



Name of Sponsor/Company Myogen, Inc.	Name of Finished Product Ambrisentan	Name of Active Ingredient Ambrisentan
<b>Protocol Number:</b> AMB-320		
<b>Title of Study:</b> ARIES-1: Ambrisentan in PAH – A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multicenter, Efficacy Study of Ambrisentan in Subjects with Pulmonary Arterial Hypertension		
<b>Investigators and Study Centers:</b> 46 Principal Investigators and 46 international investigative centers in 8 countries: Austria, Australia, Brazil, Chile, Hungary, Italy, Mexico, and United States.		
<b>Publication (reference):</b> None		
<b>Study Period (years):</b> 2.17 years <b>Date of First Enrollment:</b> 17 December 2003 <b>Date of Last Completed:</b> 21 February 2006	<b>Phase of Development:</b> Phase 3	
<p><b>Objectives:</b> The primary objective of this study was to determine the effect of ambrisentan on exercise capacity in subjects with pulmonary arterial hypertension (PAH).</p> <p>The secondary objectives of this study were to evaluate the effects of ambrisentan on other clinical measures of PAH, as well as the safety and tolerability of the study drug.</p>		
<p><b>Methodology:</b> After a 2 week screening period, eligible subjects were stratified based on the underlying etiology of PAH (idiopathic pulmonary arterial hypertension [IPAH] or non-IPAH) and were randomized to 1 of 3 treatment groups (placebo, 5 or 10 mg ambrisentan) in a ratio of 1:1:1. One blinded dose reduction was permitted during the 12-week treatment period in the event of study drug intolerance (e.g., 10 to 5 mg, 5 to 2.5 mg, placebo to placebo). Subjects received a daily dose of 2.5 mg of ambrisentan only if they reduced from the 5 mg dose group. Subjects were assessed for efficacy and safety at monthly intervals.</p> <p>Due to the placebo-controlled design of this study, there was a 1 out of 3 chance that a subject did not receive ambrisentan for a period of 12 weeks. Therefore, after a minimum treatment period of 4 weeks, subjects who met 2 or more of the following predefined early escape criteria may have been removed from the study:</p> <ul style="list-style-type: none"> <li>• A decrease from baseline of at least 20% in the distance walked during the 6-minute walk test (6MWT)</li> <li>• An increase of 1 or more World Health Organization (WHO) functional class</li> <li>• Worsening right ventricular failure (e.g., as indicated by increased jugular venous pressure, new/worsening hepatomegaly, ascites, or peripheral edema)</li> <li>• Rapidly progressing cardiogenic, hepatic, or renal failure</li> <li>• Refractory systolic hypotension (systolic blood pressure [SBP] less than 85 mmHg)</li> </ul> <p>Subjects receiving placebo who were removed from the study due to 2 or more early escape criteria were eligible to enter a long-term extension study, AMB-320/321-E and receive active treatment with</p>		

