ClinicalTrials.gov Protocol and Results Registration System (PRS) Receipt
Release Date: 02/27/2014

Grantor: CDER IND/IDE Number: 101,039 Serial Number: 0000

(ARTEMIS-IPF) Randomized, Placebo-Controlled Study to Evaluate Safety and Effectiveness of Ambrisentan in IPF

This study has been terminated.
(Lack of efficacy)

Sponsor:	Gilead Sciences
Collaborators:	
Information provided by (Responsible Party):	Gilead Sciences
ClinicalTrials.gov Identifier:	NCT00768300

Purpose

The ARTEMIS-IPF study was conducted to determine if ambrisentan was effective in delaying disease progression and death in participants with idiopathic pulmonary fibrosis (IPF), to evaluate its safety, and to evaluate its effect on development of pulmonary hypertension, quality of life, and dyspnea (shortness of breath) symptoms in this participant population. Participants were randomized in a 2:1 ratio to receive ambrisentan or placebo, respectively. Participation in the study was to be up to 4 years, depending on how long it would take to enroll participants and observe study events. After randomization, visits to the clinic took place every 3 months, and laboratory procedures were performed every month.

Condition	Intervention	Phase
Idiopathic Pulmonary Fibrosis	Drug: Ambrisentan Drug: Placebo	Phase 3

Study Type: Interventional
Study Design: Treatment, Parallel Assignment, Double Blind (Subject, Investigator), Randomized, Safety/Efficacy Study
Official Title: ARTEMIS-IPF: A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multi-Center, Parallel-Group, Event Driven Study to Evaluate the Efficacy and Safety of Ambrisentan in Subjects With Early Idiopathic Pulmonary Fibrosis (IPF)

Further study details as provided by Gilead Sciences:

Primary Outcome Measure:

- Time to Death or Disease (IPF) Progression. [Time Frame: Up to 48 months] [Designated as safety issue: No]
  The median time to death or disease progression was based on Kaplan-Meier (KM) estimates of pooling over strata, and was defined as the first occurrence of any of the following: • Either 1) a decrease of ≥ 10% in FVC (L) and a decrease of ≥ 5% in diffuse lung capacity for carbon monoxide (DLCO) (ml/min/mmHg), or 2) a decrease of ≥ 5% in FVC (L) and a decrease of ≥ 15% in DLCO (ml/min/mmHg); deterioration in FVC and DLCO must be confirmed at the subsequent visit within 28 (± 14) days • Respiratory hospitalization (hospitalization involving worsening of, or deterioration in respiratory symptoms, gas exchange/hypoxemia, or radiographic findings on chest x-ray or high-resolution computerised tomography (HRCT) scan • All-cause mortality

Secondary Outcome Measures:

- Proportion of Participants With No Disease Progression or Death at 48 Weeks [Time Frame: Baseline and Week 48] [Designated as safety issue: No]
  The proportion of participants with no disease progression or death is presented as a percentage using a Kaplan-Meier (KM) estimate of survival or not experiencing disease progression.
- Change in FVC % Predicted at Week 48 [Time Frame: Baseline and Week 48] [Designated as safety issue: No]
  FVC is defined as the volume of air (liters) that can forcibly be blown out after taking a full breath. FVC % predicted is defined as FVC % of the participant divided by the average FVC % in the population for any person of similar age, sex, and body composition.
- Change in DLCO % Predicted at Week 48 [Time Frame: Baseline and Week 48] [Designated as safety issue: No]
  DLCO is the extent to which oxygen passes from the air sacs of the lungs into the blood. DLCO % predicted is defined as DLCO % of the participant divided by the average DLCO % in the population for any person of similar age, sex and body composition.
- Change in 6MWT at Week 48 [Time Frame: Baseline and Week 48] [Designated as safety issue: No]
  The 6MWT 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.
- Change in Quality of Life (QOL) Score at Week 48 as Assessed by the Short-Form 36® (SF-36) [Time Frame: Baseline and Week 48] [Designated as safety issue: No]
  The range of each health domain score is 0-100, with 0 indicating a poorer health state and 100 indicating a better health state. An increase in score indicates an improvement in health state.
- Change in Quality of Life (QOL) Score at Week 48 as Assessed by the St. George's Respiratory Questionnaire (SGRQ) [Time Frame: Baseline and Week 48] [Designated as safety issue: No]
  The SGRQ is designed to measure impact on overall health, daily life, and perceived well-being in participants with obstructive airways disease. The range of each score is 0-100, with 0 indicating fewer limitations and 100 indicating more limitations; an increase in score indicates an increase in limitations.
- Change in Dyspnea Score at Week 48 as Assessed by the Transitional Dyspnea Index (TDI) [Time Frame: Baseline and Week 48] [Designated as safety issue: No]
  The transitional focal score (-9 to 9) is the sum of relative change from baseline for the Functional Impairment, Magnitude of Task, and Magnitude of Effort scores (each -3 to 3 scale). A TDI score of -9 represents a maximum degradation of all three tests; a score of 9 represents a maximum improvement of all three tests.
- Percentage of Participants Who Developed PH on Study [Time Frame: Up to 48 weeks] [Designated as safety issue: No]
  The percentage of participants known to have developed pulmonary hypertension on study documented by right heart catheterization (RHC) was analyzed. RHC was done at baseline and 48 weeks, or at the early termination visit.

