

Ambrisentan for the Treatment of Pulmonary Arterial Hypertension

Results of the Ambrisentan in Pulmonary Arterial Hypertension, Randomized, Double-Blind, Placebo-Controlled, Multicenter, Efficacy (ARIES) Study 1 and 2

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Background—Ambrisentan is a propanoic acid-based, A-selective endothelin receptor antagonist for the once-daily treatment of pulmonary arterial hypertension.

Methods and Results—Ambrisentan in Pulmonary Arterial Hypertension, Randomized, Double-Blind, Placebo-Controlled, Multicenter, Efficacy Study 1 and 2 (ARIES-1 and ARIES-2) were concurrent, double-blind, placebo-controlled studies that randomized 202 and 192 patients with pulmonary arterial hypertension, respectively, to placebo or ambrisentan (ARIES-1, 5 or 10 mg; ARIES-2, 2.5 or 5 mg) orally once daily for 12 weeks. The primary end point for each study was change in 6-minute walk distance from baseline to week 12. Clinical worsening, World Health Organization functional class, Short Form-36 Health Survey score, Borg dyspnea score, and B-type natriuretic peptide plasma concentrations also were assessed. In addition, a long-term extension study was performed. The 6-minute walk distance increased in all ambrisentan groups; mean placebo-corrected treatment effects were 31 m ($P=0.008$) and 51 m ($P<0.001$) in ARIES-1 for 5 and 10 mg ambrisentan, respectively, and 32 m ($P=0.022$) and 59 m ($P<0.001$) in ARIES-2 for 2.5 and 5 mg ambrisentan, respectively. Improvements in time to clinical worsening (ARIES-2), World Health Organization functional class (ARIES-1), Short Form-36 score (ARIES-2), Borg dyspnea score (both studies), and B-type natriuretic peptide (both studies) were observed. No patient treated with ambrisentan developed aminotransferase concentrations >3 times the upper limit of normal. In 280 patients completing 48 weeks of treatment with ambrisentan monotherapy, the improvement from baseline in 6-minute walk at 48 weeks was 39 m.

Conclusions—Ambrisentan improves exercise capacity in patients with pulmonary arterial hypertension. Improvements were observed for several secondary end points in each of the studies, although statistical significance was more variable. Ambrisentan is well tolerated and is associated with a low risk of aminotransferase abnormalities. (*Circulation*. 2008;117:3010-3019.)

Key Words: ambrisentan ■ drugs ■ endothelin ■ hypertension, pulmonary ■ receptors

Pulmonary arterial hypertension (PAH) is a progressive disease characterized by an elevated pulmonary vascular resistance leading to right ventricular failure and premature death.¹ Current therapies approved for the

treatment of PAH in the United States and/or Europe include prostacyclin analogues administered by intravenous, inhaled, and subcutaneous routes; the oral endothelin-receptor antagonists bosentan and sitaxsentan; and the oral phosphodiesterase

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type 5 inhibitor sildenafil. Although these agents are efficacious, each has safety-, tolerability-, or drug delivery-related adverse effects.^{2–6}

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Endothelin-1 is a 21-amino acid peptide that plays a key role in the pathobiology of PAH,^{7,8} exerting vasoconstrictor and mitogenic effects by binding to 2 distinct receptor isoforms in the pulmonary vascular smooth muscle cells, endothelin A and B receptors.⁹ Endothelin B receptors also are present in endothelial cells, and their activation leads to release of vasodilators and antiproliferative substances such as nitric oxide and prostacyclin that may counterbalance the deleterious effects of endothelin-1.⁹ Despite potential differences in receptor isoform activity, the efficacy in PAH of the dual endothelin A and B receptor antagonist bosentan and of the selective endothelin A receptor antagonist sitaxsentan appears to be comparable.^{6,10} However, the percentage of subjects with elevations of serum aminotransferase concentrations >3 times the upper limit of normal, a major side effect of endothelin-1 receptor antagonists, appears to be lower for patients treated with sitaxsentan (3% to 5%) compared with bosentan (11% to 12%), supporting possible differences among agents of this class of drugs.^{6,10}

