

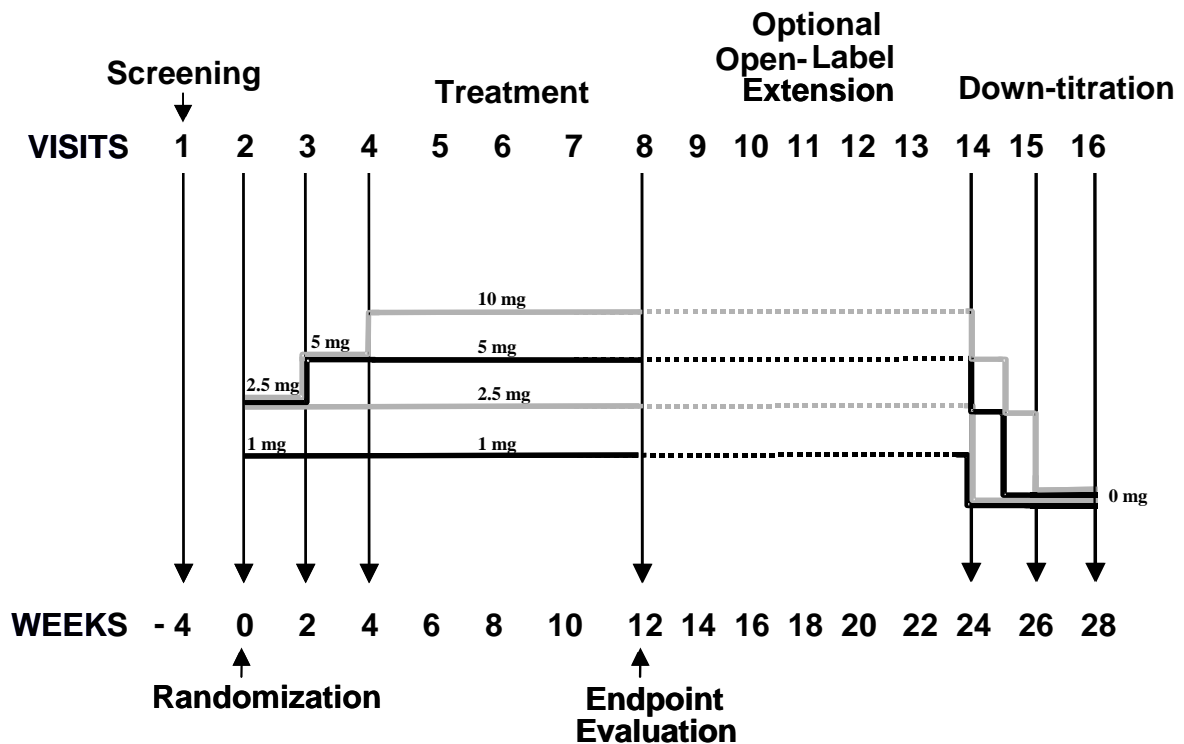


Name of Sponsor/Company Myogen, Inc.	Name of Finished Product Ambrisentan	Name of Active Ingredient Ambrisentan
Protocol Number: AMB-220		
Title of Study: A Phase 2, Randomized, Double-Blind, Dose-Controlled, Dose-Ranging Multicenter Study of Ambrisentan (BSF 208075) Evaluating Exercise Capacity in Patients with Moderate to Severe Pulmonary Arterial Hypertension		
Investigators and Study Centers: 21 Principal Investigators at 21 international investigative sites in 6 countries (US, Germany, France, Belgium, Italy, Australia).		
Publication (reference): Galiè, N, Badesch, D, Oudiz, R et. al. Ambrisentan Therapy for Pulmonary Arterial Hypertension. J Am Coll Cardiol 2005; 46:529-35.		
Studied period (years): 1 Date of First Enrollment: 23 Oct 2002 Date of Last Completed: 03 Sep 2003	Phase of Development: Phase 2	
<p>Objectives: The primary objectives of this study were to examine the effect of ambrisentan on improvement in exercise capacity in subjects with moderate to severe pulmonary arterial hypertension (PAH), and to identify the minimally effective dose and define a dose-response relationship between ambrisentan and improvement in exercise capacity.</p> <p>The secondary objectives of this study were to evaluate:</p> <ul style="list-style-type: none"> • The safety and tolerability of ambrisentan over the planned dose range and duration of exposure • The effect of ambrisentan on the Subject Global Assessment (SGA), World Health Organization (WHO) functional classification, and a composite of clinical outcomes • The effect of ambrisentan on dyspnea as scored by the Borg dyspnea index (BDI) immediately following the 6-minute walk test (6MWT) • The effect of ambrisentan on cardiopulmonary hemodynamics in a selected subset of subjects with moderate to severe PAH • The first-dose and steady-state plasma pharmacokinetics (PK) of ambrisentan in a selected subset of subjects with moderate to severe PAH • The effect of ambrisentan on plasma endothelin-1 (ET-1) levels in a selected subset of subjects with moderate to severe PAH 		
Methodology: The study consisted of 4 periods: a 4-week screening period was followed by a 12-week blinded treatment period (non-OLE), an optional open-label extension (OLE) period, and a 4-week down-titration period. Due to the severity of the disease and the availability of marketed treatments for PAH, a placebo control group was not considered appropriate in this study. Rather, the study was dose-controlled and efficacy assessments at		

