RESEARCH

Cardiovascular Therapeutics

ARIES-3: Ambrisentan Therapy in a Diverse Population of Patients with Pulmonary Hypertension

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SUMMARY

Introduction: Ambrisentan is an oral, once daily, endothelin receptor antagonist approved for treatment of pulmonary arterial hypertension (PAH). Previous studies of ambrisentan were limited to patients with Group 1 PAH and often excluded patients receiving other pulmonary hypertension (PH) therapies. **Aims:** ARIES-3 was an open-label study evaluating efficacy and safety of ambrisentan in patients with various PH etiologies and background PH medications. Patients received 5 mg ambrisentan once daily for 24 weeks. The primary endpoint was change from baseline in 6-minute walk distance (6MWD) at week 24. **Results:** A total of 224 patients with PH due to idiopathic and familial PAH (31%), connective tissue disease (18%), chronic hypoxemia (22%), chronic thromboembolic disease (13%), or other etiologies (16%) were enrolled and 53% of patients received stable background PAH therapies. After 24 weeks of therapy, an increase in 6MWD (+21 m; 95% CI: 12–29) and a decrease in B-type natriuretic peptide (–26%; 95% CI: –34 to –16%) was observed in the overall population compared to baseline; however, increases in 6MWD were not observed in several non-Group 1 PH subpopulations. Peripheral edema, headache, and dyspnea were the most common adverse events. **Conclusion:** This study reconfirms the results of previous placebo-controlled studies, which demonstrate that ambrisentan is well tolerated and provides benefit in patients with PAH. Definitive conclusions regarding the safety and efficacy of ambrisentan in specific non-Group 1 PH etiologies cannot be determined and larger, controlled studies will be necessary to determine the efficacy and safety of ambrisentan in these populations.

Introduction

Patients with Group 1 pulmonary arterial hypertension (PAH) have been the most widely studied pulmonary hypertension (PH) population. Although the number of approved therapies for PAH has increased over the past 10 years, many patients have PH associated with other conditions including left-sided heart disease (Group 2), chronic hypoxemia (Group 3), chronic thromboembolic disease (Group 4), or other miscellaneous conditions such as sarcoidosis (Group 5) [1]. PH is a progressive disease of the pulmonary vasculature, characterized by vasoconstriction and abnormal proliferation of vascular smooth muscle cells in the walls of the pulmonary artery leading to elevation of pulmonary artery pressure and pulmonary vascular resistance, and eventually right ventricular failure and death [1–4]. PH has adverse effects on morbidity and mortality in chronic thromboembolic disease [5], sarcoidosis [6], and chronic lung diseases such as chronic obstructive lung disease [7] or interstitial lung disease [8–11]. Effective

therapy with PAH medication for those conditions could potentially improve clinical outcomes.

Endothelin receptor antagonists inhibit endothelin-1-mediated vasoconstriction and mitogenic activity [12–14]. Ambrisentan (Letairis®, Gilead Sciences, Inc., Foster City, CA, USA, or Volibris®, GlaxoSmithKline, Inc., Middlesex, UK), is an orally active, once daily, type A selective endothelin receptor antagonist approved for treatment of PAH patients (Group 1) [14]; however, it has not been evaluated in a non-Group 1 PH patient population or in a population receiving background PH therapy.

Methods

Selection of Patients

Patients ≥18 years of age with PH due to the following etiologies were included: (1) Group I PAH including idiopathic, and familial PAH associated with connective tissue disease, congenital heart disease, human immunodeficiency virus infection, drugs and toxins, thyroid disorders, glycogen storage disease, Gaucher's disease, hemoglobinopathies, or splenectomy; (2) Group 3 patients with PH associated with chronic hypoxemia including chronic obstructive pulmonary disease, interstitial lung disease, sleep-disordered breathing, alveolar hypoventilation disorders; (3) Group 4 patients with PH due to proximal or distal chronic thromboembolic obstruction; and (4) Group 5 patients with PH due to sarcoidosis. Patients with left heart disease or left heart failure were excluded.