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<p>ambrisentan.</p> <p>Serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, gamma glutamyl aminotransferase (GGT), and total bilirubin were closely monitored in all subjects throughout the study. Female subjects of childbearing potential were required to undergo monthly pregnancy tests and to use a double method of contraception to reduce the risk of pregnancy during the course of the study. Male subjects were required to undergo complete semen and hormone analyses to evaluate the potential effects of ambrisentan on male fertility.</p> <p>An independent Data and Safety Monitoring Committee (DSMC) monitored the safety and welfare of the study subjects. The DSMC met at designated intervals to review accumulated, unblinded data.</p> <p>After completion of the 12-week study, subjects may have been eligible to enroll in the separate, long-term extension study.</p>		
<p><b>Number of Subjects (planned and analyzed):</b> It was anticipated that a total of 186 subjects (62 per dose group) at approximately 40 international investigative sites would be enrolled. The actual number of subjects enrolled was 202 at 46 investigative sites. The disposition of subjects is presented in Synopsis Table 1.</p>		
<p><b>Diagnosis and Main Criteria for Inclusion:</b> Men and women, 18 years of age or older, with IPAH or PAH associated with connective tissue disease (CTD; e.g., mixed CTD, CREST syndrome, systemic sclerosis [scleroderma], overlap syndrome or systemic lupus erythematosus), anorexigen use, or human immunodeficiency virus (HIV) infection were enrolled in this study. Subjects were to have a documented mean pulmonary artery pressure (mPAP) <math>\geq 25</math> mmHg, pulmonary vascular resistance (PVR) <math>&gt; 3</math> mmHg/L/min, and pulmonary capillary wedge pressure (PCWP) or left ventricle end diastolic pressure (LVEDP) <math>&lt; 15</math> mmHg. Subjects must have been able to walk a distance of at least 150 meters (m) but no more than 450 m during 2 consecutive 6MWTs to be eligible for randomization.</p>		
<p><b>Test Product, Dose and Mode of Administration, Batch Number:</b> Study drug was provided in round, biconvex, oral tablets that were identical in appearance. Three strengths of active study drug containing 2.5, 5, or 10 mg of ambrisentan were used in this study. All study drug was packaged in blister cards. Subjects were instructed to take study drug once daily (qd) by mouth (po) in the morning with or without food. The lot numbers used were: 2.5 mg = L0001849, 5 mg = L0001851, and 10 mg = L0001848.</p>		
<p><b>Duration of Treatment:</b> The maximum study duration was up to 14 weeks from the time of initial screening procedures to the final study visit (Week 12). Screening procedures were performed a maximum of 2 weeks prior to the first dose of study drug. The maximum duration of study drug treatment was 12 weeks.</p>		
<p><b>Reference Therapy, Dose and Mode of Administration, Batch Number:</b> Placebo was indistinguishable from active treatment.</p> <p>The lot number used was: placebo = L0001850.</p>		

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**Endpoints for Evaluation:**

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

The secondary efficacy endpoints included:

- Time to clinical worsening of PAH, as defined by the time from randomization to the first occurrence of death, lung transplantation, hospitalization for PAH, atrial septostomy, study discontinuation due to the addition of other PAH therapeutic agents, or study discontinuation due to 2 or more early escape criteria
- Change from baseline measured after 12 weeks of treatment compared to placebo in the:
  - WHO functional class
  - SF-36<sup>®</sup> Health Survey physical functioning scale
  - Borg dyspnea index (BDI) immediately following exercise
- An assessment of the safety and tolerability of the study drug

**Statistical Methods:**

Determination of Sample Size:

A test of the null hypothesis of no treatment group difference in change from baseline in the 6-minute walk distance (6MWD) with 62 subjects per group had approximately 90% power to detect an average placebo-adjusted treatment effect of 35 m based on a 2-sample t-test and a standard deviation (SD) of 55 m.

Analysis Populations:

The intention-to-treat (ITT) population was defined as all randomized subjects who received at least 1 dose of study drug. For the ITT population, subjects were considered as belonging to their randomized treatment group, regardless of the actual treatment received.

The safety population was defined as all randomized subjects who received at least 1 dose of study drug. Subjects were considered as belonging to a treatment group according to the highest actual treatment received. Any subject who received 10 mg ambrisentan on any day was included in the 10 mg group for safety analyses in the entire study. Any subject who received 5 mg ambrisentan on any day and never received 10 mg ambrisentan on any day was included in the 5 mg group for safety analyses in the entire study. Otherwise, any subject who received only placebo was included in the placebo group for safety analyses in the study.

The ITT population was used in all efficacy summaries. The safety population was used in all safety summaries.

Interim Analysis:

An independent DSMC monitored the safety and welfare of study subjects at designated time intervals by reviewing accumulated unblinded data. Efficacy data were summarized for the DSMC to

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assist members in assessing the benefit risk profile of ambrisentan; however, the DSMC did not conduct a formal interim analysis of efficacy and was not empowered to make recommendations of early discontinuation of the study or a given treatment arm based on efficacy considerations.

**Primary Endpoint:**

The primary efficacy endpoint was the change from baseline in 6MWD evaluated after 12 weeks of treatment compared to placebo, where the last observation was carried forward (LOCF). Baseline was defined as the mean 6MWD of the last two 6MWDs prior to randomization.