specific time points were primarily compared to mean baseline values for each dose group. Following the Screening Visit, eligible subjects were randomized to receive 1, 2.5, 5, or 10 mg of ambrisentan orally (po), once daily in the blinded treatment period. Subjects randomized to the 1 or 2.5 mg dose groups received their respective doses of ambrisentan each day throughout the 12-week blinded treatment period. Subjects in the 2 other dose groups began treatment at 2.5 mg per day for 2 weeks and then their dose was increased to 5 mg for an additional 2 weeks. After 2 weeks of treatment at 5 mg, subjects randomized to the 10 mg dose group underwent a final up-titration. After reaching the randomized dose level, subjects received their assigned dose throughout the blinded treatment period. Subjects were to remain on the randomized treatment through Week 12. In the event that a subject was not tolerating study drug, dose adjustment was permitted during the treatment period. Upon completion of the 12-week blinded treatment period, subjects either completed a 4-week down-titration period or entered the optional 12-week OLE period without down-titration. All subjects that chose to participate in the OLE were unblinded and had their dose of ambrisentan optimized based on the subject's response and tolerance during the initial 12-week blinded treatment period.

Because the additional 12 week open-label extension period was termed the OLE period, the initial 12-week, blinded treatment period was referred to in the summary tables, listings, and figures as the non-OLE period. However, throughout this report, the initial 12-weeks of treatment will be called the blinded treatment period.

Study Schematic



Number of Patients (planned and analyzed): It was anticipated that 60 subjects (15 per dose group) at approximately 15 international investigative sites would be enrolled. The

actual number of subjects enrolled was 64 at 21 investigative sites.

Diagnosis and Main Criteria for Inclusion: Male and female subjects 18 years of age or older with moderate to severe idiopathic pulmonary arterial hypertension (IPAH) or PAH associated with connective tissue disease (e.g., mixed connective tissue disease, systemic lupus erythematosus, systemic sclerosis [scleroderma], or overlap syndrome), anorexigen use, or human immunodeficiency virus (HIV) infection. Subjects were to have a documented mean pulmonary arterial pressure (mPAP) ≥ 25 mmHg, pulmonary vascular resistance (PVR) > 3 mmHg/L/min, and pulmonary wedge pressure or left ventricle end diastolic pressure of < 15 mmHg. Subjects must have been able to walk at least 150 meters (m), but no more than 450 m, in the 6MWT to be eligible for this study.

Test Product, Dose and Mode of Administration, Batch Number: Study drug was supplied for oral administration as round, biconvex, pink, film-coated, immediate release tablets that were identical in size and appearance. Four strengths of study drug were used in this study, containing 0 (placebo), 1, 2.5, and 5 mg of ambrisentan. Two tablets were combined to create a daily dose of 1, 2.5, 5, and 10 mg of ambrisentan per day. All study drug was packaged in blister cards. Each 2-week blister card contained 36 tablets of study drug. Subjects were instructed to take 2 tablets once daily in the morning, at approximately 8:00 a.m. with or without food.

Lot numbers: 0 mg (placebo) = L0001850, 1 mg = L0001852, 2.5 mg = L0001849, 5 mg = L0001851.

