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ARTEMIS-PH - Study of Ambrisentan in Subjects With Pulmonary Hypertension Associated With Idiopathic Pulmonary Fibrosis

This study has been terminated.

Sponsor:	Gilead Sciences
Collaborators:	
Information provided by (Responsible Party):	Gilead Sciences
ClinicalTrials.gov Identifier:	NCT00879229

Purpose

Ambrisentan is an endothelin receptor antagonist used for the treatment of pulmonary hypertension (PH). Based on research suggesting a role for endothelin-1 in the pathogenesis of idiopathic pulmonary fibrosis (IPF) and the poor prognosis for patients with IPF who are also diagnosed with PH, this study was designed to evaluate the effectiveness and safety of ambrisentan in that patient population.

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

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

Further study details as provided by Gilead Sciences:

Primary Outcome Measure:

- Change From Baseline in Six-minute Walk Distance (6MWD). [Time Frame: Baseline to Week 16] [Designated as safety issue: No]

The change from baseline in 6MWD at Week 16 (end of blinded treatment) was evaluated.

Secondary Outcome Measures:

- Long-term Survival [Time Frame: Week 48] [Designated as safety issue: No]
  Long-term survival was assessed as a Kaplan-Meier (KM) estimate of the percent probability of survival, with censoring at Week 48.
- Transition Dyspnea Index (TDI) [Time Frame: Baseline to Week 16] [Designated as safety issue: No]
  The change in TDI at Week 16 (end of blinded treatment) was evaluated. TDI measures the change from the baseline characteristic "Baseline Dyspnea Index." The TDI range is -9 to +9 (worst to best; 0 = no change).
- Change From Baseline in WHO Functional Class [Time Frame: Baseline to Week 16] [Designated as safety issue: No]
  WHO functional class rates severity of pulmonary hypertension, with 4 categories on a scale of 1 to 4 with the worst category being 4. Change is represented as an increase ("+1: Improved"), decrease ("-1: Deteriorated"), or no change ("0: No change") on the scale.
- Change From Baseline in Forced Vital Capacity (FVC) Percent Predicted [Time Frame: Baseline to Week 16] [Designated as safety issue: No]
  FVC is a pulmonary function test, and is defined as the volume of air that can forcibly be blown out after taking a full breath. FVC% predicted is defined as FVC% of the patient divided by the average FVC% in the population for any person of similar age, sex and body composition.
- Change From Baseline in N-terminal Pro-B-type Natriuretic Peptide (NT-proBNP) [Time Frame: Baseline to Week 16] [Designated as safety issue: No]
  Assessment of the the level of the amino acid fragment NT-proBNP is used to establish prognosis in cardiovascular disease.
- Change From Baseline in the Borg Dyspnea Index (BORG) Immediately Following Exercise [Time Frame: Baseline to Week 16] [Designated as safety issue: No]
  Borg Dyspnea Index is a measure of perceived shortness of breath: 0 units on a scale (none) to 10 units on a scale (maximum breathlessness).
- Hemoglobin-corrected Diffusing Capacity for Carbon Monoxide (DLCO) Percent Predicted [Time Frame: Baseline to Week 16] [Designated as safety issue: No]
  DLCO is a pulmonary function test, and measures the partial pressure difference between inspired and expired carbon monoxide. DLCO% predicted is defined as DLCO% of the patient divided by the average DLCO% in the population for any person of similar age, sex and body composition.
- Change in Quality of Life (QOL) Score as Assessed by the Short-Form 36® (SF-36) [Time Frame: Baseline to Week 16] [Designated as safety issue: No]
  Each SF-36 score is directly transformed into a 0-100 scale on the assumption that each question carries equal weight. An increase in score indicates an improvement in health state.
- Change in QOL Score as Assessed by the St. George's Respiratory Questionnaire (SRGQ) [Time Frame: Baseline to Week 16] [Designated as safety issue: No]
  The SRGQ is designed to measure impact on overall health, daily life, and perceived well-being in patients with obstructive airways disease. Patients respond to questions about symptoms (frequency & severity) and impact components (social functioning and psychological disturbances resulting from airways disease). Scores range from 0 to 100, with higher scores indicating more limitations.

