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A Long Term Study of Ambrisentan in Pulmonary Arterial Hypertension Subjects Having Completed AMB-320 (NCT00423748) or AMB-321 (NCT00423202)

This study has been completed.

Sponsor:	Gilead Sciences
Collaborators:	
Information provided by (Responsible Party):	Gilead Sciences
ClinicalTrials.gov Identifier:	NCT00578786

Purpose

AMB-320/321-E was designed to provide long-term, controlled monitoring of pulmonary arterial hypertension (PAH) patients treated with ambrisentan (AMB) in order to properly define the adverse event profile associated with this endothelin receptor antagonist (ERA), including the incidence and severity of elevated serum liver function tests (LFTs). In addition, this study continued the efficacy assessments of the previous studies, examined long-term AMB treatment success, and compared long-term survival of subjects treated with AMB to the NIH registry of patients with PAH.

Condition	Intervention	Phase
Pulmonary Arterial Hypertension	Drug: ambrisentan	Phase 3

Study Type: Interventional
Study Design: Treatment, Parallel Assignment, Double Blind (Subject, Investigator, Outcomes Assessor), Randomized, Safety/Efficacy Study
Official Title: A Long Term Study of Ambrisentan in Pulmonary Arterial Hypertension Subjects Having Completed AMB-320 (NCT00423748) or AMB-321 (NCT00423202)

Further study details as provided by Gilead Sciences:

Primary Outcome Measure:

- Frequently Reported (15% or More Overall) Adverse Events by Severity [Time Frame: Baseline to Week 295] [Designated as safety issue: Yes]

The primary endpoint of this study is the incidence and severity of adverse events associated with long-term exposure to AMB in participants with PAH. The most frequently occurring adverse events (occurring in 15% or more of the participants in the combined group) are presented, by severity, that began after entering this extension study. Adverse events that were serious are included. Adverse events are coded according to the Medical Dictionary for Regulatory Activities (MedDRA) Version 6.1 and are presented by MedDRA preferred term. Severity was graded as follows: mild (AE did not interfere with routine activities; subject may have experienced slight discomfort), moderate (AE interfered with routine activities; subject may have experienced significant discomfort), and severe (AE made it impossible to perform routine activities; subject may have experienced intolerable discomfort or pain).

- Serum Aminotransferases Relative to the Upper Limit of the Normal Range (ULN) [Time Frame: Baseline to Week 295] [Designated as safety issue: Yes]
  The number of participants with serum alanine aminotransferase (ALT) and serum aspartate aminotransferase (AST) falling into the following categories: >3.0 and </= 5.0 x ULN, >5.0 and </= 8.0 x ULN, and >8.0 x ULN. Includes the highest value per participant across all visits as well as values from early termination visits.

Secondary Outcome Measures:

- Baseline Exercise Capacity as Measured by the 6-Minute Walk Distance Test [Time Frame: Baseline] [Designated as safety issue: No]
  The 6-minute walk distance (6MWD) test was conducted according to the American Thoracic Society guidelines (ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med 2002; 166(1):111-117.).
- Change From Baseline to Week 24 in Exercise Capacity as Measured by the 6-Minute Walk Distance Test [Time Frame: Baseline to Week 24] [Designated as safety issue: No]
  The 6-minute walk distance (6MWD) test was conducted according to the American Thoracic Society guidelines (ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med 2002; 166(1):111-117.). Missing values were imputed using LOCF method based on post-baseline observations. Baseline (BL) values from the screening/randomization visit of the 2 prior studies defined the BL of this long-term analysis for those receiving ambrisentan in the prior studies. The Screening/Randomization Visit of the present study was the BL for subjects receiving placebo in the prior studies.
- Change From Baseline to Week 48 (Year 1) in Exercise Capacity as Measured by the 6-Minute Walk Distance Test [Time Frame: Baseline to Week 48] [Designated as safety issue: No]
  The 6-minute walk distance (6MWD) test was conducted according to the American Thoracic Society guidelines (ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med 2002; 166(1):111-117.). The last-observation-carried-forward (LOCF) imputation method was used. Baseline (BL) values from the screening/randomization visit of the 2 prior studies defined the BL of this long-term analysis for those receiving AMB in the prior studies. The Screening/Randomization Visit of the present study was the BL for subjects receiving placebo in the prior studies.
- Change From Baseline to Year 2 in Exercise Capacity as Measured by the 6-Minute Walk Distance Test [Time Frame: Baseline to Year 2] [Designated as safety issue: No]
  The 6-minute walk distance (6MWD) test was conducted according to the American Thoracic Society guidelines (ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med 2002; 166(1):111-117.). The last-observation-carried-forward (LOCF) imputation method was used. Baseline (BL) values from the screening/randomization visit of the 2 prior studies defined the BL of this long-term analysis for those receiving AMB in the prior studies. The Screening/Randomization Visit of the present study was the BL for subjects receiving placebo in the prior studies.
- Change From Baseline to Year 3 in Exercise Capacity as Measured by the 6-Minute Walk Distance Test [Time Frame: Baseline to Year 3] [Designated as safety issue: No]
  Thoracic Society guidelines (ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med 2002; 166(1):111-117.). The last-observation-carried-forward (LOCF) imputation method was used. Baseline (BL) values from the screening/randomization visit of the 2 prior studies defined the BL of this long-term analysis for those receiving AMB in the prior studies. The Screening/Randomization Visit of the present study was the BL for subjects receiving placebo in the prior studies.
- Baseline Borg Dyspnea Index [Time Frame: Baseline] [Designated as safety issue: No]
  Borg Dyspnea Index is a measure of perceived shortness of breath: 0 units on a scale (none) to 10 units on a scale (maximum breathlessness).
- Change From Baseline to Year 1 in Borg Dyspnea Index [Time Frame: Baseline to Year 1] [Designated as safety issue: No]

Borg Dyspnea Index is a measure of perceived shortness of breath: 0 units on a scale (none) to 10 units on a scale (maximum breathlessness). Baseline (BL) values from the screening/randomization visit of the 2 prior studies defined the BL of this long-term analysis for those receiving ambrisentan in the prior studies. The Screening/Randomization Visit of the present study was the BL for subjects receiving placebo in the prior studies.

- Change From Baseline to Year 2 in Borg Dyspnea Index [Time Frame: Baseline to Year 2] [Designated as safety issue: No]
  Borg Dyspnea Index is a measure of perceived shortness of breath: 0 units on a scale (none) to 10 units on a scale (maximum breathlessness). Baseline (BL) values from the screening/randomization visit of the 2 prior studies defined the BL of this long-term analysis for those receiving AMB in the prior studies. The Screening/Randomization Visit of the present study was the BL for subjects receiving placebo in the prior studies.
- Change From Baseline to Year 3 in Borg Dyspnea Index [Time Frame: Baseline to Year 3] [Designated as safety issue: No]
  Borg Dyspnea Index is a measure of perceived shortness of breath: 0 units on a scale (none) to 10 units on a scale (maximum breathlessness). Baseline (BL) values from the screening/randomization visit of the 2 prior studies defined the BL of this long-term analysis for those receiving AMB in the prior studies. The Screening/Randomization Visit of the present study was the BL for subjects receiving placebo in the prior studies.
- Baseline World Health Organization (WHO) Functional Class [Time Frame: Baseline] [Designated as safety issue: No]
  WHO Classes: I) pulmonary hypertension (PH); ordinary physical activity not limited or causes increased dyspnea, fatigue, chest pain, or presyncope. II) PH; ordinary physical activity mildly limited and causes increased dyspnea, fatigue, chest pain, or presyncope; comfortable at rest. III) PH; physical activity markedly limited and less than ordinary physical activity causes increased dyspnea, fatigue, chest pain, or presyncope; comfortable at rest. IV) PH; physical activity causes symptoms; signs of right heart failure; dyspnea/fatigue possible at rest.
- Change From Baseline to Year 1 in World Health Organization (WHO) Functional Class [Time Frame: Baseline to Year 1] [Designated as safety issue: No]
  WHO Classes: I) pulmonary hypertension (PH); ordinary physical activity not limited or causes increased dyspnea, fatigue, chest pain, or presyncope. II) PH; ordinary physical activity mildly limited and causes increased dyspnea, fatigue, chest pain, or presyncope; comfortable at rest. III) PH; physical activity markedly limited and less than ordinary physical activity causes increased dyspnea, fatigue, chest pain, or presyncope; comfortable at rest. IV) PH; physical activity causes symptoms; signs of right heart failure; dyspnea/fatigue possible at rest.
- Change From Baseline to Year 2 in World Health Organization (WHO) Functional Class [Time Frame: Baseline to Year 2] [Designated as safety issue: No]
  WHO Classes: I) pulmonary hypertension (PH); ordinary physical activity not limited or causes increased dyspnea, fatigue, chest pain, or presyncope. II) PH; ordinary physical activity mildly limited and causes increased dyspnea, fatigue, chest pain, or presyncope; comfortable at rest. III) PH; physical activity markedly limited and less than ordinary physical activity causes increased dyspnea, fatigue, chest pain, or presyncope; comfortable at rest. IV) PH; physical activity causes symptoms; signs of right heart failure; dyspnea/fatigue possible at rest.
- Change From Baseline to Year 3 in World Health Organization (WHO) Functional Class [Time Frame: Baseline to Year 3] [Designated as safety issue: No]
  WHO Classes: I) pulmonary hypertension (PH); ordinary physical activity not limited or causes increased dyspnea, fatigue, chest pain, or presyncope. II) PH; ordinary physical activity mildly limited and causes increased dyspnea, fatigue, chest pain, or presyncope; comfortable at rest. III) PH; physical activity markedly limited and less than ordinary physical activity causes increased dyspnea, fatigue, chest pain, or presyncope; comfortable at rest. IV) PH; physical activity causes symptoms; signs of right heart failure; dyspnea/fatigue possible at rest.
- Baseline SF-36 Health Survey Scales for the Combined Ambrisentan Group [Time Frame: Baseline] [Designated as safety issue: No]
  The 8 scales of the SF-36 Health Survey measured included physical functioning, role physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health, and the summary measures included physical health and mental health. Scores for each scale are transformed and the transformed scores range from 0 (worst health) to 100 (best health). The scores are then standardized with the 1998 General United States (US) population mean and standard deviation (SD). Finally, the scores are transformed to the norm-based scoring with a mean of 50 and SD of 10.
- Change From Baseline to Week 12 in SF-36 Health Survey Scales for the Combined Ambrisentan Group [Time Frame: Baseline to Week 12] [Designated as safety issue: No]
  The 8 scales of the SF-36 Health Survey measured included physical functioning, role physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health, and the summary measures included physical health and mental health. Scores for each scale are transformed and the transformed scores range from 0 (worst health) to 100 (best health). The scores are then standardized with the 1998 General US population mean and SD. Finally, the scores are transformed to the norm-based scoring with a mean of 50 and SD of 10.
- Change From Baseline to Week 24 in SF-36 Health Survey Scales for the Combined Ambrisentan Group [Time Frame: Baseline to Week 24] [Designated as safety issue: No]

The 8 scales of the SF-36 Health Survey measured included physical functioning, role physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health, and the summary measures included physical health and mental health. Scores for each scale are transformed and the transformed scores range from 0 (worst health) to 100 (best health). The scores are then standardized with the 1998 General US population mean and SD. Finally, the scores are transformed to the norm-based scoring with a mean of 50 and SD of 10.

- Change From Baseline to Week 36 in SF-36 Health Survey Scales for the Combined Ambrisentan Group [Time Frame: Baseline to Week 36] [Designated as safety issue: No]
  The 8 scales of the SF-36 Health Survey measured included physical functioning, role physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health, and the summary measures included physical health and mental health. Scores for each scale are transformed and the transformed scores range from 0 (worst health) to 100 (best health). The scores are then standardized with the 1998 General US population mean and SD. Finally, the scores are transformed to the norm-based scoring with a mean of 50 and SD of 10.
- Percentage of Participants With No Clinical Worsening of PAH [Time Frame: Baseline to Year 3] [Designated as safety issue: No]
  Clinical worsening of PAH was defined as the time from randomization to ambrisentan therapy to the first occurrence of death, lung transplantation, hospitalization for PAH, atrial septostomy, addition of approved prostanoid therapy, study withdrawal due to the addition of other clinically approved PAH therapeutics, or study withdrawal due to 2 or more early escape criteria (for subjects randomized to AMB in NCT00423748 or NCT00423202). Results are presented as the Kaplan-Meier estimate (% probability) of not having clinical worsening after a given time.
- Percentage of Participants With Failure-Free Treatment Status [Time Frame: Baseline to Year 4] [Designated as safety issue: No]
  Treatment failure was defined as the time from randomization to ambrisentan therapy to the first occurrence of death, lung transplantation, addition of approved prostanoid therapy, study withdrawal due to the addition of other clinically approved PAH therapeutics, or study withdrawal due to 2 or more early escape criteria (for subjects randomized to ambrisentan in NCT00423748 or NCT00423202). Results are presented as the Kaplan-Meier estimate (% probability) of not having treatment failure after a given time.
- Long-term Survival [Time Frame: Baseline to Year 4] [Designated as safety issue: No]
  Long-term survival was defined as the time from initiation of active treatment to death. Results are presented as the Kaplan-Meier estimate (% probability) of survival after a given time.

Enrollment: 383
Study Start Date: February 2004
Primary Completion Date: March 2010
Study Completion Date: March 2010

Arms	Assigned Interventions
Experimental: Ambrisentan 2.5, 5 or 10 mg ambrisentan	Drug: ambrisentan 2.5, 5.0 or 10.0 mg ambrisentan po, qd, long-term Other Names: Letairis(TM)

Detailed Description:

AMB-320 (ARIES-1; NCT00423748) and AMB-321 (ARIES-2; NCT00423202) were 12-week, Phase 3, randomized, double-blind, placebo-controlled, multicenter, efficacy studies of AMB in subjects with PAH. The objectives of these studies were to determine the effect of three doses of AMB (2.5, 5.0, and 10.0 mg) on exercise capacity, as well as several clinical measures of PAH. The current study (NCT00578786) was unblinded (by design) prior to completion. The ARIES studies were identical except for the dose groups assessed and the geographic locations where the studies were conducted. Both studies evaluated placebo and 5.0-mg AMB dose groups; however, AMB-320 (NCT00423748) also examined an AMB dose of 10.0 mg, while AMB-321 (NCT00423202) included an AMB

dose of 2.5 mg. AMB-320/321-E was an optional study for subjects who had participated in AMB-320 (NCT00423748) or AMB-321 (NCT00423202) that allowed continued long-term treatment with AMB.

Eligibility

Ages Eligible for Study: 18 Years and older
Genders Eligible for Study: Both
Accepts Healthy Volunteers: No

Criteria

Inclusion Criteria:

1. Subject must have completed Week 12 of AMB-320 (NCT00423748) or AMB-321 (NCT00423202) or must have received placebo during AMB-320 (NCT00423748) or AMB-321 (NCT00423202) and met two or more early escape criteria;
2. Subject must be competent to understand the information given in the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) approved informed consent form and must sign the form prior to the initiation of any study procedures.
3. Female subject of childbearing potential must agree to use two reliable methods of contraception until study completion and for at least four weeks following their final study visit. Reliable methods include: birth control pills/implants/injections, intrauterine devices (IUDs), spermicide, diaphragms, or condoms.