PH was determined by right heart catheterization (RHC) and defined as mean pulmonary arterial pressure ≥25 mmHg, pulmonary vascular resistance >3 mmHg/L/min (240 dynes seconds/cm^5), and pulmonary capillary wedge pressure or left ventricular end diastolic pressure of <15 mmHg. Patients with interstitial lung disease or chronic obstructive pulmonary disease were included only if the PH was considered disproportionate to the severity of the underlying disease, defined by a higher mean pulmonary arterial pressure (>35 mmHg) and a higher pulmonary vascular resistance (>3.5 mmHg/L/min; 280 dynes seconds/cm^5). Patients were included only if they had ventilatory reserve defined as a total lung capacity ≥70% of predicted and a forced expiratory volume in 1 second ≥65% of predicted, except for interstitial lung disease (total lung capacity ≥60%) and chronic obstructive pulmonary disease patients (forced expiratory volume in 1 second ≥50%). Six-minute walk distance (6MWD) was required to be between 150 and 450 m at baseline. Patients who had previously discontinued bosentan or sitaxsentan due to serum aminotransferase concentrations >3 × upper limit of normal were included, only if these values were <3 × upper limit of normal at screening. Patients could receive the following background PAH therapies: chronic prostacyclin analog therapy (IV epoprostenol, Flolan®, GlaxoSmithKline, Inc., IV or SC treprostinil, Remodulin®, United Therapeutics Corp., Research Triangle Park, NC, USA, or inhaled iloprost, Ventavis®, Actelion Pharmaceuticals Ltd., Allschwil, Switzerland) or sildenafil (Revatio®, Pfizer, New York, NY, USA) therapy (maximum dose of 80 mg TID). Patients with serum aminotransferase concentrations ≥3 × upper limit of normal were excluded.

The study was conducted in accordance with the amended Declaration of Helsinki and in adherence with applicable guidelines for Good Clinical Practice. Local institutional review boards or independent ethics committees approved the protocol, and written informed consent was obtained from all patients.

Study Design

ARIES-3 was a long-term, open-label, single-arm, safety, and efficacy study of ambrisentan in patients with PH conducted between September 2006 and July 2009 in 42 centers in the United States, Australia, and Canada. Eligible patients received 5 mg of ambrisentan (Letairis®, Gilead Sciences, Inc.), once daily for 24 weeks. One dose reduction was permitted during the 24-week treatment period if a patient did not tolerate the study drug. Patients were assessed for efficacy at baseline and after 4, 12, and 24 weeks of treatment; safety was assessed every 4 weeks.

Outcome Measures

The primary endpoint was the 6MWD [15] change from baseline evaluated after 24 weeks of therapy. Secondary efficacy measures included change in plasma B-type natriuretic peptide concentration (BNP), Borg dyspnea index [15], and WHO functional class, as well as time to clinical worsening of PH and survival. Time to clinical worsening was defined as the time from initiation of ambrisentan treatment to the first occurrence of death, lung transplantation, hospitalization for PH, atrial septostomy, an addition or change to chronic prostacyclin analogs or sildenafil treatment due to protocol-defined worsening criteria (≥20% decrease in 6MWD, increase in WHO functional class, or worsening right ventricular failure), or study withdrawal due to the addition of other clinically approved PH therapeutic agents.

Data Analysis

The analysis population included all enrolled patients who received at least one dose of study medication. Descriptive statistics was presented for the change from baseline to week 24 for 6MWD and Borg dyspnea index, and analyzed with two-sided paired *t*-tests.