Duration of Treatment: The maximum study duration was up to 32 weeks from the time of initial screening procedures to the end of the down-titration period. Screening procedures were to take place up to 4 weeks prior to the start of study drug dosing. The blinded treatment period of the study was from Week 0 through Week 12 (i.e., non-OLE period), and the OLE period from Week 13 to Week 24. The maximum duration of study drug treatment was up to 28 weeks, depending upon study drug dose level and participation in the optional OLE period.

Reference Therapy, Dose and Mode of Administration, Batch Number: None

Endpoints for Evaluation:

Efficacy:

The primary efficacy endpoint was the change from baseline in the 6-minute walk distance (6MWD) evaluated after 12 weeks of therapy.

The secondary endpoints included a change from baseline (Week 0) in:

- The SGA after 12 weeks of treatment
- The WHO functional class after 12 weeks of treatment
- A composite of clinical outcomes for worsening PAH after 12 weeks of treatment (time to clinical worsening). The composite of clinical outcomes was defined as death, all-cause hospitalizations, doubling of the dose of diuretics after randomization, or study withdrawal because of a need for the addition of other PAH therapeutic agents.

- The BDI immediately following exercise measured after 12 weeks of treatment
- Cardiopulmonary hemodynamics in a selected subset of subjects after 12 weeks of treatment

Other:

- The safety and tolerability of ambrisentan over the planned dose range and duration of exposure
- The first-dose and steady-state plasma pharmacokinetics of ambrisentan in a selected subset of subjects with moderate to severe PAH
- The effect of ambrisentan on plasma ET-1, B-type natriuretic peptide (BNP) and cardiac troponin T concentrations (cTnT) in a selected subset of subjects with moderate to severe PAH

Statistical Methods:

Determination of sample size:

The primary efficacy endpoint was the change from baseline distance in the 6MWD evaluated after 12 weeks of therapy. Assuming the changes from baseline were normally distributed, a 1-sample test of the null hypothesis of no change from baseline in the 6MWD for a single dose level based on 15 subjects and 2-sided alpha = 0.05 would have 80% power to detect a mean change equal to 0.72 times the standard deviation of the changes. Assuming a similar variability to that observed with bosentan (69.5 m), this would correspond to a detectable mean change from baseline of approximately 50 m. Therefore, this study was designed to enroll a total of 60 subjects in 4 dose groups (15 subjects per group).

Analysis populations:

The analysis populations evaluated for the first 12 weeks in this study included:

- The intention to treat (ITT) population consisted of all randomized subjects who received at least 1 dose of double-blind study drug. Subjects were classified according to their randomized treatment group, regardless of the actual treatment received, and imputation was not performed for subjects who had no post-baseline data. The ITT population was used for all efficacy and safety analyses.
- The interim analysis population included the first 30 subjects to complete 12 weeks of therapy and any subject that would have completed 12 weeks of therapy at the same time or before these 30 subjects if they had not discontinued before Week 12
- The PK population included all subjects who participated in the PK/ET-1 substudy
- The hemodynamics population included all subjects who participated in the cardiopulmonary hemodynamics substudy

The OLE population included all subjects who participated in the OLE period of the study.

Interim Analysis:

An interim analysis was performed on the interim analysis population in order to assess the

validity of the statistical assumptions for the variability of the primary endpoint, the appropriateness of the selected doses for establishing a dose-response relationship, and the utility and safety of continuing the study as originally designed. The interim analysis confirmed the original statistical assumptions, and the study continued without interruption.

Primary Efficacy Endpoint:

The primary efficacy endpoint was the change from baseline distance in the 6MWD evaluated after 12 weeks of therapy.

Descriptive statistics were provided for Week 0 and Week 12 6MWD and the change from baseline (Week 0) to Week 12. In each ambrisentan dose group, a paired t-test was used to test the null hypothesis of no change from Week 0 and a 95% confidence interval was provided.

The shape of the dose-response relationship was explored by plotting the change from baseline versus ambrisentan dose. Based on the linearity of the plot, linear regression of change in distance walked on dose was used to test for dose responsiveness.

Secondary Efficacy Endpoint:

Mean changes in 6MWD for Weeks 4, 8, and 12 and their 95% confidence intervals were plotted.

The time to clinical worsening of PAH, defined as death, all-cause hospitalizations, doubling of the dose of diuretics after randomization, or study withdrawal secondary to the addition of other PAH therapeutic agents was displayed as a Kaplan-Meier curve for each dose level. Differences between curves were tested for significance by the log-rank statistic. The Cox proportional hazards model was used to test for a linear or logarithmic effect of dose on remaining free of clinical worsening of PAH.