Enrollment: 40
Study Start Date: July 2009
Primary Completion Date: February 2011
Study Completion Date: February 2011

Arms	Assigned Interventions
Experimental: Ambrisentan Participants were randomized to receive ambrisentan treatment at an initial dose of 5 mg for 4 weeks, followed by ambrisentan at the target dose of 10 mg for an additional 52 weeks	Drug: Ambrisentan Ambrisentan (5 mg or 10 mg tablet) administered orally once daily. Other Names: Letairis

Arms	Assigned Interventions
Placebo Comparator: Placebo Participants were randomized to receive placebo to match ambrisentan for 48 weeks, then transition to ambrisentan treatment at the initial dose of 5 mg for 4 weeks, followed by ambrisentan at the target dose of 10 mg for an additional 4 weeks.	Drug: Ambrisentan Ambrisentan (5 mg or 10 mg tablet) administered orally once daily. Other Names: Letairis Drug: Placebo Placebo to match ambrisentan administered orally once daily.

Eligibility

Ages Eligible for Study: 35 Years to 80 Years
Genders Eligible for Study: Both
Accepts Healthy Volunteers: No

Criteria

Selected Inclusion Criteria:

- Weight ≥ 40 kg at screening
- Diagnosis of IPF based on modified American Thoracic Society-European Respiratory Society guidelines
- Diagnosis of PH based on the following hemodynamic requirements: mean pulmonary artery pressure (mPAP ≥ 25 mm Hg; pulmonary vascular resistance > 240 dyne.sec/cm^5; pulmonary capillary wedge pressure or left ventricular end-diastolic pressure ≤ 15 mm Hg
- Forced vital capacity (FVC) ≥ 40%
- Able to walk at least 50 meters during two 6-minute walk tests
- If receiving calcium channel blockers, low-dose oral corticosteroids, immunosuppressive, cytoxic, or antifibrotic drugs dose must have been stable.

Selected Exclusion Criteria:

- Diagnosis of PH primarily due to an etiology other than IPF
- Surgical lung biopsy diagnosis other than Usual Interstitial Pneumonia
- Other known cause of interstitial lung disease
- Evidence of significant obstructive lung disease
- Recent hospitalization for an acute exacerbation of IPF
- Recent active pulmonary or upper respiratory tract infection
- Left ventricular ejection fraction < 40%
- Serum creatinine ≥ 2.5 mg/dL
- Required hemodialysis, peritoneal dialysis, or hemofiltration
- Female subject who was pregnant or breastfeeding
- Recent treatment for PH with an endothelin receptor antagonist (ERA), phosphodiesterase type 5 inhibitor, or prostacyclin derivative
- Recent treatment with high dose oral corticosteroids
- Recent treatment (within 4 weeks prior to screening) with imatinib mesylate (Gleevec)
- Alanine aminotransferase or aspartate aminotransferase lab value that was greater than 1.5 x the upper limit of the normal range

- Discontinued other ERA treatment for any adverse reaction other than those associated with liver function test abnormalities

Contacts and Locations

Locations

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Investigators

Study Director:	Hunter Gillies, M.D.	Gilead Sciences

More Information

Responsible Party:	Gilead Sciences
Study ID Numbers:	GS-US-300-0128
Health Authority:	United States: Food and Drug Administration

Study Results

Participant Flow

Recruitment Details	Subjects were enrolled in a total of 29 study sites in Australia, Europe, and North America. The first participant was screened on 21 October 2009. The last participant observation was on 22 February 2011.
Pre-Assignment Details	96 participants were screened; 40 participants were randomized and treated, and comprise the Safety Analysis Set and the Full Analysis Set.

Reporting Groups

	Description
Ambrisentan	Participants were randomized to receive ambrisentan treatment for 56 weeks
Placebo	Participants were randomized to receive placebo for 48 weeks, followed by ambrisentan treatment for 8 weeks.

Overall Study

	Ambrisentan	Placebo
Started	25	15
Completed	3	1
Not Completed	22	14
Study terminated by Sponsor	13	12
Death	4	2
Adverse Event	2	0
Withdrawal by Subject	1	0
Clinical status did not improve	1	0
Unknown	1	0

Baseline Characteristics

Analysis Population Description

Full Analysis Set: participants who were randomized and received at least one dose of study drug

Reporting Groups

	Description
Ambrisentan	Participants were randomized to receive ambrisentan treatment for 56 weeks
Placebo	Participants were randomized to receive placebo for 48 weeks, followed by ambrisentan treatment for 8 weeks.

