 7.2)
- Record all AEs
- Collect all used and unused ambrisentan drug containers
- Call IVRS and complete the Premature Discontinuation Module
- Contact the subject by telephone 72 hours following discontinuation of study to check on their health status, and document the telephone contact. If the subject has experienced any AEs or changes to medications (including PH therapy), collect all pertinent information and record on the appropriate case report form CRF(s).

6.6. Criteria for Discontinuation of Study Treatment

The subject's participation in this clinical study may be prematurely discontinued due to:

- Development of an AE where continuation of the subject's participation in the study is thought by the Investigator to be inappropriate
- Clinical status did not improve or deteriorated
- Subject begins treatment with a prohibited concomitant therapy
- Subject requests to discontinue for any reason
- Noncompliance to any of the protocol procedures

- Positive pregnancy test (every attempt should be made to follow the subject through the term of the pregnancy for safety)
- Discretion of the Investigator
- Lost to follow-up
- Discontinuation of the study at the request of Gilead, a regulatory agency, or an IRB/IEC
- Ambrisentan treatment may also be discontinued when ambrisentan becomes commercially available in the country where the subject is participating and the subject qualifies for commercial therapy per the current prescribing information of that country.

7. DESCRIPTION OF STUDY PROCEDURES

7.1. Medical History

All ongoing conditions and relevant/significant medical history (including all major hospitalizations and surgeries) will be recorded at the Screening/Enrollment Visit. Symptoms and signs related to PH and/or the underlying etiology of the disease need not be listed on the medical history form; however, worsening of any symptoms or signs during the course of this study must be captured as an AE.

Current medical status, subject demographics, height, and weight will be recorded at the Screening/Enrollment Visit. Body weight will be recorded at all subsequent Clinic Visits.

7.2. Concomitant Medications

At the Screening/Enrollment Visit, review all medications taken 30 days prior to screening; document and capture on the appropriate CRF.

At each study visit, all medications will be reviewed and any changes will be captured on the appropriate CRF. Document any changes in concomitant medication (including PAH therapy) via a telephone call 72 hours following discontinuation of study.

7.3. Vital Signs and Body Weight

Vital signs (including heart rate and blood pressure) will be collected at each Clinic Visit. One measurement of blood pressure and heart rate after the subject has been sitting quietly for at least 5 minutes should be taken. This same procedure should be followed throughout the study.

Vital signs must be assessed prior to, or at least 1 hour after, a blood draw. All measures of blood pressure will be performed using standard sphygmomanometry. If possible, the same sphygmomanometer and arm should be used.

In addition, body weight will be collected at each Clinic Visit.

7.4. Clinical Laboratory Tests

Chemistry (including LFTs), hematology, and coagulation will be collected every 24 weeks at the Clinic Visits. Additionally, LFTs will be collected every 4 weeks at the Laboratory Visits. Serum or urine pregnancy tests will also be collected at all Clinic and Laboratory Visits for female subjects of childbearing potential.

A central laboratory will not be used for this study. Local laboratories will analyze all protocol-specified laboratory tests at the Laboratory Visits. Additional laboratory tests will be performed by a local laboratory if clinically relevant abnormal values are obtained at any

time during the course of the study. Local lab reports must be immediately reviewed by the Investigator. Laboratory values that are not within normal limits will be captured on the CRF, along with the normal ranges.

Chemistry: The following chemistry tests are required at Clinic Visits: serum ALT, AST, alkaline phosphatase, GGT, total bilirubin, creatinine, amylase, blood urea nitrogen (BUN), sodium, potassium, chloride, bicarbonate, calcium, total cholesterol, uric acid, glucose, total protein and albumin.

The following chemistry tests are required at Laboratory Visits: serum ALT, AST, alkaline phosphatase, GGT, and total bilirubin.

Hematology: The following hematology tests are required at Clinic Visits: hemoglobin, hematocrit, red cell count, red cell indices, white blood cell count (total and differential) and platelet count.

Coagulation: At Clinic Visits, INR will be evaluated for subjects who are receiving warfarin (Coumadin®) or any other warfarin-like anticoagulants.

Pregnancy Test: Serum or urine pregnancy tests will be performed for all female subjects of childbearing potential at the Screening/Enrollment Visit, at each subsequent study visit, including Laboratory Visits, and premature discontinuation, if applicable.