Change from baseline in the WHO functional class was presented categorically and analyzed with a 7-point scale: –3, –2, –1 (improved), 0 (no change), 1, 2, and 3 (deteriorated) using a Wilcoxon signed-rank test. Percentage change in plasma BNP was assessed with the geometric mean ratio (GMR). Kaplan–Meier analysis was used to estimate the rates of clinical worsening of PH (event-free) and survival at 24 weeks; patients who discontinued the study or reached week 24 without experiencing an event were censored at the time of discontinuation or their week 24 visit, respectively.

The primary analysis was conducted using a last observation carried forward imputation for missing data and included all patients with postbaseline data. An analysis of observed data with no imputation for missing data (observed case) was also performed for supportive analysis. No adjustment of the type-1 error rate for multiple comparisons was made and descriptive statistics are presented without formal hypothesis testing for subgroup analyses.

The database and all statistical outputs were retained by the sponsor, Gilead Sciences, Inc. All authors had access to the data to enable confirmation of the findings. The authors assume full responsibility for the completeness and accuracy of the content of the manuscript.

Results

Study Population and Patient Disposition

A total of 224 patients were enrolled between September 2006 and December 2007. The etiology of the PH was classified as: Idiopathic PAH/Familial PAH (31%); PH associated with connective tissue disease (18%); proximal or distal chronic thromboembolic obstruction (13%); chronic obstructive pulmonary disease (11%); interstitial lung disease (9%); drugs and toxins (6%); congenital heart disease (4%); sarcoidosis (3%); human immunodeficiency virus (2%); sleep-disordered breathing (2%); and other PAH etiologies (1%;) which included hypothyroidism, sickle cell anemia, and Takayasu arteritis. Mean age was 55 ± 16 years (mean ± standard deviation) with 86% Caucasian and 70% female (Table 1). The WHO functional class at baseline was predominantly class II (29%) or III (65%). Just over half of the patients were receiving background PAH therapies at baseline: sildenafil (41%), prostacyclin analogs (5%), or both (7%).

Thirty-four subjects (15%) discontinued prior to the week-24 visit. Six patients died during the 24-week treatment period, 17 patients discontinued due to adverse events, and 11 discontinued due to other reasons: withdrawal of consent (n = 5), noncompliance (n = 2), addition of IV epoprostenol (n = 1), patient moved (n = 1), preplanned lung transplant (n = 1), and lost to follow-up (n = 1). Two of the patients who withdrew consent provided a 6MWD assessment. Eleven other patients did not provide a week-24 6MWD; therefore 181 patients (81%) contributed to the primary endpoint.

Exercise Capacity

The 6MWD at baseline was 318 ± 84 m (mean ± standard deviation). Compared to baseline, a significant increase in mean 6MWD was observed at week 4 for all patients; this was maintained through the 24 weeks of treatment (Figure 1). For the primary analysis (last observation carried forward), the mean treatment effect at week 24 was +21 m (95% confidence interval [CI]: 12–29, $P < 0.001$); similar results were observed when the data were analyzed with no imputation for missing data (+28 m; 95% CI: 19–37, $P < 0.001$). An increase in mean 6MWD from baseline was observed in several PH etiology subgroups except for interstitial lung disease and chronic obstructive pulmonary disease subgroups (Table 2). 6MWD change from baseline at 24 weeks was similar in Group 1 PAH patients receiving no

Table 1 Demographics and baseline characteristics for all PH patients and by PH etiology subgroups

