ClinicalTrials.gov Protocol and Results Registration System (PRS) Receipt
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Phase 2 Study of Ambrisentan for Liver Function Test Rescue in Pulmonary Arterial Hypertension

This study has been completed.

Sponsor:	Gilead Sciences
Collaborators:	
Information provided by (Responsible Party):	Gilead Sciences
ClinicalTrials.gov Identifier:	NCT00423592

Purpose

This Phase 2 study was to determine the incidence of increased serum aminotransferase concentrations (alanine aminotransferase [ALT] and/or aspartate aminotransferase [AST]), as well as the overall safety and tolerability of ambrisentan, in participants with pulmonary arterial hypertension (PAH), idiopathic PAH (IPAH), or familial PAH (FPAH) who had previously discontinued ERA therapy (bosentan or sitaxsentan) due to increased serum ALT or AST concentrations.

Condition	Intervention	Phase
Pulmonary Hypertension	Drug: ambrisentan	Phase 2

Study Type: Interventional
Study Design: Treatment, Single Group Assignment, Open Label, Non-Randomized, Safety/Efficacy Study
Official Title: A Phase 2, Open-label, Multicenter Study Evaluating Ambrisentan in Subjects With Pulmonary Arterial Hypertension Who Have Previously Discontinued Endothelin Receptor Antagonist Therapy Due to Serum Aminotransferase Abnormalities

Further study details as provided by Gilead Sciences:

Primary Outcome Measure:

- The Incidence of Confirmed Serum Alanine Aminotransferase (ALT) or Aspartate Aminotransferase (AST) Concentrations > 3 x the Upper Limit of Normal (ULN) Considered to be Related to Ambrisentan and Resulted in Discontinuation of Study Drug. [Time Frame: Week 12] [Designated as safety issue: Yes]

The number of participants in the safety analysis set with confirmed serum ALT or AST concentrations > 3 x ULN during 12 weeks of ambrisentan therapy that were related to ambrisentan and resulted in discontinuation of study drug. Safety analysis set included all participants who received at least 1 dose of study drug.

Secondary Outcome Measures:

- The Incidence of Confirmed Serum ALT or AST Concentrations > 5 x ULN That Were Related to Ambrisentan and Resulted in Discontinuation of Study Drug. [Time Frame: Week 12] [Designated as safety issue: Yes]
  The number of participants in the safety analysis set with confirmed serum ALT or AST concentrations > 5 x ULN during 12 weeks of ambrisentan therapy that were related to ambrisentan and resulted in discontinuation of drug. Safety analysis set included all participants who received at least 1 dose of study drug.
- The Incidence of Confirmed Serum ALT or AST Concentrations > 3 x ULN That Were Related to Ambrisentan and Resulted in Dose Reduction [Time Frame: Week 12] [Designated as safety issue: Yes]
  The number of participants in the safety analysis set with confirmed serum ALT or AST concentrations > 3 x ULN during 12 weeks of ambrisentan therapy that were related to ambrisentan and resulted in dose reduction. Safety analysis set included all participants who received at least 1 dose of study drug.
- A Change From Baseline Evaluated After 12 Weeks of Ambrisentan Therapy in the 6-Minute Walk Distance Test (6MWD) [Time Frame: Baseline to Week 12] [Designated as safety issue: No]
  The 6MWD test is a measure of exercise tolerance, and measures the distance an individual is able to walk over a total of six minutes on a hard, flat surface.
- A Change From Baseline Evaluated After 12 Weeks of Ambrisentan Therapy in Borg Dyspnea Index Immediately Following Exercise [Time Frame: Baseline to Week 12] [Designated as safety issue: No]
  Change from baseline evaluated after 12 weeks of ambrisentan therapy in Borg dyspnea index (measured as units on a scale) immediately following exercise. Borg Dyspnea Index, a measure of perceived shortness of breath: 0 units on a scale (none) to 10 units on a scale (maximum breathlessness).
- A Change From Baseline Evaluated After 12 Weeks of Ambrisentan Therapy in WHO Functional Class [Time Frame: Baseline to Week 12] [Designated as safety issue: No]
  Classes: I) pulmonary hypertension (PH); ordinary physical activity not limited or causes undue dyspnea or fatigue, chest pain, or near syncope. II) PH; ordinary physical activity slightly limited and causes undue dyspnea or fatigue, chest pain, or near syncope; comfortable at rest. III) PH; physical activity markedly limited and less than ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope; comfortable at rest. IV) PH; physical activity causes symptoms and increased discomfort; signs of right heart failure; dyspnea/fatigue possibly at rest.
- A Change From Baseline Evaluated After 12 Weeks of Ambrisentan Therapy in Short Form 36 (SF-36) Health Survey Scale - Composite Physical Health [Time Frame: Baseline to Week 12] [Designated as safety issue: No]
  The SF-36 Health Survey is a self-reporting, multi-item scale measuring 8 health concepts: 1) physical functioning, 2) role limitations due to physical health problems, 3) bodily pain, 4) general health, 5) vitality (energy/fatigue), 6) social functioning, 7) role limitations due to emotional problems and 8) mental health (psychological distress and psychological well-being). The first 6 concepts constitute the physical component summary. Each item is scored from 0 to 100 (least healthy to most healthy).
- Secondary Outcome: A Change From Baseline Evaluated After 12 Weeks of Ambrisentan Therapy in SF-36 Health Survey Scale - Composite Mental Health [Time Frame: Baseline to Week 12] [Designated as safety issue: No]
  The SF-36 Health Survey is a self-reporting, multi-item scale measuring 8 health concepts: 1) physical functioning, 2) role limitations due to physical health problems, 3) bodily pain, 4) general health, 5) vitality (energy/fatigue), 6) social functioning, 7) role limitations due to emotional problems and 8) mental health (psychological distress and psychological well-being). The last 5 concepts constitute the mental component summary. Each item is scored from 0 to 100 (least healthy to most healthy).
- Secondary Outcome: A Change From Baseline Evaluated After 12 Weeks of Ambrisentan Therapy in SF-36 Health Survey Scale - Physical Functioning [Time Frame: Baseline to Week 12] [Designated as safety issue: No]

The SF-36 Health Survey is a self-reporting, multi-item scale measuring 8 health concepts: 1) physical functioning, 2) role limitations due to physical health problems, 3) bodily pain, 4) general health, 5) vitality (energy/fatigue), 6) social functioning, 7) role limitations due to emotional problems and 8) mental health (psychological distress and psychological well-being). Each item is scored from 0 to 100 (least healthy to most healthy).