Ambrisentan is a nonsulfonamide, propanoic acid-based, A-selective endothelin receptor antagonist with a bioavailability and half-life that allow once-daily dosing.¹¹ A phase 2 study suggested beneficial effects with ambrisentan in the treatment of PAH.¹²

The objectives of the Ambrisentan in Pulmonary Arterial Hypertension, Randomized, Double-Blind, Placebo-Controlled, Multicenter, Efficacy Study 1 and 2 (ARIES-1 and ARIES-2) were to assess the efficacy and tolerability of 3 doses of ambrisentan—2.5, 5, and 10 mg—orally once daily in patients with PAH.

Methods

Selection of Patients

Patients were included if they had PAH (idiopathic or associated with connective tissue disease, HIV infection, or anorexigen use) defined according to current guidelines.^{2,3} Treatment with bosentan, sitaxsentan, sildenafil, epoprostenol, iloprost, or treprostinil was prohibited. Patients with a 6-minute walk distance <150 or >450 m were excluded. Local institutional review boards or independent ethics committees approved the protocol, and written informed consent was obtained from all patients.

Study Design

ARIES-1 and ARIES-2 were concurrent, phase 3, randomized, double-blind, placebo-controlled studies conducted between December 2003 and February 2006 that were identical in design except for the investigative sites and the doses of ambrisentan studied. ARIES-1 was conducted in 46 centers in the United States, Mexico, South America, Australia, and Europe; ARIES-2 was conducted in 41 centers in Europe, Israel, and South America.

In each study, a central randomization scheme stratified by PAH cause (idiopathic versus other PAH causes) was used to assign patients to 3 treatment groups in a 1:1:1 ratio (ARIES-1, placebo or ambrisentan 5 or 10 mg PO daily; ARIES-2, placebo or ambrisentan 2.5 or 5 mg PO daily).

For safety reasons, patients who met 2 early escape criteria after a minimum of 4 weeks of treatment could discontinue the study prematurely. Early escape criteria were (1) >20% decrease in the 6-minute walk distance, (2) an increase in World Health Organization (WHO) functional class,¹³ (3) a worsening right ventricular failure (as indicated by increased jugular venous pressure, new/worsening hepatomegaly, ascites, or peripheral edema), (4) progressing hepatic or renal failure, and (5) systolic blood pressure <85 mm Hg. All requests for early escape were adjudicated in a blinded fashion by the ARIES Steering Committee, and all study assessments were collected before unblinding of treatment.

All patients who completed the study and all placebo patients who discontinued the study because of early escape were eligible to enter a long-term study. Patients remained blinded and continued to receive their last ambrisentan dose assignment. Placebo patients were randomized 1:1 to blinded ambrisentan treatment using the doses of their specific study.

Outcome Measures

The primary measure of efficacy was the change from baseline to week 12 in exercise capacity as measured by the distance walked in 6 minutes.¹⁴ Additional efficacy measures were the time to clinical worsening, the change in WHO functional classification of PAH, Short Form-36 (SF-36) Health Survey,¹⁵ Borg dyspnea score,¹⁴ and plasma B-type natriuretic peptide concentration.

Time to clinical worsening was defined as the time from randomization to the first occurrence of death, lung transplantation, hospitalization for PAH, atrial septostomy, study withdrawal because of the addition of other PAH medications, or early escape criteria. Laboratory tests were performed and adverse events were recorded throughout both studies.

Statistical Analysis

The database was retained by the sponsor. The statistical analysis was performed by the sponsor and was reviewed by an academic statistician (E.B.R.). The 2 studies were analyzed separately according to each study protocol, and a prespecified analysis of the combined 5-mg and placebo groups (stratified by study and cause) is presented for descriptive purposes.

For each study, a test of the null hypothesis of no treatment group difference in change from baseline in the 6-minute walk distance with 62 subjects per treatment arm had $\approx 90\%$ power to detect a placebo-corrected treatment effect of 35 m on the basis of a 2-sample *t* test with 2-sided $\alpha=0.025$ and equal SDs for the change from baseline of 55 m. Placebo-corrected treatment effect corresponds to the mean change from baseline of an ambrisentan treatment group minus the mean change from baseline of the placebo group.