Baseline Measures

	Ambrisentan	Placebo	Total
Number of Participants	25	15	40
Age, Continuous [units: years] Mean (Standard Deviation)	68 (7.7)	68 (5.2)	68 (6.8)
Gender, Male/Female [units: participants]			
Female	5	5	10
Male	20	10	30
Race/Ethnicity, Customized			

	Ambrisentan	Placebo	Total
[units: participants]			
White	25	14	39
Asian	0	1	1
Region of Enrollment [units: participants]			
United States	14	9	23
Australia	3	2	5
Italy	4	1	5
Canada	3	1	4
Germany	1	2	3
Baseline Dyspnea Index (BDI) [1] [units: units on a scale] Mean (Standard Deviation)	5.0 (2.15)	4.4 (2.10)	4.8 (2.13)

[1] BDI range is 0 to 12 (worst to best).

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Change From Baseline in Six-minute Walk Distance (6MWD).
Measure Description	The change from baseline in 6MWD at Week 16 (end of blinded treatment) was evaluated.
Time Frame	Baseline to Week 16
Safety Issue?	No

Analysis Population Description

Participants in the Full Analysis Set (randomized and received at least one dose of study medication) with evaluable data were analyzed.

Reporting Groups

	Description
Ambrisentan	Participants were randomized to receive ambrisentan treatment for 56 weeks
Placebo	Participants were randomized to receive placebo for 48 weeks, followed by ambrisentan treatment for 8 weeks.

Measured Values

	Ambrisentan	Placebo
Number of Participants Analyzed	21	9
Change From Baseline in Six-minute Walk Distance (6MWD). [units: meters] Mean (Standard Error)	-96 (38)	-67 (51)

Statistical Analysis 1 for Change From Baseline in Six-minute Walk Distance (6MWD).

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	0.696
	Comments	This is an exact Wilcoxon rank sum test p-value for testing equality of ambrisentan and placebo distributions.
	Method	Wilcoxon (Mann-Whitney)
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-29
	Confidence Interval	(2-Sided) 95% -54 to 17
	Parameter Dispersion	Type: Standard Error of the mean Value: 67
	Estimation Comments	[Not specified]

2. Secondary Outcome Measure:

Measure Title	Long-term Survival
Measure Description	Long-term survival was assessed as a Kaplan-Meier (KM) estimate of the percent probability of survival, with censoring at Week 48.

Time Frame	Week 48
Safety Issue?	No

Analysis Population Description
Full Analysis Set

Reporting Groups

	Description
Ambrisentan	Participants were randomized to receive ambrisentan treatment for 56 weeks
Placebo	Participants were randomized to receive placebo for 48 weeks, followed by ambrisentan treatment for 8 weeks.

Measured Values

	Ambrisentan	Placebo
Number of Participants Analyzed	25	15
Long-term Survival [units: percent probability (KM% estimate)] Number (95% Confidence Interval)	22 (2.6 to 41.0)	23 (0.0 to 52.5)

3. Secondary Outcome Measure:

Measure Title	Transition Dyspnea Index (TDI)
Measure Description	The change in TDI at Week 16 (end of blinded treatment) was evaluated. TDI measures the change from the baseline characteristic "Baseline Dyspnea Index." The TDI range is -9 to +9 (worst to best; 0 = no change).
Time Frame	Baseline to Week 16
Safety Issue?	No

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

Reporting Groups

	Description
Ambrisentan	Participants were randomized to receive ambrisentan treatment for 56 weeks
Placebo	Participants were randomized to receive placebo for 48 weeks, followed by ambrisentan treatment for 8 weeks.

Measured Values

	Ambrisentan	Placebo
Number of Participants Analyzed	14	8
Transition Dyspnea Index (TDI) [units: units on a scale] Mean (Standard Deviation)	-1.5 (3.08)	-1.4 (3.78)

4. Secondary Outcome Measure:

Measure Title	Change From Baseline in WHO Functional Class
Measure Description	WHO functional class rates severity of pulmonary hypertension, with 4 categories on a scale of 1 to 4 with the worst category being 4. Change is represented as an increase ("+1: Improved"), decrease ("-1: Deteriorated"), or no change ("0: No change") on the scale.
Time Frame	Baseline to Week 16
Safety Issue?	No

Analysis Population Description

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

Reporting Groups

	Description
Ambrisentan	Participants were randomized to receive ambrisentan treatment for 56 weeks
Placebo	Participants were randomized to receive placebo for 48 weeks, followed by ambrisentan treatment for 8 weeks.