7.5. Protocol Deviations

This study will be conducted as described in this protocol except for emergency situations in which the protection, safety, and well being of the subject requires immediate intervention based upon the judgment of the Investigator (or a responsible, appropriately trained and credentialed professional(s) designated by the Investigator). In the event of any deviation from the protocol, the Investigator or a specified designee must notify Gilead and/or specified designee immediately. This will allow an early joint decision to be made as to whether or not the subject should continue in the study. Both the Investigator and Gilead or specified designee will document this decision.

8. ADVERSE EVENTS AND TOXICITY MANAGEMENT

8.1. Adverse Events

An adverse event (AE) is any untoward medical occurrence in a clinical investigation subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

AEs may also include the following:

- Pre- or post-treatment complications that occur as a result of a protocol-associated procedure (e.g., invasive procedures such as venipuncture, biopsy) during or after screening (before the administration of study drug)

- Any pre-existing condition that increases in severity or changes in nature during or as a consequence of the study drug phase of this clinical study

- Complication and termination of pregnancy (see Section 8.7 for additional information)

- All AEs that occur from the time the subject consents to participate in the study and throughout the duration of the study, including the follow-up off study medication period should be recorded as an AE. For Post-Study Reporting Requirements, see Section 8.5.3.

An AE does not include the following:

- Medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, transfusion) performed; the condition that leads to the procedure is an AE

- Pre-existing diseases or conditions or laboratory abnormalities present or detected before the screening visit that do not worsen

- Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery, social and/or convenience admissions)

- Overdose without clinical sequelae; however, all overdoses, asymptomatic and symptomatic, must be reported using the overdose form.

Any medical condition or clinically significant laboratory abnormality with an onset date before the screening visit and not related to a protocol-associated procedure is not an AE. It is considered to be pre-existing and should be documented on the Medical History CRF.

Anticipated day-to-day fluctuations of pre-existing conditions that do not represent a clinically significant exacerbation or worsening need not be considered AEs. Any

pre-existing conditions or signs and/or symptoms not related to PH or underlying etiology present in a subject prior to the start of the study should be recorded on the Medical History CRF.

8.2. Assessment of Adverse Events

All AEs will be assessed by the Investigator and recorded on the AE CRF page. The AE entry should indicate whether or not the AE was serious, the start date (AE onset), the stop date (date of AE resolution), whether or not the AE was related to study drug, or to a study procedure, the action taken with study drug due to the AE, the severity of the AE, and the outcome of the AE.

AEs already documented in the CRF (i.e., at a previous assessment) and designated as "ongoing" should be reviewed at subsequent visits as necessary. Upon resolution, the date and time (if applicable) of resolution should be recorded in the CRF. If an AE increases in frequency or severity during a study period, a new record of the event should be started.

AEs should be documented in terms of a medical diagnosis. When this is not possible, the AE should be documented in terms of signs and/or symptoms observed by the Investigator or reported by the subject at each study visit.

For AEs associated with laboratory abnormalities, the AE should be assessed on the basis of the clinical severity in the context of the underlying conditions. Collection of changes in laboratory values as AEs should be restricted to those considered clinically significant by the Investigator that result in a change, interruption, or discontinuation of study drug, are considered an SAE, or require medical intervention or treatment. Laboratory values associated with clinical signs and symptoms should be reported as an AE based on the clinical signs and symptoms not as the laboratory value.

8.2.1. Assessment of Causality

The relationship to study drug (ambrisentan/placebo) therapy should be assessed using clinical judgment and the following definitions:

- No: Evidence exists that the AE has an etiology other than the study drug. For SAEs, an alternative causality must be provided (e.g., pre-existing condition, underlying disease, intercurrent illness, or concomitant medication).

- Yes: A temporal relationship exists between the AE onset and administration of the study drug that cannot be readily explained by the subject's clinical state or concomitant therapies. Furthermore, the AE appears with some degree of certainty to be related, based on the known therapeutic and pharmacologic actions or AE profile of the study drug. In case of cessation or reduction of the dose, the AE abates or resolves and reappears upon rechallenge.

It should be emphasized that ineffective treatment should not be considered as causally related in the context of AE reporting.

The relationship to study procedures (e.g., invasive procedures such as venipuncture) should be assessed using the following definitions:

- No: Evidence exists that the AE has an etiology other than the study procedure.
- Yes: The AE occurred as a result of protocol-mandated procedures such as venipuncture.

8.2.2. Assessment of Intensity

Adverse events will be graded on a 3-point scale, and reported as indicated on the CRF. Maximum intensity should be assigned to 1 of the following categories:

Mild: The AE does not interfere with routine activities. The subject may experience slight discomfort.

Moderate: The AE interferes with routine activities. The subject may experience significant discomfort.