Exclusion Criteria:

- Subjects must have met the exclusion criteria of the AMB-320 (NCT00423748) and AMB-321 (NCT00423202)studies. In addition, a subject who meets any one of the following criteria is ineligible for participation in the study:

    1. Subject receiving bosentan, sildenafil, or iv inotropes at any time within four weeks prior to the AMB-320/321-E Screening/Randomization Visit;
    2. Subject receiving chronic prostanoid therapy (epoprostenol, treprostinil, iloprost, beraprost, or any other investigational prostacyclin derivative) within four weeks prior to the AMB-320/321-E Screening/RandomizationVisit;
    3. Female subject who is pregnant or breastfeeding;
    4. Subject with cardiovascular, liver, renal, hematologic, gastrointestinal, immunologic, endocrine, metabolic, or central nervous system disease that, in the opinion of the Investigator, may adversely affect the safety of the subject and/or efficacy of the study drug or severely limit the lifespan of the subject;
    5. Subject who has demonstrated noncompliance with previous medical regimens;
    6. Subject who has a recent history of abusing alcohol or illicit drugs;
    7. Subject who has participated in a clinical study involving another investigational drug or device at any time within four weeks prior to the AMB-320/321-E Screening/Randomization Visit.

Contacts and Locations

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Investigators

Study Chair:	Chris Dufton, PhD	Gilead Sciences, Inc

More Information

Responsible Party:	Gilead Sciences
Study ID Numbers:	AMB-320/321-E ARIES-E
Health Authority:	United States: Food and Drug Administration

Study Results

Participant Flow

Recruitment Details	Participants completing Week 12 of NCT00423748 or NCT00423202 could enroll in extension (E) study. Participants on placebo in parent study and d/c treatment due to >/=2 early escape criteria were eligible. Total randomized: 361 (completed/early escape in prior study), 19 (d/c prior study), and 3 (completed prior study, did not enroll in E study).
Pre-Assignment Details	Participants on active treatment in NCT00423748 or NCT00423202 continued to receive their last assigned blinded ambrisentan (AMB) dose from the prior study. Those on placebo in NCT00423748 were randomized to receive either 5 or 10 mg of AMB in the extension study. Those on placebo in NCT00423202 were randomized to either 2.5 or 5 mg of AMB.

Reporting Groups

	Description
Ambrisentan 2.5 mg	Original randomized dose group in the prior study (NCT00423748 and NCT00423202) or in the current study (for subjects originally randomized to placebo in one of the prior studies). Analysis included those not enrolling in this study but received AMB in 1 of the 2 parent studies. It should be noted that by Year 3, almost half of those randomized to AMB 2.5 mg were titrated to 5 mg and 10 mg.
Ambrisentan 5 mg	Original randomized dose group in the prior study (NCT00423748 and NCT00423202) or in the current study (for subjects originally randomized to placebo in one of the prior studies). Analysis included those not enrolling in this study but received AMB in 1 of the 2 parent studies. It should be noted that by Year 3, a third starting at 5 mg were titrated to 10 mg.
Ambrisentan 10 mg	Original randomized dose group in the prior study (NCT00423748 and NCT00423202) or in the current study (for subjects originally randomized to placebo in one of the prior studies).

Overall Study

	Ambrisentan 2.5 mg	Ambrisentan 5 mg	Ambrisentan 10 mg
Started	96	190	97
Completed	57	124	67
Not Completed	39	66	30
Adverse Event	27	37	17
Lack of Efficacy	2	5	2
Early Escape from Prior Study	2	1	2
Withdrawal by Subject	7	8	5
Protocol Violation	0	3	1
Physician Decision	1	0	1
Sponsor Decision	0	0	1
Lost to Follow-up	0	4	0
Pregnancy	0	1	0
Not Otherwise Specified	0	4	1
Qualified but Not Enrolled in Extension	0	3	0

Baseline Characteristics

Reporting Groups

	Description
Ambrisentan 2.5 mg	Original randomized dose group in the prior study (NCT00423748 and NCT00423202) or in the current study (for subjects originally randomized to placebo in one of the prior studies). Analysis included those not enrolling in this study but received AMB in 1 of the 2 parent studies. It should be noted that by Year 3, almost half of those randomized to AMB 2.5 mg were titrated to 5 mg and 10 mg.
Ambrisentan 5 mg	Original randomized dose group in the prior study (NCT00423748 and NCT00423202) or in the current study (for subjects originally randomized to placebo in one of the prior studies). Analysis included those not enrolling in this study but received AMB in 1 of the 2 parent studies. It should be noted that by Year 3, a third starting at 5 mg were titrated to 10 mg.
Ambrisentan 10 mg	Original randomized dose group in the prior study (NCT00423748 and NCT00423202) or in the current study (for subjects originally randomized to placebo in one of the prior studies).

Baseline Measures

	Ambrisentan 2.5 mg	Ambrisentan 5 mg	Ambrisentan 10 mg	Total
Number of Participants	96	190	97	383
Age, Continuous [1] [units: years] Mean (Standard Deviation)	52.27 (14.968)	51.46 (14.429)	49.09 (16.572)	51.06 (15.139)
Gender, Male/Female [units: participants]				
Female	69	154	79	302
Male	27	36	18	81
Race/Ethnicity, Customized [1] [units: participants]				
Caucasian	81	148	65	294
Black	0	5	6	11
Asian	1	6	2	9
Hispanic	14	29	22	65
Other	0	2	2	4
Pulmonary Arterial Hypertension Stratification [2] [units: participants]				
Idiopathic PAH (IPAH)	63	119	59	241
Non-IPAH	33	71	38	142
6-Minute Walk Distance (6MWD) [3] [units: meters] Mean (Standard Deviation)	350.3 (86.640)	347.7 (87.333)	342.3 (80.840)	347.0 (85.389)
World Heath Organization (WHO) Class [4] [units: participants]				
WHO Class I	1	7	4	12
WHO Class II	51	77	35	163
WHO Class III	39	91	48	178
WHO Class IV	5	15	10	30

	Ambrisentan 2.5 mg	Ambrisentan 5 mg	Ambrisentan 10 mg	Total
Borg Dyspnea Index (BDI) [5] [units: units on a scale] Mean (Standard Deviation)	4.14 (2.684)	3.80 (2.332)	3.78 (2.133)	3.88 (2.377)
Body Mass Index (BMI) [6] [units: kg/m^2] Mean (Standard Deviation)	26.68 (5.038)	26.86 (5.632)	28.26 (7.212)	27.17 (5.958)

[1] Baseline data values established at the screening/randomization visit of the 2 prior (parent) studies defined the baseline of this long-term analysis for subjects who first received 2.5, 5, or 10 mg ambrisentan in the prior studies. The Screening/Randomization Visit of the present extension study defined the baseline for subjects who received placebo in the 2 prior studies.

[2] Participants were classified as diagnosed with idiopathic pulmonary arterial hypertension (IPAH) or non-idiopathic PAH (non-IPAH). Baseline data values established at the screening/randomization visit of the 2 prior (parent) studies defined the baseline of this long-term analysis for subjects who first received 2.5, 5, or 10 mg ambrisentan in the prior studies. The Screening/Randomization Visit of the present extension study defined the baseline for subjects who received placebo in the 2 prior studies.

[3] A measure of the distance participants could walk in 6 minutes. Baseline data values established at the screening/randomization visit of the 2 prior (parent) studies defined the baseline of this long-term analysis for subjects who first received 2.5, 5, or 10 mg ambrisentan in the prior studies. The Screening/Randomization Visit of the present extension study defined the baseline for subjects who received placebo in the 2 prior studies.

[4] WHO Classes: I) pulmonary hypertension (PH); ordinary physical activity not limited or causes increased dyspnea, fatigue, chest pain, or presyncope. II) PH; ordinary physical activity mildly limits/causes increased dyspnea, fatigue, chest pain, or presyncope; comfortable at rest. III) PH; physical activity markedly limited and less than ordinary physical activity causes increased dyspnea, fatigue, chest pain, or presyncope; comfortable at rest. IV) PH; physical activity causes symptoms; signs of right heart failure; dyspnea/fatigue possible at rest. Baseline defined as previously described.

[5] Borg Dyspnea Index is a measure of perceived shortness of breath: 0 units on a scale (none) to 10 units on a scale (maximum breathlessness). Baseline data values established at the screening/randomization visit of the 2 prior (parent) studies defined the baseline of this long-term analysis for subjects who first received 2.5, 5, or 10 mg ambrisentan in the prior studies. The Screening/Randomization Visit of the present extension study defined the baseline for subjects who received placebo in the 2 prior studies.

[6] Adult body mass index (BMI) is calculated by dividing weight in kg by height in meters squared.BMI below 18.5 = underweight; BMI 18.5 to 24.9 = normal; BMI 25.0 to 29.9 = overweight; BMI 30.0 and above = obese. Note that 1 subject was not included in the denominator for the Ambrisentan 5 mg group (N=189) and the combined group (N=382). Baseline was defined as previously described.

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Frequently Reported (15% or More Overall) Adverse Events by Severity

Measure Description	The primary endpoint of this study is the incidence and severity of adverse events associated with long-term exposure to AMB in participants with PAH. The most frequently occurring adverse events (occurring in 15% or more of the participants in the combined group) are presented, by severity, that began after entering this extension study. Adverse events that were serious are included. Adverse events are coded according to the Medical Dictionary for Regulatory Activities (MedDRA) Version 6.1 and are presented by MedDRA preferred term. Severity was graded as follows: mild (AE did not interfere with routine activities; subject may have experienced slight discomfort), moderate (AE interfered with routine activities; subject may have experienced significant discomfort), and severe (AE made it impossible to perform routine activities; subject may have experienced intolerable discomfort or pain).
Time Frame	Baseline to Week 295
Safety Issue?	Yes

Analysis Population Description

Safety Analysis Set: Includes all participants who received at least 1 dose of AMB in one of the 2 prior studies (NCT00423748 or NCT00423202) or in the current extension study. Treatment group assignments for the safety analysis set were based upon the highest dose of AMB received at any time during the parent or extension studies.

Reporting Groups

	Description
Ambrisentan 2.5 mg	Participants were classified based on their randomized dose of AMB in the 2 prior studies (NCT00423748 or NCT00423202) or in the current extension study. Study drug was taken once daily.
Ambrisentan 5 mg	Participants were classified based on their randomized dose of AMB in the 2 prior studies (NCT00423748 or NCT00423202) or in the current extension study. Study drug was taken once daily.
Ambrisentan 10 mg	Participants were classified based on their randomized dose of AMB in the 2 prior studies (NCT00423748 or NCT00423202) or in the current extension study. Study drug was taken once daily.

Measured Values

	Ambrisentan 2.5 mg	Ambrisentan 5 mg	Ambrisentan 10 mg
Number of Participants Analyzed	43	146	194
Frequently Reported (15% or More Overall) Adverse Events by Severity [units: participants]			
Headache - Mild	1	20	36
Headache - Moderate	0	14	17
Headache - Severe	0	0	8
Pulmonary hypertension (worsening) - Mild	2	2	7
Pulmonary hypertension (worsening) - Moderate	4	10	29

	Ambrisentan 2.5 mg	Ambrisentan 5 mg	Ambrisentan 10 mg
Pulmonary hypertension (worsening) - Severe	6	6	19
Right ventricular failure - Mild	0	2	6
Right ventricular failure - Moderate	2	7	14
Right ventricular failure - Severe	5	12	26
Cough - Mild	1	23	24
Cough - Moderate	1	2	22
Cough - Severe	0	1	0
Upper respiratory tract infection - Mild	3	13	23
Upper respiratory tract infection - Moderate	2	4	26
Upper respiratory tract infection - Severe	0	0	1
Dizziness - Mild	1	8	31
Dizziness - Moderate	2	7	14
Dizziness - Severe	0	0	3
Dyspnoea exacerbated - Mild	1	4	8
Dyspnoea exacerbated - Moderate	3	14	22
Dyspnoea exacerbated - Severe	1	2	7
Arthralgia - Mild	1	5	19
Arthralgia - Moderate	3	11	18
Arthralgia - Severe	1	2	1
Diarrhoea - Mild	2	12	17
Diarrhoea - Moderate	1	10	15
Diarrhoea - Severe	0	2	1
Nasopharyngitis - Mild	1	14	19
Nasopharyngitis - Moderate	1	8	15
Nasopharyngitis - Severe	0	0	0
Oedema peripheral - Mild	6	31	48
Oedema peripheral - Moderate	6	19	50

	Ambrisentan 2.5 mg	Ambrisentan 5 mg	Ambrisentan 10 mg
Oedema peripheral - Severe	1	3	4

2. Primary Outcome Measure:

Measure Title	Serum Aminotransferases Relative to the Upper Limit of the Normal Range (ULN)
Measure Description	The number of participants with serum alanine aminotransferase (ALT) and serum aspartate aminotransferase (AST) falling into the following categories: >3.0 and </= 5.0 x ULN, >5.0 and </= 8.0 x ULN, and >8.0 x ULN. Includes the highest value per participant across all visits as well as values from early termination visits.
Time Frame	Baseline to Week 295
Safety Issue?	Yes

Analysis Population Description

Safety Analysis Set: Includes all participants who received at least 1 blinded dose of AMB in one of the 2 prior studies (NCT00423748 or NCT00423202) or in the current extension study.

Reporting Groups

	Description
Ambrisentan 2.5 mg	Participants were classified based on the highest dose of AMB received at any time during the 2 prior studies (NCT00423748 or NCT00423202) or in the current extension study. Study drug was taken once daily.
Ambrisentan 5 mg	Participants were classified based on the highest dose of AMB received at any time during the 2 prior studies (NCT00423748 or NCT00423202) or in the current extension study. Study drug was taken once daily.
Ambrisentan 10 mg	Participants were classified based on the highest dose of AMB received at any time during the 2 prior studies (NCT00423748 or NCT00423202) or in the current extension study. Study drug was taken once daily.

Measured Values

	Ambrisentan 2.5 mg	Ambrisentan 5 mg	Ambrisentan 10 mg
Number of Participants Analyzed	43	155	205
Serum Aminotransferases Relative to the Upper Limit of the Normal Range (ULN) [units: participants]			
ALT >3.0 and </=5.0 x ULN	0	2	4
ALT >5.0 and </= 8.0 x ULN	0	1	0
ALT >8.0 x ULN	0	3	5

	Ambrisentan 2.5 mg	Ambrisentan 5 mg	Ambrisentan 10 mg
Total ALT results >3.0 x ULN	0	0	1
AST >3.0 and </=5.0 x ULN	1	3	7
AST >5.0 and </= 8.0 x ULN	0	1	0
AST >8.0 x ULN	0	0	1
Total AST results >3.0 x ULN	1	4	8

3. Secondary Outcome Measure:

Measure Title	Baseline Exercise Capacity as Measured by the 6-Minute Walk Distance Test
Measure Description	The 6-minute walk distance (6MWD) test was conducted according to the American Thoracic Society guidelines (ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med 2002; 166(1):111-117.).
Time Frame	Baseline
Safety Issue?	No

Analysis Population Description

All assessments of efficacy were performed using the randomized analysis set; subjects were allotted to an individual dose group based upon their randomized treatment assignment in the 2 prior studies (NCT00423748 or NCT00423202) or in the extension study. The LOCF method of imputation was used; only postbaseline observations were carried forward.