		PH etiology subgroups, (n)[a]						
Demographics and baseline characteristics	All patients (n = 224)	IPAH/FPAH (n = 69)	CTD (n = 40)	CHD (n = 10)	Drugs or toxins (n = 13)	COPD (n = 24)	ILD (n = 21)	CTEPH (n = 29)
Female sex, N (%)	156 (70)	50 (73)	36 (90)	10 (100)	9 (69)	7 (29)	7 (33)	20 (69)
Age, years	55 ± 16	49 ± 15	55 ± 15	34 ± 9	49 ± 13	68 ± 11	66 ± 9	63 (16)
Caucasian, N (%)	193 (86)	65 (94)	33 (83)	6 (60)	13 (100)	22 (92)	19 (91)	23 (79)
WHO class, N (%)								
I	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
II	65 (29)	29 (42)	12 (30)	3 (30)	6 (46)	1 (4)	0 (0)	8 (28)
III	146 (65)	37 (54)	27 (68)	7 (70)	7 (54)	17 (71)	18 (86)	21 (72)
IV	12 (5)	2 (3)	1 (2)	0 (0)	0 (0)	6 (25)	3 (14)	0 (0)
6-min walk distance, m	318 ± 84	344 ± 82	324 ± 83	387 ± 48	335 ± 66	241 ± 84	271 ± 65	325 ± 71
Borg Dyspnea Index, units	3.9 ± 2.1	3.4 ± 2.2	3.5 ± 1.8	2.4 ± 1.4	3.5 ± 1.9	4.4 ± 2.2	5.2 ± 2.2	4.4 ± 1.9
BNP (ng/L)	335 ± 413	269 ± 332	417 ± 543	145 ± 104	316 ± 306	243 ± 245	485 ± 580	390 ± 387
mPAP (mmHg)	49 ± 14	53 ± 15	45 ± 13	64 ± 16	53 ± 11	45 ± 10	41 ± 7	46 ± 11
mRAP (mmHg)	8.7 ± 4.9	8.7 ± 4.9	8.5 ± 4.7	6.2 ± 4.6	10.4 ± 5.9	9.2 ± 5.2	7.6 ± 4.1	8.7 ± 4.9
Cardiac index (L/min/m^2)	2.3 ± 0.7	2.3 ± 0.7	2.4 ± 0.7	2.4 ± 0.5	1.9 ± 0.7	2.3 ± 0.6	2.4 ± 0.6	2.5 ± 0.8
PVR (mmHg/L/min)	10.5 ± 6.6	11.8 ± 6.4	10.1 ± 6.5	14 ± 5.1	16.1 ± 12.4	8.4 ± 4.3	6.8 ± 2.6	9.6 ± 5.5
PCWP (mmHg)	9.9 ± 3.4	9.9 ± 3.2	10.2 ± 3.0	8.3 ± 3.2	8.9 ± 2.9	10.7 ± 3.4	11 ± 3.3	10 ± 3.6

Values are mean ± SD unless otherwise stated.

[a]Table 1 only shows PH Etiology subgroups with ≥10 patients.

BNP, plasma B-type natriuretic peptide concentration (normal value for patients ≥ 18 years: <150 pg/mL); CHD, congenital heart disease (repaired [≥ 1 year] congenital systemic-to-pulmonary shunts or unrepaired secundum atrial septal defect); COPD, chronic obstructive pulmonary disease; CTD, connective tissue disease; CTEPH, PH with chronic chronic thromboembolic obstruction of proximal and distal pulmonary artery; ILD, interstitial lung disease; IPAH/FPAH, idiopathic and familial PAH; mPAP, mean pulmonary artery pressure; mRAP, mean right atrial pressure; PAH, pulmonary arterial hypertension; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; WHO class, WHO functional class.

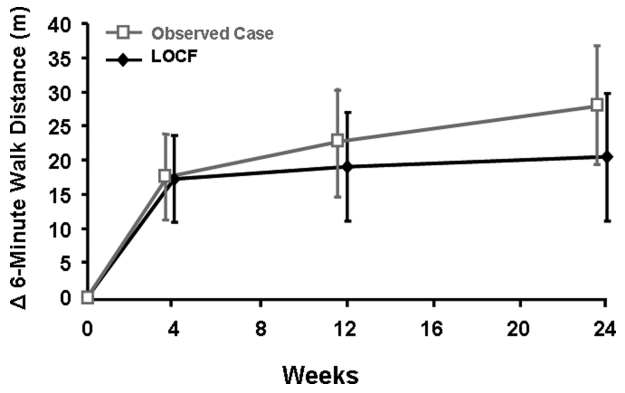

Figure 1 Mean (± 95% CI) change from baseline in 6-minute walk distance through week 24 with imputation of missing data using last observation carried forward (LOCF, n = 220), and with no imputation of data (observed case, n = 181).