- Secondary Outcome: A Change From Baseline Evaluated After 12 Weeks of Ambrisentan Therapy in SF-36 Health Survey Scale - Role Physical [Time Frame: Baseline to Week 12] [Designated as safety issue: No]

  The SF-36 Health Survey is a self-reporting, multi-item scale measuring 8 health concepts: 1) physical functioning, 2) role limitations due to physical health problems, 3) bodily pain, 4) general health, 5) vitality (energy/fatigue), 6) social functioning, 7) role limitations due to emotional problems and 8) mental health (psychological distress and psychological well-being). Each item is scored from 0 to 100 (least healthy to most healthy).
- Secondary Outcome: A Change From Baseline Evaluated After 12 Weeks of Ambrisentan Therapy in SF-36 Health Survey Scale - Bodily Pain [Time Frame: Baseline to Week 12] [Designated as safety issue: No]

  The SF-36 Health Survey is a self-reporting, multi-item scale measuring 8 health concepts: 1) physical functioning, 2) role limitations due to physical health problems, 3) bodily pain, 4) general health, 5) vitality (energy/fatigue), 6) social functioning, 7) role limitations due to emotional problems and 8) mental health (psychological distress and psychological well-being). Each item is scored from 0 to 100 (least healthy to most healthy).
- Secondary Outcome: A Change From Baseline Evaluated After 12 Weeks of Ambrisentan Therapy in SF-36 Health Survey Scale - General Health [Time Frame: Baseline to Week 12] [Designated as safety issue: No]

  The SF-36 Health Survey is a self-reporting, multi-item scale measuring 8 health concepts: 1) physical functioning, 2) role limitations due to physical health problems, 3) bodily pain, 4) general health, 5) vitality (energy/fatigue), 6) social functioning, 7) role limitations due to emotional problems and 8) mental health (psychological distress and psychological well-being). Each item is scored from 0 to 100 (least healthy to most healthy).
- Secondary Outcome: A Change From Baseline Evaluated After 12 Weeks of Ambrisentan Therapy in SF-36 Health Survey Scale - Vitality [Time Frame: Baseline to Week 12] [Designated as safety issue: No]

  The SF-36 Health Survey is a self-reporting, multi-item scale measuring 8 health concepts: 1) physical functioning, 2) role limitations due to physical health problems, 3) bodily pain, 4) general health, 5) vitality (energy/fatigue), 6) social functioning, 7) role limitations due to emotional problems and 8) mental health (psychological distress and psychological well-being). Each item is scored from 0 to 100 (least healthy to most healthy).
- Secondary Outcome: A Change From Baseline Evaluated After 12 Weeks of Ambrisentan Therapy in SF-36 Health Survey Scale - Social Functioning [Time Frame: Baseline to Week 12] [Designated as safety issue: No]

  The SF-36 Health Survey is a self-reporting, multi-item scale measuring 8 health concepts: 1) physical functioning, 2) role limitations due to physical health problems, 3) bodily pain, 4) general health, 5) vitality (energy/fatigue), 6) social functioning, 7) role limitations due to emotional problems and 8) mental health (psychological distress and psychological well-being). Each item is scored from 0 to 100 (least healthy to most healthy).
- Secondary Outcome: A Change From Baseline Evaluated After 12 Weeks of Ambrisentan Therapy in SF-36 Health Survey Scale - Role Emotional [Time Frame: Baseline to Week 12] [Designated as safety issue: No]

  The SF-36 Health Survey is a self-reporting, multi-item scale measuring 8 health concepts: 1) physical functioning, 2) role limitations due to physical health problems, 3) bodily pain, 4) general health, 5) vitality (energy/fatigue), 6) social functioning, 7) role limitations due to emotional problems and 8) mental health (psychological distress and psychological well-being). Each item is scored from 0 to 100 (least healthy to most healthy).
- Secondary Outcome: A Change From Baseline Evaluated After 12 Weeks of Ambrisentan Therapy in SF-36 Health Survey Scale - Mental Health [Time Frame: Baseline to Week 12] [Designated as safety issue: No]

  The SF-36 Health Survey is a self-reporting, multi-item scale measuring 8 health concepts: 1) physical functioning, 2) role limitations due to physical health problems, 3) bodily pain, 4) general health, 5) vitality (energy/fatigue), 6) social functioning, 7) role limitations due to emotional problems and 8) mental health (psychological distress and psychological well-being). Each item is scored from 0 to 100 (least healthy to most healthy).

Enrollment: 36
Study Start Date: May 2005
Primary Completion Date: January 2006
Study Completion Date: March 2009

Number of arms: 1

Intervention Details:

Drug: ambrisentan

All eligible subjects received 2.5 mg ambrisentan once daily for a period of 4 weeks before increasing the dose to 5 mg once daily. After Week 24, investigators were allowed to adjust the dose of ambrisentan as clinically indicated (available doses were 2.5, 5, and 10 mg).

Eligibility

Ages Eligible for Study: 12 Years to 75 Years
Genders Eligible for Study: Both
Accepts Healthy Volunteers: No

Criteria

Summary of Inclusion Criteria:

- Males and Females between 12 and 75 years of age
- Current diagnosis of IPAH, FPAH, or PAH associated with collagen vascular disease, congenital systemic-to-pulmonary shunts, anorexigen use, HIV infection
- Must have previously discontinued bosentan or sitaxsentan therapy due to serum aminotransferase (ALT and/or AST) concentrations > 3 x ULN
- Must have normal (< 1 x ULN) serum ALT and AST concentrations at screening
- Six-minute Walk distance of at least 150 meters at screening
- If receiving sildenafil or a clinically approved prostanoid for PAH, must have been on stable therapy for at least 4 weeks prior to screening
- Subjects with a diagnosis of HIV must have stable disease status during the screening period

More Information

http://www.myogen.com

Responsible Party:	Gilead Sciences
Study ID Numbers:	AMB-222
Health Authority:	United States: Food and Drug Administration

Study Results

Participant Flow

Reporting Groups

	Description
Ambrisentan	All eligible subjects received 2.5 mg ambrisentan once daily for a period of 4 weeks before increasing the dose to 5 mg once daily. After Week 24, investigators were allowed to adjust the dose of ambrisentan as clinically indicated (available doses were 2.5, 5, and 10 mg).

Overall Study

	Ambrisentan
Started	36 [1]
Completed Preliminary Analysis Cut-off	34 [2]
Completed	29 [3]
Not Completed	7
Adverse Event (through Week 12)	2
Adverse Event (post Week 12)	5

[1] Enrolled
[2] Preliminary analysis cut-off at Week 12 for primary/secondary endpoint analysis
[3] Completed study

Baseline Characteristics

Reporting Groups

	Description
Ambrisentan	All eligible subjects received 2.5 mg ambrisentan once daily for a period of 4 weeks before increasing the dose to 5 mg once daily. After Week 24, investigators were allowed to adjust the dose of ambrisentan as clinically indicated (available doses were 2.5, 5, and 10 mg).

Baseline Measures

	Ambrisentan
Number of Participants	36
Age, Categorical [units: participants]	
<=18 years	0
Between 18 and 65 years	22
>=65 years	14
Age, Continuous [units: years] Mean (Standard Deviation)	57.2 (13.39)
Gender, Male/Female	

	Ambrisentan
[units: participants]	
Female	31
Male	5
Race/Ethnicity, Customized [units: participants]	
Caucasian	28
Black	2
Asian	2
Hispanic	3
Other	1
Region of Enrollment [units: participants]	
United States	26
Australia	5
Netherlands	3
Belgium	2
Pulmonary Arterial Hypertension Etiology [units: participants]	
Idiopathic pulmonary arterial hypertension	23
Familial pulmonary arterial hypertension	1
Associated pulmonary arterial hypertension	12
Pulmonary Arterial Hypertension Treatment [1] [units: participants]	
Ambrisentan only	11
Ambrisentan/sildenafil	12
Ambrisentan/prostanoid	8

	Ambrisentan
Ambrisentan/sildenafil/ prostanoid	5
World Health Organization (WHO) Functional Class [2] [units: participants]	
Class I	0
Class II	13
Class III	23
Class IV	0
Baseline 6-Minute Walk Distance [units: meters] Mean (Standard Deviation)	397.2 (104.59)
Body Mass Index [units: kg/m^2] Mean (Standard Deviation)	27.2 (5.44)
Borg dyspnea index [3] [units: units on a scale] Mean (Standard Deviation)	4.2 (2.31)
Cardiac index [4] [units: L/min/m^2] Mean (Standard Deviation)	2.7 (1.02)
Height [units: cm] Mean (Standard Deviation)	165.1 (7.22)
Mean pulmonary artery pressure [4] [units: mmHg] Mean (Standard Deviation)	48.4 (13.50)
Pulmonary arterial hypertension present [5] [units: year] Mean (Standard Deviation)	3.8 (4.99)
Pulmonary capillary wedge pressure [4] [units: mmHg] Mean (Standard Deviation)	10.1 (5.38)

	Ambrisentan
Pulmonary vascular resistance [4] [units: mmHg/L/min] Mean (Standard Deviation)	10.3 (5.75)
Right atrial pressure [4] [units: mmHg] Mean (Standard Deviation)	7.9 (5.29)
Weight [units: kg] Mean (Standard Deviation)	74.1 (15.36)

[1] Ambrisentan treatment was started on study Day 1. Concomitant sildenafil and prostanoids had to be stable for 4 weeks before screening.