Measured Values

	Ambrisentan	Placebo
Number of Participants Analyzed	14	8
Change From Baseline in WHO Functional Class [units: units on a scale]		
-1: Deteriorated	0	1
0: No change	11	5
+1: Improved	3	2

5. Secondary Outcome Measure:

Measure Title	Change From Baseline in Forced Vital Capacity (FVC) Percent Predicted
Measure Description	FVC is a pulmonary function test, and is defined as the volume of air that can forcibly be blown out after taking a full breath. FVC% predicted is defined as FVC% of the patient divided by the average FVC% in the population for any person of similar age, sex and body composition.
Time Frame	Baseline to Week 16
Safety Issue?	No

Analysis Population Description

Insufficient data due to study termination

Reporting Groups

	Description
Ambrisentan	Participants were randomized to receive ambrisentan treatment for 56 weeks
Placebo	Participants were randomized to receive placebo for 48 weeks, followed by ambrisentan treatment for 8 weeks.

Measured Values

	Ambrisentan	Placebo
Number of Participants Analyzed	0	0

No data displayed because Outcome Measure has zero total participants analyzed.

6. Secondary Outcome Measure:

Measure Title	Change From Baseline in N-terminal Pro-B-type Natriuretic Peptide (NT-proBNP)
Measure Description	Assessment of the the level of the amino acid fragment NT-proBNP is used to establish prognosis in cardiovascular disease.
Time Frame	Baseline to Week 16
Safety Issue?	No

Analysis Population Description

Insufficient data due to study termination

Reporting Groups

	Description
Ambrisentan	Participants were randomized to receive ambrisentan treatment for 56 weeks

	Description
Placebo	Participants were randomized to receive placebo for 48 weeks, followed by ambrisentan treatment for 8 weeks.

Measured Values

	Ambrisentan	Placebo
Number of Participants Analyzed	0	0

No data displayed because Outcome Measure has zero total participants analyzed.

7. Secondary Outcome Measure:

Measure Title	Change From Baseline in the Borg Dyspnea Index (BORG) Immediately Following Exercise
Measure Description	Borg Dyspnea Index is a measure of perceived shortness of breath: 0 units on a scale (none) to 10 units on a scale (maximum breathlessness).
Time Frame	Baseline to Week 16
Safety Issue?	No

Analysis Population Description

Insufficient data due to study termination

Reporting Groups

	Description
Ambrisentan	Participants were randomized to receive ambrisentan treatment for 56 weeks
Placebo	Participants were randomized to receive placebo for 48 weeks, followed by ambrisentan treatment for 8 weeks.

Measured Values

	Ambrisentan	Placebo
Number of Participants Analyzed	0	0

No data displayed because Outcome Measure has zero total participants analyzed.

8. Secondary Outcome Measure:

Measure Title	Hemoglobin-corrected Diffusing Capacity for Carbon Monoxide (DLCO) Percent Predicted
Measure Description	DLCO is a pulmonary function test, and measures the partial pressure difference between inspired and expired carbon monoxide. DLCO% predicted is defined as DLCO% of the patient divided by the average DLCO% in the population for any person of similar age, sex and body composition.

Time Frame	Baseline to Week 16
Safety Issue?	No

Analysis Population Description
Insufficient data due to study termination

Reporting Groups

	Description
Ambrisentan	Participants were randomized to receive ambrisentan treatment for 56 weeks
Placebo	Participants were randomized to receive placebo for 48 weeks, followed by ambrisentan treatment for 8 weeks.

Measured Values

	Ambrisentan	Placebo
Number of Participants Analyzed	0	0

No data displayed because Outcome Measure has zero total participants analyzed.

9. Secondary Outcome Measure:

Measure Title	Change in Quality of Life (QOL) Score as Assessed by the Short-Form 36® (SF-36)
Measure Description	Each SF-36 score is directly transformed into a 0-100 scale on the assumption that each question carries equal weight. An increase in score indicates an improvement in health state.
Time Frame	Baseline to Week 16
Safety Issue?	No

Analysis Population Description
Insufficient data due to study termination

Reporting Groups

	Description
Ambrisentan	Participants were randomized to receive ambrisentan treatment for 56 weeks
Placebo	Participants were randomized to receive placebo for 48 weeks, followed by ambrisentan treatment for 8 weeks.

Measured Values

	Ambrisentan	Placebo
Number of Participants Analyzed	0	0

No data displayed because Outcome Measure has zero total participants analyzed.