The primary analysis plan was as follows. Comparisons of individual ambrisentan dose groups with placebo for change in 6-minute walk distance, WHO functional class, Borg dyspnea score, and B-type natriuretic peptide plasma concentrations were analyzed with the Wilcoxon test with stratification by cause. Change from baseline WHO functional class at week 12 was analyzed categorically with a 7-point scale: -3, -2, -1 (improved), 0 (no change), 1, 2, and 3 (deteriorated). B-type natriuretic peptide plasma concentrations were summarized with logarithmic transformation. Time to clinical worsening was tested with a log-rank test stratified by PAH cause. Change in SF-36 score was analyzed as described elsewhere.¹⁵

Multiple comparisons for efficacy end points were controlled with a fixed sequence procedure in each study. For the primary end point, the higher dose of ambrisentan was compared with placebo. If this comparison showed a significant effect ($\alpha=0.05$), then the lower dose was compared with placebo. If at least 1 ambrisentan dose was significant for the primary end point, then time to clinical worsening and change in WHO functional class were tested with a weighted version of the Hommel¹⁶ test. If time to clinical worsening showed an effect at $\alpha=0.04$, change in WHO functional class showed an effect at $\alpha=0.01$, or both

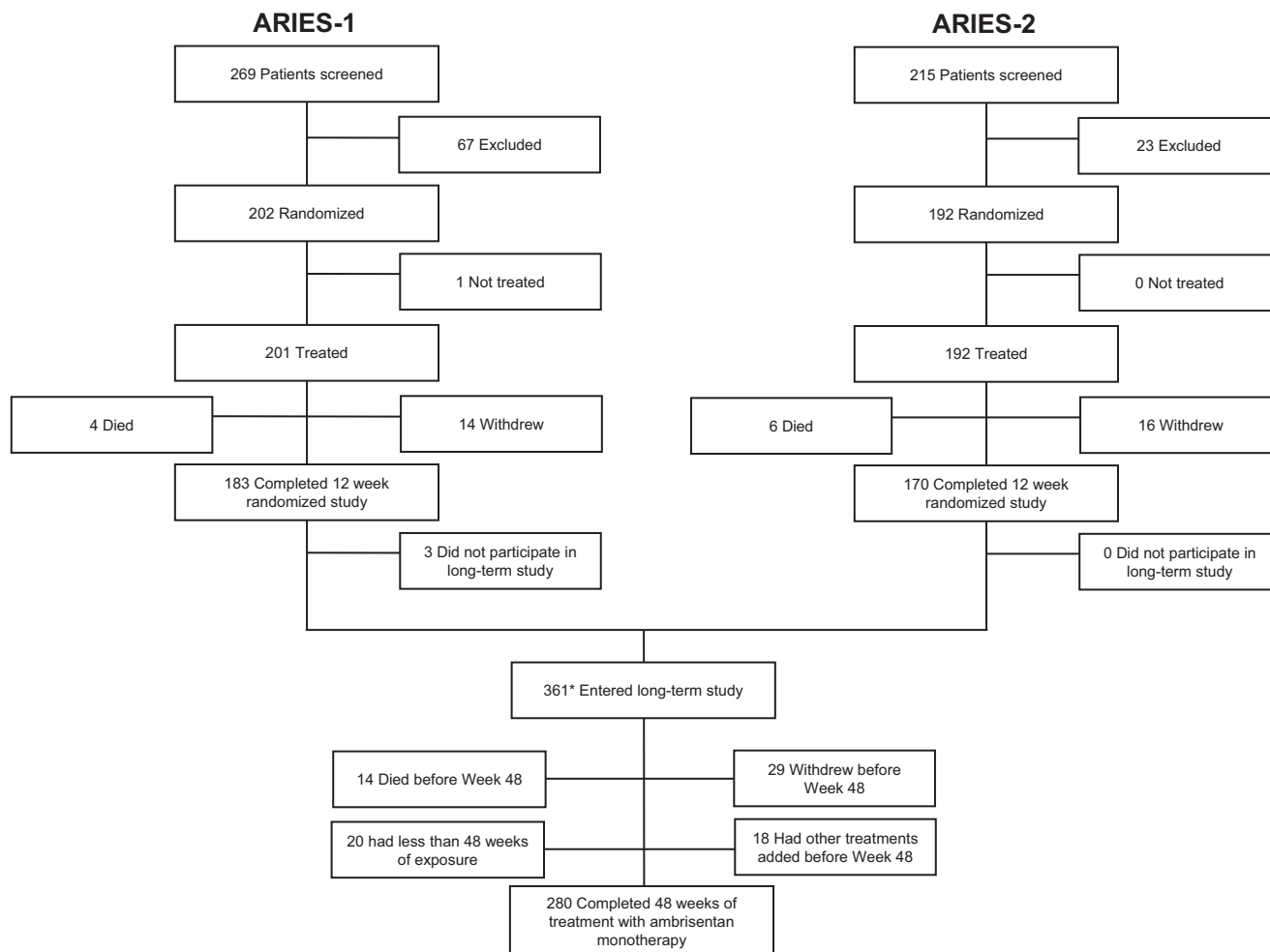


Figure 1. Numbers of patients enrolled in ARIES-1 and ARIES-2 and in the long-term extension study who underwent screening and randomization. The data cutoff for patients in the long-term extension study was November 30, 2006. *Includes 11 patients who discontinued the 12-week study because of early escape criteria while receiving placebo and entered the long-term extension study.

showed an effect at $\alpha=0.05$, then the SF-36 Physical Functioning scale was tested at the previous α level. If SF-36 showed an effect, Borg dyspnea score was tested at the previous α level. In each study, the primary comparison for secondary end points was the combined ambrisentan dose groups that were significant for the primary end point versus the placebo group.