Enrollment: 494
Study Start Date: December 2008
Primary Completion Date: February 2011
Study Completion Date: February 2011

Arms	Assigned Interventions
Experimental: Ambrisentan	Drug: Ambrisentan Ambrisentan (5mg or 10 mg tablet) was administered orally once daily. Other Names: Letairis®
Placebo Comparator: Placebo	Drug: Placebo Placebo to match ambrisentan was administered orally once daily.

Eligibility

Ages Eligible for Study: 40 Years to 80 Years
Genders Eligible for Study: Both
Accepts Healthy Volunteers: No

Criteria

Inclusion Criteria:

- Male or females from 40 to 80 years of age
- Diagnosis of IPF
- Honeycombing (fibrosis in the lung) on high-resolution computerised tomography (HRCT) scan of less than or equal to 5%
- Willing and able to have 2 right heart catheterizations performed
- Willing to have monthly lab tests to monitor liver function
- Able to perform the 6 minute walk test (indicated adequate physical function)
- Must have meet lung function requirements
- Normal liver function tests
- Negative serum pregnancy test
- Willing to use at least 2 reliable methods of contraception
- Able to understand and willing to sign informed consent form

Exclusion Criteria:

- No restrictive lung disease (other than usual interstitial pneumonia or IPF)
- No obstructive lung disease
- No recent or active respiratory exacerbations
- No recent hospitalization for an IPF exacerbation
- No recent history of alcohol abuse
- Chronic sildenafil (or same drug class) use for pulmonary hypertension
- Chronic treatment with certain medications for IPF within 30 days of randomization
- No other serious medical conditions

Contacts and Locations

Locations

United States, Alabama
University of Alabama at Birmingham Hospital
Birmingham, Alabama, United States, 35294
United States, Arizona
Pulmonary Associates
Phoenix, Arizona, United States, 85006
Scottsdale, Arizona, United States, 85258
United States, California
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University of California, Davis
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Stanford University
Stanford, California, United States, 94305
United States, Colorado
National Jewish Medical And Research Center
Denver, Colorado, United States, 80206
United States, Delaware
Newark, Delaware, United States, 19713
United States, Florida
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Tampa, Florida, United States, 33606
United States, Georgia
Emory University
Atlanta, Georgia, United States, 30322
United States, Illinois
University of Chicago
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United States, Iowa
Council Bluffs, Iowa, United States, 51503
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Louisville, Kentucky, United States, 40202
Louisville, Kentucky, United States, 40202
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Baltimore, Maryland, United States, 21205

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Boston, Massachusetts, United States, 02215
Boston, Massachusetts, United States, 02115
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United States, Missouri
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United States, New Jersey
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Pittsburgh, Pennsylvania, United States, 15212

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Provo, Utah, United States, 84604
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Prahran, Victoria, Australia, 3181
Australia, Western Australia
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- Innsbruck, Austria, 6020
- Linz, Austria, 4020
- Wien, Austria, 1090

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- Bruxelles, Belgium, 1200
- Leuven, Belgium, 3000
- Yvoir, Belgium, 5530

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- Florianopolis, Brazil, 88040-970
- Goiania, Brazil, 74605-050
- Porto Alegre, Brazil, 90035-074
- Porto Alegre, Brazil, 90610-000
- Porto Alegre, Brazil, 91350-200
- Rio de Janeiro, Brazil, 21949-900
- Santo Andre, Brazil, 09060-650
- Sao Paolo, Sao Paolo, Brazil, 04023-062

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Lima, Peru, Lima 27
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Investigators

Study Chair:	Ganesh Raghu, MD	University of Washington, Div. of Pulmonary and Critical Care Medicine Chair

More Information

Results Publications:

Raghu G, Behr J, Brown KK, Egan JJ, Kawut SM, Flaherty KR, Martinez FJ, Nathan SD, Wells AU, Collard HR, Costabel U, Richeldi L, de Andrade J, Khalil N, Morrison LD, Lederer DJ, Shao L, Li X, Pedersen PS, Montgomery AB, Chien JW, O'Riordan TG; ARTEMIS-IPF Investigators*. Treatment of idiopathic pulmonary fibrosis with ambrisentan: a parallel, randomized trial. Ann Intern Med. 2013 May 7;158(9):641-9. doi: 10.7326/0003-4819-158-9-201305070-00003. Erratum in: Ann Intern Med. 2014 May 6;160(9):658.

Responsible Party:	Gilead Sciences
Study ID Numbers:	GS-US-231-0101
Health Authority:	United States: Food and Drug Administration

Study Results

Participant Flow

Recruitment Details	Participants were enrolled in a total of 136 study sites in North and South America, Europe, and Australia. The first participant was screened on 10 December 2008. The last participant observation was on 28 February 2011.
Pre-Assignment Details	494 participants were randomized; 492 participants were treated, and comprise the Safety Analysis Set and the Full Analysis Set.