Severe: The AE makes it impossible to perform routine activities. The subject may experience intolerable discomfort or pain.

8.3. Serious Adverse Events

A **serious adverse event** (SAE) is defined as follows:

Any adverse drug experience occurring at any dose that results in any of the following outcomes:

- Death
- Life-threatening situation (subject is at **immediate** risk of death)
- In-patient hospitalization or prolongation of existing hospitalization (excluding those for study therapy or placement of an indwelling catheter, unless associated with other SAEs)
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect in the offspring of a subject who received study drug
- Other: medically significant events that may not be immediately life-threatening or result in death or hospitalization, but based upon appropriate medical and scientific judgment, may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed above

Examples of such events are as follows:

— Intensive treatment in an emergency room or at home for allergic bronchospasm

— Blood dyscrasias or convulsions that do not result in hospitalization

— Development of drug dependency or drug abuse

— Infections resulting from contaminated Gilead medicinal product

- Study specific:
- Pregnancies (Section 8.7)
- Elevated serum aminotransferase concentrations (Section 6.2)

Clarification of Serious Adverse Events

- Death is an outcome of an AE, and not an AE in itself. In reports of death due to "Disease Progression," where no other information is provided, the death will be assumed to have resulted from progression of the disease being treated with the study drug(s).
- "Occurring at any dose" does not imply that the subject is receiving study drug at the time of the event. Dosing may have been given as treatment cycles or interrupted temporarily before the onset of the SAE, but may have contributed to the event.
- "Life-threatening" means that the subject was at immediate risk of death from the event as it occurred. This does not include an event that might have led to death if it had occurred with greater severity.
- Complications that occur during hospitalizations are AEs. If a complication prolongs the hospitalization, it is a SAE.
- "In-patient hospitalization" means the subject has been formally admitted to a hospital for medical reasons, for any length of time. This may or may not be overnight. It does not include presentation and care within an emergency department.
- The Investigator should attempt to establish a diagnosis of the event on the basis of signs, symptoms and/or other clinical information. In such cases, the diagnosis should be documented as the AE and/or SAE and not the individual signs/symptoms.

A distinction should be drawn between seriousness and severity of AEs. An AE that is assessed as severe should not be confused with a SAE. Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe. An event is defined as "serious" when it meets one of the predefined outcomes described above.

8.4. Special Situations Reports

8.4.1. Definitions of Special Situations

Special situation reports include all reports of medication error, abuse, misuse, overdose, and pregnancy reports regardless of an associated AE. Also includes reports of adverse reactions associated with product complaints and reports arising from occupational exposure.

A pregnancy report is used to report any pregnancy following maternal exposure to the medicinal product (see Section 8.7).

Medication error is any unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the health care provider, subject, or consumer.

Abuse is defined as persistent or sporadic intentional excessive use of a medicinal product by a subject.

Misuse is defined as any intentional or inappropriate use of a medicinal product that is not in accordance with the protocol instructions or the local prescribing information.

An overdose is defined as an accidental or intentional administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose as per protocol or in the product labelling (as it applies to the daily dose of the subject in question). In cases of a discrepancy in drug accountability, overdose will be established only when it is clear that the subject has taken the excess dose(s). Overdose cannot be established when the subject cannot account for the discrepancy except in cases in which the investigator has reason to suspect that the subject has taken the additional dose(s).

Product complaint is defined as complaints arising from potential deviations in the manufacture, packaging, or distribution of the medicinal product.

8.4.2. Instructions for Reporting Special Situations

8.4.2.1. Instructions for Reporting Pregnancies (see Section 8.7)

8.4.2.2. Reporting Other Special Situations

All other special situation reports must be reported on the special situations report form and forwarded to designated Pharmcovigilance Officeror Gilead DSPH within 24 hours of the investigator becoming aware of the situation. These reports must consist of situations that involve study IMP, but do not apply to concomitant medications. Except for situations that result in AEs, special situations involving concomitant medications will not be reported. Any inappropriate use of medications prohibited by this protocol should not be reported as “misuse,” but may be more appropriately documented as a protocol deviation.

Special Situations should be reported to the designated Pharmacovigilance Officer using the Special Situations Report form. If the special situation occurs after the study has been completed, the special situations report should be reported directly to Gilead DSPH. Gilead DSPH contact information is as follows: Email: PPD and Fax: PPD

All clinical sequelae in relation to these special situation reports will be reported as AEs or SAEs at the same time using the AE CRF/eCRF and/or the SAE report form. Details of the symptoms and signs, clinical management, and outcome will be reported, when available.