Reporting Groups

	Description
Ambrisentan 2.5 mg	Participants were classified based on their randomized dose of AMB in the 2 prior studies (NCT00423748 or NCT00423202) or in the current extension study. Study drug was taken once daily.
Ambrisentan 5 mg	Participants were classified based on their randomized dose of AMB in the 2 prior studies (NCT00423748 or NCT00423202) or in the current extension study. Study drug was taken once daily.
Ambrisentan 10 mg	Participants were classified based on their randomized dose of AMB in the 2 prior studies (NCT00423748 or NCT00423202) or in the current extension study. Study drug was taken once daily.
Combined Ambrisentan Group	All dose groups combined.

Measured Values

	Ambrisentan 2.5 mg	Ambrisentan 5 mg	Ambrisentan 10 mg	Combined Ambrisentan Group
Number of Participants Analyzed	96	190	97	383
Baseline Exercise Capacity as Measured by the 6-Minute Walk Distance Test [units: Meters] Mean (Standard Deviation)	350.3 (86.64)	347.7 (87.33)	342.3 (80.84)	347.0 (85.39)

4. Secondary Outcome Measure:

Measure Title	Change From Baseline to Week 24 in Exercise Capacity as Measured by the 6-Minute Walk Distance Test
Measure Description	The 6-minute walk distance (6MWD) test was conducted according to the American Thoracic Society guidelines (ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med 2002; 166(1):111-117.). Missing values were imputed using LOCF method based on post-baseline observations. Baseline (BL) values from the screening/ randomization visit of the 2 prior studies defined the BL of this long-term analysis for those receiving ambrisentan in the prior studies. The Screening/Randomization Visit of the present study was the BL for subjects receiving placebo in the prior studies.
Time Frame	Baseline to Week 24
Safety Issue?	No

Analysis Population Description

All assessments of efficacy were performed using the randomized analysis set; subjects were allotted to an individual dose group based upon their randomized treatment assignment in the 2 prior studies (NCT00423748 or NCT00423202) or in the extension study. The LOCF method of imputation was used; only postbaseline observations were carried forward.

Reporting Groups

	Description
Ambrisentan 2.5 mg	Participants were classified based on their randomized dose of ambrisentan in the 2 prior studies (NCT00423748 or NCT00423202) or in the current extension study. Study drug was taken once daily.
Ambrisentan 5 mg	Participants were classified based on their randomized dose of ambrisentan in the 2 prior studies (NCT00423748 or NCT00423202) or in the current extension study. Study drug was taken once daily.
Ambrisentan 10 mg	Participants were classified based on their randomized dose of ambrisentan in the 2 prior studies (NCT00423748 or NCT00423202) or in the current extension study. Study drug was taken once daily.
Combined Ambrisentan Group	All dose groups combined.

Measured Values

	Ambrisentan 2.5 mg	Ambrisentan 5 mg	Ambrisentan 10 mg	Combined Ambrisentan Group
Number of Participants Analyzed	93	186	96	375
Change From Baseline to Week 24 in Exercise Capacity as Measured by the 6-Minute Walk Distance Test [units: Meters] Mean (Standard Deviation)	38.0 (74.28)	32.5 (78.55)	40.9 (72.85)	36.0 (75.97)

Statistical Analysis 1 for Change From Baseline to Week 24 in Exercise Capacity as Measured by the 6-Minute Walk Distance Test

Statistical Analysis Overview	Comparison Groups	Ambrisentan 2.5 mg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Net)
	Estimated Value	38.0
	Confidence Interval	(2-Sided) 95% 22.7 to 53.3
	Parameter Dispersion	Type: Standard Deviation Value: 74.28
	Estimation Comments	Applies to Ambrisentan 2.5 mg group only. Missing values were imputed using last-observation-carried forward method (LOCF) based on post-baseline observations.

Statistical Analysis 2 for Change From Baseline to Week 24 in Exercise Capacity as Measured by the 6-Minute Walk Distance Test

Statistical Analysis Overview	Comparison Groups	Ambrisentan 5 mg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Net)

	Estimated Value	32.5
	Confidence Interval	(2-Sided) 95% 21.1 to 43.8
	Parameter Dispersion	Type: Standard Deviation Value: 78.55
	Estimation Comments	Applies to Ambrisentan 5 mg group only. Missing values were imputed using last-observation-carried forward method (LOCF) based on post-baseline observations.

Statistical Analysis 3 for Change From Baseline to Week 24 in Exercise Capacity as Measured by the 6-Minute Walk Distance Test

Statistical Analysis Overview	Comparison Groups	Ambrisentan 10 mg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Net)
	Estimated Value	40.9
	Confidence Interval	(2-Sided) 95% 26.1 to 55.7
	Parameter Dispersion	Type: Standard Deviation Value: 72.85
	Estimation Comments	Applies to Ambrisentan 10 mg group only. LOCF method of imputation. Missing values were imputed using last-observation-carried forward method (LOCF) based on post-baseline observations.

Statistical Analysis 4 for Change From Baseline to Week 24 in Exercise Capacity as Measured by the 6-Minute Walk Distance Test

Statistical Analysis Overview	Comparison Groups	Combined Ambrisentan Group
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Net)
	Estimated Value	36.0
	Confidence Interval	(2-Sided) 95%

		28.3 to 43.7
	Parameter Dispersion	Type: Standard Deviation Value: 75.97
	Estimation Comments	Applies to Ambrisentan combined group only. LOCF method of imputation.

5. Secondary Outcome Measure:

Measure Title	Change From Baseline to Week 48 (Year 1) in Exercise Capacity as Measured by the 6-Minute Walk Distance Test
Measure Description	The 6-minute walk distance (6MWD) test was conducted according to the American Thoracic Society guidelines (ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med 2002; 166(1):111-117.). The last-observation-carried-forward (LOCF) imputation method was used. Baseline (BL) values from the screening/ randomization visit of the 2 prior studies defined the BL of this long-term analysis for those receiving AMB in the prior studies. The Screening/Randomization Visit of the present study was the BL for subjects receiving placebo in the prior studies.
Time Frame	Baseline to Week 48
Safety Issue?	No

Analysis Population Description

All assessments of efficacy were performed using the randomized analysis set; subjects were allotted to an individual dose group based upon their randomized treatment assignment in the 2 prior studies (NCT00423748 or NCT00423202) or in the extension study. The LOCF method of imputation was used; only postbaseline observations were carried forward.

Reporting Groups

	Description
Ambrisentan 2.5 mg	Participants were classified based on their randomized dose of AMB in the 2 prior studies (NCT00423748 or NCT00423202) or in the current extension study. Study drug was taken once daily.
Ambrisentan 5 mg	Participants were classified based on their randomized dose of AMB in the 2 prior studies (NCT00423748 or NCT00423202) or in the current extension study. Study drug was taken once daily.
Ambrisentan 10 mg	Participants were classified based on their randomized dose of AMB in the 2 prior studies (NCT00423748 or NCT00423202) or in the current extension study. Study drug was taken once daily.
Ambrisentan Combined Group	All dose groups combined.

Measured Values

	Ambrisentan 2.5 mg	Ambrisentan 5 mg	Ambrisentan 10 mg	Ambrisentan Combined Group
Number of Participants Analyzed	93	186	96	375

	Ambrisentan 2.5 mg	Ambrisentan 5 mg	Ambrisentan 10 mg	Ambrisentan Combined Group
Change From Baseline to Week 48 (Year 1) in Exercise Capacity as Measured by the 6-Minute Walk Distance Test [units: Meters] Mean (Standard Deviation)	24.9 (96.14)	27.9 (94.50)	37.2 (72.97)	29.5 (89.81)

Statistical Analysis 1 for Change From Baseline to Week 48 (Year 1) in Exercise Capacity as Measured by the 6-Minute Walk Distance Test

Statistical Analysis Overview	Comparison Groups	Ambrisentan 2.5 mg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Net)
	Estimated Value	24.9
	Confidence Interval	(2-Sided) 95% 5.1 to 44.7
	Parameter Dispersion	Type: Standard Deviation Value: 96.14
	Estimation Comments	Applies to Ambrisentan 2.5 mg group only. Missing values were imputed using last-observation-carried forward method (LOCF) based on post-baseline observations.

Statistical Analysis 2 for Change From Baseline to Week 48 (Year 1) in Exercise Capacity as Measured by the 6-Minute Walk Distance Test

Statistical Analysis Overview	Comparison Groups	Ambrisentan 5 mg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Net)
	Estimated Value	27.9
	Confidence Interval	(2-Sided) 95%

		14.2 to 41.6
	Parameter Dispersion	Type: Standard Deviation Value: 94.50
	Estimation Comments	Applies to Ambrisentan 5.0 mg group only. Missing values were imputed using last-observation-carried forward method (LOCF) based on post-baseline observations.

Statistical Analysis 3 for Change From Baseline to Week 48 (Year 1) in Exercise Capacity as Measured by the 6-Minute Walk Distance Test

Statistical Analysis Overview	Comparison Groups	Ambrisentan 10 mg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Net)
	Estimated Value	37.2
	Confidence Interval	(2-Sided) 95% 22.4 to 52.0
	Parameter Dispersion	Type: Standard Deviation Value: 72.97
	Estimation Comments	Applies to Ambrisentan 10 mg group only. Missing values were imputed using last-observation-carried forward method (LOCF) based on post-baseline observations.

Statistical Analysis 4 for Change From Baseline to Week 48 (Year 1) in Exercise Capacity as Measured by the 6-Minute Walk Distance Test

Statistical Analysis Overview	Comparison Groups	Ambrisentan Combined Group
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Median Difference (Net)
	Estimated Value	29.5
	Confidence Interval	(2-Sided) 95% 20.4 to 38.7
	Parameter Dispersion	Type: Standard Deviation Value: 89.81

	Estimation Comments	Applies to Ambrisentan combined group only. LOCF method of imputation.

6. Secondary Outcome Measure:

Measure Title	Change From Baseline to Year 2 in Exercise Capacity as Measured by the 6-Minute Walk Distance Test
Measure Description	The 6-minute walk distance (6MWD) test was conducted according to the American Thoracic Society guidelines (ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med 2002; 166(1):111-117.). The last-observation-carried-forward (LOCF) imputation method was used. Baseline (BL) values from the screening/ randomization visit of the 2 prior studies defined the BL of this long-term analysis for those receiving AMB in the prior studies. The Screening/Randomization Visit of the present study was the BL for subjects receiving placebo in the prior studies.
Time Frame	Baseline to Year 2
Safety Issue?	No

Analysis Population Description

All assessments of efficacy were performed using the randomized analysis set; subjects were allotted to an individual dose group based upon their randomized treatment assignment in the 2 prior studies (NCT00423748 or NCT00423202) or in the extension study. The LOCF method of imputation was used; only postbaseline observations were carried forward.

Reporting Groups

	Description
Ambrisentan 2.5 mg	Participants were classified based on their randomized dose of AMB in the 2 prior studies (NCT00423748 or NCT00423202) or in the current extension study. Study drug was taken once daily.
Ambrisentan 5 mg	Participants were classified based on their randomized dose of AMB in the 2 prior studies (NCT00423748 or NCT00423202) or in the current extension study. Study drug was taken once daily.
Ambrisentan 10 mg	Participants were classified based on their randomized dose of AMB in the 2 prior studies (NCT00423748 or NCT00423202) or in the current extension study. Study drug was taken once daily.
Combined Ambrisentan Group	All dose groups combined.

Measured Values

	Ambrisentan 2.5 mg	Ambrisentan 5 mg	Ambrisentan 10 mg	Combined Ambrisentan Group
Number of Participants Analyzed	93	186	96	375
Change From Baseline to Year 2 in Exercise Capacity as Measured by the 6-Minute Walk Distance Test [units: Meters] Mean (Standard Deviation)	6.7 (97.48)	23.2 (100.69)	28.0 (84.38)	20.3 (96.05)

Statistical Analysis 1 for Change From Baseline to Year 2 in Exercise Capacity as Measured by the 6-Minute Walk Distance Test

Statistical Analysis Overview	Comparison Groups	Ambrisentan 2.5 mg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Net)
	Estimated Value	6.7
	Confidence Interval	(2-Sided) 95% -13.4 to 26.8
	Parameter Dispersion	Type: Standard Deviation Value: 97.48
	Estimation Comments	Applies to Ambrisentan 2.5 mg group only. LOCF method of imputation.

Statistical Analysis 2 for Change From Baseline to Year 2 in Exercise Capacity as Measured by the 6-Minute Walk Distance Test

Statistical Analysis Overview	Comparison Groups	Ambrisentan 5 mg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Net)
	Estimated Value	23.2
	Confidence Interval	(2-Sided) 95% 8.7 to 37.8
	Parameter Dispersion	Type: Standard Deviation Value: 100.69
	Estimation Comments	Applies to Ambrisentan 5 mg group only. LOCF method of imputation.

Statistical Analysis 3 for Change From Baseline to Year 2 in Exercise Capacity as Measured by the 6-Minute Walk Distance Test

Statistical Analysis Overview	Comparison Groups	Ambrisentan 10 mg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Net)
	Estimated Value	28.0
	Confidence Interval	(2-Sided) 95% 10.9 to 45.1
	Parameter Dispersion	Type: Standard Deviation Value: 84.38
	Estimation Comments	Applies to Ambrisentan 10 mg group only. LOCF method of imputation.

Statistical Analysis 4 for Change From Baseline to Year 2 in Exercise Capacity as Measured by the 6-Minute Walk Distance Test

Statistical Analysis Overview	Comparison Groups	Combined Ambrisentan Group
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Median Difference (Net)
	Estimated Value	20.3
	Confidence Interval	(2-Sided) 95% 10.6 to 30.1
	Parameter Dispersion	Type: Standard Deviation Value: 96.05
	Estimation Comments	Applies to Ambrisentan combined group only. Missing values were imputed using last-observation-carried forward method (LOCF) based on post-baseline observations.

7. Secondary Outcome Measure:

Measure Title	Change From Baseline to Year 3 in Exercise Capacity as Measured by the 6-Minute Walk Distance Test

Measure Description	Thoracic Society guidelines (ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med 2002; 166(1):111-117.). The last-observation-carried-forward (LOCF) imputation method was used. Baseline (BL) values from the screening/randomization visit of the 2 prior studies defined the BL of this long-term analysis for those receiving AMB in the prior studies. The Screening/Randomization Visit of the present study was the BL for subjects receiving placebo in the prior studies.
Time Frame	Baseline to Year 3
Safety Issue?	No

Analysis Population Description

All assessments of efficacy were performed using the randomized analysis set; subjects were allotted to an individual dose group based upon their randomized treatment assignment in the 2 prior studies (NCT00423748 or NCT00423202) or in the extension study. The LOCF method of imputation was used; only postbaseline observations were carried forward.

Reporting Groups

	Description
Ambrisentan 2.5 mg	Participants were classified based on their randomized dose of AMB in the 2 prior studies (NCT00423748 or NCT00423202) or in the current extension study. Study drug was taken once daily.
Ambrisentan 5 mg	Participants were classified based on their randomized dose of AMB in the 2 prior studies (NCT00423748 or NCT00423202) or in the current extension study. Study drug was taken once daily.
Ambrisentan 10 mg	Participants were classified based on their randomized dose of AMB in the 2 prior studies (NCT00423748 or NCT00423202) or in the current extension study. Study drug was taken once daily.
Combined Ambrisentan Group	All dose groups combined.