Reporting Groups

	Description
Ambrisentan	Ambrisentan (5 mg or 10 mg tablet) administered orally once daily

	Description
Placebo	Placebo to match ambrisentan administered orally once daily

Overall Study

	Ambrisentan	Placebo
Started	330	164
Randomized and Treated	329	163
Completed	1	1
Not Completed	329	163
Randomized but not treated	1	1
Adverse Event	10	2
Protocol Violation	6	1
Withdrawal by Subject	13	7
Physician Decision	2	3
Study discontinued by Sponsor	271	140
Death	21	5
Subject moved to pursue lung transplant	1	1
Screen failure following randomization	1	0
Received lung transplant	1	1
Lost to Follow-up	0	1
Began prohibited concomitant medication	0	1
Treated but never dosed with Study drug	1	0
Missing data	1	0

Baseline Characteristics

Analysis Population Description

Full Analysis Set: participants who were randomized and treated

Reporting Groups

	Description
Ambrisentan	Ambrisentan (5 mg or 10 mg tablet) administered orally once daily
Placebo	Placebo to match ambrisentan administered orally once daily

Baseline Measures

	Ambrisentan	Placebo	Total
Number of Participants	329	163	492
Age, Continuous [units: years] Mean (Standard Deviation)	65.8 (7.4)	66.1 (7.1)	65.9 (7.3)
Gender, Male/Female [units: participants]			
Female	85	52	137
Male	244	111	355
Race/Ethnicity, Customized [units: participants]			
Black or African Heritage	1	0	1
White	293	145	438
Asian	4	1	5
American Indian or Alaskan Native	1	1	2
Other	27	16	43
Not Permitted	3	0	3
Region of Enrollment [1] [units: participants]			
United States	141	62	203
Canada	25	14	39
Australia	22	12	34
France	21	10	31
Germany	17	9	26
Brazil	18	6	24

	Ambrisentan	Placebo	Total
Peru	12	6	18
Czech Republic	10	6	16
Israel	8	7	15
Italy	11	3	14
Belgium	7	6	13
Colombia	8	3	11
Mexico	5	4	9
United Kingdom	3	6	9
Spain	7	1	8
Poland	3	3	6
Switzerland	5	1	6
Austria	2	2	4
Chile	3	1	4
Argentina	1	2	3
Ireland	1	0	1
Baseline Pulmonary Hypertension (PH) per interactive voice response system (IVRS) [units: participants]			
No	293	145	438
Yes	36	18	54
Smoking status [2] [units: participants]			
Never	105	53	158
Current	7	5	12
Former	217	104	321
Surgical lung biopsy (SLB) to Confirm Diagnosis of IPF (per IVRS) [units: participants]			

	Ambrisentan	Placebo	Total
No	175	87	262
Yes	154	76	230
Disease duration [units: years] Mean (Standard Deviation)	1.13 (1.39)	0.91 (1.19)	1.06 (1.33)
Forced vital capacity (FVC) percent predicted [units: percentage of FVC % predicted] Least Squares Mean (Standard Deviation)	68.74 (13.12)	69.86 (13.75)	69.11 (13.33)
Six mile walk test (6MWT) [units: meters] Mean (Standard Deviation)	410.4 (118.7)	420.5 (121.4)	413.7 (119.6)
Hemoglobin Adjusted Diffusing lung capacity for carbon monoxide (DLCO) percent predicted [units: percentage of DLCO % predicted] Least Squares Mean (Standard Deviation)	42.04 (13.77)	45.57 (13.25)	43.20 (13.69)
Prior IPF Medications [3] [units: participants]			
No	205	97	302
Yes	124	65	189
N-acetylcysteine (NAC) Use [4] [units: participants]			
No	310	153	463
Yes	19	8	27

[1] All participants who were randomized are presented in Region of Enrollment (ambrisentan = 330; placebo = 164)

[2] Smoking status data is missing for one participant randomized to placebo.

[3] Prior IPF Medications data is missing for one participant randomized to placebo.

[4] NAC is a therapy commonly used in the treatment of IPF. NAC use data is missing for two participants randomized to placebo.

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Time to Death or Disease (IPF) Progression.
Measure Description	The median time to death or disease progression was based on Kaplan-Meier (KM) estimates of pooling over strata, and was defined as the first occurrence of any of the following: • Either 1) a decrease of ≥ 10% in FVC (L) and a decrease of ≥ 5% in diffuse lung capacity for carbon monoxide (DLCO) (ml/min/mmHg), or 2) a decrease of ≥ 5% in FVC (L) and a decrease of ≥ 15% in DLCO (ml/min/mmHg); deterioration in FVC and DLCO must be confirmed at the subsequent visit within 28 (± 14) days • Respiratory hospitalization (hospitalization involving worsening of, or deterioration in respiratory symptoms, gas exchange/hypoxemia, or radiographic findings on chest x-ray or high-resolution computerised tomography (HRCT) scan • All-cause mortality
Time Frame	Up to 48 months
Safety Issue?	No

Analysis Population Description

Full Analysis Set: participants who were randomized and treated

Reporting Groups

	Description
Ambrisentan	Ambrisentan (5 mg or 10 mg tablet) administered orally once daily
Placebo	Placebo to match ambrisentan administered orally once daily

Measured Values

	Ambrisentan	Placebo
Number of Participants Analyzed	329	163
Time to Death or Disease (IPF) Progression. [units: weeks] Median (Inter-Quartile Range)	84.14 (36.00 to NA) [1]	NA (60.00 to NA) [1]

[1] Insufficient data for estimation due to study termination

Statistical Analysis 1 for Time to Death or Disease (IPF) Progression.