[2] Classes: I) pulmonary hypertension (PH); ordinary physical activity not limited or causes undue dyspnea or fatigue, chest pain, or near syncope. II) PH; ordinary physical activity slightly limited and causes undue dyspnea or fatigue, chest pain, or near syncope; comfortable at rest. III) PH; physical activity markedly limited and less than ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope; comfortable at rest. IV) PH; physical activity causes symptoms and increased discomfort; signs of right heart failure; dyspnea/fatigue possibly at rest.

[3] Borg Dyspnea Index, a measure of perceived shortness of breath: 0 units on a scale (none) to 10 units on a scale (maximum breathlessness).

[4] Historical values from most recent catheterization.

[5] Duration (in years) of pulmonary arterial hypertension at baseline.

Outcome Measures

1. Primary Outcome Measure:

Measure Title	The Incidence of Confirmed Serum Alanine Aminotransferase (ALT) or Aspartate Aminotransferase (AST) Concentrations > 3 x the Upper Limit of Normal (ULN) Considered to be Related to Ambrisentan and Resulted in Discontinuation of Study Drug.
Measure Description	The number of participants in the safety analysis set with confirmed serum ALT or AST concentrations > 3 x ULN during 12 weeks of ambrisentan therapy that were related to ambrisentan and resulted in discontinuation of study drug. Safety analysis set included all participants who received at least 1 dose of study drug.
Time Frame	Week 12
Safety Issue?	Yes

Analysis Population Description

The Safety analysis set was defined as all subjects who received at least 1 dose of study drug. All subjects who received at least 1 dose of ambrisentan were followed (to the extent possible) to the end of the study and included in the analyses of safety.

Reporting Groups

	Description
Ambrisentan	All eligible subjects received 2.5 mg ambrisentan once daily for a period of 4 weeks before increasing the dose to 5 mg once daily. After Week 24, investigators were allowed to adjust the dose of ambrisentan as clinically indicated (available doses were 2.5, 5, and 10 mg).

Measured Values

	Ambrisentan
Number of Participants Analyzed	36
The Incidence of Confirmed Serum Alanine Aminotransferase (ALT) or Aspartate Aminotransferase (AST) Concentrations > 3 x the Upper Limit of Normal (ULN) Considered to be Related to Ambrisentan and Resulted in Discontinuation of Study Drug. [units: Participants]	0

Statistical Analysis 1 for The Incidence of Confirmed Serum Alanine Aminotransferase (ALT) or Aspartate Aminotransferase (AST) Concentrations > 3 x the Upper Limit of Normal (ULN) Considered to be Related to Ambrisentan and Resulted in Discontinuation of Study Drug.

Statistical Analysis Overview	Comparison Groups	Ambrisentan
	Comments	Sample size: 30 participants; 80% power to rule out 50% recurrence rate of serum ALT/ AST abnormalities following ambrisentan treatment (assumes 25% recurrence rate); 99% power to rule out 75% recurrence rate (assumes 37.5% recurrence rate). H_0 = proportion of subjects experiencing primary endpoint at 12% vs 1-sided alternative of < 12%. P-value from exact binomial test. Summary statistics included the estimated proportion, 95% confidence interval (CI), and the p-value of the hypothesis test.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.01
	Comments	[Not specified]
	Method	Other [Exact binomial test]
	Comments	A 1-sample test for a binomial proportion was performed.

Method of Estimation	Estimation Parameter	Other [Proportion]
	Estimated Value	0
	Confidence Interval	(2-Sided) 95% 0.0 to 9.7
	Parameter Dispersion	Type: Standard Deviation Value: 0.0
	Estimation Comments	[Not specified]

2. Secondary Outcome Measure:

Measure Title	The Incidence of Confirmed Serum ALT or AST Concentrations > 5 x ULN That Were Related to Ambrisentan and Resulted in Discontinuation of Study Drug.
Measure Description	The number of participants in the safety analysis set with confirmed serum ALT or AST concentrations > 5 x ULN during 12 weeks of ambrisentan therapy that were related to ambrisentan and resulted in discontinuation of drug. Safety analysis set included all participants who received at least 1 dose of study drug.
Time Frame	Week 12
Safety Issue?	Yes

Analysis Population Description

The Safety analysis set was defined as all subjects who received at least 1 dose of study drug. All subjects who received at least 1 dose of ambrisentan were followed (to the extent possible) to the end of the study and included in the analyses of safety.

Reporting Groups

	Description
Ambrisentan	All eligible subjects received 2.5 mg ambrisentan once daily for a period of 4 weeks before increasing the dose to 5 mg once daily. After Week 24, investigators were allowed to adjust the dose of ambrisentan as clinically indicated (available doses were 2.5, 5, and 10 mg).

Measured Values

	Ambrisentan
Number of Participants Analyzed	36
The Incidence of Confirmed Serum ALT or AST Concentrations > 5 x ULN That Were Related to Ambrisentan and Resulted in Discontinuation of Study Drug. [units: participants]	0

3. Secondary Outcome Measure:

Measure Title	The Incidence of Confirmed Serum ALT or AST Concentrations > 3 x ULN That Were Related to Ambrisentan and Resulted in Dose Reduction
Measure Description	The number of participants in the safety analysis set with confirmed serum ALT or AST concentrations > 3 x ULN during 12 weeks of ambrisentan therapy that were related to ambrisentan and resulted in dose reduction. Safety analysis set included all participants who received at least 1 dose of study drug.
Time Frame	Week 12
Safety Issue?	Yes

Analysis Population Description

The Safety analysis set was defined as all subjects who received at least 1 dose of study drug. All subjects who received at least 1 dose of ambrisentan were followed (to the extent possible) to the end of the study and included in the analyses of safety.

Reporting Groups

	Description
Ambrisentan	All eligible subjects received 2.5 mg ambrisentan once daily for a period of 4 weeks before increasing the dose to 5 mg once daily. After Week 24, investigators were allowed to adjust the dose of ambrisentan as clinically indicated (available doses were 2.5, 5, and 10 mg).

Measured Values

	Ambrisentan
Number of Participants Analyzed	36
The Incidence of Confirmed Serum ALT or AST Concentrations > 3 x ULN That Were Related to Ambrisentan and Resulted in Dose Reduction [units: participants]	0

4. Secondary Outcome Measure:

Measure Title	A Change From Baseline Evaluated After 12 Weeks of Ambrisentan Therapy in the 6-Minute Walk Distance Test (6MWD)
Measure Description	The 6MWD test is a measure of exercise tolerance, and measures the distance an individual is able to walk over a total of six minutes on a hard, flat surface.
Time Frame	Baseline to Week 12

Safety Issue?	No

Analysis Population Description

The Intention-to-Treat (ITT) analysis set was defined as all subjects who received at least 1 dose of study drug and had at least 1 postdose efficacy value.