Measured Values

	Ambrisentan 2.5 mg	Ambrisentan 5 mg	Ambrisentan 10 mg	Combined Ambrisentan Group
Number of Participants Analyzed	93	186	96	375
Change From Baseline to Year 3 in Exercise Capacity as Measured by the 6-Minute Walk Distance Test [units: Meters] Mean (Standard Deviation)	0.7 (95.21)	18.8 (101.22)	27.8 (87.07)	16.6 (96.54)

Statistical Analysis 1 for Change From Baseline to Year 3 in Exercise Capacity as Measured by the 6-Minute Walk Distance Test

Statistical Analysis Overview	Comparison Groups	Ambrisentan 2.5 mg
	Comments	[Not specified]

	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Net)
	Estimated Value	0.7
	Confidence Interval	(2-Sided) 95% -18.9 to 20.3
	Parameter Dispersion	Type: Standard Deviation Value: 95.21
	Estimation Comments	Applies to Ambrisentan 2.5 mg group only. Missing values were imputed using last-observation-carried forward method (LOCF) based on post-baseline observations.

Statistical Analysis 2 for Change From Baseline to Year 3 in Exercise Capacity as Measured by the 6-Minute Walk Distance Test

Statistical Analysis Overview	Comparison Groups	Ambrisentan 5 mg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Net)
	Estimated Value	18.8
	Confidence Interval	(2-Sided) 95% 4.2 to 33.5
	Parameter Dispersion	Type: Standard Deviation Value: 101.22
	Estimation Comments	Applies to Ambrisentan 5 mg group only. Missing values were imputed using last-observation-carried forward method (LOCF) based on post-baseline observations.

Statistical Analysis 3 for Change From Baseline to Year 3 in Exercise Capacity as Measured by the 6-Minute Walk Distance Test

Statistical Analysis Overview	Comparison Groups	Ambrisentan 10 mg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Net)
	Estimated Value	27.8
	Confidence Interval	(2-Sided) 95% 10.1 to 45.4
	Parameter Dispersion	Type: Standard Deviation Value: 87.07
	Estimation Comments	Applies to Ambrisentan 10 mg group only. Missing values were imputed using last-observation-carried forward method (LOCF) based on post-baseline observations.

Statistical Analysis 4 for Change From Baseline to Year 3 in Exercise Capacity as Measured by the 6-Minute Walk Distance Test

Statistical Analysis Overview	Comparison Groups	Combined Ambrisentan Group
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Net)
	Estimated Value	16.6
	Confidence Interval	(2-Sided) 95% 6.8 to 26.4
	Parameter Dispersion	Type: Standard Deviation Value: 96.54
	Estimation Comments	Applies to Ambrisentan combined group only. Missing values were imputed using last-observation-carried forward method (LOCF) based on post-baseline observations.

8. Secondary Outcome Measure:

Measure Title	Baseline Borg Dyspnea Index
Measure Description	Borg Dyspnea Index is a measure of perceived shortness of breath: 0 units on a scale (none) to 10 units on a scale (maximum breathlessness).
Time Frame	Baseline
Safety Issue?	No

Analysis Population Description

All assessments of efficacy were performed using the randomized analysis set, such that subjects were allotted to an individual dose group based upon their randomized treatment assignment in the 2 prior studies (NCT00423748 or NCT00423202) or in the current extension study.

Reporting Groups

	Description
Ambrisentan 2.5 mg	Participants were classified based on their randomized dose of AMB in the 2 prior studies (NCT00423748 or NCT00423202) or in the current extension study. Study drug was taken once daily.
Ambrisentan 5 mg	Participants were classified based on their randomized dose of AMB in the 2 prior studies (NCT00423748 or NCT00423202) or in the current extension study. Study drug was taken once daily.
Ambrisentan 10 mg	Participants were classified based on their randomized dose of AMB in the 2 prior studies (NCT00423748 or NCT00423202) or in the current extension study. Study drug was taken once daily.
Combined Ambrisentan Group	All dose groups combined.

Measured Values

	Ambrisentan 2.5 mg	Ambrisentan 5 mg	Ambrisentan 10 mg	Combined Ambrisentan Group
Number of Participants Analyzed	96	189	97	382
Baseline Borg Dyspnea Index [units: units on a scale] Mean (Standard Deviation)	4.14 (2.684)	3.80 (2.332)	3.78 (2.133)	3.88 (2.377)

9. Secondary Outcome Measure:

Measure Title	Change From Baseline to Year 1 in Borg Dyspnea Index
Measure Description	Borg Dyspnea Index is a measure of perceived shortness of breath: 0 units on a scale (none) to 10 units on a scale (maximum breathlessness). Baseline (BL) values from the screening/randomization visit of the 2 prior studies defined the BL of this long-term analysis for those receiving ambrisentan in the prior studies. The Screening/Randomization Visit of the present study was the BL for subjects receiving placebo in the prior studies.
Time Frame	Baseline to Year 1
Safety Issue?	No

Analysis Population Description

All assessments of efficacy were performed using the randomized analysis set; subjects were allotted to an individual dose group based upon their randomized treatment assignment in the 2 prior studies (NCT00423748 or NCT00423202) or in the extension study. The LOCF method of imputation was used; only postbaseline observations were carried forward.

Reporting Groups

	Description
Ambrisentan 2.5 mg	Participants were classified based on their randomized dose of AMB in the 2 prior studies (NCT00423748 or NCT00423202) or in the current extension study. Study drug was taken once daily.
Ambrisentan 5 mg	Participants were classified based on their randomized dose of AMB in the 2 prior studies (NCT00423748 or NCT00423202) or in the current extension study. Study drug was taken once daily.
Ambrisentan 10 mg	Participants were classified based on their randomized dose of AMB in the 2 prior studies (NCT00423748 or NCT00423202) or in the current extension study. Study drug was taken once daily.
Combined Ambrisentan Group	All dose groups combined.

Measured Values

	Ambrisentan 2.5 mg	Ambrisentan 5 mg	Ambrisentan 10 mg	Combined Ambrisentan Group
Number of Participants Analyzed	93	185	96	374
Change From Baseline to Year 1 in Borg Dyspnea Index [units: units on a scale] Mean (Standard Deviation)	-0.08 (2.254)	-0.59 (2.450)	-0.51 (2.400)	-0.44 (2.393)

Statistical Analysis 1 for Change From Baseline to Year 1 in Borg Dyspnea Index

Statistical Analysis Overview	Comparison Groups	Ambrisentan 2.5 mg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Net)
	Estimated Value	-0.08
	Confidence Interval	(2-Sided) 95% -0.55 to 0.38
	Parameter Dispersion	Type: Standard Deviation Value: 2.254
	Estimation Comments	Applies to Ambrisentan 2.5 mg group only. Missing values were imputed using last-observation-carried forward method (LOCF) based on post-baseline observations.

Statistical Analysis 2 for Change From Baseline to Year 1 in Borg Dyspnea Index

Statistical Analysis Overview	Comparison Groups	Ambrisentan 5 mg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Net)
	Estimated Value	-0.59
	Confidence Interval	(2-Sided) 95% -0.94 to -0.23
	Parameter Dispersion	Type: Standard Deviation Value: 2.450
	Estimation Comments	Applies to Ambrisentan 5 mg group only. Missing values were imputed using last-observation-carried forward method (LOCF) based on post-baseline observations.

Statistical Analysis 3 for Change From Baseline to Year 1 in Borg Dyspnea Index

Statistical Analysis Overview	Comparison Groups	Ambrisentan 10 mg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Net)
	Estimated Value	-0.51
	Confidence Interval	(2-Sided) 95% -1.00 to -0.03
	Parameter Dispersion	Type: Standard Deviation Value: 2.400
	Estimation Comments	Applies to Ambrisentan 10 mg group only. Missing values were imputed using last-observation-carried forward method (LOCF) based on post-baseline observations.

Statistical Analysis 4 for Change From Baseline to Year 1 in Borg Dyspnea Index

Statistical Analysis Overview	Comparison Groups	Combined Ambrisentan Group
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-0.44
	Confidence Interval	(2-Sided) 95% -0.69 to -0.20
	Parameter Dispersion	Type: Standard Deviation Value: 2.393
	Estimation Comments	Applies to Ambrisentan combined group only. Missing values were imputed using last-observation-carried forward method (LOCF) based on post-baseline observations.

10. Secondary Outcome Measure:

Measure Title	Change From Baseline to Year 2 in Borg Dyspnea Index
Measure Description	Borg Dyspnea Index is a measure of perceived shortness of breath: 0 units on a scale (none) to 10 units on a scale (maximum breathlessness). Baseline (BL) values from the screening/randomization visit of the 2 prior studies defined the BL of this long-term analysis for those receiving AMB in the prior studies. The Screening/Randomization Visit of the present study was the BL for subjects receiving placebo in the prior studies.
Time Frame	Baseline to Year 2
Safety Issue?	No

Analysis Population Description

All assessments of efficacy were performed using the randomized analysis set; subjects were allotted to an individual dose group based upon their randomized treatment assignment in the 2 prior studies (NCT00423748 or NCT00423202) or in the extension study. The LOCF method of imputation was used; only postbaseline observations were carried forward.

Reporting Groups

	Description
Ambrisentan 2.5 mg	Participants were classified based on their randomized dose of AMB in the 2 prior studies (NCT00423748 or NCT00423202) or in the current extension study. Study drug was taken once daily.

	Description
Ambrisentan 5 mg	Participants were classified based on their randomized dose of AMB in the 2 prior studies (NCT00423748 or NCT00423202) or in the current extension study. Study drug was taken once daily.
Ambrisentan 10 mg	Participants were classified based on their randomized dose of AMB in the 2 prior studies (NCT00423748 or NCT00423202) or in the current extension study. Study drug was taken once daily.
Combined Ambrisentan Group	All dose groups combined.

Measured Values

	Ambrisentan 2.5 mg	Ambrisentan 5 mg	Ambrisentan 10 mg	Combined Ambrisentan Group
Number of Participants Analyzed	93	185	96	374
Change From Baseline to Year 2 in Borg Dyspnea Index [units: units on a scale] Mean (Standard Deviation)	0.23 (2.603)	-0.33 (2.477)	-0.65 (2.305)	-0.27 (2.480)

Statistical Analysis 1 for Change From Baseline to Year 2 in Borg Dyspnea Index

Statistical Analysis Overview	Comparison Groups	Ambrisentan 2.5 mg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Net)
	Estimated Value	0.23
	Confidence Interval	(2-Sided) 95% -0.31 to 0.76
	Parameter Dispersion	Type: Standard Deviation Value: 2.603
	Estimation Comments	Applies to Ambrisentan 2.5 mg group only. Missing values were imputed using last-observation-carried forward method (LOCF) based on post-baseline observations.

Statistical Analysis 2 for Change From Baseline to Year 2 in Borg Dyspnea Index

Statistical Analysis Overview	Comparison Groups	Ambrisentan 5 mg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Net)
	Estimated Value	-0.33
	Confidence Interval	(2-Sided) 95% -0.68 to 0.03
	Parameter Dispersion	Type: Standard Deviation Value: 2.477
	Estimation Comments	Applies to Ambrisentan 5 mg group only. Missing values were imputed using last-observation-carried forward method (LOCF) based on post-baseline observations.

Statistical Analysis 3 for Change From Baseline to Year 2 in Borg Dyspnea Index

Statistical Analysis Overview	Comparison Groups	Ambrisentan 10 mg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Net)
	Estimated Value	-0.65
	Confidence Interval	(2-Sided) 95% -1.12 to -0.18
	Parameter Dispersion	Type: Standard Deviation Value: 2.305
	Estimation Comments	Applies to Ambrisentan 10 mg group only. Missing values were imputed using last-observation-carried forward method (LOCF) based on post-baseline observations.

Statistical Analysis 4 for Change From Baseline to Year 2 in Borg Dyspnea Index

Statistical Analysis Overview	Comparison Groups	Combined Ambrisentan Group
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Net)
	Estimated Value	-0.27
	Confidence Interval	(2-Sided) 95% -0.52 to -0.02
	Parameter Dispersion	Type: Standard Deviation Value: 2.480
	Estimation Comments	Applies to Ambrisentan combined group only. Missing values were imputed using last-observation-carried forward method (LOCF) based on post-baseline observations.

11. Secondary Outcome Measure:

Measure Title	Change From Baseline to Year 3 in Borg Dyspnea Index
Measure Description	Borg Dyspnea Index is a measure of perceived shortness of breath: 0 units on a scale (none) to 10 units on a scale (maximum breathlessness). Baseline (BL) values from the screening/randomization visit of the 2 prior studies defined the BL of this long-term analysis for those receiving AMB in the prior studies. The Screening/Randomization Visit of the present study was the BL for subjects receiving placebo in the prior studies.
Time Frame	Baseline to Year 3
Safety Issue?	No

Analysis Population Description

All assessments of efficacy were performed using the randomized analysis set; subjects were allotted to an individual dose group based upon their randomized treatment assignment in the 2 prior studies (NCT00423748 or NCT00423202) or in the extension study. The LOCF method of imputation was used; only postbaseline observations were carried forward.

Reporting Groups

	Description
Ambrisentan 2.5 mg	Participants were classified based on their randomized dose of AMB in the 2 prior studies (NCT00423748 or NCT00423202) or in the current extension study. Study drug was taken once daily.

	Description
Ambrisentan 5 mg	Participants were classified based on their randomized dose of AMB in the 2 prior studies (NCT00423748 or NCT00423202) or in the current extension study. Study drug was taken once daily.
Ambrisentan 10 mg	Participants were classified based on their randomized dose of AMB in the 2 prior studies (NCT00423748 or NCT00423202) or in the current extension study. Study drug was taken once daily.
Combined Ambrisentan Group	All dose groups combined.

Measured Values

	Ambrisentan 2.5 mg	Ambrisentan 5 mg	Ambrisentan 10 mg	Combined Ambrisentan Group
Number of Participants Analyzed	93	185	96	374
Change From Baseline to Year 3 in Borg Dyspnea Index [units: units on a scale] Mean (Standard Deviation)	0.20 (2.593)	-0.14 (2.514)	-0.48 (2.215)	-0.14 (2.467)

Statistical Analysis 1 for Change From Baseline to Year 3 in Borg Dyspnea Index

Statistical Analysis Overview	Comparison Groups	Ambrisentan 2.5 mg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Net)
	Estimated Value	0.20
	Confidence Interval	(2-Sided) 95% -0.33 to 0.74
	Parameter Dispersion	Type: Standard Deviation Value: 2.593
	Estimation Comments	Applies to Ambrisentan 2.5 mg group only. Missing values were imputed using last-observation-carried forward method (LOCF) based on post-baseline observations.

Statistical Analysis 2 for Change From Baseline to Year 3 in Borg Dyspnea Index

Statistical Analysis Overview	Comparison Groups	Ambrisentan 5 mg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Net)
	Estimated Value	-0.14
	Confidence Interval	(2-Sided) 95% -0.51 to 0.22
	Parameter Dispersion	Type: Standard Deviation Value: 2.514
	Estimation Comments	Applies to Ambrisentan 5 mg group only. Missing values were imputed using last-observation-carried forward method (LOCF) based on post-baseline observations.