Statistical Analysis Overview	Comparison Groups	Ambrisentan, Placebo
	Comments	[Not specified]

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

Statistical Test of Hypothesis	P-Value	0.010
	Comments	P-value was based on a stratified log-rank test with strata of baseline presence of pulmonary hypertension and whether a surgical lung biopsy was performed with definite or probable usual interstitial pneumonia (UIP) based on core pathology review.
	Method	Log Rank
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Hazard Ratio (HR)
	Estimated Value	1.74
	Confidence Interval	(2-Sided) 95% 1.14 to 2.66
	Estimation Comments	The hazard ratio was based on a stratified Cox proportional hazards model with strata of baseline presence of pulmonary hypertension and whether a surgical lung biopsy was performed with definite or probable UIP based on core pathology review.

2. Secondary Outcome Measure:

Measure Title	Proportion of Participants With No Disease Progression or Death at 48 Weeks
Measure Description	The proportion of participants with no disease progression or death is presented as a percentage using a Kaplan-Meier (KM) estimate of survival or not experiencing disease progression.
Time Frame	Baseline and Week 48
Safety Issue?	No

Analysis Population Description
Full Analysis Set

Reporting Groups

	Description
Ambrisentan	Ambrisentan (5 mg or 10 mg tablet) administered orally once daily
Placebo	Placebo to match ambrisentan administered orally once daily

Measured Values

	Ambrisentan	Placebo
Number of Participants Analyzed	329	163
Proportion of Participants With No Disease Progression or Death at 48 Weeks [units: percentage of participants]	65	80

3. Secondary Outcome Measure:

Measure Title	Change in FVC % Predicted at Week 48
Measure Description	FVC is defined as the volume of air (liters) that can forcibly be blown out after taking a full breath. FVC % predicted is defined as FVC % of the participant divided by the average FVC % in the population for any person of similar age, sex, and body composition.
Time Frame	Baseline and Week 48
Safety Issue?	No

Analysis Population Description

Participants in the Full Analysis Set with evaluable change data were analyzed.

Reporting Groups

	Description
Ambrisentan	Ambrisentan (5 mg or 10 mg tablet) administered orally once daily
Placebo	Placebo to match ambrisentan administered orally once daily

Measured Values

	Ambrisentan	Placebo
Number of Participants Analyzed	163	80
Change in FVC % Predicted at Week 48 [units: percent change in FVC % predicted] Mean (Standard Deviation)	-10.24 (25.95)	-5.28 (15.68)

Statistical Analysis 1 for Change in FVC % Predicted at Week 48

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

Statistical Test of Hypothesis	P-Value	0.086
	Comments	P-value was calculated using the Van Elteren test with strata of baseline presence of PH and whether a SLB was performed with definite or probable UIP based on core pathology review.
	Method	Other [Van Elteren test]
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Other [Point estimate]
	Estimated Value	4.29
	Confidence Interval	(2-Sided) 95% -0.805 to 9.376
	Estimation Comments	The point estimate and 95% confidence interval (CI) were based on the Hodges-Lehmann Estimate of treatment effect for percent change from baseline.

4. Secondary Outcome Measure:

Measure Title	Change in DLCO % Predicted at Week 48
Measure Description	DLCO is the extent to which oxygen passes from the air sacs of the lungs into the blood. DLCO % predicted is defined as DLCO % of the participant divided by the average DLCO % in the population for any person of similar age, sex and body composition.
Time Frame	Baseline and Week 48
Safety Issue?	No

Analysis Population Description

Participants in the Full Analysis Set with evaluable change data were analyzed.

Reporting Groups

	Description
Ambrisentan	Ambrisentan (5 mg or 10 mg tablet) administered orally once daily

	Description
Placebo	Placebo to match ambrisentan administered orally once daily

Measured Values

	Ambrisentan	Placebo
Number of Participants Analyzed	163	80
Change in DLCO % Predicted at Week 48 [units: percent change in DLCO % predicted] Mean (Standard Deviation)	-2.68 (27.60)	-11.28 (32.06)

Statistical Analysis 1 for Change in DLCO % Predicted at Week 48

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

Statistical Test of Hypothesis	P-Value	0.250
	Comments	P-value was calculated using the Van Elteren test with strata of baseline presence of PH and whether a SLB was performed with definite or probable UIP based on core pathology review.
	Method	Other [Van Elteren test]
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Other [Point estimate]
	Estimated Value	2.85
	Confidence Interval	(2-Sided) 95% -2.20 to 7.90
	Estimation Comments	The point estimate and its 95% CI were based on the Hodges-Lehmann Estimate of treatment effect for percent change from baseline.

5. Secondary Outcome Measure:

Measure Title	Change in 6MWT at Week 48

Measure Description	The 6MWT 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 and Week 48
Safety Issue?	No

Analysis Population Description

Participants in the Full Analysis Set with evaluable change data were analyzed.