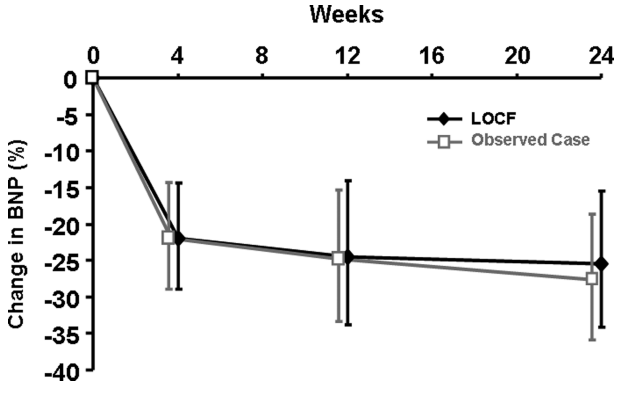

Figure 2 Percentage (± 95% CI) change from baseline in B-type natriuretic peptide concentration (BNP) through week 24 comparing LOCF (n = 214) and observed case analyses (n = 176). BNP, B-type natriuretic peptide concentration.

background therapy (+32 m; 95% CI: 17–48) compared to patients receiving background therapy with sildenafil alone (+25m; 95% CI: 11–40) or patients receiving background prostacyclin analog therapy with or without sildenafil (+46 m; 95% CI: 7–85).

Other Measures of Clinical Outcome

Baseline plasma BNP concentrations were 335 ± 413 ng/L. At week 24, a decrease compared to baseline was observed in the overall population (–26%; 95% CI: –34% to –16%; Figure 2) and decreases were also observed in most subgroups (Table 2). The WHO functional class improved in 23% of patients and deteriorated in 7% of patients ($P < 0.001$). Dyspnea, as assessed by the Borg dyspnea index, decreased at week 24 compared to baseline (–0.5; 95% CI: –0.8 to –0.3).

Long-Term Survival and Clinical Worsening

Six subjects died during this 24-week study: cardio-respiratory arrest (n = 2), worsening PH (n = 2), left ventricular failure (n = 1), and illicit drug toxicity (n = 1). None of these events were considered related to study drug by the investigator. At week 24, Kaplan–Meier estimates for survival and freedom from clinical

Table 2 Change from baseline in 6MWD and BNP at week 24 by PH etiology and background PH therapy subgroups (last observation carried forward analysis)

	6MWD (m)			BNP (% GMR)[a]	
	n	Mean (95% CI)	Median (95% CI)[b]	n	% GMR (95% CI)
All patients	220	21 (12, 29)	20 (12, 27)	214	−26 (−34, −16)
PH etiology[c]					
IPAH/FPAH	67	34 (21, 48)	37 (18, 49)	65	−27 (−42, −8)
CTD	39	24 (−3, 50)	11 (3, 47)	40	−9 (−32, 21)
CHD	10	26 (−11, 64)	17 (−24, 100)	9	−14 (−55, 63)
Drugs & toxins	13	32 (12, 52)	40 (−6, 63)	13	−35 (−59, 2)
COPD	24	−5 (−34, 24)	3 (−6, 20)	23	−38 (−54, −17)
ILD	21	−23 (−60, 14)	6 (−66, 33)	20	−30 (−50, −2)
CTEPH	28	17 (1, 33)	10 (0, 25)	25	−22 (−40, 1)
Background PAH therapy					
All patients receiving background PAH therapy	114	25 (13, 37)	24 (15, 38)	111	−25 (−36, −12)
Group 1 PAH none	57	32 (17, 48)	27 (11, 47)	55	−19 (−37, 5)
Group 1 PAH sildenafil	57	25 (11, 40)	29 (14, 47)	57	−34 (−48, −16)
Group 1 PAH prostacyclin analogs[d]	22	46 (7, 85)	25 (12, 72)	22	2 (−28, 46)

[a]BNP (% GMR), plasma B-type natriuretic peptide concentration (percentage geometric mean ratio).