Change from baseline for Weeks 4, 8, and 12 in each of the 2 ambrisentan treatment groups were compared to placebo. The mean change was reported with 2-sided 95% confidence intervals (CIs) calculated by normal theory. The primary comparison was the change from baseline to Week 12. The Wilcoxon rank sum test stratified by IPAH and non-IPAH subjects was used for inference. A fixed sequence approach was used to control the type I error rate accounting for the 2 comparisons. The higher dose was first compared to placebo. Because the p-value from the Wilcoxon rank sum test was less than 0.05 for the 10 mg dose group, the difference was considered significant, and the lower dose was compared to placebo, again at the full 0.05  $\alpha$ -level.

The 2 ambrisentan dose groups were also combined and compared to the placebo group. A p-value was reported, but for descriptive purposes only, with no impact on the fixed sequence procedure used for comparing the 2 individual dose groups to the placebo group.

**Secondary Endpoints:**

If both ambrisentan dose groups were superior to placebo for the primary endpoint, evaluation of the secondary endpoints was done by combining the subjects from the 2 dose groups for comparison to the placebo group. However, if only the 10 mg dose group was significant for the primary endpoint, evaluation of the secondary endpoints was done only for that dose group. Secondary endpoint analyses were stratified by IPAH and non-IPAH subjects.

The 2 most important secondary endpoints, time to clinical worsening of PAH and change in WHO functional class, were compared to placebo using a weighted version of Hommel's extension of the Simes' test, with an overall  $\alpha$  of 0.05. Time to clinical worsening was assigned a weight of 80% while change in WHO functional class received 20% of the weight. These 2 tests served as a parallel gatekeeper, allowing the physical functioning scale of the SF-36<sup>®</sup> Health Survey to be tested if at least 1 of the first 2 secondary endpoints was significant. Lastly, the BDI was tested conditional on a significant result from the test of the SF-36<sup>®</sup> physical functioning scale.

**Safety Analysis:**

All adverse events (AEs) reported during the course of the study were coded to a body system and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA<sup>®</sup>) version 6.1 and summarized by body system, preferred term, and treatment. A global summary of all AEs presents frequencies and percentages of the following:

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<ul style="list-style-type: none"> <li>• Subjects with at least 1 AE</li> <li>• Subjects with possibly or probably drug-related AEs</li> <li>• Subjects with at least 1 serious AE (SAE)</li> <li>• Subjects with an AE leading to study discontinuation</li> <li>• Subjects who died</li> </ul> <p>Additional tables presented summaries of all AEs, AEs by severity and AEs by relationship to study drug.</p> <p>The following liver function test (LFT) assessments were summarized separately by severity relative to the upper limit of normal (ULN): ALT, AST, alkaline phosphatase, and total bilirubin.</p> <p>Descriptive statistics for numeric clinical laboratory tests (including LFTs) are presented for each scheduled assessment time by treatment. Descriptive statistics are also presented for the change from predose Week 0 to each subsequent scheduled assessment by treatment. Change from baseline to Week 12 was compared for all pairs of treatment groups by reporting the p-value for a Wilcoxon rank sum test stratified by IPAH and non-IPAH subjects.</p> <p>For subjects who were on anticoagulants at any point during the study (regular visit or between visits), coagulation tests (PT, PTT, and INR) were completed. In addition to summary statistics by study visit, changes in PT and INR were examined relative to changes in warfarin-type anticoagulant dose. These analyses focused on the values at Week 0 and Week 12 and the percentage change from Week 0 to Week 12.</p> <p>The results of semen samples and their normality/abnormality were assessed by an independent male fertility expert and summarized through frequency counts and percentages by treatment. Descriptive statistics for male hormone data are presented by treatment for the Week 0 and Week 12 visits when data were collected. Change from Week 0 to Week 12 was determined and descriptive statistics are displayed by treatment. The male fertility hormone results were analyzed in combination with the semen sample results by a second independent male fertility expert.</p> <p>Frequency counts and percentages are presented to summarize the frequency of normal, abnormal but not clinically significant, and abnormal clinically significant ECG results for each scheduled assessment time by treatment. All ECG data was digitally recorded and analyzed by a central reader. The following variables were analyzed: heart rate, RR and PR intervals, QRS duration, QT interval, QTcB, QTcF, and ECG diagnostic variables. Descriptive statistics were used to summarize the ECG results by treatment group and by week of ECG assessment.</p> <p>Descriptive statistics for vital signs are presented for each scheduled assessment time by treatment and for the change from predose Week 0 to each subsequent scheduled assessment by treatment. Physical examination results are listed in subject data listings.</p>		