Statistical Analysis 3 for Change From Baseline to Year 3 in Borg Dyspnea Index

Statistical Analysis Overview	Comparison Groups	Ambrisentan 10 mg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Net)
	Estimated Value	-0.48
	Confidence Interval	(2-Sided) 95% -0.93 to -0.03
	Parameter Dispersion	Type: Standard Deviation Value: 2.215
	Estimation Comments	Applies to Ambrisentan 10 mg group only. Missing values were imputed using last-observation-carried forward method (LOCF) based on post-baseline observations.

Statistical Analysis 4 for Change From Baseline to Year 3 in Borg Dyspnea Index

Statistical Analysis Overview	Comparison Groups	Combined Ambrisentan Group
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Net)
	Estimated Value	-0.14
	Confidence Interval	(2-Sided) 95% -0.39 to 0.11
	Parameter Dispersion	Type: Standard Deviation Value: 2.467
	Estimation Comments	Applies to Ambrisentan combined group only. Missing values were imputed using last-observation-carried forward method (LOCF) based on post-baseline observations.

12. Secondary Outcome Measure:

Measure Title	Baseline World Health Organization (WHO) Functional Class
Measure Description	WHO Classes: I) pulmonary hypertension (PH); ordinary physical activity not limited or causes increased dyspnea, fatigue, chest pain, or presyncope. II) PH; ordinary physical activity mildly limited and causes increased dyspnea, fatigue, chest pain, or presyncope; comfortable at rest. III) PH; physical activity markedly limited and less than ordinary physical activity causes increased dyspnea, fatigue, chest pain, or presyncope; comfortable at rest. IV) PH; physical activity causes symptoms; signs of right heart failure; dyspnea/fatigue possible at rest.
Time Frame	Baseline
Safety Issue?	No

Analysis Population Description

All assessments of efficacy were performed using the randomized analysis set, such that subjects were allotted to an individual dose group based upon their randomized treatment assignment in the 2 prior studies (NCT00423748 or NCT00423202) or in the current extension study.

Reporting Groups

	Description
Ambrisentan 2.5 mg	Participants were classified based on their randomized dose of AMB in the 2 prior studies (NCT00423748 or NCT00423202) or in the current extension study. Study drug was taken once daily.

	Description
Ambrisentan 5 mg	Participants were classified based on their randomized dose of AMB in the 2 prior studies (NCT00423748 or NCT00423202) or in the current extension study. Study drug was taken once daily.
Ambrisentan 10 mg	Participants were classified based on their randomized dose of AMB in the 2 prior studies (NCT00423748 or NCT00423202) or in the current extension study. Study drug was taken once daily.
Ambrisentan Combined Group	All dose groups combined.

Measured Values

	Ambrisentan 2.5 mg	Ambrisentan 5 mg	Ambrisentan 10 mg	Ambrisentan Combined Group
Number of Participants Analyzed	96	190	97	383
Baseline World Health Organization (WHO) Functional Class [units: participants]				
WHO Functional Class I	1	7	4	12
WHO Functional Class II	51	77	35	163
WHO Functional Class III	39	91	48	178
WHO Functional Class IV	5	15	10	30

13. Secondary Outcome Measure:

Measure Title	Change From Baseline to Year 1 in World Health Organization (WHO) Functional Class
Measure Description	WHO Classes: I) pulmonary hypertension (PH); ordinary physical activity not limited or causes increased dyspnea, fatigue, chest pain, or presyncope. II) PH; ordinary physical activity mildly limited and causes increased dyspnea, fatigue, chest pain, or presyncope; comfortable at rest. III) PH; physical activity markedly limited and less than ordinary physical activity causes increased dyspnea, fatigue, chest pain, or presyncope; comfortable at rest. IV) PH; physical activity causes symptoms; signs of right heart failure; dyspnea/fatigue possible at rest.
Time Frame	Baseline to Year 1
Safety Issue?	No

Analysis Population Description

All assessments of efficacy were performed using the randomized analysis set; subjects were allotted to an individual dose group based upon their randomized treatment assignment in the 2 prior studies (NCT00423748 or NCT00423202) or in extension study. Missing values imputed using LOCF based on post-baseline observations.

Reporting Groups

	Description
Ambrisentan 2.5 mg	Participants were classified based on their randomized dose of AMB in the 2 prior studies (NCT00423748 or NCT00423202) or in the current extension study. Study drug was taken once daily.
Ambrisentan 5 mg	Participants were classified based on their randomized dose of AMB in the 2 prior studies (NCT00423748 or NCT00423202) or in the current extension study. Study drug was taken once daily.
Ambrisentan 10 mg	Participants were classified based on their randomized dose of AMB in the 2 prior studies (NCT00423748 or NCT00423202) or in the current extension study. Study drug was taken once daily.
Ambrisentan Combined Group	All dose groups combined.

Measured Values

	Ambrisentan 2.5 mg	Ambrisentan 5 mg	Ambrisentan 10 mg	Ambrisentan Combined Group
Number of Participants Analyzed	96	190	97	383
Change From Baseline to Year 1 in World Health Organization (WHO) Functional Class [units: participants]				
Improved	16	56	36	108
No Change	68	122	46	236
Deteriorated	10	9	14	33
Missing	2	3	1	6

14. Secondary Outcome Measure:

Measure Title	Change From Baseline to Year 2 in World Health Organization (WHO) Functional Class
Measure Description	WHO Classes: I) pulmonary hypertension (PH); ordinary physical activity not limited or causes increased dyspnea, fatigue, chest pain, or presyncope. II) PH; ordinary physical activity mildly limited and causes increased dyspnea, fatigue, chest pain, or presyncope; comfortable at rest. III) PH; physical activity markedly limited and less than ordinary physical activity causes increased dyspnea, fatigue, chest pain, or presyncope; comfortable at rest. IV) PH; physical activity causes symptoms; signs of right heart failure; dyspnea/fatigue possible at rest.
Time Frame	Baseline to Year 2
Safety Issue?	No

Analysis Population Description

All assessments of efficacy were performed using the randomized analysis set; subjects were allotted to an individual dose group based upon their randomized treatment assignment in the 2 prior studies (NCT00423748 or NCT00423202) or in extension study. Missing values were imputed using LOCF based on post-baseline observations.

Reporting Groups

	Description
Ambrisentan 2.5 mg	Participants were classified based on their randomized dose of AMB in the 2 prior studies (NCT00423748 or NCT00423202) or in the current extension study. Study drug was taken once daily.
Ambrisentan 5 mg	Participants were classified based on their randomized dose of AMB in the 2 prior studies (NCT00423748 or NCT00423202) or in the current extension study. Study drug was taken once daily.
Ambrisentan 10 mg	Participants were classified based on their randomized dose of AMB in the 2 prior studies (NCT00423748 or NCT00423202) or in the current extension study. Study drug was taken once daily.
Combined Ambrisentan Group	All dose groups combined.

Measured Values

	Ambrisentan 2.5 mg	Ambrisentan 5 mg	Ambrisentan 10 mg	Combined Ambrisentan Group
Number of Participants Analyzed	96	190	97	383
Change From Baseline to Year 2 in World Health Organization (WHO) Functional Class [units: participants]				
Improved	16	58	39	113
No Change	58	109	43	210
Deteriorated	20	20	14	54
Missing	2	3	1	6

15. Secondary Outcome Measure:

Measure Title	Change From Baseline to Year 3 in World Health Organization (WHO) Functional Class
Measure Description	WHO Classes: I) pulmonary hypertension (PH); ordinary physical activity not limited or causes increased dyspnea, fatigue, chest pain, or presyncope. II) PH; ordinary physical activity mildly limited and causes increased dyspnea, fatigue, chest pain, or presyncope; comfortable at rest. III) PH; physical activity markedly limited and less than ordinary physical activity causes increased dyspnea, fatigue, chest pain, or presyncope; comfortable at rest. IV) PH; physical activity causes symptoms; signs of right heart failure; dyspnea/fatigue possible at rest.

Time Frame	Baseline to Year 3
Safety Issue?	No

Analysis Population Description

All assessments of efficacy were performed using the randomized analysis set; subjects were allotted to an individual dose group based upon their randomized treatment assignment in the 2 prior studies (NCT00423748 or NCT00423202) or in the extension study. Missing values were imputed using LOCF based on post-baseline observations.

Reporting Groups

	Description
Ambrisentan 2.5 mg	Participants were classified based on their randomized dose of AMB in the 2 prior studies (NCT00423748 or NCT00423202) or in the current extension study. Study drug was taken once daily.
Ambrisentan 5 mg	Participants were classified based on their randomized dose of AMB in the 2 prior studies (NCT00423748 or NCT00423202) or in the current extension study. Study drug was taken once daily.
Ambrisentan 10 mg	Participants were classified based on their randomized dose of AMB in the 2 prior studies (NCT00423748 or NCT00423202) or in the current extension study. Study drug was taken once daily.
Combined Ambrisentan Group	All dose groups combined.

Measured Values

	Ambrisentan 2.5 mg	Ambrisentan 5 mg	Ambrisentan 10 mg	Combined Ambrisentan Group
Number of Participants Analyzed	96	190	97	383
Change From Baseline to Year 3 in World Health Organization (WHO) Functional Class [units: participants]				
Improved	17	61	32	110
No Change	57	109	49	215
Deteriorated	20	17	15	52
Missing	2	3	1	6

16. Secondary Outcome Measure:

Measure Title	Baseline SF-36 Health Survey Scales for the Combined Ambrisentan Group

Measure Description	The 8 scales of the SF-36 Health Survey measured included physical functioning, role physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health, and the summary measures included physical health and mental health. Scores for each scale are transformed and the transformed scores range from 0 (worst health) to 100 (best health). The scores are then standardized with the 1998 General United States (US) population mean and standard deviation (SD). Finally, the scores are transformed to the norm-based scoring with a mean of 50 and SD of 10.
Time Frame	Baseline
Safety Issue?	No

Analysis Population Description

All participants were combined into one group for this analysis (all doses) and an observed-case approach was used.

Reporting Groups

	Description
Combined Ambrisentan Group	All dose groups combined.

Measured Values

	Combined Ambrisentan Group
Number of Participants Analyzed	355
Baseline SF-36 Health Survey Scales for the Combined Ambrisentan Group [units: units on a scale] Mean (Standard Deviation)	
Physical Functioning	30.0 (9.02)
Role Physical	35.2 (10.21)
Bodily Pain	46.3 (11.93)
General Health	36.0 (8.65)
Vitality	42.1 (10.23)
Social Functioning	39.6 (11.8)
Role Emotional	39.2 (13.47)
Mental Health	43.3 (12.12)
Physical Component Summary	35.1 (8.52)
Mental Component Summary	44.5 (11.98)

17. Secondary Outcome Measure:

Measure Title	Change From Baseline to Week 12 in SF-36 Health Survey Scales for the Combined Ambrisentan Group
Measure Description	The 8 scales of the SF-36 Health Survey measured included physical functioning, role physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health, and the summary measures included physical health and mental health. Scores for each scale are transformed and the transformed scores range from 0 (worst health) to 100 (best health). The scores are then standardized with the 1998 General US population mean and SD. Finally, the scores are transformed to the norm-based scoring with a mean of 50 and SD of 10.
Time Frame	Baseline to Week 12
Safety Issue?	No

Analysis Population Description

All participants were combined into one group for this analysis (all doses) and an observed-case approach was used.

Reporting Groups

	Description
Combined Ambrisentan Group	All dose groups combined.

Measured Values

	Combined Ambrisentan Group
Number of Participants Analyzed	303
Change From Baseline to Week 12 in SF-36 Health Survey Scales for the Combined Ambrisentan Group [units: units on a scale] Mean (Standard Deviation)	
Physical Functioning (n=299)	3.9 (7.40)
Role Physical (n=298)	5.6 (10.81)
Bodily Pain (n=303)	1.8 (11.27)
General Health (n=297)	3.1 (7.85)
Vitality (n=301)	4.6 (9.12)
Social Functioning (n=303)	3.9 (10.63)
Role Emotional (n=286)	3.9 (14.69)
Mental Health (n=301)	3.2 (9.72)

	Combined Ambrisentan Group
Physical Component Summary (n=276)	3.8 (7.59)
Mental Component Summary (n=276)	3.4 (10.77)

18. Secondary Outcome Measure:

Measure Title	Change From Baseline to Week 24 in SF-36 Health Survey Scales for the Combined Ambrisentan Group
Measure Description	The 8 scales of the SF-36 Health Survey measured included physical functioning, role physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health, and the summary measures included physical health and mental health. Scores for each scale are transformed and the transformed scores range from 0 (worst health) to 100 (best health). The scores are then standardized with the 1998 General US population mean and SD. Finally, the scores are transformed to the norm-based scoring with a mean of 50 and SD of 10.
Time Frame	Baseline to Week 24
Safety Issue?	No

Analysis Population Description

All participants were combined into one group for this analysis (all doses) and an observed-case approach was used.

Reporting Groups

	Description
Combined Ambrisentan Group	(All Doses)

Measured Values

	Combined Ambrisentan Group
Number of Participants Analyzed	230
Change From Baseline to Week 24 in SF-36 Health Survey Scales for the Combined Ambrisentan Group [units: units on a scale] Mean (Standard Deviation)	
Physical Functioning (n=226)	4.7 (8.75)
Role Physical (n=227)	5.7 (13.37)
Bodily Pain (n=230)	1.0 (13.28)
General Health (n=223)	3.2 (8.11)
Vitality (n=227)	4.5 (9.55)

	Combined Ambrisentan Group
Social Functioning (n=230)	3.5 (11.50)
Role Emotional (n=220)	4.3 (14.45)
Mental Health (n=227)	2.6 (10.57)
Physical Component Summary (n=212)	3.8 (9.06)
Mental Component Summary (n=212)	3.2 (11.06)

19. Secondary Outcome Measure:

Measure Title	Change From Baseline to Week 36 in SF-36 Health Survey Scales for the Combined Ambrisentan Group
Measure Description	The 8 scales of the SF-36 Health Survey measured included physical functioning, role physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health, and the summary measures included physical health and mental health. Scores for each scale are transformed and the transformed scores range from 0 (worst health) to 100 (best health). The scores are then standardized with the 1998 General US population mean and SD. Finally, the scores are transformed to the norm-based scoring with a mean of 50 and SD of 10.
Time Frame	Baseline to Week 36
Safety Issue?	No

Analysis Population Description

All participants were combined into one group for this analysis (all doses) and an observed-case approach was used.

Reporting Groups

	Description
Combined Ambrisentan Group	All dose groups combined.