[b]Ref. 16.

[c] Table 2 only shows PH Etiology subgroups with ≥10 patients.

[d]Group 1 PAH prostacyclin analogs without and with sildenafil (15 patients were also receiving background sildenafil therapy).

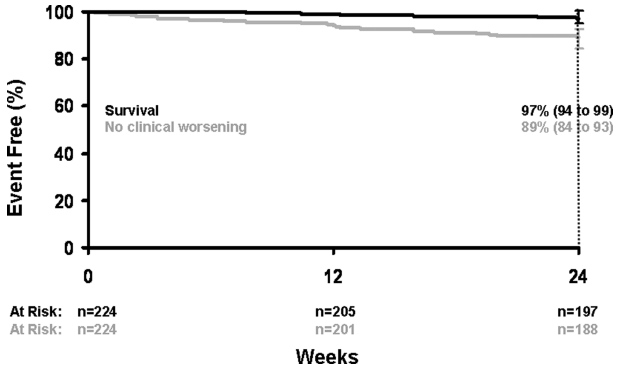

Figure 3 Kaplan–Meier analysis (95% CI) for survival and freedom from clinical worsening of PH with point estimates shown through week 24. The number at risk is presented above at each time point.

Table 3 Clinical worsening: cumulative incidence of events through Week 24

	All patients (n = 224)
Patients with at least one clinical worsening event, n (%)	23 (10)
Death, n (%)	6 (3)
Lung transplantation, n (%)	2 (1)
Hospitalization for PH, n (%)	16 (7)
Atrial septostomy, n (%)	0 (0)
Addition to or change of chronic prostacyclin analog therapy or sildenafil, n (%)	9 (4)
Study withdrawal due to addition of other PH therapy, n (%)	2 (1)

Patients can be included in more than one category of clinical worsening. Clinical worsening was defined as first occurrence of death, lung transplantation, hospitalization for PH, atrial septostomy, a change to chronic prostacyclin analogs, or sildenafil treatment due to protocol-defined worsening criteria (i.e., ≥20% decrease in 6MWD, increase in WHO functional class, and/or worsening right ventricular failure), or study withdrawal due to the addition of other clinically approved PH therapeutic agents.

worsening of PH were 97% (95% CI: 94–99%) and 89% (95% CI: 84–93%), respectively (Figure 3). The most frequent clinical worsening events reported were hospitalization for PH, change of chronic sildenafil or prostacyclin analog therapy, and death (Table 3).

Safety

Ambrisentan was generally well tolerated, with most adverse events being mild to moderate in intensity. The most common treatment-emergent adverse events were peripheral edema, headache, dyspnea, upper respiratory tract infection, nasal congestion, fatigue, and nausea; however, discontinuation of ambrisentan treatment due to these adverse events was infrequent (Table 4). The most frequent serious adverse events were right ventricular failure (n = 12), pneumonia (n = 9), and worsening PH (n = 6). Similar adverse events were observed in the non-Group 1 PH subgroups and the PAH population, with peripheral edema and headache generally being the most common events. Four of the six patients who discontinued therapy due to peripheral edema also experienced other adverse events at the time of discontinuation, consistent with disease progression such as right ventricular failure, dyspnea, increased weight, increased BNP, and renal failure.