All patients who received at least 1 dose of study drug were analyzed for efficacy (intention to treat). Missing data at week 12 were imputed by use of the last observation carried forward with 1 exception: If a patient discontinued the study because of clinical worsening and did not have a premature discontinuation visit, a 6-minute walk distance of 0 m, a WHO functional class of IV, and a Borg dyspnea score of 10 were imputed.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

ARIES-1 patients were randomized to placebo ($n=67$) or 5 mg ($n=67$) or 10 mg ($n=68$) ambrisentan once daily; ARIES-2 patients were randomized to placebo ($n=65$) or 2.5 mg ($n=64$) or 5 mg ($n=63$) ambrisentan once daily. All randomized patients received at least 1 dose of study drug, except for 1 patient in the 10-mg group of ARIES-1 who was not included in the analysis of safety or efficacy

(Figure 1 and Figures 1a and 1b of the online-only Data Supplement).

Baseline Characteristics

Baseline characteristics were similar among all 6 treatment groups (Table 1). Idiopathic PAH was the most frequent diagnosis; WHO functional classification at baseline was predominantly class II (38%) and class III (55%).

Exercise Capacity

An increase in 6-minute walk distance was observed in each ambrisentan dose group at week 4, and this effect was maintained at weeks 8 and 12, whereas in the placebo group, it deteriorated by week 12 (Figure 2). The mean placebo-corrected treatment effects at week 12 were 31 m (95% confidence interval [CI], 3 to 59; $P=0.008$) for ambrisentan 5 mg and 51 m (95% CI, 27 to 76; $P<0.001$) for ambrisentan 10 mg in ARIES-1; 32 m (95% CI, 2 to 63; $P=0.022$) for ambrisentan 2.5 mg and 59 m (95% CI, 30 to 89; $P<0.001$) for ambrisentan 5 mg in ARIES-2; and 45 m (95% CI, 24 to 65; $P<0.001$) for the combined 5-mg group from both studies.