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**Summary of Results:**

Study Population:

**Synopsis Table 1. Subject Disposition (Population: Randomized Subjects)**

Treatment group	Placebo	5 mg ambrisentan	10 mg ambrisentan	Combined ambrisentan
Disposition, n (%)	(N = 67)	(N = 67)	(N = 68)	(N = 135)
Randomized	67 (100.0)	67 (100.0)	68 (100.0)	135 (100.0)
Completed	57 (85.1)	63 (94.0)	63 (92.6)	126 (93.3)
Withdrew	10 (14.9)	4 (6.0)	5 (7.4)	9 (6.7)

- A total of 201 subjects, with a mean age of 50.1 years, received at least 1 dose of study drug and were included in the ITT and safety populations. A majority of the subjects enrolled were female (83.6%) and Caucasian (69.2%). More than two-thirds (68.7%) of the subjects were residents of the US. The remainder was distributed in Central/South America (20.9%) and the Rest of the World (10.4% in Australia, Austria, Hungary, or Italy).
- Sixty-three percent of the subjects had the diagnosis of IPAH prior to enrollment, and 37% had PAH associated with CTD, anorexigen use, or HIV infection; IPAH and non-IPAH subjects were equally distributed between the treatment groups. Nearly all of the subjects had either WHO class II (32.3 %) or WHO class III (58.2%) symptoms at baseline; only a small percentage of subjects had WHO class I (2.5 %) or IV (7.0 %) symptoms at baseline. Overall, the mean baseline 6MWD was  $341.0 \pm 75.80$  m, and the mean BDI was  $3.8 \pm 2.02$ .
- In general, demographic and baseline characteristics of the subjects participating were well-balanced between the treatment groups. However, there were more class IV subjects in the 5 mg (9.0%) and 10 mg (10.4%) dose groups than in the placebo group (1.5%). There was also a difference in baseline 6MWD between WHO class II and WHO class III subjects for both the placebo and combined ambrisentan group: class I/II, 377.5 m and 372.0 m; and class III/IV, 320.6 m and 324.6 m, respectively.
- The most frequently used concomitant medications by preferred term were furosemide (47.3%), warfarin sodium (36.8%), and oxygen (26.4%). Minor differences were observed between dose groups in the use of concomitant medications.

Efficacy Results:

- The primary efficacy endpoint was statistically significant for both doses of ambrisentan compared to placebo. The placebo-adjusted improvement in mean 6MWD at Week 12 was +51.4 m (95% CI: 26.6 to 76.2;  $p < 0.001$ ) for the 10 mg group and +30.6 m (95% CI: 2.9 to 58.3;  $p = 0.008$ ) for the 5 mg group. For subjects in the placebo group, the mean 6MWD decreased from baseline by -7.8 m. For subjects receiving ambrisentan, improvement in 6MWD compared to placebo was observed as early as Week 4, and by Week 8 there was evidence of a dose response.

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- The secondary endpoint of time to clinical worsening of PAH demonstrated that ambrisentan (combined ambrisentan group) did not significantly delay the time to clinical worsening of PAH compared to placebo. However, twice as many subjects in the placebo group (n = 6) had an event of clinical worsening compared to each of the ambrisentan dose groups (3 subjects each in the 5 mg and 10 mg dose groups). Furthermore, the hazard ratio showed a 50% reduction in the probability of clinical worsening occurring at any given time for a subject receiving ambrisentan, when compared to placebo.
- The combined ambrisentan group demonstrated a clinically relevant improvement in the change in WHO functional class at Week 12 compared to placebo (p = 0.036); similar trends were observed for each ambrisentan treatment group. Due to the multiple comparisons procedure, a statistically significant improvement compared to placebo could not be stated for this secondary endpoint. Moreover, a more than 5-fold greater percentage of subjects in the placebo group (16.4%) deteriorated by at least 1 WHO class compared to subjects in the combined ambrisentan group (3.0%). In addition, a 3-fold greater percentage of subjects in the combined ambrisentan group (4.5%) had an improvement of 2 WHO classes compared to subjects in the placebo group (1.5%).
- An increase in the physical function scale of the SF-36<sup>®</sup> Health Survey was observed in the combined ambrisentan group at Week 12 (4.10 ± 8.39); however, this increase was not significantly different than placebo (2.31 ± 7.65). For most of the SF-36<sup>®</sup> scales there was a general trend of greater increases for the 10 mg group compared to the 5 mg and placebo groups.
- A clinically relevant improvement in BDI was observed at Week 12 for the combined ambrisentan group, with a placebo-adjusted BDI of -0.6 (95% CI: -1.2 to 0.0; p = 0.017). Dose-dependent improvements in BDI were also observed for both the 5 and 10 mg dose groups compared to placebo. Due to the multiple comparisons procedure, a statistically significant improvement compared to placebo could not be stated for this secondary endpoint.