10. Secondary Outcome Measure:

Measure Title	Change in QOL Score as Assessed by the St. George's Respiratory Questionnaire (SRGQ)
Measure Description	The SRGQ is designed to measure impact on overall health, daily life, and perceived well-being in patients with obstructive airways disease. Patients respond to questions about symptoms (frequency & severity) and impact components (social functioning and psychological disturbances resulting from airways disease). Scores range from 0 to 100, with higher scores indicating more limitations.
Time Frame	Baseline to Week 16
Safety Issue?	No

Analysis Population Description

Insufficient data due to study termination

Reporting Groups

	Description
Ambrisentan	Participants were randomized to receive ambrisentan treatment for 56 weeks
Placebo	Participants were randomized to receive placebo for 48 weeks, followed by ambrisentan treatment for 8 weeks.

Measured Values

	Ambrisentan	Placebo
Number of Participants Analyzed	0	0

No data displayed because Outcome Measure has zero total participants analyzed.

Reported Adverse Events

Time Frame	Baseline to end of treatment
Additional Description	Adverse events were collected based on the randomization group and not with regards to the specific treatment received.

Reporting Groups

	Description
Ambrisentan	Participants were randomized to receive ambrisentan treatment for 56 weeks
Placebo	Participants were randomized to receive placebo for 48 weeks, followed by ambrisentan treatment for 8 weeks.

Serious Adverse Events

	Ambrisentan	Placebo
	Affected/At Risk (%)	Affected/At Risk (%)
Total	12/25 (48%)	3/15 (20%)
Blood and lymphatic system disorders		
Anaemia [A] †	1/25 (4%)	0/15 (0%)
Cardiac disorders		
Atrioventricular block complete [A] †	1/25 (4%)	0/15 (0%)
Bradycardia [A] †	1/25 (4%)	0/15 (0%)
Gastrointestinal disorders		
Abdominal pain lower [A] †	1/25 (4%)	0/15 (0%)
Infections and infestations		
Pneumonia [A] †	2/25 (8%)	0/15 (0%)
Respiratory tract infection [A] †	0/25 (0%)	1/15 (6.67%)
Injury, poisoning and procedural complications		
Procedural complication [A] †	0/25 (0%)	1/15 (6.67%)
Investigations		
Electrocardiogram T wave inversion [A] †	1/25 (4%)	0/15 (0%)
Metabolism and nutrition disorders		
Hyperkalaemia [A] †	1/25 (4%)	0/15 (0%)
Musculoskeletal and connective tissue disorders		
Groin pain [A] †	1/25 (4%)	0/15 (0%)

	Ambrisentan	Placebo
	Affected/At Risk (%)	Affected/At Risk (%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Breast cancer [A] †	1/25 (4%)	0/15 (0%)
Renal and urinary disorders		
Renal failure [A] †	1/25 (4%)	0/15 (0%)
Respiratory, thoracic and mediastinal disorders		
Acute respiratory failure [A] †	1/25 (4%)	0/15 (0%)
Dyspnoea [A] †	2/25 (8%)	0/15 (0%)
Haemoptysis [A] †	1/25 (4%)	0/15 (0%)
Hypoxia [A] †	2/25 (8%)	0/15 (0%)
Idiopathic pulmonary fibrosis [A] †	3/25 (12%)	1/15 (6.67%)
Interstitial lung disease [A] †	1/25 (4%)	0/15 (0%)
Pulmonary fibrosis [A] †	1/25 (4%)	0/15 (0%)
Respiratory failure [A] †	1/25 (4%)	0/15 (0%)

† Indicates events were collected by systematic assessment.
A Term from vocabulary, MedDRA (13.1)

Other Adverse Events

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

	Ambrisentan	Placebo
	Affected/At Risk (%)	Affected/At Risk (%)
Total	18/25 (72%)	12/15 (80%)
Blood and lymphatic system disorders		
Anaemia [A] †	1/25 (4%)	1/15 (6.67%)
Cardiac disorders		
Myocardial infarction [A] †	0/25 (0%)	1/15 (6.67%)