Table 4 Most frequent adverse events for 24-week period[a]

	Patient, n = 224		
	Events[b] (%)	Mild or moderate (%)	Discontinuation of ABS[e] due to AE (%)
Peripheral edema	33	32	2.7
Headache	26	25	0.4
Dyspnea	15	13	0.9
URI[c]	13	13	0
Nasal congestion	13	13	0
Fatigue	11	11	0.4
Nausea	10	10	0
Dizziness	9	9	0.4
Cough	8	8	0
Depression	8	8	0
Pain in extremity	8	7	0.4
Diarrhea	8	6	0
Urinary tract infection	8	8	0
Increased BNP[d]	7	7	0.4
Flushing	7	7	0
Hypokalemia	7	7	0
Right ventricular failure	6	3	1.3
Chest pain	6	5	0.4
Vomiting	6	6	0
Back pain	6	6	0
Pneumonia	5	3	0
Epistaxis	5	4	0
Insomnia	5	5	0
Arthralgia	5	4	0

[a]Adverse events in patients who received at least 1 dose of ambrisentan with an incidence of >5%.
[b]Some patients reported >1 event.
[c]URI = Upper respiratory tract infection.
[d]Plasma B-type natriuretic peptide concentration.
[e]ABS = ambrisentan.

Six patients (2.7%) had alanine aminotransferase/aspartate aminotransferase (ALT/AST) elevations >3× upper limit of normal during the 24-week period. Four of the six patients had transient ALT/AST elevations <5× upper limit of normal and continued ambrisentan therapy with no additional events; one of these events was observed in the subpopulation of patients who previously failed bosentan and/or sitaxsentan due to aminotransferase abnormalities (1/27; 3.7%). Two patients had ALT/AST elevations ≥8× upper limit of normal and discontinued therapy. The first patient had a history of abnormal liver function tests and discontinued the study due to a biopsy-proven autoimmune hepatitis. The second patient also had a concurrent elevation in total bilirubin of 4.8× upper limit of normal; however baseline total bilirubin

was 1.7× upper limit of normal and remained at that level until the patient was hospitalized for worsening right heart failure with an elevated plasma BNP (829 ng/L). This patient also had elevated bile acids at baseline (3.3 × upper limit of normal) and had recently initiated acetaminophen and oxycodone at the time of this event. Within 3 weeks of discontinuation of ambrisentan, acetaminophen, and oxycodone, her transaminases normalized and total bilirubin was 2.6 × upper limit of normal.

In the overall population, the mean hemoglobin concentration was 13.3 ± 2.0 g/dL (mean ± standard deviation) at baseline and decreased by 0.92 ± 1.3 g/dL at week 24.

Discussion

Current medical therapies approved for the treatment of PAH have demonstrated efficacy and safety in a Group 1 PAH patient population [1–3,17]. Similarly, trials that had previously evaluated the efficacy and safety of ambrisentan have been limited primarily to patients with idiopathic PAH or PAH associated with connective tissue diseases, and have excluded other background PAH therapies [14,18,19]. ARIES-3 was the first examination of the safety and efficacy of ambrisentan in a more diverse PH population. Subgroup analyses were limited by the small sample size and lack of a placebo control, but were included in the prespecified analysis plan to determine potential non-Group 1 PH subgroups that could be studied in future placebo-controlled clinical studies.

An increase in mean 6MWD compared to baseline was observed in the overall study population; however, caution is advised when interpreting these data due to the relatively large number of subjects who either discontinued or had missing data. The increase in 6MWD observed in the subpopulation of PAH patients receiving ambrisentan monotherapy (Table 2) was consistent with that observed for similar PAH populations in the ARIES-1 and ARIES-2 trials [14], thus reconfirming the efficacy of ambrisentan in the population for which it is currently indicated. Similar 6MWD results were observed in this study for PAH patients receiving background sildenafil and/or chronic prostanoid therapy. It is important to note that approximately half of the patients in the overall population had PH due to etiologies other than idiopathic PAH or connective tissue disease PAH, and 52.2% were receiving other PAH therapies at baseline.