Reporting Groups

	Description
Ambrisentan	Ambrisentan (5 mg or 10 mg tablet) administered orally once daily
Placebo	Placebo to match ambrisentan administered orally once daily

Measured Values

	Ambrisentan	Placebo
Number of Participants Analyzed	162	80
Change in 6MWT at Week 48 [units: meters] Mean (Standard Deviation)	-52.5 (148.7)	-10.6 (89.8)

Statistical Analysis 1 for Change in 6MWT at Week 48

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

Statistical Test of Hypothesis	P-Value	0.150
	Comments	P-value was calculated using the Van Elteren test with strata of baseline presence of PH and whether a SLB was performed with definite or probable UIP based on core pathology review.
	Method	Other [Van Elteren test]
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Other [Point estimate]
	Estimated Value	16.00
	Confidence Interval	(2-Sided) 95% -5.00 to 37.00
	Estimation Comments	The point estimate and 95% CI were based on the Hodges-Lehmann Estimate of treatment effect for percent change from baseline.

6. Secondary Outcome Measure:

Measure Title	Change in Quality of Life (QOL) Score at Week 48 as Assessed by the Short-Form 36® (SF-36)
Measure Description	The range of each health domain score is 0-100, with 0 indicating a poorer health state and 100 indicating a better health state. An increase in score indicates an improvement in health state.
Time Frame	Baseline and Week 48
Safety Issue?	No

Analysis Population Description

Participants in the Full Analysis Set with evaluable change data were analyzed.

Reporting Groups

	Description
Ambrisentan	Ambrisentan (5 mg or 10 mg tablet) administered orally once daily
Placebo	Placebo to match ambrisentan administered orally once daily

Measured Values

	Ambrisentan	Placebo
Number of Participants Analyzed	158	78
Change in Quality of Life (QOL) Score at Week 48 as Assessed by the Short-Form 36® (SF-36) [units: units on a scale] Mean (Standard Deviation)		
Physical function	-1.65 (10.86)	-2.60 (7.25)
General Health	-2.81 (9.77)	-1.95 (8.63)
Vitality	-1.67 (12.67)	-0.12 (7.69)

7. Secondary Outcome Measure:

Measure Title	Change in Quality of Life (QOL) Score at Week 48 as Assessed by the St. George's Respiratory Questionnaire (SGRQ)
Measure Description	The SGRQ is designed to measure impact on overall health, daily life, and perceived well-being in participants with obstructive airways disease. The range of each score is 0-100, with 0 indicating fewer limitations and 100 indicating more limitations; an increase in score indicates an increase in limitations.
Time Frame	Baseline and Week 48
Safety Issue?	No

Analysis Population Description

Participants in the Full Analysis Set with evaluable change data were analyzed.

Reporting Groups

	Description
Ambrisentan	Ambrisentan (5 mg or 10 mg tablet) administered orally once daily
Placebo	Placebo to match ambrisentan administered orally once daily

Measured Values

	Ambrisentan	Placebo
Number of Participants Analyzed	159	78
Change in Quality of Life (QOL) Score at Week 48 as Assessed by the St. George's Respiratory Questionnaire (SGRQ) [units: units on a scale] Mean (Standard Deviation)		
Symptoms Score	3.30 (22.11)	2.84 (20.43)
Activity Score	5.54 (19.38)	2.05 (16.47)
Impacts Score	4.68 (24.07)	3.09 (15.80)
Total Score	4.70 (19.92)	3.04 (13.80)

8. Secondary Outcome Measure:

Measure Title	Change in Dyspnea Score at Week 48 as Assessed by the Transitional Dyspnea Index (TDI)

Measure Description	The transitional focal score (-9 to 9) is the sum of relative change from baseline for the Functional Impairment, Magnitude of Task, and Magnitude of Effort scores (each -3 to 3 scale). A TDI score of -9 represents a maximum degradation of all three tests; a score of 9 represents a maximum improvement of all three tests.
Time Frame	Baseline and Week 48
Safety Issue?	No

Analysis Population Description

Participants in the Full Analysis Set with evaluable change data were analyzed.

Reporting Groups

	Description
Ambrisentan	Ambrisentan (5 mg or 10 mg tablet) administered orally once daily
Placebo	Placebo to match ambrisentan administered orally once daily

Measured Values

	Ambrisentan	Placebo
Number of Participants Analyzed	163	80
Change in Dyspnea Score at Week 48 as Assessed by the Transitional Dyspnea Index (TDI) [units: units on a scale] Mean (Standard Deviation)	-1.23 (3.74)	-0.84 (2.99)

Statistical Analysis 1 for Change in Dyspnea Score at Week 48 as Assessed by the Transitional Dyspnea Index (TDI)

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

Statistical Test of Hypothesis	P-Value	0.793
	Comments	The p-value was based on a Wilcoxon rank sum test stratified by baseline pulmonary hypertension (Yes/No) and surgical lung biopsy was performed with definite or probable UIP based on core pathology review (Yes/No).
	Method	Wilcoxon (Mann-Whitney)

	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Other [Point estimate]
	Estimated Value	0.50
	Confidence Interval	(2-Sided) 95% 0.00 to 1.00
	Estimation Comments	The point estimate and 95% confidence interval were based on the Hodges-Lehmann Estimate of treatment effect

9. Secondary Outcome Measure:

Measure Title	Percentage of Participants Who Developed PH on Study
Measure Description	The percentage of participants known to have developed pulmonary hypertension on study documented by right heart catheterization (RHC) was analyzed. RHC was done at baseline and 48 weeks, or at the early termination visit.
Time Frame	Up to 48 weeks
Safety Issue?	No

Analysis Population Description

Participants in the Full Analysis Set without PH at baseline were analyzed.