8.5. Serious Adverse Event Reporting Requirements

8.5.1. All Serious Adverse Events

Gilead is required to expedite reports of SAEs, Serious Adverse Drug Reactions, or Suspected Unexpected Serious Adverse Reactions (SUSAR) in line with relevant legislation, including the European Commission Clinical Trial Directive (2001/20/EC) to worldwide regulatory authorities; therefore, Gilead (or the Clinical Research Organization [CRO] on the behalf of Gilead) must be notified immediately regarding the occurrence of any SAE that occurs after the subject consents to participate in the study, including SAEs resulting from protocol-associated procedures as defined in relevant legislation including 2001/20/EC, performed from screening onwards. The procedures for reporting all SAEs, regardless of causal relationship, are as follows:

- Record the SAE on the AE CRF and complete the "Serious Adverse Event Report" form.
- Fax or e-mail the SAE form to the attention of designated Pharmacovigilance Officer within 24 hours of the Investigator's knowledge of the event. For fatal or life-threatening events, also fax copies of hospital case reports, autopsy reports, and other documents when requested and applicable.

Gilead may request additional information from the Investigator to ensure the timely completion of accurate safety reports. Any subject data sent to Gilead must be made anonymous (while remaining traceable by the sender) before sending.

The Investigator must take all therapeutic measures necessary for resolution of the SAE. Any medications necessary for treatment of the SAE must be recorded onto the CONMED Section of the subject's CRF.

Follow-up of AEs/SAEs will continue through the last day on study and/or until the Investigator and/or Gilead determine that the subject's condition is stable. Gilead may request that certain AEs/SAEs be followed until resolution.

8.5.2. Investigator and Sponsor Reporting Requirements for SAEs

An SAE may qualify for expedited reporting to worldwide regulatory authorities if it is a SAE, Serious Adverse Event, or SUSAR in line with relevant legislation, including the European Commission Clinical Trials Directive (2001/20/EC). Expectedness of SAEs will be determined by Gilead using reference safety information specified in the IB.

All Investigators will receive a safety letter notifying them of relevant SUSAR reports. The Investigator should notify the IRB or IEC as soon as is practical, of serious events in writing where this is required by local regulatory authorities, and in accordance with the local institutional policy.

In accordance with the EU Clinical Trials Directive (2001/20/EC), Gilead will notify worldwide regulatory authorities and the relevant Ethics Committees in concerned Member States of applicable SUSARs as individual notifications or through a period line listing.

8.5.3. Post-Study Reporting Requirements

All AEs and SAEs, including deaths, regardless of cause or relationship, must be reported for subjects on study. Any SAEs that occur within 30 days of last study drug dose, regardless of causality, should also be reported.

Investigators are not obligated to actively seek out SAEs beyond the follow-up period for subjects. However, if the Investigator learns of an AE or SAE occurring after the completion/termination visit and the event is deemed by the Investigator to be relevant to the use of study drug (ambrisentan), he/she should promptly document and report the event to the designated Pharmacovigilance Officer or, if the study has been completed, to Gilead DSPH. Gilead DSPH contact information is as follows: Email: PPD and Fax: PPD

8.6. Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or Serious Adverse Events

Laboratory abnormalities are usually not recorded as AEs or SAEs. However, laboratory abnormalities (e.g. clinical chemistry, hematology, urinalysis) independent of the underlying medical condition that require medical or surgical intervention or lead to study drug interruption or discontinuation must be recorded as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (e.g., vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE (or SAE) as described in Section 8.1 (or 8.3). If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis.

If the changes are mild and in the opinion of the Investigator not clinically significant, the Investigator should continue to carefully monitor the values. Laboratory tests may be repeated, as clinically indicated, without prior approval by Gilead or specified designee.

Special attention must be paid to the results of LFTs for all subjects enrolled into this study. Section 6.2 Monitoring of Liver Function Test Abnormalities, provides specific guidance for dose adjustment and monitoring of subjects who develop serum aminotransferase elevations. Investigators are required to follow these guidelines. All confirmed elevations in serum aminotransferase concentrations >3xULN must be immediately reported as a SAE.

8.7. Pregnancy

Subjects who become pregnant during the study must discontinue study drug immediately, and the pregnancy must be reported as an SAE. The Investigator should report all pregnancies to the designated Pharmacovigilance Officer within 24 hours of becoming aware of the pregnancy. The Investigator should counsel the subject regarding the possible effects of prior study drug exposure on the fetus (see Section 1.2.4.2.3 and the IB) and the need to inform the study site of the outcome of the pregnancy. The SAE reporting process, as identified in Section 8.5 must be followed.