Reporting Groups

	Description
Ambrisentan	All eligible subjects received 2.5 mg ambrisentan once daily for a period of 4 weeks before increasing the dose to 5 mg once daily. After Week 24, investigators were allowed to adjust the dose of ambrisentan as clinically indicated (available doses were 2.5, 5, and 10 mg).

Measured Values

	Ambrisentan
Number of Participants Analyzed	35
A Change From Baseline Evaluated After 12 Weeks of Ambrisentan Therapy in the 6-Minute Walk Distance Test (6MWD) [units: meters] Mean (Standard Deviation)	23.4 (49.60)

Statistical Analysis 1 for A Change From Baseline Evaluated After 12 Weeks of Ambrisentan Therapy in the 6-Minute Walk Distance Test (6MWD)

Statistical Analysis Overview	Comparison Groups	Ambrisentan
	Comments	Hypothesis testing and descriptive statistics were carried out on the last-observation-carried-forward (LOCF) 6-minute walk distance change from baseline.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.009
	Comments	[Not specified]
	Method	t-test, 2 sided
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	23.4

	Confidence Interval	(2-Sided) 95% 6.3 to 40.4
	Parameter Dispersion	Type: Standard Deviation Value: 49.60
	Estimation Comments	[Not specified]

5. Secondary Outcome Measure:

Measure Title	A Change From Baseline Evaluated After 12 Weeks of Ambrisentan Therapy in Borg Dyspnea Index Immediately Following Exercise
Measure Description	Change from baseline evaluated after 12 weeks of ambrisentan therapy in Borg dyspnea index (measured as units on a scale) immediately following exercise. Borg Dyspnea Index, a measure of perceived shortness of breath: 0 units on a scale (none) to 10 units on a scale (maximum breathlessness).
Time Frame	Baseline to Week 12
Safety Issue?	No

Analysis Population Description

The Intention-to-Treat (ITT) analysis set was defined as all subjects who received at least 1 dose of study drug and had at least 1 postdose efficacy value.

Reporting Groups

	Description
Ambrisentan	All eligible subjects received 2.5 mg ambrisentan once daily for a period of 4 weeks before increasing the dose to 5 mg once daily. After Week 24, investigators were allowed to adjust the dose of ambrisentan as clinically indicated (available doses were 2.5, 5, and 10 mg).

Measured Values

	Ambrisentan
Number of Participants Analyzed	35
A Change From Baseline Evaluated After 12 Weeks of Ambrisentan Therapy in Borg Dyspnea Index Immediately Following Exercise [units: Units on a scale] Mean (Standard Deviation)	-0.5 (1.51)

Statistical Analysis 1 for A Change From Baseline Evaluated After 12 Weeks of Ambrisentan Therapy in Borg Dyspnea Index Immediately Following Exercise

Statistical Analysis Overview	Comparison Groups	Ambrisentan
	Comments	Hypothesis testing and descriptive statistics were carried out on the last-observation-carried-forward (LOCF) Borg dyspnea index change from baseline.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.046
	Comments	[Not specified]
	Method	t-test, 2 sided
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-0.5
	Confidence Interval	(2-Sided) 95% -1.0 to 0.0
	Parameter Dispersion	Type: Standard Deviation Value: 1.51
	Estimation Comments	[Not specified]

6. Secondary Outcome Measure:

Measure Title	A Change From Baseline Evaluated After 12 Weeks of Ambrisentan Therapy in WHO Functional Class
Measure Description	Classes: I) pulmonary hypertension (PH); ordinary physical activity not limited or causes undue dyspnea or fatigue, chest pain, or near syncope. II) PH; ordinary physical activity slightly limited and causes undue dyspnea or fatigue, chest pain, or near syncope; comfortable at rest. III) PH; physical activity markedly limited and less than ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope; comfortable at rest. IV) PH; physical activity causes symptoms and increased discomfort; signs of right heart failure; dyspnea/fatigue possibly at rest.
Time Frame	Baseline to Week 12
Safety Issue?	No

Analysis Population Description

The Intention-to-Treat (ITT) analysis set was defined as all subjects who received at least 1 dose of study drug and had at least 1 postdose efficacy value.

Reporting Groups

	Description
Ambrisentan	All eligible subjects received 2.5 mg ambrisentan once daily for a period of 4 weeks before increasing the dose to 5 mg once daily. After Week 24, investigators were allowed to adjust the dose of ambrisentan as clinically indicated (available doses were 2.5, 5, and 10 mg).

Measured Values

	Ambrisentan
Number of Participants Analyzed	35
A Change From Baseline Evaluated After 12 Weeks of Ambrisentan Therapy in WHO Functional Class [units: Participants]	
Improved	15
No Change	18
Deteriorated	2

7. Secondary Outcome Measure:

Measure Title	A Change From Baseline Evaluated After 12 Weeks of Ambrisentan Therapy in Short Form 36 (SF-36) Health Survey Scale - Composite Physical Health
Measure Description	The SF-36 Health Survey is a self-reporting, multi-item scale measuring 8 health concepts: 1) physical functioning, 2) role limitations due to physical health problems, 3) bodily pain, 4) general health, 5) vitality (energy/fatigue), 6) social functioning, 7) role limitations due to emotional problems and 8) mental health (psychological distress and psychological well-being). The first 6 concepts constitute the physical component summary. Each item is scored from 0 to 100 (least healthy to most healthy).
Time Frame	Baseline to Week 12
Safety Issue?	No

Analysis Population Description

The Intention-to-Treat (ITT) analysis set was defined as all subjects who received at least 1 dose of study drug and had at least 1 postdose efficacy value.

Reporting Groups

	Description
Ambrisentan	All eligible subjects received 2.5 mg ambrisentan once daily for a period of 4 weeks before increasing the dose to 5 mg once daily. After Week 24, investigators were allowed to adjust the dose of ambrisentan as clinically indicated (available doses were 2.5, 5, and 10 mg).

Measured Values

	Ambrisentan
Number of Participants Analyzed	28
A Change From Baseline Evaluated After 12 Weeks of Ambrisentan Therapy in Short Form 36 (SF-36) Health Survey Scale - Composite Physical Health [units: Units on a scale] Mean (Standard Deviation)	4.6 (6.44)

Statistical Analysis 1 for A Change From Baseline Evaluated After 12 Weeks of Ambrisentan Therapy in Short Form 36 (SF-36) Health Survey Scale - Composite Physical Health

Statistical Analysis Overview	Comparison Groups	Ambrisentan
	Comments	Seven subjects were evaluated by the incorrect version of the SF-36 questionnaire at the baseline visit and were not included in the analysis; therefore n = 28 for mean baseline scores, and n = 28 for mean change from baseline at Week 12.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.001
	Comments	[Not specified]
	Method	t-test, 2 sided
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	4.6
	Confidence Interval	(2-Sided) 95% 2.1 to 7.1
	Parameter Dispersion	Type: Standard Deviation

		Value: 6.44
	Estimation Comments	[Not specified]

8. Secondary Outcome Measure:

Measure Title	Secondary Outcome: A Change From Baseline Evaluated After 12 Weeks of Ambrisentan Therapy in SF-36 Health Survey Scale - Composite Mental Health
Measure Description	The SF-36 Health Survey is a self-reporting, multi-item scale measuring 8 health concepts: 1) physical functioning, 2) role limitations due to physical health problems, 3) bodily pain, 4) general health, 5) vitality (energy/fatigue), 6) social functioning, 7) role limitations due to emotional problems and 8) mental health (psychological distress and psychological well-being). The last 5 concepts constitute the mental component summary. Each item is scored from 0 to 100 (least healthy to most healthy).
Time Frame	Baseline to Week 12
Safety Issue?	No

Analysis Population Description

The Intention-to-Treat (ITT) analysis set was defined as all subjects who received at least 1 dose of study drug and had at least 1 postdose efficacy value.