Measured Values

	Combined Ambrisentan Group
Number of Participants Analyzed	186
Change From Baseline to Week 36 in SF-36 Health Survey Scales for the Combined Ambrisentan Group [units: units on a scale] Mean (Standard Deviation)	
Physical Functioning (n=183)	4.9 (8.27)
Role Physical (n=181)	4.5 (12.34)

	Combined Ambrisentan Group
Bodily Pain (n=186)	1.9 (13.16)
General Health (n=181)	4.5 (12.34)
Vitality (n=185)	4.6 (9.16)
Social Functioning (n=186)	3.7 (12.26)
Role Emotional (n=178)	3.6 (15.17)
Mental Health (n=185)	2.9 (11.00)
Physical Component Summary (n=169)	3.9 (8.79)
Mental Component Summary (n=169)	2.9 (11.34)

20. Secondary Outcome Measure:

Measure Title	Percentage of Participants With No Clinical Worsening of PAH
Measure Description	Clinical worsening of PAH was defined as the time from randomization to ambrisentan therapy to the first occurrence of death, lung transplantation, hospitalization for PAH, atrial septostomy, addition of approved prostanoid therapy, study withdrawal due to the addition of other clinically approved PAH therapeutics, or study withdrawal due to 2 or more early escape criteria (for subjects randomized to AMB in NCT00423748 or NCT00423202). Results are presented as the Kaplan-Meier estimate (% probability) of not having clinical worsening after a given time.
Time Frame	Baseline to Year 3
Safety Issue?	No

Analysis Population Description

All assessments of efficacy were performed using the randomized analysis set, such that subjects were allotted to an individual dose group based upon their randomized treatment assignment in the 2 prior studies (NCT00423748 or NCT00423202) or in the current extension study.

Reporting Groups

	Description
Ambrisentan 2.5 mg	Participants were classified based on their randomized dose of AMB in the 2 prior studies (NCT00423748 or NCT00423202) or in the current extension study. Study drug was taken once daily.
Ambrisentan 5 mg	Participants were classified based on their randomized dose of AMB in the 2 prior studies (NCT00423748 or NCT00423202) or in the current extension study. Study drug was taken once daily.
Ambrisentan 10 mg	Participants were classified based on their randomized dose of AMB in the 2 prior studies (NCT00423748 or NCT00423202) or in the current extension study. Study drug was taken once daily.

	Description
Ambrisentan Combined Group	All dose groups combined.

Measured Values

	Ambrisentan 2.5 mg	Ambrisentan 5 mg	Ambrisentan 10 mg	Ambrisentan Combined Group
Number of Participants Analyzed	96	190	97	383
Percentage of Participants With No Clinical Worsening of PAH [units: percent probability (KM estimate)] Number (95% Confidence Interval)				
No clinical worsening after 1 year of treatment	80.4 (70.7 to 87.2)	83.9 (77.7 to 88.5)	82.8 (73.5 to 89.1)	82.7 (78.4 to 86.2)
No clinical worsening after 2 years of treatment	67.8 (57.0 to 76.4)	72.4 (65.1 to 78.5)	72.2 (61.7 to 80.3)	71.1 (66.1 to 75.6)
No clinical worsening after 3 years of treatment	60.7 (49.7 to 70.0)	67.4 (59.7 to 74.0)	59.9 (48.0 to 69.9)	63.8 (58.4 to 68.8)

21. Secondary Outcome Measure:

Measure Title	Percentage of Participants With Failure-Free Treatment Status
Measure Description	Treatment failure was defined as the time from randomization to ambrisentan therapy to the first occurrence of death, lung transplantation, addition of approved prostanoid therapy, study withdrawal due to the addition of other clinically approved PAH therapeutics, or study withdrawal due to 2 or more early escape criteria (for subjects randomized to ambrisentan in NCT00423748 or NCT00423202). Results are presented as the Kaplan-Meier estimate (% probability) of not having treatment failure after a given time.
Time Frame	Baseline to Year 4
Safety Issue?	No

Analysis Population Description

All assessments of efficacy were performed using the randomized analysis set, such that subjects were allotted to an individual dose group based upon their randomized treatment assignment in the 2 prior studies (NCT00423748 or NCT00423202) or in the current extension study.

Reporting Groups

	Description
Ambrisentan 2.5 mg	Participants were classified based on their randomized dose of AMB in the 2 prior studies (NCT00423748 or NCT00423202) or in the current extension study. Study drug was taken once daily.

	Description
Ambrisentan 5 mg	Participants were classified based on their randomized dose of AMB in the 2 prior studies (NCT00423748 or NCT00423202) or in the current extension study. Study drug was taken once daily.
Ambrisentan 10 mg	Participants were classified based on their randomized dose of AMB in the 2 prior studies (NCT00423748 or NCT00423202) or in the current extension study. Study drug was taken once daily.
Ambrisentan Combined Group	All dose groups combined.

Measured Values

	Ambrisentan 2.5 mg	Ambrisentan 5 mg	Ambrisentan 10 mg	Ambrisentan Combined Group
Number of Participants Analyzed	96	190	97	383
Percentage of Participants With Failure-Free Treatment Status [units: percent probability (KM estimate)] Number (95% Confidence Interval)				
No treatment failure after 1 year of treatment	86.8 (77.9 to 92.3)	89.0 (83.3 to 92.9)	90.1 (81.8 to 94.7)	88.7 (85.0 to 91.6)
No treatment failure after 2 years of treatment	77.6 (67.4 to 84.9)	79.8 (72.8 to 85.1)	81.4 (71.4 to 88.2)	79.6 (75.0 to 83.5)
No treatment failure after 3 years of treatment	69.1 (58.3 to 77.7)	73.8 (66.2 to 80.0)	67.9 (55.5 to 77.6)	71.3 (65.9 to 76.0)
No treatment failure after 4 years of treatment	60.8 (49.4 to 70.5)	69.0 (60.3 to 76.2)	63.2 (49.9 to 73.9)	66.4 (59.0 to 70.4)

22. Secondary Outcome Measure:

Measure Title	Long-term Survival
Measure Description	Long-term survival was defined as the time from initiation of active treatment to death. Results are presented as the Kaplan-Meier estimate (% probability) of survival after a given time.
Time Frame	Baseline to Year 4
Safety Issue?	No

Analysis Population Description

All assessments of efficacy were performed using the randomized analysis set, such that subjects were allotted to an individual dose group based upon their randomized treatment assignment in the 2 prior studies (NCT00423748 or NCT00423202) or in the current extension study.

Reporting Groups

	Description
Ambrisentan 2.5 mg	Participants were classified based on their randomized dose of AMB in the 2 prior studies (NCT00423748 or NCT00423202) or in the current extension study. Study drug was taken once daily.
Ambrisentan 5 mg	Participants were classified based on their randomized dose of AMB in the 2 prior studies (NCT00423748 or NCT00423202) or in the current extension study. Study drug was taken once daily.
Ambrisentan 10 mg	Participants were classified based on their randomized dose of AMB in the 2 prior studies (NCT00423748 or NCT00423202) or in the current extension study. Study drug was taken once daily.
Ambrisentan Combined Group	All dose groups combined.

Measured Values

	Ambrisentan 2.5 mg	Ambrisentan 5 mg	Ambrisentan 10 mg	Ambrisentan Combined Group
Number of Participants Analyzed	96	190	97	383
Long-term Survival [units: percent probability (KM estimate)] Number (95% Confidence Interval)				
Survival after 1 year of treatment	96.8 (90.4 to 99.0)	93.1 (88.1 to 96.0)	94.5 (87.2 to 97.7)	94.4 (91.4 to 96.3)
Survival after 2 years of treatment	84.7 (75.1 to 90.8)	87.3 (81.2 to 91.6)	90.7 (82.3 to 95.3)	87.5 (83.5 to 90.6)
Survival after 3 years of treatment	78.4 (67.9 to 85.8)	84.2 (77.4 to 89.1)	82.7 (71.7 to 89.7)	82.2 (77.5 to 86.1)
Survival After 4 Years of Treatment	71.1 (59.6 to 79.9)	78.1 (69.5 to 84.6)	82.7 (71.7 to 89.7)	76.5 (70.7 to 81.3)

Reported Adverse Events

Time Frame	Serious adverse event data collected through 288 weeks are presented.
Additional Description	For the safety population, subjects were classified based on the highest dose of ambrisentan received at any time during the 2 prior studies (NCT00423748 or NCT00423202) or in the current extension study.

Reporting Groups

	Description
Ambrisentan 2.5 mg	Participants were classified based on the highest dose of ambrisentan received at any time during the 2 prior studies (NCT00423748 or NCT00423202) or in the current extension study. Study drug was taken once daily.

	Description
Ambrisentan 5 mg	Participants were classified based on the highest dose of ambrisentan received at any time during the 2 prior studies (NCT00423748 or NCT00423202) or in the current extension study. Study drug was taken once daily.
Ambrisentan 10 mg	Participants were classified based on the highest dose of ambrisentan received at any time during the 2 prior studies (NCT00423748 or NCT00423202) or in the current extension study. Study drug was taken once daily.

Serious Adverse Events

	Ambrisentan 2.5 mg		Ambrisentan 5 mg		Ambrisentan 10 mg	
	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events
Total	26/43 (60.47%)		76/146 (52.05%)		103/194 (53.09%)	
Blood and lymphatic system disorders						
Anaemia [A] †	0/43 (0%)	0	2/146 (1.37%)	2	3/194 (1.55%)	3
Bone marrow depression [A] †	0/43 (0%)	0	1/146 (0.68%)	1	0/194 (0%)	0
Iron deficiency anaemia [A] †	0/43 (0%)	0	0/146 (0%)	0	2/194 (1.03%)	2
Lymphadenopathy [A] †	0/43 (0%)	0	0/146 (0%)	0	2/194 (1.03%)	2
Microcytic anaemia [A] †	0/43 (0%)	0	0/146 (0%)	0	1/194 (0.52%)	1
Thrombocytopenia [A] †	0/43 (0%)	0	0/146 (0%)	0	1/194 (0.52%)	1
Cardiac disorders						
AV dissociation [A] †	1/43 (2.33%)	1	0/146 (0%)	0	0/194 (0%)	0
Acute coronary syndrome [A] †	1/43 (2.33%)	1	0/146 (0%)	0	0/194 (0%)	0
Acute myocardial infarction [A] †	0/43 (0%)	0	0/146 (0%)	0	1/194 (0.52%)	1
Angina pectoris [A] †	1/43 (2.33%)	1	2/146 (1.37%)	2	2/194 (1.03%)	2
Arrhythmia supraventricular [A] †	0/43 (0%)	0	0/146 (0%)	0	1/194 (0.52%)	1
Atrial fibrillation [A] †	1/43 (2.33%)	1	4/146 (2.74%)	4	2/194 (1.03%)	2
Atrial flutter [A] †	0/43 (0%)	0	1/146 (0.68%)	1	2/194 (1.03%)	2
Atrial tachycardia [A] †	0/43 (0%)	0	1/146 (0.68%)	1	0/194 (0%)	0

	Ambrisentan 2.5 mg		Ambrisentan 5 mg		Ambrisentan 10 mg	
	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events
Cardiac arrest [A] †	1/43 (2.33%)	1	1/146 (0.68%)	1	2/194 (1.03%)	2
Cardiac failure congestive [A] †	0/43 (0%)	0	0/146 (0%)	0	1/194 (0.52%)	1
Cardio-respiratory arrest [A] †	0/43 (0%)	0	0/146 (0%)	0	1/194 (0.52%)	1
Cardiogenic shock [A] †	0/43 (0%)	0	1/146 (0.68%)	1	0/194 (0%)	0
Cor pulmonale [A] †	0/43 (0%)	0	0/146 (0%)	0	1/194 (0.52%)	1
Diastolic dysfunction [A] †	0/43 (0%)	0	0/146 (0%)	0	1/194 (0.52%)	1
Left ventricular failure [A] †	0/43 (0%)	0	0/146 (0%)	0	2/194 (1.03%)	2
Myocardial infarction [A] †	0/43 (0%)	0	1/146 (0.68%)	1	1/194 (0.52%)	1
Pericardial effusion [A] †	0/43 (0%)	0	1/146 (0.68%)	1	0/194 (0%)	0
Right ventricular failure [A] †	6/43 (13.95%)	6	14/146 (9.59%)	18	34/194 (17.53%)	55
Supraventricular tachycardia [A] †	1/43 (2.33%)	1	0/146 (0%)	0	3/194 (1.55%)	5
Tachyarrhthmia [A] †	1/43 (2.33%)	1	0/146 (0%)	0	0/194 (0%)	0
Tachycardia [A] †	0/43 (0%)	0	0/146 (0%)	0	1/194 (0.52%)	1
Ventricular fibrillation [A] †	0/43 (0%)	0	1/146 (0.68%)	1	0/194 (0%)	0
Congenital, familial and genetic disorders						
Dermoid cyst of ovary [A] †	0/43 (0%)	0	1/146 (0.68%)	1	0/194 (0%)	0
Eye disorders						
Cataract [A] †	0/43 (0%)	0	1/146 (0.68%)	1	1/194 (0.52%)	1
Gastrointestinal disorders						
Abdominal distension [A] †	0/43 (0%)	0	0/146 (0%)	0	1/194 (0.52%)	1
Abdominal pain [A] †	0/43 (0%)	0	1/146 (0.68%)	1	1/194 (0.52%)	1
Abdominal pain upper [A] †	1/43 (2.33%)	1	0/146 (0%)	0	1/194 (0.52%)	1

	Ambrisentan 2.5 mg		Ambrisentan 5 mg		Ambrisentan 10 mg	
	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events
Colonic polyp [A] †	0/43 (0%)	0	0/146 (0%)	0	1/194 (0.52%)	1
Diverticulum [A] †	0/43 (0%)	0	1/146 (0.68%)	1	0/194 (0%)	0
Duodenal ulcer haemorrhage [A] †	0/43 (0%)	0	1/146 (0.68%)	1	0/194 (0%)	0
Enteritis [A] †	0/43 (0%)	0	1/146 (0.68%)	1	0/194 (0%)	0
Gastric haemorrhage [A] †	0/43 (0%)	0	1/146 (0.68%)	1	0/194 (0%)	0
Gastrointestinal haemorrhage [A] †	1/43 (2.33%)	1	2/146 (1.37%)	2	1/194 (0.52%)	1
Hypoaesthesia oral [A] †	0/43 (0%)	0	0/146 (0%)	0	1/194 (0.52%)	1
Inguinal hernia [A] †	0/43 (0%)	0	0/146 (0%)	0	1/194 (0.52%)	1
Intestinal functional disorder [A] †	0/43 (0%)	0	1/146 (0.68%)	1	0/194 (0%)	0
Mesenteric occlusion [A] †	0/43 (0%)	0	0/146 (0%)	0	1/194 (0.52%)	1
Oesophageal perforation [A] †	0/43 (0%)	0	1/146 (0.68%)	1	0/194 (0%)	0
Parotid gland enlargement [A] †	0/43 (0%)	0	0/146 (0%)	0	1/194 (0.52%)	1
Peritoneal hemorrhage [A] †	0/43 (0%)	0	0/146 (0%)	0	1/194 (0.52%)	1
Rectal haemorrhage [A] †	0/43 (0%)	0	1/146 (0.68%)	1	0/194 (0%)	0
Retroperitoneal haemorrhage [A] †	0/43 (0%)	0	0/146 (0%)	0	2/194 (1.03%)	2
General disorders						
Catheter related complication [A] †	0/43 (0%)	0	0/146 (0%)	0	1/194 (0.52%)	1
Chest discomfort [A] †	0/43 (0%)	0	0/146 (0%)	0	1/194 (0.52%)	1
Chest pain [A] †	0/43 (0%)	0	0/146 (0%)	0	2/194 (1.03%)	2
Microlithiasis [A] †	0/43 (0%)	0	1/146 (0.68%)	1	0/194 (0%)	0
Multi-organ failure [A] †	0/43 (0%)	0	2/146 (1.37%)	2	1/194 (0.52%)	1
Noncardiac chest pain [A] †	0/43 (0%)	0	1/146 (0.68%)	1	4/194 (2.06%)	5