The change from baseline (Week 0) in SGA to Week 12 was summarized using descriptive statistics. For each dose group and across all subjects, a paired t-test was used to test the null hypothesis of no mean change from baseline.

The change from baseline in WHO functional class to Week 12 was summarized by tabulating, for each dose group, the number and percentage of subjects in each discrete category at each visit. The proportional odds model was used to test for evidence of a dose-response relationship in the measurements obtained at Week 12.

The change from baseline in BDI at Week 12 was summarized for each dose group using descriptive statistics. In each dose group and across all subjects, a paired t-test was used to test the null hypothesis of no mean change from baseline.

A subset of subjects at selected investigative sites participated in a substudy for evaluation of cardiopulmonary hemodynamics. The goal was to evaluate at least one-third of all enrolled subjects in the hemodynamics substudy. The cardiopulmonary hemodynamics change from baseline (Week 0) to 12 weeks were summarized with descriptive statistics, for each dose and for the combined ambrisentan group.

Other:

ET-1, BNP, and cTnT plasma concentrations were determined at baseline (Week 0) and

Week 12 for the PK subset of subjects. For each molecular marker, descriptive statistics were performed for predose and 2- and 24-hours postdose at baseline and Week 12, as well as for change from predose baseline concentrations.

Pharmacokinetic Analysis:

PK analysis was performed in a subset of subjects, after the first dose of study drug (single-dose PK) and again after 12 weeks of daily dosing (steady-state PK) for each dose. Twenty-four hour plasma concentrations following a single-dose and steady-state dose were summarized with descriptive statistics. Single-dose PK parameters were calculated for the 1 and 2.5 mg ambrisentan dose, and steady-state PK parameters were determined for all 4 doses of study drug.

Safety Analysis:

Adverse events (AEs) reported during the study were summarized by the number and percentage of subjects having an AE, by body system and preferred term, for each dose group separately and for all groups combined. The Fisher exact test was to be used to test for any dose-response relationship in the rate of an event among the 4 treatment groups. Additional summaries were presented by severity and relationship to study drug. Serious adverse events (SAEs) and AEs leading to study withdrawal were reported separately.

Laboratory and physical examination measures were to be summarized with descriptive statistics for raw values, and change from baseline values at each visit. Vital signs and electrocardiogram (ECG) measures were summarized with descriptive statistics for raw values and change from baseline values at each visit.

Serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, gamma glutamyl aminotransferase (GGT), and total bilirubin results, as well as change from baseline, were summarized by treatment at each visit. ALT and AST concentrations were also summarized by treatment at each visit according to the following categories:

- ≤ 1.0 times the upper limit of normal (xULN)
- > 1.0 and ≤ 1.5 xULN
- > 1.5 and ≤ 3 xULN
- > 3 and ≤ 5 xULN
- > 5 and ≤ 8 xULN
- > 8 xULN

Myogen required that any confirmed increase in any serum aminotransferase concentration greater than > 3 xULN be reported as a SAE.

Open-label Extension Analysis:

An analysis was performed for efficacy and safety endpoints for which data were collected in the OLE period.

For most endpoints, data from the OLE period was also combined with data from the blinded treatment period to show data from the total study (Week 0 to Week 24). In these

presentations, subjects were classified according to their randomized treatment group, regardless of the actual treatment received.

Summary of Results:

Subject Disposition:

**Synopsis Table 1: Subject Disposition for the Blinded Treatment Period
(Population: Randomized Subjects)**

Treatment group	1 mg	2.5 mg	5 mg	10 mg	Total
Disposition, n (%)	(N = 16)	(N = 19)	(N = 16)	(N = 13)	(N = 64)
Randomized	16 (100.0)	19 (100.0)	16 (100.0)	13 (100.0)	64 (100.0)
Completed	15 (93.8)	16 (84.2)	15 (93.8)	12 (92.3)	58 (90.6)
Withdrew	1 (6.3)	3 (15.8)	1 (6.3)	1 (7.7)	6 (9.4)

- Sixty-four subjects were randomized and 58 (90.6%) subjects completed the 12-week blinded treatment period. Fifty-six subjects entered the 12-week OLE period and 54 (96.4%) completed this period.
- During the 12-week blinded treatment period a total of 64 subjects were randomized to 1 mg (n = 16), 2.5 mg (n = 19), 5 mg (n = 16), or 10 mg (n = 13). During the OLE Period, dose adjustment was allowed and by Week 24 a total of 56 subjects were distributed as follows: 1 mg (n = 2), 2.5 mg (n = 11), 5 mg (n = 16), or 10 mg (n = 27).