	Ambrisentan	Placebo
	Affected/At Risk (%)	Affected/At Risk (%)
Palpitations [A] †	0/25 (0%)	1/15 (6.67%)
Endocrine disorders		
Hyperparathyroidism secondary [A] †	0/25 (0%)	1/15 (6.67%)
Gastrointestinal disorders		
Abdominal discomfort [A] †	0/25 (0%)	1/15 (6.67%)
Abdominal distension [A] †	2/25 (8%)	0/15 (0%)
Abdominal pain [A] †	0/25 (0%)	1/15 (6.67%)
Abdominal pain upper [A] †	1/25 (4%)	1/15 (6.67%)
Constipation [A] †	4/25 (16%)	1/15 (6.67%)
Diarrhoea [A] †	0/25 (0%)	2/15 (13.33%)
Dry mouth [A] †	0/25 (0%)	1/15 (6.67%)
Dyspepsia [A] †	0/25 (0%)	1/15 (6.67%)
Nausea [A] †	0/25 (0%)	2/15 (13.33%)
Vomiting [A] †	0/25 (0%)	1/15 (6.67%)
General disorders		
Chest discomfort [A] †	0/25 (0%)	1/15 (6.67%)
Chest pain [A] †	0/25 (0%)	1/15 (6.67%)
Fatigue [A] †	1/25 (4%)	4/15 (26.67%)
Malaise [A] †	0/25 (0%)	1/15 (6.67%)
Oedema peripheral [A] †	5/25 (20%)	3/15 (20%)
Pyrexia [A] †	2/25 (8%)	0/15 (0%)
Infections and infestations		
Bronchitis [A] †	0/25 (0%)	1/15 (6.67%)

	Ambrisentan	Placebo
	Affected/At Risk (%)	Affected/At Risk (%)
Diverticulitis [A] †	0/25 (0%)	2/15 (13.33%)
Influenza [A] †	0/25 (0%)	1/15 (6.67%)
Lower respiratory tract infection [A] †	0/25 (0%)	2/15 (13.33%)
Nasopharyngitis [A] †	0/25 (0%)	1/15 (6.67%)
Pneumonia [A] †	1/25 (4%)	1/15 (6.67%)
Respiratory tract infection [A] †	1/25 (4%)	1/15 (6.67%)
Rhinitis [A] †	0/25 (0%)	1/15 (6.67%)
Sinusitis [A] †	1/25 (4%)	1/15 (6.67%)
Upper respiratory tract infection [A] †	4/25 (16%)	1/15 (6.67%)
Urinary tract infection [A] †	0/25 (0%)	3/15 (20%)
Viral infection [A] †	0/25 (0%)	1/15 (6.67%)
Injury, poisoning and procedural complications		
Joint sprain [A] †	0/25 (0%)	1/15 (6.67%)
Investigations		
Cardiac murmur [A] †	2/25 (8%)	0/15 (0%)
Eosinophil count increased [A] †	0/25 (0%)	1/15 (6.67%)
Metabolism and nutrition disorders		
Decreased appetite [A] †	0/25 (0%)	1/15 (6.67%)
Hypercalcaemia [A] †	0/25 (0%)	1/15 (6.67%)
Musculoskeletal and connective tissue disorders		
Back pain [A] †	2/25 (8%)	3/15 (20%)
Muscle spasms [A] †	1/25 (4%)	1/15 (6.67%)
Musculoskeletal chest pain [A] †	0/25 (0%)	1/15 (6.67%)

	Ambrisentan	Placebo
	Affected/At Risk (%)	Affected/At Risk (%)
Neck pain [A] †	0/25 (0%)	1/15 (6.67%)
Pain in extremity [A] †	0/25 (0%)	1/15 (6.67%)
Nervous system disorders		
Dizziness [A] †	0/25 (0%)	2/15 (13.33%)
Headache [A] †	5/25 (20%)	3/15 (20%)
Neuropathy peripheral [A] †	0/25 (0%)	1/15 (6.67%)
Syncope [A] †	0/25 (0%)	1/15 (6.67%)
Psychiatric disorders		
Anxiety [A] †	0/25 (0%)	1/15 (6.67%)
Renal and urinary disorders		
Proteinuria [A] †	0/25 (0%)	1/15 (6.67%)
Respiratory, thoracic and mediastinal disorders		
Cough [A] †	3/25 (12%)	2/15 (13.33%)
Dyspnoea [A] †	6/25 (24%)	5/15 (33.33%)
Hypoxia [A] †	2/25 (8%)	1/15 (6.67%)
Nasal congestion [A] †	6/25 (24%)	1/15 (6.67%)
Orthopnoea [A] †	0/25 (0%)	1/15 (6.67%)
Skin and subcutaneous tissue disorders		
Alopecia [A] †	0/25 (0%)	1/15 (6.67%)
Ecchymosis [A] †	0/25 (0%)	1/15 (6.67%)
Hyperhidrosis [A] †	2/25 (8%)	0/15 (0%)
Vascular disorders		
Flushing [A] †	1/25 (4%)	2/15 (13.33%)

† Indicates events were collected by systematic assessment.
A Term from vocabulary, MedDRA (13.1)

Limitations and Caveats

Study GS-US-300-0128 was terminated early with enrollment of 40 of 225 planned subjects.

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

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