Reporting Groups

	Description
Ambrisentan	Ambrisentan (5 mg or 10 mg tablet) administered orally once daily
Placebo	Placebo to match ambrisentan administered orally once daily

Measured Values

	Ambrisentan	Placebo
Number of Participants Analyzed	293	145
Percentage of Participants Who Developed PH on Study [units: percentage of participants]	0.7	2.1

Reported Adverse Events

Time Frame	Up to 48 months
Additional Description	[Not specified]

Reporting Groups

	Description
Ambrisentan	Ambrisentan (5 mg or 10 mg tablet) administered orally once daily
Placebo	Placebo to match ambrisentan administered orally once daily

Serious Adverse Events

	Ambrisentan	Placebo
	Affected/At Risk (%)	Affected/At Risk (%)
Total	73/329 (22.19%)	25/163 (15.34%)
Blood and lymphatic system disorders		
Anaemia [A] †	1/329 (0.3%)	0/163 (0%)
Cardiac disorders		
Acute myocardial infarction [A] †	3/329 (0.91%)	0/163 (0%)
Angina pectoris [A] †	1/329 (0.3%)	0/163 (0%)
Angina unstable [A] †	1/329 (0.3%)	0/163 (0%)
Atrial fibrillation [A] †	2/329 (0.61%)	0/163 (0%)
Cardiac failure congestive [A] †	4/329 (1.22%)	0/163 (0%)
Cardiac ventricular disorder [A] †	1/329 (0.3%)	0/163 (0%)
Cardiomegaly [A] †	1/329 (0.3%)	0/163 (0%)
Dilatation atrial [A] †	1/329 (0.3%)	0/163 (0%)
Electromechanical dissociation [A] †	1/329 (0.3%)	0/163 (0%)
Extrasystoles [A] †	1/329 (0.3%)	0/163 (0%)
Palpitations [A] †	1/329 (0.3%)	0/163 (0%)

	Ambrisentan	Placebo
	Affected/At Risk (%)	Affected/At Risk (%)
Sinus tachycardia [A] †	1/329 (0.3%)	0/163 (0%)
Tricuspid valve incompetence [A] †	1/329 (0.3%)	0/163 (0%)
Ear and labyrinth disorders		
Acute vestibular syndrome [A] †	1/329 (0.3%)	0/163 (0%)
Eye disorders		
Cataract [A] †	0/329 (0%)	1/163 (0.61%)
Choroidal haemorrage [A] †	0/329 (0%)	1/163 (0.61%)
Visual impairment [A] †	1/329 (0.3%)	0/163 (0%)
Gastrointestinal disorders		
Abdominal pain upper [A] †	0/329 (0%)	1/163 (0.61%)
Aptyalism [A] †	0/329 (0%)	1/163 (0.61%)
Colitis [A] †	1/329 (0.3%)	1/163 (0.61%)
Colonic polyp [A] †	1/329 (0.3%)	0/163 (0%)
Constipation [A] †	4/329 (1.22%)	0/163 (0%)
Diarrhoea [A] †	1/329 (0.3%)	1/163 (0.61%)
Gastrooesophageal reflux disease [A] †	2/329 (0.61%)	2/163 (1.23%)
Nausea [A] †	2/329 (0.61%)	0/163 (0%)
Small intestinal obstruction [A] †	1/329 (0.3%)	0/163 (0%)
Upper gastrointestinal haemorrhage [A] †	1/329 (0.3%)	0/163 (0%)
General disorders		
Catheter site haemorrhage [A] †	1/329 (0.3%)	0/163 (0%)
Chest pain [A] †	2/329 (0.61%)	1/163 (0.61%)
Fatigue [A] †	2/329 (0.61%)	0/163 (0%)

	Ambrisentan	Placebo
	Affected/At Risk (%)	Affected/At Risk (%)
Hyperthermia [A] †	1/329 (0.3%)	0/163 (0%)
Influenza like illness [A] †	1/329 (0.3%)	0/163 (0%)
Oedema [A] †	1/329 (0.3%)	0/163 (0%)
Oedema peripheral [A] †	4/329 (1.22%)	1/163 (0.61%)
Pain [A] †	2/329 (0.61%)	0/163 (0%)
Pyrexia [A] †	2/329 (0.61%)	0/163 (0%)
Infections and infestations		
Appendicitis [A] †	0/329 (0%)	1/163 (0.61%)
Bacteraemia [A] †	0/329 (0%)	1/163 (0.61%)
Bronchitis [A] †	3/329 (0.91%)	0/163 (0%)
Bronchopneumonia [A] †	1/329 (0.3%)	0/163 (0%)
Cellulitis [A] †	2/329 (0.61%)	0/163 (0%)
Conjunctivitis viral [A] †	1/329 (0.3%)	0/163 (0%)
Endocarditis bacterial [A] †	1/329 (0.3%)	1/163 (0.61%)
Infection [A] †	1/329 (0.3%)	0/163 (0%)
Influenza [A] †	2/329 (0.61%)	0/163 (0%)
Lobar pneumonia [A] †	1/329 (0.3%)	1/163 (0.61%)
Lower respiratory tract infection [A] †	0/329 (0%)	1/163 (0.61%)
Nasopharyngitis [A] †	2/329 (0.61%)	2/163 (1.23%)
Oral candidiasis [A] †	1/329 (0.3%)	0/163 (0%)
Pharyngitis [A] †	1/329 (0.3%)	0/163 (0%)
Pneumonia [A] †	9/329 (2.74%)	2/163 (1.23%)