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. Whenever possible, a pregnancy should be followed by the study site to term, and the status of the mother and child should be reported to the designated Pharmacovigilance Officer after delivery. Any premature terminations of pregnancy must be reported.

All pregnancies that occur during the study should be reported using the SAE and Pregnancy Report forms and faxed to the designated Pharmacovigilance Officer. Monitoring of the subject should continue until the conclusion of the pregnancy. The outcome should be reported to the designated Pharmacovigilance Officer (Section 8.5) using the Pregnancy Outcome Report form. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead DSPH. Gilead DSPH contact information is as follows: Email: PPD and Fax: PPD

Of note, the effects of ambrisentan on pregnancy in female partners have not been evaluated; please refer to the IB for additional information.

8.7.1. Reliable Forms of Contraception

Female subjects of childbearing potential (see definition below) must agree to utilize TWO reliable methods of contraception from the Screening/Enrollment Visit throughout the study period and for 30 days following the last dose of study drug. Reliable methods of contraception are: birth control pills/implants/injections, intrauterine devices (IUDs), spermicide, diaphragms, or condoms. If a subject has undergone tubal sterilization or has had a Copper T 380A IUD or LNg 20 IUD inserted, no other contraception is needed. The Investigator should counsel subjects on the most effective method(s) for avoiding pregnancy during the study.

8.7.2. Definition of Childbearing Potential and Post-Menopausal

A female patient of childbearing potential is a nonmenopausal female who has not had a hysterectomy, bilateral oophorectomy, or medically documented ovarian failure. This definition includes a young woman who has not yet started menstruating. A woman who has had a tubal sterilization is considered to be of childbearing potential.

Menopause can be assumed to have occurred in a woman when there is either:

- Appropriate medical documentation of prior complete bilateral oophorectomy (i.e., surgical removal of the ovaries, resulting in "surgical menopause" and occurring at the age at which the procedure was performed) or

- Permanent cessation of previously occurring menses as a result of ovarian failure with documentation of hormonal deficiency by a certified healthcare provider (i.e., "spontaneous menopause," which occurs in the United States at a mean age of 51.5 years).

- A hormonal deficiency should be properly documented in the case of suspected spontaneous menopause as follows:

- If age ≥54 years and with the absence of normal menses: serum follicle stimulating hormone (FSH) level elevated to within the post-menopausal range based on the laboratory reference range where the hormonal assay is performed;

- If age <54 years and with the absence of normal menses: negative serum or urine human chorionic gonadotropin (hCG) with concurrently elevated serum FSH level in the post-menopausal range, depressed estradiol (E2) level in the post-menopausal range, and absent serum progesterone level, based on the laboratory reference ranges where the hormonal assays are performed.

Female subjects who were determined to be post-menopausal (i.e., not of childbearing potential) at the time enrollment in the previous ambrisentan study will be considered post-menopausal for this study. Female subjects who were of childbearing potential at the time of enrollment in the previous study must meet the criteria outlined above in order to be considered post-menopausal.

9. STATISTICAL CONSIDERATIONS

9.1. Primary Endpoint

The primary endpoint of this study is the incidence and severity of AEs associated with long-term exposure to ambrisentan in subjects with PH.

9.2. Measures of Interest

Additional safety measures of interest include:

- Shift from baseline (low/normal/high) over time in clinical laboratory values
- Change from baseline over time in vital signs

9.3. Methods of Analysis

9.3.1. Analysis Sets

The primary analysis set for safety analyses will include all enrolled subjects who received at least one dose of ambrisentan in this study (referred to hereafter as the safety full analysis set [FAS]).

9.3.2. General Methodology

Most continuous data will be summarized using the following descriptive statistics: number of observations, mean, standard deviation, standard error, median, minimum and maximum. Categorical data will be summarized using frequencies and percentages. Changes from baseline will be calculated as the later value minus the baseline value. Baseline will be defined for all endpoints as the time of enrollment into this study.

9.3.3. Data Handling Conventions

Safety data will be used according to availability, with no imputation for missing data.

9.3.4. Timing of Analyses

Interim analyses for this study will be performed periodically to generate safety data. This data may be used for regulatory submissions and publications.

The data from this study will also be reviewed on a regular basis by an unblinded DMC charged with protecting the safety of the study subjects. This committee will have the authority to recommend stopping the study early or modifying the study design for safety concerns.