Key Demographics:

- A total of 64 subjects with a mean age 51.4 years received at least 1 dose of study drug. A majority of the subjects enrolled were female (84.4%) and Caucasian (70.3%). The mean and median number of years PAH was present was 3.2 and 2.0 years, respectively. In general, the distribution of gender, race, and age were similar between treatment groups.
- The majority of subjects participating in the study had the diagnosis of IPAH (39; 60.9%). The remaining 25 (39.1%) subjects had PAH associated with mixed connective tissue disease (7; 10.9%), systemic sclerosis (scleroderma, 4; 6.3%), anorexigen use (4; 6.3%), systemic lupus erythematosus (3; 4.7%), HIV infection (2; 3.1%), or overlap syndrome (1; 1.6%). Four (6.3%) subjects had an unspecified diagnosis of PAH associated with a cause other than those listed above, which were determined to be CREST syndrome for 3 subjects and scleroderma for 1 subject.
- The study population included subjects with WHO functional class II (23; 35.9%) and class III (41; 64.1%) symptoms. There was a clear difference in baseline 6MWD between WHO class II (390.1 ± 59.76 m) and WHO class III (315.9 ± 76.92 m) subjects. There were no WHO class I or class IV subjects at baseline. The 5 mg dose group had a slightly higher percentage of class II subjects compared to the other dose groups, but in general the distribution of WHO functional class was similar across dose groups.
- The mean baseline 6MWD for all subjects was 342.5 ± 79.33 m. The 10 mg dose group had a slightly lower mean baseline 6MWD (288.8 ± 91.27 m) compared to the other dose groups.

Efficacy Results:

- A significant increase in the mean change from baseline in 6MWD at Week 12 was observed for each ambrisentan dose: 1 mg, +36.2 m (95% confidence interval (CI): 14.9 to 57.5 m; $p = 0.003$); 2.5 mg, +39.1 m (95% CI: 20.5 to 57.7 m; $p < 0.001$); 5 mg, +38.1 m (95% CI: 10.0 to 66.1 m; $p = 0.011$); 10 mg, +35.1 m (95% CI: 10.9 to 59.2 m; $p = 0.008$). A regression analysis of individual subject 6MWD change by ambrisentan dose did not indicate that the change in 6MWD varied with dose.
- Improvements in 6MWD were observed as early as Week 4 in all dose groups and in the combined ambrisentan group (+24.3 m; 95% CI: 13.0 to 35.6 m). During the 12-week OLE period the dose of ambrisentan was increased for a substantial number of subjects. Subsequently, the significant improvement in 6MWD observed at Week 12 for the combined ambrisentan group (+37.3 m; 95% CI: 26.7 to 47.8 m) increased further at Week 24 (+55.9 m; 95% CI: 42.6 to 69.1 m). Similar effects were observed in each dose group.
- At Week 12, a decrease in BDI (improvement) was observed in the 1 mg (-0.6; 95% CI: -1.7 to 0.6), 2.5 mg (-0.9; 95% CI: -1.8 to -0.1), 5 mg (-1.0; 95% CI: -2.3 to 0.3) and 10 mg (-1.0; 95% CI: -2.2 to 0.2) groups. The combined ambrisentan group had a decrease from baseline at Week 12 of -0.9 (95% CI: -1.4 to -0.3; $p = 0.002$). In the combined ambrisentan group, improvements in BDI were observed as early as Week 4 (-0.7; 95% CI: -1.1 to -0.2) and were maintained through Week 24 (-1.3; 95% CI: -1.9 to -0.7).
- At baseline, 37.1% of subjects were WHO class II and 62.9% were WHO class III in the combined ambrisentan group; whereas, at Week 12, 7 (12.1%) subjects were WHO class I, 29 (50.0%) subjects were WHO class II, and 22 (37.9%) were WHO class III. Improvements in WHO functional class were observed at Week 12 for 21 (36.2%) subjects in the combined ambrisentan group, while only 2 subjects had a worsening (3.4%). In general, the improvements observed at Week 12 were similar in each of the dose groups and a proportional odds model did not suggest a dose-response relationship. The improvement in WHO class for the combined ambrisentan group at Week 12 was maintained through Week 24.
- At Week 12, an increase in SGA was observed for the 1 mg (+12.4 mm; 95% CI: 2.5 to 22.3 mm), 2.5 mg (+12.3 mm; 95% CI: 3.0 to 21.5 mm), 5 mg (+7.9 mm; 95% CI: -0.8 to 16.7 mm) and 10 mg (+12.8 mm; 95% CI: -2.5 to 28.0 mm) groups. For the combined ambrisentan group, the mean change in SGA at Week 12 was +11.3 mm (95% CI: 6.5 to 16.1 mm; $p < 0.001$). The improvements observed at Week 12 were maintained through Week 24.
- During the 12-week blinded treatment period 13 (20.3%) subjects experienced clinical worsening of PAH. Kaplan-Meier and Cox proportional hazards model analyses did not indicate a difference between dose groups. Nearly half of the clinical worsening events were due to doubling the dose of diuretic. For the 24-week study period, 21 (32.8%) subjects had clinical worsening and nearly two-thirds of these events were due to doubling the dose of diuretic.
- At Week 12, mean cardiac index increased (+0.3 L/min/m²; 95% CI: 0.15 to 0.51 L/min/m²; $p < 0.001$), mPAP decreased (-5.2 mmHg; 95% CI: -7.6 to -2.9 mmHg; p