	Ambrisentan	Placebo
	Affected/At Risk (%)	Affected/At Risk (%)
Respiratory tract infection [A] †	2/329 (0.61%)	1/163 (0.61%)
Sepsis [A] †	2/329 (0.61%)	0/163 (0%)
Sinusitis [A] †	1/329 (0.3%)	0/163 (0%)
Upper respiratory tract infection [A] †	1/329 (0.3%)	1/163 (0.61%)
Urinary tract infection [A] †	1/329 (0.3%)	0/163 (0%)
Injury, poisoning and procedural complications		
Rib fracture [A] †	1/329 (0.3%)	0/163 (0%)
Road traffic accident [A] †	1/329 (0.3%)	0/163 (0%)
Investigations		
Alanine aminotransferase increased [A] †	0/329 (0%)	2/163 (1.23%)
Aspartate aminotransferase increased [A] †	0/329 (0%)	1/163 (0.61%)
Computerised tomogram thorax abnormal [A] †	1/329 (0.3%)	0/163 (0%)
Electrocardiogram ST-T segment abnormal [A] †	1/329 (0.3%)	0/163 (0%)
Electrocardiogram T wave inversion [A] †	1/329 (0.3%)	0/163 (0%)
Hepatic enzyme increased [A] †	0/329 (0%)	1/163 (0.61%)
Metabolism and nutrition disorders		
Anorexia [A] †	1/329 (0.3%)	0/163 (0%)
Diabetic ketoacidosis [A] †	1/329 (0.3%)	0/163 (0%)
Hyperglycaemia [A] †	2/329 (0.61%)	0/163 (0%)
Hyperkalaemia [A] †	4/329 (1.22%)	0/163 (0%)
Hypokalaemia [A] †	2/329 (0.61%)	0/163 (0%)

	Ambrisentan	Placebo
	Affected/At Risk (%)	Affected/At Risk (%)
Hypophosphataemia [A] †	1/329 (0.3%)	0/163 (0%)
Musculoskeletal and connective tissue disorders		
Back pain [A] †	1/329 (0.3%)	0/163 (0%)
Clubbing [A] †	1/329 (0.3%)	0/163 (0%)
Joint swelling [A] †	0/329 (0%)	1/163 (0.61%)
Musculoskeletal pain [A] †	1/329 (0.3%)	0/163 (0%)
Myalgia [A] †	1/329 (0.3%)	0/163 (0%)
Osteoarthritis [A] †	2/329 (0.61%)	1/163 (0.61%)
Pain in jaw [A] †	1/329 (0.3%)	0/163 (0%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Basal cell carcinoma [A] †	0/329 (0%)	1/163 (0.61%)
Lung neoplasm malignant [A] †	1/329 (0.3%)	0/163 (0%)
Malignant melanoma [A] †	0/329 (0%)	1/163 (0.61%)
Prostate cancer [A] †	1/329 (0.3%)	0/163 (0%)
Prostate cancer metastatic [A] †	1/329 (0.3%)	0/163 (0%)
Squamous cell carcinoma [A] †	1/329 (0.3%)	0/163 (0%)
Nervous system disorders		
Carotid artery stenosis [A] †	1/329 (0.3%)	0/163 (0%)
Cerebrovascular accident [A] †	1/329 (0.3%)	0/163 (0%)
Coma [A] †	1/329 (0.3%)	0/163 (0%)
Grand mal convulsion [A] †	1/329 (0.3%)	0/163 (0%)
Headache [A] †	5/329 (1.52%)	1/163 (0.61%)

	Ambrisentan	Placebo
	Affected/At Risk (%)	Affected/At Risk (%)
Hypoaesthesia [A] †	1/329 (0.3%)	0/163 (0%)
Ischaemic stroke [A] †	1/329 (0.3%)	0/163 (0%)
Nerve compression [A] †	1/329 (0.3%)	0/163 (0%)
Somnolence [A] †	1/329 (0.3%)	0/163 (0%)
Syncope [A] †	1/329 (0.3%)	1/163 (0.61%)
Psychiatric disorders		
Anxiety [A] †	3/329 (0.91%)	0/163 (0%)
Delirium [A] †	1/329 (0.3%)	0/163 (0%)
Insomnia [A] †	1/329 (0.3%)	0/163 (0%)
Renal and urinary disorders		
Renal failure [A] †	1/329 (0.3%)	0/163 (0%)
Renal failure acute [A] †	2/329 (0.61%)	0/163 (0%)
Reproductive system and breast disorders		
Benign prostatic hyperplasia [A] †	1/329 (0.3%)	0/163 (0%)
Prostatomegaly [A] †	0/329 (0%)	1/163 (0.61%)
Respiratory, thoracic and mediastinal disorders		
Acute respiratory failure [A] †	5/329 (1.52%)	1/163 (0.61%)
Choking [A] †	1/329 (0.3%)	0/163 (0%)
Cough [A] †	4/329 (1.22%)	1/163 (0.61%)
Dyspnoea [A] †	17/329 (5.17%)	2/163 (1.23%)
Emphysema [A] †	2/329 (0.61%)	0/163 (0%)
Epistaxis [A] †	0/329 (0%)	1/163 (0.61%)
Haemoptysis [A] †	4/329 (1.22%)	0/163 (0%)