9.4. Demographic Data and Baseline Characteristics

Demographic and baseline characteristics will be summarized by treatment group for the FAS using descriptive statistics.

Data to be included in this summary are gender, race, region, age, height, weight, body mass index (BMI), childbearing potential, smoking status, PH etiology, years PH present, and previous ambrisentan study.

9.5. Efficacy Analysis

Efficacy will not be examined in this study.

9.6. Safety Analysis

All safety data collected on or after the date that ambrisentan was first administered in this study up to the date of last dose of ambrisentan (including any SAEs occurring as specified in Section 8.5.3) will be summarized by treatment group and all subjects combined. Subjects will be assigned to a treatment group by 2 different methods: by ambrisentan dose at enrollment and by maximum ambrisentan dose received at any time in the study. A data listing of all information relating to AEs will be provided.

In general, safety data will be summarized by treatment group and all subjects combined for cumulative 24-week intervals (weeks 1–24, weeks 1–48, etc…) and for the entire study.

9.6.1. Extent of Exposure

Exposure data will be summarized by ambrisentan dose at enrollment and by maximum ambrisentan dose received at any time in the study.

9.6.2. Dose Migration

Dose migration will be summarized using shift tables of the subjects' doses at baseline versus doses at 24-week intervals throughout the study.

9.6.3. Adverse Events

Clinical and laboratory AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Events will be summarized on the basis of the date of onset for the event. A treatment-emergent AE will be defined as any AE that begins on or after the date of first dose of ambrisentan in this study up to the date of last dose of ambrisentan (including any SAEs occurring as specified in Section 8.5.3).

AEs reported during the study will be summarized by tabulating, for each treatment group, the number and percentage of subjects having AEs by System Organ Class [SOC] and Preferred Term. Incidence of AEs will also be summarized by severity and by relationship to

the study drug. AEs which led to treatment discontinuation, death, or that were considered serious will be tabulated separately by treatment group.

9.6.4. Laboratory Evaluations

Laboratory data will be summarized using shift from baseline (low/normal/high) over time.

The percentage of subjects with serum aminotransferase concentrations ≤1xULN, >1xULN and ≤3xULN, >3xULN and ≤5x ULN, >5xULN and ≤8xULN, and >8xULN and the percentage of subjects with alkaline phosphatase or bilirubin ≥2xULN will be summarized for cumulative 24-week intervals and for the entire study.

9.6.5. Other Safety Evaluations

Vital sign data collected at Clinic Visits will be summarized with descriptive statistics of raw values and of change from baseline across time.

9.7. Pharmacokinetic Analysis

Pharmacokinetic data are not being collected in this study.

9.8. Sample Size

This is a study of the safety of long-term ambrisentan administration to subjects with PH. Only subjects who are discontinuing an ambrisentan PH study due to study closure by the Sponsor and for whom ambrisentan is not yet currently available may enroll in this study. It is estimated that approximately 300 subjects will be eligible to enroll in this study at its inception. This number will vary as subjects discontinue this study, or as additional clinical studies of ambrisentan in PH are completed and subjects participating in these studies become eligible per the inclusion and exclusion criteria specified in Sections 4.2 and 4.3.

10. RESPONSIBILITIES

10.1. Investigator Responsibilities

10.1.1. Good Clinical Practice

The Investigator will ensure that this study is conducted in accordance with the principles of the "Declaration of Helsinki" (as amended in Edinburgh, Tokyo, Venice, Hong Kong, and South Africa), International Conference on Harmonisation (ICH) guidelines, or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the study subject.

Gilead and Investigators will follow requirements as set forth in the U.S. Code of Federal Regulations, 21 CFR Parts 50, 54, 56, and 312 and the ICH E6 Good Clinical Practice (GCP) Consolidated Guidance (ICH 1996). Investigator responsibilities are set out in Section 4 of the E6 Guideline (as published in the Federal Register May 1997). Sponsor responsibilities are set out in Section 5 of the E6 ICH Guideline (as published in the Federal Register May 1997).

Since this is a "covered" clinical trial, the Investigator will ensure that 21 CFR Part 54, 1998, is adhered to; a "covered" clinical trial is any "study of a drug or device in humans submitted in a marketing application or reclassification petition subject to this part that the applicant or FDA relies on to establish that the product is effective (including studies that show equivalence to an effective product) or that make a significant contribution to the demonstration of safety." This requires that Investigators and all sub-investigators must provide documentation of their financial interest or arrangements with Gilead, or proprietary interests in the drug being studied. This documentation must be provided before participation of the Investigator and any sub-investigator. The Investigator and sub-investigator agree to notify Gilead of any change in reportable interests during the study and for one year following completion of the study. Study completion is defined as the date that the last subject has completed the protocol defined activities.