<0.001), and mean PVR decreased (-2.8 mmHg/L/min; 95% CI: -3.8 to -1.8 mmHg/L/min; p <0.001) for the combined ambrisentan group. With the exception of the 1 mg dose group, a non-significant trend toward a reduction in right atrial pressure (RAP) was observed.

- No treatment-related or dose-dependent effects in plasma ET-1 concentrations were apparent.
- At baseline, the mean plasma BNP concentration was 244.0 ± 371.55 ng/L for the combined ambrisentan group (n = 18), with a median of 111.2 ng/L. At Week 12, the mean plasma BNP concentration was 137.3 ± 164.04 ng/L for the combined ambrisentan group (n =16), with a median of 64.4 ng/L.
- At Week 0, nearly all plasma cTnT concentrations were below the level of quantification (0.01 ng/mL). The changes in cTnT concentrations during the 12-week study were minor and not remarkably different from zero.

Pharmacokinetic Results:

- Plasma concentration-time profiles appeared to be biphasic, suggesting a rapid distribution phase followed by the elimination phase. The PK of ambrisentan was best described by a 2-compartment model.
- Absorption rates based on t_{max} values were similar after a single-dose and at steady-state dosing.
- Steady-state PK was predictable based upon data from single doses; calculated accumulation ratios were comparable to theoretical accumulation ratios.
- At steady-state, mean t_{max} was approximately 2-3 hours and the mean t_{1/2} ranged from 9-15 hours; no apparent dose-related or time-on-dose-related trends in t_{1/2} were noted.

Safety:

A global summary of AEs for the blinded treatment period is presented below.

Synopsis Table 2: Global Summary of Adverse Events During the Blinded Treatment Period (Population: ITT)

Treatment Group	1 mg (N = 16)	2.5 mg (N = 19)	5 mg (N = 16)	10 mg (N = 13)	Total (N = 64)
Subjects, n (%)					
with at least 1 AE	16 (100.0)	17 (89.5)	14 (87.5)	11 (84.6)	58 (90.6)
with at least 1 related AE	8 (50.0)	9 (47.4)	10 (62.5)	8 (61.5)	35 (54.7)
with at least 1 SAE	3 (18.8)	1 (5.3)	6 (37.5)	1 (7.7)	11 (17.2)
with AE leading to study discontinuation	1 (6.3)	0 (0.0)	1 (6.3)	1 (7.7)	3 (4.7)
who died	1 (6.3)	0 (0.0)	0 (0.0)	1 (7.7)	2 (3.1)

- During the 12-week blinded treatment period, 58 (90.6%) subjects experienced 1 or more

AEs. The difference in the incidence of AEs across dose groups did not appear to be dose-related and most AEs occurred in the first 12 weeks of treatment. For the 24-week study period, the AE profile was consistent with that observed during the blinded treatment period.