#### Safety Results:

A Global Summary of AEs is displayed below.

**Synopsis Table 2. Global Summary of Adverse Events (Population: Safety)**

Treatment group	Placebo (N = 67)	5 mg ambrisentan (N = 67)	10 mg ambrisentan (N = 67)	Combined ambrisentan (N = 134)
Subjects, n (%)				
with at least 1 AE	56 (83.5)	56 (83.6)	53 (79.1)	109 (81.3)
with at least 1 related AE	21 (31.3)	34 (50.7)	29 (43.3)	63 (47.0)
with at least 1 SAE	7 (10.4)	4 (6.0)	7 (10.4)	11 (8.2)
with AE leading to study discontinuation	4 (6.0)	2 (3.0)	2 (3.0)	4 (3.0)
who discontinued the study via early escape	4 (6.0)	0 (0.0)	2 (3.0)	2 (1.5)
who died	2 (3.0)	1 (1.5)	1 (1.5)	2 (1.5)

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<ul style="list-style-type: none"> <li>• During this 12-week study, 83.5% of the subjects in the placebo group experienced at least 1 AE. Similarly, 83.6% of subjects in the 5 mg dose group and 79.1% of subjects in the 10 mg dose group experienced at least 1 AE during the study.</li> <li>• Overall, more subjects in the placebo group compared to the ambrisentan groups prematurely discontinued from the study due to death, SAEs, AEs, and/or the early escape procedure. Of note, a greater percentage of subjects in the placebo group (6.0%, 4/67) met the criteria for early escape, compared to subjects in the combined ambrisentan group (1.5%, 2/134).</li> <li>• The most frequently reported SAE was right ventricular failure: placebo group, 4.5%, 5 mg, 1.5%, and 10 mg dose group, 1.5%.</li> <li>• The most frequent AEs in the combined ambrisentan group were peripheral edema (27.6%), headache (18.7%), nasal congestion (8.2%), upper respiratory infection (7.5%), dizziness (7.5%), and cough (7.5%); whereas, the most frequent AEs in the placebo group were headache (20.9%), urinary tract infection (11.9%), dizziness (11.9%), nausea (10.4%), peripheral edema (10.4%), and upper respiratory infection (10.4%).</li> <li>• In general AEs were not dose-dependent; however, there was an apparent dose-dependence in the frequency of nasal congestion (5 mg, 6.0%; and 10 mg, 10.4%).</li> <li>• Differences of at least 5% in incidences of AEs between the treatment groups were infrequent. The most notable difference between treatment groups was for peripheral edema. A total of 10.4% of subjects in the placebo group had an event of peripheral edema; whereas, this AE was reported for 26.9% and 28.4% of subjects in the 5 and 10 mg ambrisentan groups, respectively.</li> <li>• In general, a similar percentage of AEs were assessed as severe in the placebo and 10 mg groups (19.4% and 17.9%, respectively); whereas, a lower percentage of AEs were assessed as severe in the 5 mg group (6.0%). Furthermore, a similar percentage of AEs were assessed as moderate in the placebo and 10 mg groups (38.8% and 37.3%, respectively); whereas, a higher percentage of AEs were assessed as moderate in the 5 mg group (50.7%).</li> <li>• The incidence of AEs related to study drug was greater in the ambrisentan groups than in the placebo group. At least 1 AE considered possibly or probably related to study drug was experienced by 31.3% of subjects in the placebo group and 47.0% of subjects in the combined ambrisentan group.</li> <li>• None of the 134 subjects who received ambrisentan developed any elevated serum aminotransferase concentrations &gt;3xULN, compared to 2 subjects in the placebo group. Further, there were no notable mean changes from baseline at Week 12 for serum ALT and AST, and no differences between treatment groups.</li> <li>• The changes in total bilirubin at Week 12 were shown to be substantially decreased in the 10 mg and combined ambrisentan groups, compared to placebo. The changes in alkaline phosphatase at Week 12 were shown to be substantially decreased in the 5 mg, 10 mg, and combined ambrisentan groups, compared to placebo.</li> <li>• Mean decreases in hemoglobin concentration were observed at Week 12 for both ambrisentan</li> </ul>		