This study is also subject to and will be conducted in accordance with 21 CFR Part 320, 1993, "Retention of Bioavailability and Bioequivalence Testing Samples."

10.1.2. Institutional Review Board (IRB)/Independent Ethics Committee (IEC) Approval

This protocol and any accompanying material to be provided to the subject (such as advertisements, subject information sheets, or descriptions of the study used to obtain informed consent) will be submitted by the Investigator to an IRB/IBC. Approval from the IRB/IEC must be obtained before starting the study and should be documented in a letter to the Investigator specifying the protocol number, protocol version, protocol date, documents reviewed, and date on which the committee met and granted the approval.

All documents subject to review during the study, including, but not limited to, any modifications made to the protocol after receipt of IRB/IEC approval and SAE safety reports must also be submitted to the Committee for review and/or approval prior to implementation (if applicable).

As part of the written application to the IRB/IEC, the Investigator should provide the Committee with a current copy of the IB. If the IB is updated during the study, the Investigator should supply an updated copy to the Committee.

10.1.3. Informed Consent

The Investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study and before undertaking any study-related procedures. The Investigator must utilize an IRB/IEC-approved consent form for documenting written informed consent. Each informed consent will be appropriately signed and dated by the subject or the subject's legally authorized representative and the person obtaining consent.

10.1.4. Confidentiality

The Investigator must assure that subjects' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only subject initials, date of birth and an identification code (i.e., not names) should be recorded on any form or biological sample submitted to the sponsor, IRB/IEC, or laboratory. The Investigator must keep a screening log showing codes, names, and addresses for all subjects screened and for all subjects enrolled in the trial.

The Investigator agrees that all information received from Gilead, including but not limited to the IB, this protocol, CRFs, the study drug, and any other study information, remain the sole and exclusive property of Gilead during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from Gilead. The Investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

10.1.5. Study Files and Retention of Records

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least the following two categories: (1) Investigator's study file, and (2) subject clinical source documents.

The Investigator's study file will contain the protocol/amendments, CRF and query forms, IRB/IEC and governmental approval with correspondence, informed consent, drug records,

staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

Subject clinical source documents (usually defined by the project in advance to record key efficacy/safety parameters independent of the CRFs) would include (although not be limited to) the following: subject hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, electrocardiogram (ECG), electroencephalogram (EEG), X-ray, pathology and special assessment reports, consultant letters, screening and enrollment log, etc.

All clinical study documents must be retained by the Investigator until at least 2 years after the last approval of a marketing application in an ICH region (i.e., United States, Europe, or Japan) and until there are no pending or contemplated marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and regulatory authorities have been notified. Investigators may be required to retain documents longer if required by applicable regulatory requirements or an agreement with Gilead. The Investigator must notify Gilead before destroying any clinical study records.

Should the Investigator wish to assign the study records to another party or move them to another location, Gilead must be notified in advance.

If the Investigator cannot guarantee this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the Investigator and Gilead to store these in sealed containers outside of the site so that they can be returned sealed to the Investigator in case of a regulatory audit. When source documents are required for the continued care of the subject, appropriate copies should be made for storage outside of the site.

CCI [redacted]

10.1.6. Case Report Forms

For each subject enrolled, a CRF must be completed and signed by the Principal Investigator or sub-investigator within a reasonable time period after data collection. This also applies to records for those subjects who fail to complete the study (even during a prerandomization screening period if a CRF was initiated). If a subject withdraws from the study, the reason must be noted on the CRF. If a subject is withdrawn from the study because of a treatment-limiting AE, thorough efforts should be made to clearly document the outcome.

All protocol required data will be collected in a CRF or via electronic means. A list of systems used to create, modify, maintain, archive, retrieve, or transmit data will be maintained by the sponsor or their designee.

10.1.7. Drug Accountability

The Investigator or designee (i.e., pharmacist) is responsible for ensuring adequate accountability of all used and unused study drug. This includes acknowledgment of receipt of each shipment of study product (quantity and condition) and subject dispensing records and returned or destroyed study product. Dispensing records will document quantities received from Gilead and quantities dispensed to subjects, including lot number, date dispensed, subject identifier number, subject initials, and the initials of the person dispensing the medication.