	Ambrisentan	Placebo
	Affected/At Risk (%)	Affected/At Risk (%)
Hiccups [A] †	1/329 (0.3%)	0/163 (0%)
Hypoxia [A] †	1/329 (0.3%)	0/163 (0%)
Idiopathic pulmonary fibrosis [A] †	20/329 (6.08%)	4/163 (2.45%)
Nasal congestion [A] †	4/329 (1.22%)	0/163 (0%)
Pleurisy [A] †	1/329 (0.3%)	0/163 (0%)
Pneumonitis [A] †	1/329 (0.3%)	0/163 (0%)
Pneumothorax [A] †	1/329 (0.3%)	0/163 (0%)
Productive cough [A] †	1/329 (0.3%)	0/163 (0%)
Pulmonary alveolar haemorrhage [A] †	1/329 (0.3%)	0/163 (0%)
Pulmonary embolism [A] †	0/329 (0%)	1/163 (0.61%)
Pulmonary fibrosis [A] †	2/329 (0.61%)	0/163 (0%)
Respiratory arrest [A] †	1/329 (0.3%)	0/163 (0%)
Respiratory failure [A] †	4/329 (1.22%)	0/163 (0%)
Rhinitis allergic [A] †	1/329 (0.3%)	0/163 (0%)
Rhinorrhoea [A] †	1/329 (0.3%)	0/163 (0%)
Skin and subcutaneous tissue disorders		
Rash [A] †	0/329 (0%)	1/163 (0.61%)
Vascular disorders		
Flushing [A] †	1/329 (0.3%)	0/163 (0%)
Hot flush [A] †	1/329 (0.3%)	0/163 (0%)
Hypertension [A] †	3/329 (0.91%)	0/163 (0%)
Hypotension [A] †	4/329 (1.22%)	1/163 (0.61%)

	Ambrisentan	Placebo
	Affected/At Risk (%)	Affected/At Risk (%)
Peripheral ischaemia [A] †	1/329 (0.3%)	0/163 (0%)
Subclavian vein thrombosis [A] †	1/329 (0.3%)	0/163 (0%)

† Indicates events were collected by systematic assessment.
A Term from vocabulary, MedDRA (11.1)

Other Adverse Events

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

	Ambrisentan	Placebo
	Affected/At Risk (%)	Affected/At Risk (%)
Total	227/329 (69%)	104/163 (63.8%)
Gastrointestinal disorders		
Constipation [A] †	19/329 (5.78%)	10/163 (6.13%)
Diarrhoea [A] †	20/329 (6.08%)	8/163 (4.91%)
Nausea [A] †	15/329 (4.56%)	9/163 (5.52%)
General disorders		
Fatigue [A] †	22/329 (6.69%)	14/163 (8.59%)
Oedema peripheral [A] †	73/329 (22.19%)	14/163 (8.59%)
Infections and infestations		
Bronchitis [A] †	23/329 (6.99%)	15/163 (9.2%)
Nasopharyngitis [A] †	37/329 (11.25%)	18/163 (11.04%)
Respiratory tract infection [A] †	9/329 (2.74%)	12/163 (7.36%)
Sinusitis [A] †	20/329 (6.08%)	6/163 (3.68%)
Musculoskeletal and connective tissue disorders		
Back pain [A] †	18/329 (5.47%)	5/163 (3.07%)
Nervous system disorders		

	Ambrisentan	Placebo
	Affected/At Risk (%)	Affected/At Risk (%)
Dizziness [A] †	20/329 (6.08%)	2/163 (1.23%)
Headache [A] †	47/329 (14.29%)	17/163 (10.43%)
Respiratory, thoracic and mediastinal disorders		
Cough [A] †	34/329 (10.33%)	20/163 (12.27%)
Dyspnoea [A] †	40/329 (12.16%)	11/163 (6.75%)
Idiopathic pulmonary fibrosis [A] †	19/329 (5.78%)	2/163 (1.23%)
Nasal congestion [A] †	27/329 (8.21%)	6/163 (3.68%)
Productive cough [A] †	8/329 (2.43%)	9/163 (5.52%)
Upper respiratory tract infection [A] †	47/329 (14.29%)	18/163 (11.04%)

† Indicates events were collected by systematic assessment.
A Term from vocabulary, MedDRA (11.1)

Limitations and Caveats

[Not specified]

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.

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

- The results of the study in their entirety have been publicly disclosed by or with the consent of Gilead in an abstract, manuscript, or presentation form; or
- The study has been completed at all study sites for at least 2 years

Results Point of Contact:

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