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<p>dose groups compared to placebo (placebo, 0.15 g/dL; 5 mg, -0.83 g/dL and 10 mg, -0.93 g/dL). The decreases were observed early (Week 4) in the study and did not decrease further with continued treatment.</p> <ul style="list-style-type: none"> <li>• Ambrisentan had no effect on PT, INR, or weekly warfarin-type anticoagulant dose.</li> <li>• Mean uric acid decreased slightly over the 12-week study in the placebo group (-6.5 <math>\mu\text{mol/L}</math>); whereas, a substantial decrease was observed for the 5 mg (-21.5 <math>\mu\text{mol/L}</math>) and 10 mg (-53.3 <math>\mu\text{mol/L}</math>) that appeared to be dose-dependent.</li> <li>• The analysis of male fertility hormones in combination with a limited number of subjects (n = 12) providing serial semen samples did not suggest that ambrisentan was associated with an adverse effect on male reproductive potential.</li> <li>• In the placebo group, the mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) remained unchanged at Week 12. In contrast, the mean SBP and DBP decreased -2.7 and -3.2 mmHg in the 5 mg group and -5.4 and -6.0 mmHg in the 10 mg group, respectively. The decreases in SBP and DBP were observed by Week 4.</li> <li>• The majority of ECG abnormalities, both at screening and throughout the study, were typical of those observed in subjects with PAH. Although, definitive interpretation of QT/QTc was limited, none of the subjects exposed to ambrisentan demonstrated electrocardiographic evidence of ventricular arrhythmia.</li> <li>• There were no notable physical exam findings or AEs related to physical exams reported.</li> </ul>		
<p><b>Conclusions:</b></p> <p>This study demonstrated that both the 5 mg and 10 mg dose of ambrisentan administered once-daily provided statistically significant and clinically relevant improvements in exercise capacity and symptoms in subjects with PAH. The improvements in 6MWD were evident within 4 weeks and appeared dose-dependent by Week 8. At Week 12, the increase in 6MWD was nearly twice as large in the 10 mg dose group compared to the 5 mg dose group. Improvements in 6MWD were observed in most subgroups and, in general, appeared to be dose-dependent. Both doses also demonstrated clinically relevant treatment benefits for several secondary endpoints, including WHO functional class and BDI.</p> <p>Ambrisentan was well-tolerated as indicated by the lack of dose reduction and AEs leading to premature discontinuation as well as more subjects in the placebo group discontinued due to death, SAEs, AEs, early escape, right heart failure, and/or worsening PAH. The most clinically important AEs observed in this study were peripheral edema, headache, and nasal congestion. For the most part, these events were mild in severity and none led to study discontinuation. Serum aminotransferase abnormalities, which have been observed and treatment-limiting for other ERAs, were not observed in any subjects receiving ambrisentan. Furthermore, there were no increases in mean ALT and AST and there were notable decreases in mean total bilirubin and alkaline phosphatase in subjects receiving ambrisentan. Decreases in hemoglobin concentration were observed early in the study and did not decrease further with continued treatment.</p>		

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In conclusion, the treatment benefits observed for the primary and secondary endpoints of this study were robust, internally consistent, and clinically relevant. Ambrisentan was well-tolerated and was associated with a manageable safety profile, indicating a positive risk-to-benefit profile.		