The 6WMD results for the non-Group 1 PH subgroups were mixed and warrant investigation. Of note, the increase in mean 6MWD for the proximal or distal chronic thromboembolic obstruction subpopulation was suggestive of a clinically relevant treatment effect. The lack of improvement in 6MWD in the interstitial lung disease and chronic obstructive pulmonary disease subpopulations is interesting in that this group did experience decreases in BNP of the same magnitude as those who did improve 6MWD. Exercise capacity for the chronic obstructive pulmonary disease and interstitial lung disease subgroups may have been limited by progression of the underlying lung disease. Consistent with this hypothesis, these two subpopulations had less severe PH as assessed by cardiopulmonary hemodynamics and greater 6MWD impairment at baseline when compared to other subgroups or the overall population (Table 1).

Clinical improvements compared to baseline were observed in this study for several secondary efficacy endpoints, most notably for plasma BNP, a nonsubjective marker of ventricular stress. The decrease in plasma BNP observed in the overall population was similar to that seen in the previous ARIES-1 and ARIES-2 trials [14], and trends toward decreases in plasma BNP were observed in nearly all PH subpopulations (Table 2). Changes in the WHO functional class and the Borg dyspnea index were suggestive of clinical benefit; however, these data must be viewed with caution due to the open-label design of this study and the subjective nature of these assessments.

The safety and tolerability of ambrisentan in this population was similar to that seen in previous PAH studies [14,18,19]. Peripheral edema and headache were the most common adverse events and are known side effects of the endothelin receptor antagonists class [14,19]. Although peripheral edema was observed in approximately one-third of patients during the 24-week period, nearly all events were of mild-to-moderate intensity and few patients discontinued ambrisentan treatment due to these events. Peripheral edema is also a common symptom of patients with PH and was observed in approximately 11% of placebo patients in the previous 12-week ambrisentan studies [14]. The proportion of peripheral edema events in this study that are due to ambrisentan or progression of underlying disease is unknown. Liver function test abnormalities are a common and occasionally treatment-limiting adverse event associated with the endothelin receptor antagonist bosentan [20,21]. Sitaxentan (Thelin^{TM}), another endothelin receptor antagonist indicated for the treatment of PAH, was recently withdrawn from the market due to the association with potentially life threatening liver toxicity. Increases in these tests have also been reported with ambrisentan; however, in controlled studies these events have occurred at rates less than placebo events [14]. In this study, two patients (2/224; 0.9%) had significant increases in serum aminotransferase concentrations during the 24-week treatment period requiring discontinuation of ambrisentan. Both patients had a medical history and/or concomitant events that were suggestive of other etiologies for these abnormalities; however, a causal relationship for ambrisentan cannot be excluded.

There were several limitations to this study, the most substantial of which was the lack of a placebo or active comparator; therefore, this study cannot provide precise estimates of treatment effect. As previously mentioned, sample sizes were limited in nearly all of the etiology subpopulations and were not sufficiently powered to observe clinically relevant treatment effects. Therefore, definitive conclusions regarding the efficacy of ambrisentan in these groups cannot be determined. Finally, the primary analysis was conducted using last observation carried forward imputation for missing data and did not apply a penalty for patients who died. Although six patients died during the study, a penalty analysis was not considered appropriate, as there was no placebo group to compare disease progression. However, most patients completed the study and the results were similar when analyzed without imputation for missing data; therefore, it is unlikely that the primary analysis was significantly affected by the imputation strategy.

In summary, this study reconfirms the results of previous placebo-controlled studies, which demonstrate that ambrisentan is

well tolerated and provides benefit in patients with PAH. Definitive conclusions regarding the safety and efficacy of ambrisentan in specific non-Group1 PH etiologies cannot be determined based on the subgroup analyses performed here, and larger, controlled studies will be necessary to determine the efficacy and safety of ambrisentan in these populations.

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Conflict of Interest

The authors have no conflict of interest.

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