Reporting Groups

	Description
Ambrisentan	All eligible subjects received 2.5 mg ambrisentan once daily for a period of 4 weeks before increasing the dose to 5 mg once daily. After Week 24, investigators were allowed to adjust the dose of ambrisentan as clinically indicated (available doses were 2.5, 5, and 10 mg).

Measured Values

	Ambrisentan
Number of Participants Analyzed	28
Secondary Outcome: A Change From Baseline Evaluated After 12 Weeks of Ambrisentan Therapy in SF-36 Health Survey Scale - Composite Mental Health [units: Units on a scale] Mean (Standard Deviation)	3.4 (8.98)

Statistical Analysis 1 for Secondary Outcome: A Change From Baseline Evaluated After 12 Weeks of Ambrisentan Therapy in SF-36 Health Survey Scale - Composite Mental Health

Statistical Analysis Overview	Comparison Groups	Ambrisentan
	Comments	Seven subjects were evaluated by the incorrect version of the SF-36 questionnaire at the baseline visit and were not included in the analysis; therefore n = 28 for mean baseline scores, and n = 28 for mean change from baseline at Week 12.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.059
	Comments	[Not specified]
	Method	t-test, 2 sided
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	3.4
	Confidence Interval	(2-Sided) 95% -0.1 to 6.8
	Parameter Dispersion	Type: Standard Deviation Value: 8.98
	Estimation Comments	[Not specified]

9. Secondary Outcome Measure:

Measure Title	Secondary Outcome: A Change From Baseline Evaluated After 12 Weeks of Ambrisentan Therapy in SF-36 Health Survey Scale - Physical Functioning
Measure Description	The SF-36 Health Survey is a self-reporting, multi-item scale measuring 8 health concepts: 1) physical functioning, 2) role limitations due to physical health problems, 3) bodily pain, 4) general health, 5) vitality (energy/fatigue), 6) social functioning, 7) role limitations due to emotional problems and 8) mental health (psychological distress and psychological well-being). Each item is scored from 0 to 100 (least healthy to most healthy).
Time Frame	Baseline to Week 12
Safety Issue?	No

Analysis Population Description

The Intention-to-Treat (ITT) analysis set was defined as all subjects who received at least 1 dose of study drug and had at least 1 postdose efficacy value.

Reporting Groups

	Description
Ambrisentan	All eligible subjects received 2.5 mg ambrisentan once daily for a period of 4 weeks before increasing the dose to 5 mg once daily. After Week 24, investigators were allowed to adjust the dose of ambrisentan as clinically indicated (available doses were 2.5, 5, and 10 mg).

Measured Values

	Ambrisentan
Number of Participants Analyzed	28
Secondary Outcome: A Change From Baseline Evaluated After 12 Weeks of Ambrisentan Therapy in SF-36 Health Survey Scale - Physical Functioning [units: Units on a scale] Mean (Standard Deviation)	4.4 (6.86)

Statistical Analysis 1 for Secondary Outcome: A Change From Baseline Evaluated After 12 Weeks of Ambrisentan Therapy in SF-36 Health Survey Scale - Physical Functioning

Statistical Analysis Overview	Comparison Groups	Ambrisentan
	Comments	Seven subjects were evaluated by the incorrect version of the SF-36 questionnaire at the baseline visit and were not included in the analysis; therefore n = 28 for mean baseline scores, and n = 28 for mean change from baseline at Week 12.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.002
	Comments	[Not specified]
	Method	t-test, 2 sided
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	4.4
	Confidence Interval	(2-Sided) 95% 1.7 to 7.0

	Parameter Dispersion	Type: Standard Deviation Value: 6.86
	Estimation Comments	[Not specified]

10. Secondary Outcome Measure:

Measure Title	Secondary Outcome: A Change From Baseline Evaluated After 12 Weeks of Ambrisentan Therapy in SF-36 Health Survey Scale - Role Physical
Measure Description	The SF-36 Health Survey is a self-reporting, multi-item scale measuring 8 health concepts: 1) physical functioning, 2) role limitations due to physical health problems, 3) bodily pain, 4) general health, 5) vitality (energy/fatigue), 6) social functioning, 7) role limitations due to emotional problems and 8) mental health (psychological distress and psychological well-being). Each item is scored from 0 to 100 (least healthy to most healthy).
Time Frame	Baseline to Week 12
Safety Issue?	No

Analysis Population Description

The Intention-to-Treat (ITT) analysis set was defined as all subjects who received at least 1 dose of study drug and had at least 1 postdose efficacy value.

Reporting Groups

	Description
Ambrisentan	All eligible subjects received 2.5 mg ambrisentan once daily for a period of 4 weeks before increasing the dose to 5 mg once daily. After Week 24, investigators were allowed to adjust the dose of ambrisentan as clinically indicated (available doses were 2.5, 5, and 10 mg).

Measured Values

	Ambrisentan
Number of Participants Analyzed	28
Secondary Outcome: A Change From Baseline Evaluated After 12 Weeks of Ambrisentan Therapy in SF-36 Health Survey Scale - Role Physical [units: Units on a scale] Mean (Standard Deviation)	7.2 (10.56)

Statistical Analysis 1 for Secondary Outcome: A Change From Baseline Evaluated After 12 Weeks of Ambrisentan Therapy in SF-36 Health Survey Scale - Role Physical

Statistical Analysis Overview	Comparison Groups	Ambrisentan
	Comments	Seven subjects were evaluated by the incorrect version of the SF-36 questionnaire at the baseline visit and were not included in the analysis; therefore n = 28 for mean baseline scores, and n = 28 for mean change from baseline at Week 12.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.001
	Comments	[Not specified]
	Method	t-test, 2 sided
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	7.2
	Confidence Interval	(2-Sided) 95% 3.1 to 11.3
	Parameter Dispersion	Type: Standard Deviation Value: 10.56
	Estimation Comments	[Not specified]

11. Secondary Outcome Measure:

Measure Title	Secondary Outcome: A Change From Baseline Evaluated After 12 Weeks of Ambrisentan Therapy in SF-36 Health Survey Scale - Bodily Pain
Measure Description	The SF-36 Health Survey is a self-reporting, multi-item scale measuring 8 health concepts: 1) physical functioning, 2) role limitations due to physical health problems, 3) bodily pain, 4) general health, 5) vitality (energy/fatigue), 6) social functioning, 7) role limitations due to emotional problems and 8) mental health (psychological distress and psychological well-being). Each item is scored from 0 to 100 (least healthy to most healthy).
Time Frame	Baseline to Week 12
Safety Issue?	No

Analysis Population Description

The Intention-to-Treat (ITT) analysis set was defined as all subjects who received at least 1 dose of study drug and had at least 1 postdose efficacy value.