- The most frequent AEs in the combined ambrisentan group during the blinded treatment period were peripheral edema (16; 25.0%), upper respiratory tract infection (12; 18.8%), nasal congestion (12; 18.8%), headache (10; 15.6%), flushing (8; 12.5%), and nausea (8; 12.5%). The difference in the incidence of these frequent AEs across dose groups did not appear to be dose-related.
- In the blinded treatment period, 14 (21.9%) subjects experienced at least 1 AE assessed with a maximum severity of mild, 29 (45.3%) subjects had at least 1 AE assessed with a maximum severity of moderate, and 15 (23.4%) subjects had at least 1 AE assessed as severe. The incidence of AEs by severity did not appear to be dose-related.
- Based on the most related event in the blinded treatment period, 6 (9.4%) subjects had an AE considered probably related to study drug, 29 (45.3%) subjects had an AE assessed as possibly related to study drug, and 23 (35.9%) subjects had AEs that were considered not related to study drug. No difference in the relationship of AEs to study drug was found between treatment groups.
- In the blinded treatment period, 11 (17.2%) subjects experienced SAEs, including 2 deaths (2 events of sudden death assessed not related to study drug). Three subjects did not complete the study because of AEs (2 deaths and 1 elevation of serum aminotransferases). All SAEs, with the exception of elevated serum aminotransferases were assessed as not related to study drug.
- A total of 4 subjects (2 each in the 2.5 and 5 mg groups) developed either ALT or AST increases of >3xULN at 1 or more time points. One of these subjects discontinued study drug due to the elevated aminotransferase concentrations >5xULN and 1 subject had the dose of study drug decreased. The remaining 2 subjects had transient increase in ALT and/or AST >3xULN that were not confirmed upon retest and required no dose adjustments.
- Slight decreases in mean ALT, AST, GGT, alkaline phosphatase, or total bilirubin were observed. There did not appear to be a dose-related trend in mean ALT, AST, GGT, alkaline phosphatase, or total bilirubin.
- At Week 12, decreases in hemoglobin concentration and hematocrit were observed that appeared to be dose-dependent. The decrease in hemoglobin and hematocrit were observed early in treatment (by Week 2) and were maintained without further decrease during the study.
- At Week 12 and 24, there was a trend in most treatment groups for a decrease in heart rate, systolic blood pressure and diastolic blood pressure. The mean changes in these parameters were variable throughout the study, and did not appear dose-dependent.
- The analysis of male fertility hormones in combination with a limited number of subjects (n = 6) providing serial semen samples did not suggest that ambrisentan was associated

with an adverse effect on male reproductive potential.

- It did not appear that subjects developed any clinically remarkable ECG abnormality or had worsening of an existing abnormality following study drug exposure.
- There were no notable physical exam findings or AEs related to physical exams reported.

Conclusions:

In this study, all 4 doses of ambrisentan administered once-daily provided statistically significant and clinically relevant improvements in 6MWD; however, there was little evidence of a dose-response for change in 6MWD at Week 12. The improvements in 6MWD were observed as early as Week 4, were significant at Week 12, and increased further at Week 24. Based on the primary endpoint, the minimally effective dose appeared to be 1 mg once daily (qd); however, several secondary endpoints (i.e., BDI, cardiopulmonary hemodynamics), as well as subgroup analyses, suggest that higher doses may provide additional benefit. Ambrisentan also demonstrated clinically relevant treatment benefits for several secondary endpoints, including Borg dyspnea index, WHO functional class, and SGA, as well as cardiopulmonary hemodynamics.

In subjects with PAH, ambrisentan had an onset of absorption that was rapid, with maximum concentrations observed 2-3 hours after dosing, and a plasma elimination half-life that ranged from 9-15 hours.

Ambrisentan was well tolerated in subjects with PAH at doses that ranged from 1 to 10 mg po qd. The most frequent AEs regardless of dose were peripheral edema, headache, nasal congestion, upper respiratory tract infection, cough, nausea, and flushing. There were no notable differences in the incidence of AEs among dose groups. One subject discontinued study drug due to aminotransferase concentrations $>5\times\text{ULN}$ and 1 subject had the dose reduced due to an AST $>3\times\text{ULN}$.

Overall, this study presents evidence that ambrisentan may provide a treatment benefit for patients with PAH. Ambrisentan was well-tolerated and was associated with a manageable safety profile, indicating a positive risk-to-benefit profile and supports further examination in Phase 3 studies.