At study initiation, the monitor will evaluate the site's standard operating procedure for study drug disposal/destruction in order to ensure that it complies with Gilead requirements. Drug may be returned or destroyed on an ongoing basis during the study if appropriate. At the end of the study, following final drug inventory reconciliation by the monitor, the study site will dispose of and/or destroy all unused study drug supplies, including empty containers, according these procedures. If the site cannot meet Gilead's requirements for disposal, arrangements will be made between the site and Gilead or its representative for destruction or return of unused study drug supplies.

All drug supplies and associated documentation will be periodically reviewed and verified by the study monitor over the course of the study.

10.1.8. Inspections

The Investigator should understand that source documents for this trial should be made available to appropriately qualified personnel from Gilead or its representatives, to the IRB/IEC, or to regulatory authority or health authority inspectors.

10.1.9. Protocol Compliance

The Investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

10.2. Sponsor Responsibilities

10.2.1. Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to study subjects, may be made only by Gilead. All protocol modifications must be submitted to the IRB/IEC in accordance with local requirements. Approval must be obtained before changes can be implemented.

A protocol change intended to eliminate an apparent immediate hazard to subjects may be implemented immediately, provided the IRB/IEC is notified within 5 days.

Any permanent change to the protocol must be handled as a protocol amendment. The written amendment must be submitted to the IRB/IEC and the Investigator must await approval before implementing the changes. Gilead will submit protocol amendments to the appropriate regulatory authorities for approval.

If in the judgment of the IRB/IEC, the Investigator, and/or Gilead, the amendment to the protocol substantially changes the study design and/or increases the potential risk to the subject and/or has an impact on the subject's involvement as a study participant, the currently approved written ICF will require similar modification. In such cases, informed consent will be renewed for subjects enrolled in the study before implementing protocol changes.

10.2.2. Study Report and Publications

A clinical study report will be prepared and provided to the regulatory agency(ies). Gilead will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases.

After conclusion of the study and without prior written approval from Gilead, Investigators in this study may communicate, orally present, or publish in scientific journals or other scholarly media ***only after the following conditions have been met:***

- the results of the study in their entirety have been publicly disclosed by or with the consent of Gilead in an abstract, manuscript, or presentation form; or

- the study has been completed at all study sites for at least 2 years.

No such communication, presentation, or publication will include Gilead's confidential information (see Section 10.1.4).

The Investigator will submit any proposed publication or presentation along with the respective scientific journal or presentation forum at least 30 days before submission of the publication or presentation. The Investigator will comply with Gilead's request to delete references to its confidential information (other than the study results) in any paper or presentation and agrees to withhold publication or presentation for an additional 60 days in order to obtain patent protection if deemed necessary.

10.3. Joint Investigator/Sponsor Responsibilities

10.3.1. Access to Information for Monitoring

In accordance with ICH Good Clinical Practice (ICH GCP) guidelines, the study monitor must have direct access to the Investigator's source documentation in order to verify the data recorded in the CRFs for consistency.

The monitor is responsible for routine review of the CRFs at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor should have access to any subject records needed to verify the entries on the CRFs. The Investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

10.3.2. Access to Information for Auditing or Inspections

Representatives of regulatory authorities or of Gilead may conduct inspections or audits of the clinical study. If the Investigator is notified of an inspection by a regulatory authority, the Investigator agrees to notify the designated Gilead representative immediately. The Investigator agrees to provide to representatives of a regulatory agency or Gilead access to records, facilities, and personnel for the effective conduct of any inspection or audit.

10.3.3. Study Discontinuation

Both the Sponsor and the Investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange discontinuation procedures and notify the appropriate regulatory authority(ies), IRBs, and IECs. In terminating the study, Gilead and the Investigator will assure that adequate consideration is given to the protection of the subjects' interests.

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12. APPENDICES

Appendix 1. Investigator Signature Page

GILEAD SCIENCES, INC.
333 LAKESIDE DRIVE
FOSTER CITY, CA 94404

STUDY ACKNOWLEDGEMENT
GS-US-300-0124: ABS-LT: A Phase 3, Long-Term, Open Label, Multicenter Safety Study of Ambrisentan in Subjects with Pulmonary Hypertension

Version 2.0 Rest of World 12 June 2013

This protocol has been approved by Gilead Sciences, Inc. The following signature documents this approval.

PPD

PPD

07/08/13
Date

INVESTIGATOR STATEMENT

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Gilead Sciences, Inc. I will discuss this material with them to ensure that they are fully informed about the drugs and the study.

Principal Investigator Name (Printed) | Signature

Date | Site Number