Reporting Groups

	Description
Ambrisentan	All eligible subjects received 2.5 mg ambrisentan once daily for a period of 4 weeks before increasing the dose to 5 mg once daily. After Week 24, investigators were allowed to adjust the dose of ambrisentan as clinically indicated (available doses were 2.5, 5, and 10 mg).

Measured Values

	Ambrisentan
Number of Participants Analyzed	28
Secondary Outcome: A Change From Baseline Evaluated After 12 Weeks of Ambrisentan Therapy in SF-36 Health Survey Scale - Bodily Pain [units: Units on a scale] Mean (Standard Deviation)	3.1 (6.40)

Statistical Analysis 1 for Secondary Outcome: A Change From Baseline Evaluated After 12 Weeks of Ambrisentan Therapy in SF-36 Health Survey Scale - Bodily Pain

Statistical Analysis Overview	Comparison Groups	Ambrisentan
	Comments	Seven subjects were evaluated by the incorrect version of the SF-36 questionnaire at the baseline visit and were not included in the analysis; therefore n = 28 for mean baseline scores, and n = 28 for mean change from baseline at Week 12.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.017
	Comments	[Not specified]
	Method	t-test, 2 sided
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	3.1
	Confidence Interval	(2-Sided) 95% 0.6 to 5.6

	Parameter Dispersion	Type: Standard Deviation Value: 6.40
	Estimation Comments	[Not specified]

12. Secondary Outcome Measure:

Measure Title	Secondary Outcome: A Change From Baseline Evaluated After 12 Weeks of Ambrisentan Therapy in SF-36 Health Survey Scale - General Health
Measure Description	The SF-36 Health Survey is a self-reporting, multi-item scale measuring 8 health concepts: 1) physical functioning, 2) role limitations due to physical health problems, 3) bodily pain, 4) general health, 5) vitality (energy/fatigue), 6) social functioning, 7) role limitations due to emotional problems and 8) mental health (psychological distress and psychological well-being). Each item is scored from 0 to 100 (least healthy to most healthy).
Time Frame	Baseline to Week 12
Safety Issue?	No

Analysis Population Description

The Intention-to-Treat (ITT) analysis set was defined as all subjects who received at least 1 dose of study drug and had at least 1 postdose efficacy value.

Reporting Groups

	Description
Ambrisentan	All eligible subjects received 2.5 mg ambrisentan once daily for a period of 4 weeks before increasing the dose to 5 mg once daily. After Week 24, investigators were allowed to adjust the dose of ambrisentan as clinically indicated (available doses were 2.5, 5, and 10 mg).

Measured Values

	Ambrisentan
Number of Participants Analyzed	28
Secondary Outcome: A Change From Baseline Evaluated After 12 Weeks of Ambrisentan Therapy in SF-36 Health Survey Scale - General Health [units: Units on a scale] Mean (Standard Deviation)	3.0 (7.45)

Statistical Analysis 1 for Secondary Outcome: A Change From Baseline Evaluated After 12 Weeks of Ambrisentan Therapy in SF-36 Health Survey Scale - General Health

Statistical Analysis Overview	Comparison Groups	Ambrisentan
	Comments	Seven subjects were evaluated by the incorrect version of the SF-36 questionnaire at the baseline visit and were not included in the analysis; therefore n = 28 for mean baseline scores, and n = 28 for mean change from baseline at Week 12.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.046
	Comments	[Not specified]
	Method	t-test, 2 sided
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	3.0
	Confidence Interval	(2-Sided) 95% 0.1 to 5.8
	Parameter Dispersion	Type: Standard Deviation Value: 7.45
	Estimation Comments	[Not specified]

13. Secondary Outcome Measure:

Measure Title	Secondary Outcome: A Change From Baseline Evaluated After 12 Weeks of Ambrisentan Therapy in SF-36 Health Survey Scale - Vitality
Measure Description	The SF-36 Health Survey is a self-reporting, multi-item scale measuring 8 health concepts: 1) physical functioning, 2) role limitations due to physical health problems, 3) bodily pain, 4) general health, 5) vitality (energy/fatigue), 6) social functioning, 7) role limitations due to emotional problems and 8) mental health (psychological distress and psychological well-being). Each item is scored from 0 to 100 (least healthy to most healthy).
Time Frame	Baseline to Week 12
Safety Issue?	No

Analysis Population Description

The Intention-to-Treat (ITT) analysis set was defined as all subjects who received at least 1 dose of study drug and had at least 1 postdose efficacy value.

Reporting Groups

	Description
Ambrisentan	All eligible subjects received 2.5 mg ambrisentan once daily for a period of 4 weeks before increasing the dose to 5 mg once daily. After Week 24, investigators were allowed to adjust the dose of ambrisentan as clinically indicated (available doses were 2.5, 5, and 10 mg).

Measured Values

	Ambrisentan
Number of Participants Analyzed	28
Secondary Outcome: A Change From Baseline Evaluated After 12 Weeks of Ambrisentan Therapy in SF-36 Health Survey Scale - Vitality [units: Units on a scale] Mean (Standard Deviation)	4.5 (7.23)

Statistical Analysis 1 for Secondary Outcome: A Change From Baseline Evaluated After 12 Weeks of Ambrisentan Therapy in SF-36 Health Survey Scale - Vitality

Statistical Analysis Overview	Comparison Groups	Ambrisentan
	Comments	Seven subjects were evaluated by the incorrect version of the SF-36 questionnaire at the baseline visit and were not included in the analysis; therefore n = 28 for mean baseline scores, and n = 28 for mean change from baseline at Week 12.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.003
	Comments	[Not specified]
	Method	t-test, 2 sided
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	4.5
	Confidence Interval	(2-Sided) 95% 1.7 to 7.3

	Parameter Dispersion	Type: Standard Deviation Value: 7.23
	Estimation Comments	[Not specified]

14. Secondary Outcome Measure:

Measure Title	Secondary Outcome: A Change From Baseline Evaluated After 12 Weeks of Ambrisentan Therapy in SF-36 Health Survey Scale - Social Functioning
Measure Description	The SF-36 Health Survey is a self-reporting, multi-item scale measuring 8 health concepts: 1) physical functioning, 2) role limitations due to physical health problems, 3) bodily pain, 4) general health, 5) vitality (energy/fatigue), 6) social functioning, 7) role limitations due to emotional problems and 8) mental health (psychological distress and psychological well-being). Each item is scored from 0 to 100 (least healthy to most healthy).
Time Frame	Baseline to Week 12
Safety Issue?	No

Analysis Population Description

The Intention-to-Treat (ITT) analysis set was defined as all subjects who received at least 1 dose of study drug and had at least 1 postdose efficacy value.

Reporting Groups

	Description
Ambrisentan	All eligible subjects received 2.5 mg ambrisentan once daily for a period of 4 weeks before increasing the dose to 5 mg once daily. After Week 24, investigators were allowed to adjust the dose of ambrisentan as clinically indicated (available doses were 2.5, 5, and 10 mg).