	Ambrisentan 2.5 mg		Ambrisentan 5 mg		Ambrisentan 10 mg	
	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events
Oedema peripheral [A] †	1/43 (2.33%)	1	0/146 (0%)	0	2/194 (1.03%)	2
Pyrexia [A] †	0/43 (0%)	0	1/146 (0.68%)	1	1/194 (0.52%)	1
Sudden death [A] †	0/43 (0%)	0	2/146 (1.37%)	2	1/194 (0.52%)	1
Hepatobiliary disorders						
Cholecystitis acute [A] †	0/43 (0%)	0	2/146 (1.37%)	4	1/194 (0.52%)	1
Cholelithiasis [A] †	0/43 (0%)	0	0/146 (0%)	0	4/194 (2.06%)	4
Immune system disorders						
Drug hypersensitivity [A] †	0/43 (0%)	0	0/146 (0%)	0	1/194 (0.52%)	3
Infections and infestations						
Abdominal infection [A] †	0/43 (0%)	0	0/146 (0%)	0	1/194 (0.52%)	1
Arthritis bacterial [A] †	0/43 (0%)	0	1/146 (0.68%)	1	0/194 (0%)	0
Bone infection [A] †	0/43 (0%)	0	1/146 (0.68%)	1	0/194 (0%)	0
Bronchitis [A] †	0/43 (0%)	0	2/146 (1.37%)	3	1/194 (0.52%)	1
Bronchitis acute [A] †	1/43 (2.33%)	1	1/146 (0.68%)	2	0/194 (0%)	0
Bronchopneumonia [A] †	0/43 (0%)	0	0/146 (0%)	0	3/194 (1.55%)	3
Cellulitis [A] †	0/43 (0%)	0	0/146 (0%)	0	2/194 (1.03%)	2
Cytomegalovirus colitis [A] †	0/43 (0%)	0	0/146 (0%)	0	1/194 (0.52%)	1
Escherichia urinary tract infection [A] †	0/43 (0%)	0	1/146 (0.68%)	1	0/194 (0%)	0
Gastroenteritis [A] †	0/43 (0%)	0	1/146 (0.68%)	1	0/194 (0%)	0
Gastrointestinal infection [A] †	1/43 (2.33%)	1	0/146 (0%)	0	0/194 (0%)	0
Haemophilus infection [A] †	0/43 (0%)	0	0/146 (0%)	0	1/194 (0.52%)	1
Lower respiratory tract infection [A] †	0/43 (0%)	0	0/146 (0%)	0	2/194 (1.03%)	3

	Ambrisentan 2.5 mg		Ambrisentan 5 mg		Ambrisentan 10 mg	
	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events
Lung infection [A] †	0/43 (0%)	0	0/146 (0%)	0	1/194 (0.52%)	1
Meningitis tuberculosis [A] †	0/43 (0%)	0	1/146 (0.68%)	1	0/194 (0%)	0
Oral candidiasis [A] †	0/43 (0%)	0	0/146 (0%)	0	1/194 (0.52%)	1
Pneumonia [A] †	1/43 (2.33%)	1	5/146 (3.42%)	6	9/194 (4.64%)	13
Postoperative infection [A] †	1/43 (2.33%)	1	0/146 (0%)	0	0/194 (0%)	0
Pyelonephritis [A] †	0/43 (0%)	0	1/146 (0.68%)	1	0/194 (0%)	0
Respiratory tract infection [A] †	0/43 (0%)	0	0/146 (0%)	0	3/194 (1.55%)	3
Respiratory tract infection bacterial [A] †	0/43 (0%)	0	0/146 (0%)	0	1/194 (0.52%)	1
Respiratory tract infection viral [A] †	0/43 (0%)	0	0/146 (0%)	0	1/194 (0.52%)	1
Sepsis [A] †	0/43 (0%)	0	2/146 (1.37%)	2	0/194 (0%)	0
Septic shock [A] †	0/43 (0%)	0	0/146 (0%)	0	1/194 (0.52%)	1
Sinusitis [A] †	0/43 (0%)	0	0/146 (0%)	0	2/194 (1.03%)	2
Streptococcal sepsis [A] †	0/43 (0%)	0	1/146 (0.68%)	1	0/194 (0%)	0
Tracheobronchitis [A] †	0/43 (0%)	0	0/146 (0%)	0	1/194 (0.52%)	2
Upper respiratory tract infection [A] †	0/43 (0%)	0	0/146 (0%)	0	1/194 (0.52%)	1
Urinary tract infection [A] †	0/43 (0%)	0	1/146 (0.68%)	1	2/194 (1.03%)	2
Injury, poisoning and procedural complications						
Accidental overdose [A] †	0/43 (0%)	0	1/146 (0.68%)	1	1/194 (0.52%)	1
Chest injury [A] †	0/43 (0%)	0	0/146 (0%)	0	1/194 (0.52%)	2
Fall [A] †	0/43 (0%)	0	0/146 (0%)	0	1/194 (0.52%)	2
Femoral neck fracture [A] †	0/43 (0%)	0	0/146 (0%)	0	1/194 (0.52%)	1
Femur fracture [A] †	0/43 (0%)	0	1/146 (0.68%)	1	0/194 (0%)	0

	Ambrisentan 2.5 mg		Ambrisentan 5 mg		Ambrisentan 10 mg	
	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events
Fractured coccyx [A] †	0/43 (0%)	0	0/146 (0%)	0	1/194 (0.52%)	1
Haemothorax [A] †	0/43 (0%)	0	0/146 (0%)	0	1/194 (0.52%)	1
Ligament injury [A] †	0/43 (0%)	0	1/146 (0.68%)	1	0/194 (0%)	0
Muscle strain [A] †	0/43 (0%)	0	1/146 (0.68%)	1	0/194 (0%)	0
Pacemaker complication [A] †	0/43 (0%)	0	1/146 (0.68%)	1	0/194 (0%)	0
Polytraumatism [A] †	0/43 (0%)	0	1/146 (0.68%)	1	0/194 (0%)	0
Post procedural haemorrhage [A] †	0/43 (0%)	0	1/146 (0.68%)	1	1/194 (0.52%)	1
Subdural haematoma [A] †	1/43 (2.33%)	1	1/146 (0.68%)	2	2/194 (1.03%)	2
Tendon rupture [A] †	0/43 (0%)	0	0/146 (0%)	0	1/194 (0.52%)	1
Investigations						
Alanine aminotransferase increased [A] †	0/43 (0%)	0	3/146 (2.05%)	3	1/194 (0.52%)	1
Aspartate aminotransferase increased [A] †	0/43 (0%)	0	2/146 (1.37%)	2	0/194 (0%)	0
Exercise capacity descreased [A] †	0/43 (0%)	0	0/146 (0%)	0	1/194 (0.52%)	1
Hepatic enzyme increased [A] †	0/43 (0%)	0	0/146 (0%)	0	1/194 (0.52%)	1
Hysteroscopy [A] †	0/43 (0%)	0	0/146 (0%)	0	1/194 (0.52%)	1
Liver function test abnormal [A] †	0/43 (0%)	0	0/146 (0%)	0	1/194 (0.52%)	1
Platelet count decreased [A] †	0/43 (0%)	0	0/146 (0%)	0	1/194 (0.52%)	1
Metabolism and nutrition disorders						
Dehydration [A] †	0/43 (0%)	0	1/146 (0.68%)	1	1/194 (0.52%)	1
Diabetes mellitus [A] †	0/43 (0%)	0	0/146 (0%)	0	1/194 (0.52%)	1
Fluid overload [A] †	0/43 (0%)	0	0/146 (0%)	0	3/194 (1.55%)	3
Hyperglycaemia [A] †	0/43 (0%)	0	1/146 (0.68%)	1	1/194 (0.52%)	1

	Ambrisentan 2.5 mg		Ambrisentan 5 mg		Ambrisentan 10 mg	
	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events
Hypoglycaemia [A] †	1/43 (2.33%)	1	0/146 (0%)	0	0/194 (0%)	0
Hypokalaemia [A] †	0/43 (0%)	0	0/146 (0%)	0	1/194 (0.52%)	1
Hyponatraemia [A] †	1/43 (2.33%)	1	0/146 (0%)	0	1/194 (0.52%)	1
Musculoskeletal and connective tissue disorders						
Arthralgia [A] †	1/43 (2.33%)	1	0/146 (0%)	0	0/194 (0%)	0
Back pain [A] †	0/43 (0%)	0	0/146 (0%)	0	2/194 (1.03%)	2
CREST syndrome [A] †	0/43 (0%)	0	0/146 (0%)	0	1/194 (0.52%)	1
Connective tissue disorder [A] †	0/43 (0%)	0	1/146 (0.68%)	1	1/194 (0.52%)	1
Joint swelling [A] †	0/43 (0%)	0	1/146 (0.68%)	1	0/194 (0%)	0
Localised osteoarthritis [A] †	0/43 (0%)	0	1/146 (0.68%)	2	1/194 (0.52%)	1
Pain in extremity [A] †	0/43 (0%)	0	1/146 (0.68%)	1	0/194 (0%)	0
Polymyositis [A] †	1/43 (2.33%)	1	0/146 (0%)	0	0/194 (0%)	0
Scleroderma [A] †	0/43 (0%)	0	0/146 (0%)	0	2/194 (1.03%)	2
Systemic lupus erythematosus [A] †	0/43 (0%)	0	3/146 (2.05%)	5	1/194 (0.52%)	1
Systemic sclerosis [A] †	1/43 (2.33%)	1	1/146 (0.68%)	3	2/194 (1.03%)	2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)						
Breast cancer [A] †	0/43 (0%)	0	1/146 (0.68%)	2	0/194 (0%)	0
Breast cancer metastatic [A] †	0/43 (0%)	0	0/146 (0%)	0	1/194 (0.52%)	1
Colon neoplasm [A] †	0/43 (0%)	0	1/146 (0.68%)	1	0/194 (0%)	0
Endometrial cancer metastatic [A] †	0/43 (0%)	0	0/146 (0%)	0	1/194 (0.52%)	1
Fibroadenoma of the breast [A] †	0/43 (0%)	0	0/146 (0%)	0	1/194 (0.52%)	1
Gastric cancer [A] †	0/43 (0%)	0	1/146 (0.68%)	1	0/194 (0%)	0

	Ambrisentan 2.5 mg		Ambrisentan 5 mg		Ambrisentan 10 mg	
	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events
Hepatic cancer metastatic [A] †	0/43 (0%)	0	1/146 (0.68%)	1	1/194 (0.52%)	1
Insulinoma [A] †	0/43 (0%)	0	0/146 (0%)	0	1/194 (0.52%)	1
Malignant soft tissue neoplasm [A] †	0/43 (0%)	0	0/146 (0%)	0	1/194 (0.52%)	1
Metastases to bone marrow [A] †	0/43 (0%)	0	0/146 (0%)	0	1/194 (0.52%)	1
Metastases to central nervous system [A] †	0/43 (0%)	0	0/146 (0%)	0	1/194 (0.52%)	1
Metastases to liver [A] †	0/43 (0%)	0	0/146 (0%)	0	1/194 (0.52%)	1
Metastases to lung [A] †	0/43 (0%)	0	0/146 (0%)	0	1/194 (0.52%)	1
Multiple myeloma [A] †	0/43 (0%)	0	1/146 (0.68%)	1	0/194 (0%)	0
Rectal cancer [A] †	0/43 (0%)	0	1/146 (0.68%)	1	0/194 (0%)	0
Squamous cell carcinoma [A] †	0/43 (0%)	0	0/146 (0%)	0	1/194 (0.52%)	1
Nervous system disorders						
Cerebral haemorrhage [A] †	0/43 (0%)	0	1/146 (0.68%)	1	0/194 (0%)	0
Cervicobrachial syndrome [A] †	0/43 (0%)	0	1/146 (0.68%)	1	0/194 (0%)	0
Convulsion [A] †	0/43 (0%)	0	0/146 (0%)	0	1/194 (0.52%)	1
Dizziness [A] †	0/43 (0%)	0	0/146 (0%)	0	1/194 (0.52%)	1
Encephalitis [A] †	0/43 (0%)	0	1/146 (0.68%)	1	0/194 (0%)	0
Haemorrhage intracranial [A] †	0/43 (0%)	0	0/146 (0%)	0	2/194 (1.03%)	2
Headache [A] †	0/43 (0%)	0	0/146 (0%)	0	1/194 (0.52%)	1
Hypertensive encephalopathy [A] †	0/43 (0%)	0	0/146 (0%)	0	1/194 (0.52%)	1
Hypoglycaemic coma [A] †	0/43 (0%)	0	1/146 (0.68%)	1	0/194 (0%)	0
Paraesthesia [A] †	0/43 (0%)	0	0/146 (0%)	0	1/194 (0.52%)	1
Syncope [A] †	3/43 (6.98%)	3	3/146 (2.05%)	3	5/194 (2.58%)	5

	Ambrisentan 2.5 mg		Ambrisentan 5 mg		Ambrisentan 10 mg	
	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events
Syncope vasovagal [A] †	0/43 (0%)	0	0/146 (0%)	0	1/194 (0.52%)	1
Pregnancy, puerperium and perinatal conditions						
Pregnancy [A] †	0/43 (0%)	0	5/146 (3.42%)	5	2/194 (1.03%)	2
Psychiatric disorders						
Anxiety [A] †	0/43 (0%)	0	0/146 (0%)	0	1/194 (0.52%)	1
Depressed mood [A] †	0/43 (0%)	0	0/146 (0%)	0	1/194 (0.52%)	1
Depression [A] †	0/43 (0%)	0	1/146 (0.68%)	1	1/194 (0.52%)	2
Neurosis [A] †	1/43 (2.33%)	1	0/146 (0%)	0	0/194 (0%)	0
Panic attack [A] †	0/43 (0%)	0	1/146 (0.68%)	1	0/194 (0%)	0
Panic reaction [A] †	0/43 (0%)	0	1/146 (0.68%)	1	0/194 (0%)	0
Suicide attempt [A] †	0/43 (0%)	0	0/146 (0%)	0	1/194 (0.52%)	1
Renal and urinary disorders						
Haematuria [A] †	0/43 (0%)	0	0/146 (0%)	0	1/194 (0.52%)	1
Lupus nephritis [A] †	0/43 (0%)	0	1/146 (0.68%)	1	0/194 (0%)	0
Nephrolithiasis [A] †	0/43 (0%)	0	1/146 (0.68%)	1	0/194 (0%)	0
Oliguria [A] †	0/43 (0%)	0	0/146 (0%)	0	1/194 (0.52%)	1
Renal Failure Acute [A] †	0/43 (0%)	0	3/146 (2.05%)	3	1/194 (0.52%)	1
Renal impairment [A] †	0/43 (0%)	0	1/146 (0.68%)	1	0/194 (0%)	0
Renal insufficiency [A] †	0/43 (0%)	0	2/146 (1.37%)	2	2/194 (1.03%)	2
Urinary tract disorder [A] †	0/43 (0%)	0	0/146 (0%)	0	1/194 (0.52%)	1
Reproductive system and breast disorders						
Dysfunctional uterine bleeding [A] †	0/43 (0%)	0	0/146 (0%)	0	1/194 (0.52%)	1