Measured Values

	Ambrisentan
Number of Participants Analyzed	28
Secondary Outcome: A Change From Baseline Evaluated After 12 Weeks of Ambrisentan Therapy in SF-36 Health Survey Scale - Social Functioning [units: Units on a scale] Mean (Standard Deviation)	3.5 (9.41)

Statistical Analysis 1 for Secondary Outcome: A Change From Baseline Evaluated After 12 Weeks of Ambrisentan Therapy in SF-36 Health Survey Scale - Social Functioning

Statistical Analysis Overview	Comparison Groups	Ambrisentan
	Comments	Seven subjects were evaluated by the incorrect version of the SF-36 questionnaire at the baseline visit and were not included in the analysis; therefore n = 28 for mean baseline scores, and n = 28 for mean change from baseline at Week 12.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.059
	Comments	[Not specified]
	Method	t-test, 2 sided
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	3.5
	Confidence Interval	(2-Sided) 95% -0.1 to 7.2
	Parameter Dispersion	Type: Standard Deviation Value: 9.41
	Estimation Comments	[Not specified]

15. Secondary Outcome Measure:

Measure Title	Secondary Outcome: A Change From Baseline Evaluated After 12 Weeks of Ambrisentan Therapy in SF-36 Health Survey Scale - Role Emotional
Measure Description	The SF-36 Health Survey is a self-reporting, multi-item scale measuring 8 health concepts: 1) physical functioning, 2) role limitations due to physical health problems, 3) bodily pain, 4) general health, 5) vitality (energy/fatigue), 6) social functioning, 7) role limitations due to emotional problems and 8) mental health (psychological distress and psychological well-being). Each item is scored from 0 to 100 (least healthy to most healthy).
Time Frame	Baseline to Week 12
Safety Issue?	No

Analysis Population Description

The Intention-to-Treat (ITT) analysis set was defined as all subjects who received at least 1 dose of study drug and had at least 1 postdose efficacy value.

Reporting Groups

	Description
Ambrisentan	All eligible subjects received 2.5 mg ambrisentan once daily for a period of 4 weeks before increasing the dose to 5 mg once daily. After Week 24, investigators were allowed to adjust the dose of ambrisentan as clinically indicated (available doses were 2.5, 5, and 10 mg).

Measured Values

	Ambrisentan
Number of Participants Analyzed	28
Secondary Outcome: A Change From Baseline Evaluated After 12 Weeks of Ambrisentan Therapy in SF-36 Health Survey Scale - Role Emotional [units: Units on a scale] Mean (Standard Deviation)	3.9 (13.96)

Statistical Analysis 1 for Secondary Outcome: A Change From Baseline Evaluated After 12 Weeks of Ambrisentan Therapy in SF-36 Health Survey Scale - Role Emotional

Statistical Analysis Overview	Comparison Groups	Ambrisentan
	Comments	Seven subjects were evaluated by the incorrect version of the SF-36 questionnaire at the baseline visit and were not included in the analysis; therefore n = 28 for mean baseline scores, and n = 28 for mean change from baseline at Week 12.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	0.152
	Comments	[Not specified]
	Method	t-test, 2 sided
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	3.9
	Confidence Interval	(2-Sided) 95% -1.5 to 9.3

	Parameter Dispersion	Type: Standard Deviation Value: 13.96
	Estimation Comments	[Not specified]

16. Secondary Outcome Measure:

Measure Title	Secondary Outcome: A Change From Baseline Evaluated After 12 Weeks of Ambrisentan Therapy in SF-36 Health Survey Scale - Mental Health
Measure Description	The SF-36 Health Survey is a self-reporting, multi-item scale measuring 8 health concepts: 1) physical functioning, 2) role limitations due to physical health problems, 3) bodily pain, 4) general health, 5) vitality (energy/fatigue), 6) social functioning, 7) role limitations due to emotional problems and 8) mental health (psychological distress and psychological well-being). Each item is scored from 0 to 100 (least healthy to most healthy).
Time Frame	Baseline to Week 12
Safety Issue?	No

Analysis Population Description

The Intention-to-Treat (ITT) analysis set was defined as all subjects who received at least 1 dose of study drug and had at least 1 postdose efficacy value.

Reporting Groups

	Description
Ambrisentan	All eligible subjects received 2.5 mg ambrisentan once daily for a period of 4 weeks before increasing the dose to 5 mg once daily. After Week 24, investigators were allowed to adjust the dose of ambrisentan as clinically indicated (available doses were 2.5, 5, and 10 mg).

Measured Values

	Ambrisentan
Number of Participants Analyzed	28
Secondary Outcome: A Change From Baseline Evaluated After 12 Weeks of Ambrisentan Therapy in SF-36 Health Survey Scale - Mental Health [units: Units on a scale] Mean (Standard Deviation)	3.9 (5.78)

Statistical Analysis 1 for Secondary Outcome: A Change From Baseline Evaluated After 12 Weeks of Ambrisentan Therapy in SF-36 Health Survey Scale - Mental Health

Statistical Analysis Overview	Comparison Groups	Ambrisentan
	Comments	Seven subjects were evaluated by the incorrect version of the SF-36 questionnaire at the baseline visit and were not included in the analysis; therefore n = 28 for mean baseline scores, and n = 28 for mean change from baseline at Week 12.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.001
	Comments	[Not specified]
	Method	t-test, 2 sided
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	3.9
	Confidence Interval	(2-Sided) 95% 1.7 to 6.2
	Parameter Dispersion	Type: Standard Deviation Value: 5.78
	Estimation Comments	[Not specified]

Reported Adverse Events

Time Frame	Baseline to Week 189
Additional Description	Median exposure to study drug was 108.1 weeks (2.08 years). Two subjects discontinued ambrisentan because of adverse events after 1 and 3 weeks, respectively. Reporting interval for all other subjects was from 36 to 189 weeks.

Reporting Groups

	Description
Ambrisentan	All eligible subjects received 2.5 mg ambrisentan once daily for a period of 4 weeks before increasing the dose to 5 mg once daily. After Week 24, investigators were allowed to adjust the dose of ambrisentan as clinically indicated (available doses were 2.5, 5, and 10 mg).

Serious Adverse Events

	Ambrisentan
	Affected/At Risk (%)
Total	17/36 (47.22%)
Blood and lymphatic system disorders	
anaemia [A] †	2/36 (5.56%)
microcytic anaemia [B] †	1/36 (2.78%)
Cardiac disorders	
acute coronary syndrome [B] †	1/36 (2.78%)
acute myocardial infarction [B] †	1/36 (2.78%)
atrial fibrillation [B] †	2/36 (5.56%)
atrial tachycardia [B] †	1/36 (2.78%)
cardiac arrest [B] †	1/36 (2.78%)
coronary artery disease [B] †	1/36 (2.78%)
palpitations [B] †	1/36 (2.78%)
right ventricular failure [B] †	1/36 (2.78%)
supraventricular tachycardia [B] †	1/36 (2.78%)
Congenital, familial and genetic disorders	
gastrointestinal arteriovenous malformation [B] †	1/36 (2.78%)
Gastrointestinal disorders	
diarrhoea [B] †	1/36 (2.78%)

	Ambrisentan
	Affected/At Risk (%)
General disorders	
chest pain [B] †	1/36 (2.78%)
infusion site pain [B] †	1/36 (2.78%)
Infections and infestations	
catheter site cellulitis [B] †	1/36 (2.78%)
central line infection [B] †	1/36 (2.78%)
gastroenteritis [B] †	1/36 (2.78%)
gastroenteritis viral [B] †	1/36 (2.78%)
lobar pneumonia [B] †	1/36 (2.78%)
pneumococcal sepsis [B] †	1/36 (2.78%)
pneumonia [B] †	1/36 (2.78%)
staphylococcal bacteraemia [B] †	1/36 (2.78%)
upper respiratory tract infection [B] †	1/36 (2.78%)
Investigations	
blood potassium increased [B] †	1/36 (2.78%)
Metabolism and nutrition disorders	
dehydration [B] †	2/36 (5.56%)
hypokalaemia [B] †	1/36 (2.78%)
hyponatraemia [B] †	1/36 (2.78%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	
breast cancer [B] †	1/36 (2.78%)
Nervous system disorders	
dizziness [B] †	1/36 (2.78%)

	Ambrisentan
	Affected/At Risk (%)
dizziness postural [B] †	1/36 (2.78%)
ischaemic stroke [B] †	1/36 (2.78%)
sciatica [B] †	1/36 (2.78%)
syncope [B] †	1/36 (2.78%)
Psychiatric disorders	
depression [B] †	1/36 (2.78%)
Renal and urinary disorders	
azotaemia [B] †	1/36 (2.78%)
Respiratory, thoracic and mediastinal disorders	
chronic obstructive airways disease exacerbated [B] †	1/36 (2.78%)
hypoxia [B] †	1/36 (2.78%)
pulmonary embolism [B] †	1/36 (2.78%)
pulmonary hypertension [B] †	5/36 (13.89%)

† Indicates events were collected by systematic assessment.
A Term from vocabulary, MedDRA 8.0
B Term from vocabulary, MedDRA (8.0)

Other Adverse Events

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

	Ambrisentan
	Affected/At Risk (%)
Total	36/36 (100%)
Blood and lymphatic system disorders	
anaemia [A] †	8/36 (22.22%)
lymphadenopathy [A] †	2/36 (5.56%)

	Ambrisentan
	Affected/At Risk (%)
Cardiac disorders	
atrial fibrillation [A] †	4/36 (11.11%)
bradycardia [A] †	2/36 (5.56%)
coronary artery disease [A] †	2/36 (5.56%)
palpitations [A] †	8/36 (22.22%)
tricuspid valve incompetence [A] †	3/36 (8.33%)
Ear and labyrinth disorders	
vertigo [A] †	3/36 (8.33%)
Eye disorders	
conjunctival haemorrhage [A] †	2/36 (5.56%)
vision blurred [A] †	2/36 (5.56%)
Gastrointestinal disorders	
abdominal pain [A] †	4/36 (11.11%)
abdominal pain upper [A] †	2/36 (5.56%)
constipation [A] †	3/36 (8.33%)
diarrhoea [A] †	7/36 (19.44%)
dyspepsia [A] †	3/36 (8.33%)
gastrooesophageal reflux disease [A] †	4/36 (11.11%)
nausea [A] †	9/36 (25%)
oesophagitis [A] †	2/36 (5.56%)
toothache [A] †	3/36 (8.33%)
vomiting [A] †	2/36 (5.56%)
General disorders	

	Ambrisentan
	Affected/At Risk (%)
asthenia [A] †	2/36 (5.56%)
chest discomfort [A] †	4/36 (11.11%)
chest pain [A] †	4/36 (11.11%)
chills [A] †	2/36 (5.56%)
fatigue [A] †	9/36 (25%)
influenza like illness [A] †	2/36 (5.56%)
infusion site pain [A] †	3/36 (8.33%)
non-cardiac chest pain [A] †	2/36 (5.56%)
oedema peripheral [A] †	19/36 (52.78%)
pyrexia [A] †	5/36 (13.89%)
Immune system disorders	
drug hypersensitivity [A] †	2/36 (5.56%)
Infections and infestations	
bronchitis [A] †	4/36 (11.11%)
bronchitis acute [A] †	3/36 (8.33%)
eye infection [A] †	2/36 (5.56%)
herpes zoster [A] †	2/36 (5.56%)
influenza [A] †	2/36 (5.56%)
infusion site infection [A] †	2/36 (5.56%)
localised infection [A] †	2/36 (5.56%)
lower respiratory tract infection [A] †	2/36 (5.56%)
nasopharyngitis [A] †	5/36 (13.89%)

	Ambrisentan
	Affected/At Risk (%)
pharyngitis [A] †	3/36 (8.33%)
respiratory tract infection [A] †	5/36 (13.89%)
sinusitis [A] †	7/36 (19.44%)
upper respiratory tract infection [A] †	8/36 (22.22%)
urinary tract infection [A] †	6/36 (16.67%)
viral upper respiratory tract infection [A] †	2/36 (5.56%)
Injury, poisoning and procedural complications	
contusion [A] †	2/36 (5.56%)
fall [A] †	2/36 (5.56%)
post procedural pain [A] †	2/36 (5.56%)
Investigations	
excercise capacity decreased [A] †	2/36 (5.56%)
international normalised ratio increased [A] †	4/36 (11.11%)
weight increased [A] †	3/36 (8.33%)
Metabolism and nutrition disorders	
dehydration [A] †	2/36 (5.56%)
fluid retention [A] †	3/36 (8.33%)
hypokalaemia [A] †	2/36 (5.56%)
hypomagnesaemia [A] †	2/36 (5.56%)
Musculoskeletal and connective tissue disorders	
arthralgia [A] †	4/36 (11.11%)
back pain [A] †	3/36 (8.33%)
neck pain [A] †	2/36 (5.56%)

	Ambrisentan
	Affected/At Risk (%)
pain in extremity [A] †	6/36 (16.67%)
pain in jaw [A] †	2/36 (5.56%)
shoulder pain [A] †	2/36 (5.56%)
Nervous system disorders	
dizziness [A] †	5/36 (13.89%)
dizziness postural [A] †	2/36 (5.56%)
headache [A] †	13/36 (36.11%)
tremor [A] †	2/36 (5.56%)
Psychiatric disorders	
anxiety [A] †	6/36 (16.67%)
depression [A] †	2/36 (5.56%)
insomnia [A] †	7/36 (19.44%)
Respiratory, thoracic and mediastinal disorders	
cough [A] †	6/36 (16.67%)
crackles lung [A] †	2/36 (5.56%)
dysphonia [A] †	2/36 (5.56%)
dyspnoea [A] †	4/36 (11.11%)
dyspnoea exacerbated [A] †	12/36 (33.33%)
dyspnoea exertional [A] †	4/36 (11.11%)
epistaxis [A] †	4/36 (11.11%)
hypoxia [A] †	2/36 (5.56%)
nasal congestion [A] †	5/36 (13.89%)

	Ambrisentan
	Affected/At Risk (%)
pharyngolaryngeal pain [A] †	2/36 (5.56%)
pleuritic pain [A] †	3/36 (8.33%)
pulmonary hypertension [A] †	4/36 (11.11%)
rales [A] †	2/36 (5.56%)
rhinitis allergic [A] †	3/36 (8.33%)
rhinorrhoea [A] †	3/36 (8.33%)
wheezing [A] †	2/36 (5.56%)
Skin and subcutaneous tissue disorders	
dry skin [A] †	2/36 (5.56%)
erythema [A] †	2/36 (5.56%)
pruritis [A] †	2/36 (5.56%)
rash [A] †	4/36 (11.11%)
rash macular [A] †	2/36 (5.56%)
Vascular disorders	
flushing [A] †	7/36 (19.44%)
hypotension [A] †	3/36 (8.33%)

† Indicates events were collected by systematic assessment.
A Term from vocabulary, MedDRA (8.0)

Limitations and Caveats

Seven subjects were excluded from the change from baseline analysis of the SF-36 Health Survey because the incorrect version of the SF-36 questionnaire was used for evaluation at baseline, which made comparisons problematic.

More Information

Certain Agreements:

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

There IS 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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