	Ambrisentan 2.5 mg		Ambrisentan 5 mg		Ambrisentan 10 mg	
	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events
Menorrhagia [A] †	0/43 (0%)	0	1/146 (0.68%)	1	1/194 (0.52%)	1
Metrorrhagia [A] †	0/43 (0%)	0	2/146 (1.37%)	2	0/194 (0%)	0
Ovarian cyst [A] †	1/43 (2.33%)	1	0/146 (0%)	0	1/194 (0.52%)	1
Ovarian cyst ruptured [A] †	1/43 (2.33%)	1	0/146 (0%)	0	0/194 (0%)	0
Vaginal haemorrhage [A] †	0/43 (0%)	0	0/146 (0%)	0	1/194 (0.52%)	1
Respiratory, thoracic and mediastinal disorders						
Acute respiratory failure [A] †	0/43 (0%)	0	3/146 (2.05%)	3	2/194 (1.03%)	2
Aspiration [A] †	0/43 (0%)	0	0/146 (0%)	0	1/194 (0.52%)	1
Asthma [A] †	1/43 (2.33%)	1	0/146 (0%)	0	1/194 (0.52%)	1
Dyspnoea [A] †	0/43 (0%)	0	2/146 (1.37%)	3	2/194 (1.03%)	3
Dyspnoea at rest [A] †	0/43 (0%)	0	0/146 (0%)	0	1/194 (0.52%)	1
Dyspnoea exacerbated [A] †	2/43 (4.65%)	2	1/146 (0.68%)	1	4/194 (2.06%)	4
Haemoptysis [A] †	0/43 (0%)	0	1/146 (0.68%)	1	2/194 (1.03%)	2
Hydrothorax [A] †	0/43 (0%)	0	0/146 (0%)	0	1/194 (0.52%)	1
Hypoxia [A] †	0/43 (0%)	0	1/146 (0.68%)	1	6/194 (3.09%)	8
Interstitial lung disease [A] †	0/43 (0%)	0	0/146 (0%)	0	1/194 (0.52%)	1
Pleural effusion [A] †	0/43 (0%)	0	1/146 (0.68%)	1	3/194 (1.55%)	7
Pleuritic pain [A] †	0/43 (0%)	0	1/146 (0.68%)	1	0/194 (0%)	0
Pneumomediastinum [A] †	0/43 (0%)	0	1/146 (0.68%)	1	0/194 (0%)	0
Pneumonia aspiration [A] †	0/43 (0%)	0	1/146 (0.68%)	1	1/194 (0.52%)	1
Pneumonitis [A] †	0/43 (0%)	0	2/146 (1.37%)	2	0/194 (0%)	0
Pulmonary alveolar haemorrhage [A] †	0/43 (0%)	0	1/146 (0.68%)	1	1/194 (0.52%)	1

	Ambrisentan 2.5 mg		Ambrisentan 5 mg		Ambrisentan 10 mg	
	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events
Pulmonary embolism [A] †	1/43 (2.33%)	1	1/146 (0.68%)	1	1/194 (0.52%)	1
Pulmonary fibrosis [A] †	0/43 (0%)	0	0/146 (0%)	0	1/194 (0.52%)	1
Pulmonary haemorrhage [A] †	0/43 (0%)	0	0/146 (0%)	0	1/194 (0.52%)	1
Pulmonary hypertension [A] †	7/43 (16.28%)	8	10/146 (6.85%)	12	33/194 (17.01%)	48
Respiratory arrest [A] †	1/43 (2.33%)	1	1/146 (0.68%)	1	1/194 (0.52%)	1
Respiratory failure [A] †	1/43 (2.33%)	1	3/146 (2.05%)	3	2/194 (1.03%)	2
Skin and subcutaneous tissue disorders						
Diabetic ulcer [A] †	0/43 (0%)	0	0/146 (0%)	0	1/194 (0.52%)	1
Stevens Johnson syndrome [A] †	0/43 (0%)	0	0/146 (0%)	0	1/194 (0.52%)	1
Toxic skin eruption [A] †	0/43 (0%)	0	0/146 (0%)	0	1/194 (0.52%)	1
Surgical and medical procedures						
Heart and lung transplant [A] †	1/43 (2.33%)	1	0/146 (0%)	0	0/194 (0%)	0
Therapy regimen changed [A] †	0/43 (0%)	0	1/146 (0.68%)	1	2/194 (1.03%)	2
Vascular disorders						
Aortic stenosis [A] †	0/43 (0%)	0	1/146 (0.68%)	1	0/194 (0%)	0
Deep vein thrombosis [A] †	0/43 (0%)	0	0/146 (0%)	0	1/194 (0.52%)	1
Hypertensive crisis [A] †	0/43 (0%)	0	0/146 (0%)	0	1/194 (0.52%)	1
Hypotension [A] †	0/43 (0%)	0	0/146 (0%)	0	1/194 (0.52%)	1
Hypovolaemic shock [A] †	0/43 (0%)	0	1/146 (0.68%)	1	0/194 (0%)	0

† Indicates events were collected by systematic assessment.
A Term from vocabulary, MedDRA (6.1)

Other Adverse Events

Frequency Threshold Above Which Other Adverse Events are Reported: 5%

	Ambrisentan 2.5 mg		Ambrisentan 5 mg		Ambrisentan 10 mg	
	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events
Total	36/43 (83.72%)		131/146 (89.73%)		190/194 (97.94%)	
Blood and lymphatic system disorders						
Anaemia [A] †	6/43 (13.95%)		19/146 (13.01%)		26/194 (13.4%)	
Iron deficiency anaemia [A] †	2/43 (4.65%)		1/146 (0.68%)		12/194 (6.19%)	
Cardiac disorders						
Angina pectoris [A] †	1/43 (2.33%)		3/146 (2.05%)		12/194 (6.19%)	
Cyanosis [A] †	0/43 (0%)		1/146 (0.68%)		14/194 (7.22%)	
Palpitations [A] †	3/43 (6.98%)		12/146 (8.22%)		35/194 (18.04%)	
Right ventricular failure [A] †	4/43 (9.3%)		15/146 (10.27%)		20/194 (10.31%)	
Tachycardia [A] †	0/43 (0%)		3/146 (2.05%)		12/194 (6.19%)	
Ear and labyrinth disorders						
Vertigo [A] †	0/43 (0%)		5/146 (3.42%)		19/194 (9.79%)	
Gastrointestinal disorders						
Abdominal distension [A] †	0/43 (0%)		2/146 (1.37%)		15/194 (7.73%)	
Abdominal pain [A] †	2/43 (4.65%)		11/146 (7.53%)		16/194 (8.25%)	
Abdominal pain upper [A] †	2/43 (4.65%)		6/146 (4.11%)		21/194 (10.82%)	

	Ambrisentan 2.5 mg		Ambrisentan 5 mg		Ambrisentan 10 mg	
	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events
Constipation [A] †	0/43 (0%)		12/146 (8.22%)		21/194 (10.82%)	
Diarrhoea [A] †	3/43 (6.98%)		24/146 (16.44%)		33/194 (17.01%)	
Dyspepsia [A] †	1/43 (2.33%)		7/146 (4.79%)		14/194 (7.22%)	
Gastritis [A] †	1/43 (2.33%)		13/146 (8.9%)		7/194 (3.61%)	
Gastroesophageal reflux disease [A] †	0/43 (0%)		1/146 (0.68%)		12/194 (6.19%)	
Nausea [A] †	3/43 (6.98%)		12/146 (8.22%)		38/194 (19.59%)	
Vomiting [A] †	0/43 (0%)		7/146 (4.79%)		23/194 (11.86%)	
General disorders						
Asthenia [A] †	3/43 (6.98%)		8/146 (5.48%)		9/194 (4.64%)	
Chest discomfort [A] †	1/43 (2.33%)		2/146 (1.37%)		25/194 (12.89%)	
Chest pain [A] †	1/43 (2.33%)		6/146 (4.11%)		15/194 (7.73%)	
Fatigue [A] †	3/43 (6.98%)		14/146 (9.59%)		30/194 (15.46%)	
Non-cardiac chest pain [A] †	1/43 (2.33%)		10/146 (6.85%)		19/194 (9.79%)	
Oedema peripheal [A] †	13/43 (30.23%)		53/146 (36.3%)		101/194 (52.06%)	
Pyrexia [A] †	1/43 (2.33%)		11/146 (7.53%)		18/194 (9.28%)	
Hepatobiliary disorders						
Hepatomegaly [A] †	1/43 (2.33%)		7/146 (4.79%)		13/194 (6.7%)	
Infections and infestations						

	Ambrisentan 2.5 mg		Ambrisentan 5 mg		Ambrisentan 10 mg	
	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events
Bronchitis [A] †	3/43 (6.98%)		13/146 (8.9%)		17/194 (8.76%)	
Bronchitis acute [A] †	3/43 (6.98%)		4/146 (2.74%)		7/194 (3.61%)	
Influenza [A] †	5/43 (11.63%)		13/146 (8.9%)		22/194 (11.34%)	
Nasopharyngitis [A] †	2/43 (4.65%)		22/146 (15.07%)		34/194 (17.53%)	
Respiratory tract infection [A] †	2/43 (4.65%)		6/146 (4.11%)		24/194 (12.37%)	
Sinusitis [A] †	0/43 (0%)		15/146 (10.27%)		24/194 (12.37%)	
Upper respiratory tract infection [A] †	5/43 (11.63%)		17/146 (11.64%)		50/194 (25.77%)	
Urinary tract imfection [A] †	2/43 (4.65%)		7/146 (4.79%)		26/194 (13.4%)	
Injury, poisoning and procedural complications						
Contusion [A] †	0/43 (0%)		1/146 (0.68%)		13/194 (6.7%)	
Fall [A] †	0/43 (0%)		1/146 (0.68%)		11/194 (5.67%)	
Investigations						
Blood alkaline phosphatase increased [A] †	4/43 (9.3%)		3/146 (2.05%)		6/194 (3.09%)	
Cardiac murmur [A] †	2/43 (4.65%)		4/146 (2.74%)		10/194 (5.15%)	
Gamma-glutamyltransferase increased [A] †	4/43 (9.3%)		9/146 (6.16%)		13/194 (6.7%)	
Heart sounds abnormal [A] †	0/43 (0%)		4/146 (2.74%)		13/194 (6.7%)	
International normalised ratio increased [A] †	0/43 (0%)		7/146 (4.79%)		14/194 (7.22%)	
Metabolism and nutrition disorders						

	Ambrisentan 2.5 mg		Ambrisentan 5 mg		Ambrisentan 10 mg	
	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events
Fluid retention [A] †	0/43 (0%)		2/146 (1.37%)		10/194 (5.15%)	
Hypercholesterolaemia [A] †	2/43 (4.65%)		9/146 (6.16%)		11/194 (5.67%)	
Hypokalaemia [A] †	2/43 (4.65%)		13/146 (8.9%)		23/194 (11.86%)	
Musculoskeletal and connective tissue disorders						
Arthralgia [A] †	5/43 (11.63%)		18/146 (12.33%)		38/194 (19.59%)	
Back pain [A] †	1/43 (2.33%)		11/146 (7.53%)		36/194 (18.56%)	
Muscle cramp [A] †	1/43 (2.33%)		9/146 (6.16%)		14/194 (7.22%)	
Myalgia [A] †	1/43 (2.33%)		9/146 (6.16%)		18/194 (9.28%)	
Pain in extremity [A] †	3/43 (6.98%)		7/146 (4.79%)		36/194 (18.56%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)						
Neck pain [A] †	2/43 (4.65%)		3/146 (2.05%)		10/194 (5.15%)	
Nervous system disorders						
Dizziness [A] †	3/43 (6.98%)		15/146 (10.27%)		47/194 (24.23%)	
Headache [A] †	1/43 (2.33%)		34/146 (23.29%)		61/194 (31.44%)	
Paraesthesia [A] †	0/43 (0%)		2/146 (1.37%)		11/194 (5.67%)	
Syncope [A] †	2/43 (4.65%)		7/146 (4.79%)		19/194 (9.79%)	
Psychiatric disorders						

	Ambrisentan 2.5 mg		Ambrisentan 5 mg		Ambrisentan 10 mg	
	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events
Anxiety [A] †	1/43 (2.33%)		10/146 (6.85%)		17/194 (8.76%)	
Depression [A] †	1/43 (2.33%)		11/146 (7.53%)		25/194 (12.89%)	
Insomnia [A] †	2/43 (4.65%)		13/146 (8.9%)		23/194 (11.86%)	
Respiratory, thoracic and mediastinal disorders						
Abnormal chest sound [A] †	0/43 (0%)		1/146 (0.68%)		10/194 (5.15%)	
Cough [A] †	2/43 (4.65%)		26/146 (17.81%)		46/194 (23.71%)	
Crackles lung [A] †	0/43 (0%)		5/146 (3.42%)		16/194 (8.25%)	
Dyspnoea [A] †	3/43 (6.98%)		13/146 (8.9%)		29/194 (14.95%)	
Dyspnoea exacerbated [A] †	4/43 (9.3%)		19/146 (13.01%)		35/194 (18.04%)	
Dyspnoea exertional [A] †	0/43 (0%)		3/146 (2.05%)		17/194 (8.76%)	
Epistaxis [A] †	3/43 (6.98%)		9/146 (6.16%)		31/194 (15.98%)	
Hypoxia [A] †	0/43 (0%)		3/146 (2.05%)		10/194 (5.15%)	
Nasal congestion [A] †	1/43 (2.33%)		19/146 (13.01%)		28/194 (14.43%)	
Pharyngolaryngeal pain [A] †	0/43 (0%)		3/146 (2.05%)		15/194 (7.73%)	
Pulmonary hypertension [A] †	7/43 (16.28%)		12/146 (8.22%)		32/194 (16.49%)	
Rhinitis [A] †	2/43 (4.65%)		5/146 (3.42%)		12/194 (6.19%)	

	Ambrisentan 2.5 mg		Ambrisentan 5 mg		Ambrisentan 10 mg	
	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events
Skin and subcutaneous tissue disorders						
Pruritis [A] †	1/43 (2.33%)		3/146 (2.05%)		12/194 (6.19%)	
Rash [A] †	1/43 (2.33%)		5/146 (3.42%)		12/194 (6.19%)	
Vascular disorders						
Flushing [A] †	3/43 (6.98%)		9/146 (6.16%)		8/194 (4.12%)	
Hypotension [A] †	5/43 (11.63%)		8/146 (5.48%)		16/194 (8.25%)	
Jugular vein distension [A] †	0/43 (0%)		2/146 (1.37%)		17/194 (8.76%)	

† Indicates events were collected by systematic assessment.
A Term from vocabulary, MedDRA (6.1)

Limitations and Caveats

Analysis included those not enrolling in this study but received AMB in 1 of the 2 parent studies. At Year 3, almost half of those randomized to 2.5 mg were titrated to 5 mg and 10 mg; a third starting at 5 mg were titrated to 10 mg.

More Information

Certain Agreements:

Principal Investigators are NOT employed by the organization sponsoring the study.

There is NOT an agreement between the Principal Investigator and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed.

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