In both studies, improvements in the mean placebo-corrected 6-minute walk distance were observed at week

Table 1. Baseline Characteristics of the Patients in ARIES-1 and ARIES-2*

Characteristic	ARIES-1			ARIES-2		
	Placebo (n=67)	5 mg Ambrisentan (n=67)	10 mg Ambrisentan (n=67)	Placebo (n=65)	2.5 mg Ambrisentan (n=64)	5 mg Ambrisentan (n=63)
Female sex, n (%)	59 (88)	56 (84)	53 (79)	44 (68)	48 (75)	51 (81)
Age, y	48±16	53±14	49±16	51±14	52±15	50±16
Race, n (%)						
White	49 (73)	46 (69)	44 (66)	51 (79)	54 (84)	58 (92)
Black	4 (6)	4 (6)	3 (5)	0 (0)	0 (0)	0 (0)
Asian	2 (3)	3 (5)	1 (2)	2 (3)	1 (2)	0 (0)
Hispanic	12 (18)	12 (18)	17 (25)	12 (19)	9 (14)	5 (8)
Other	0 (0)	2 (3)	2 (3)	0 (0)	0 (0)	0 (0)
Weight, kg	77±22	73±17	73±21	71±16	70±15	68±16
WHO functional class, n (%)						
I	2 (3)	1 (2)	2 (3)	2 (3)	0 (0)	1 (2)
II	23 (34)	20 (30)	22 (33)	24 (37)	34 (53)	28 (44)
III	41 (61)	40 (60)	36 (54)	37 (57)	29 (45)	33 (52)
IV	1 (2)	6 (9)	7 (10)	2 (3)	1 (2)	1 (2)
Diagnosis, n (%)						
Idiopathic PAH	43 (64)	42 (63)	41 (61)	42 (65)	42 (66)	41 (65)
Associated PAH						
Connective tissue disease	21 (31)	19 (28)	22 (33)	22 (34)	19 (30)	21 (33)
HIV infection	2 (3)	3 (5)	2 (3)	1 (2)	2 (3)	1 (2)
Anorexigen use	1 (2)	2 (3)	2 (3)	0 (0)	1 (2)	0 (0)
6-min Walk distance, m	342±73	340±77	341±78	343±86	347±84	355±84
Mean pulmonary artery pressure, mm Hg	50±15	47±13	51±16	51±13	48±14	48±14
Cardiac index, L · min ⁻¹ · m ⁻²	2.5±0.8	2.5±0.9	2.6±0.7	2.4±0.7	2.5±0.7	2.4±0.8
Pulmonary vascular resistance, dynes · s · cm ⁻⁵	868±518	834±424	912±465	971±579	800±396	931±672
Right atrial pressure, mm Hg	8±5	8±5	9±6	7±5	8±5	8±5
B-type natriuretic peptide, ng/L†	138 (99–193)	121 (94–156)	146 (101–209)	126 (87–183)	125 (86–180)	84 (56–125)
SF-36 health survey physical functioning scale	29.0±8.3	28.6±9.2	29.6±9.4	31.9±7.9	29.3±7.7	31.3±9.1

Values are mean±SD when appropriate.

*The groups shown are all treated patients.

†Geometric mean (95% CI).

12 in patients treated with ambrisentan with baseline WHO functional class II symptoms (range, 36 to 55 m) and WHO functional class III symptoms (range, 39 to 45 m). Similarly, improvements were observed in both studies for idiopathic PAH patients treated with ambrisentan (range, 50 to 66 m) and, to a lesser extent, for patients with PAH associated with connective tissue disease (range, 15 to 23 m).

Clinical Worsening

In ARIES-2, a statistically significant improvement in time to clinical worsening was observed for patients receiving ambrisentan compared with placebo ($P<0.001$); similar results were observed for the 2.5- and 5-mg ambrisentan groups separately ($P=0.005$, $P=0.008$; Table 2 and Figure 3). An improvement in time to clinical worsening also was

observed in ARIES-1 for patients receiving ambrisentan compared with placebo and for the 5- and 10-mg groups separately (Table 2 and Figure 3), but the difference was not statistically significant ($P=0.307$, $P=0.292$, and $P=0.214$, respectively).

A statistically significant improvement in time to clinical worsening was observed for the combined 5-mg group compared with the combined placebo groups from both studies ($P=0.005$).

WHO Functional Class

In ARIES-1, the distribution of WHO functional class improved from baseline to week 12 for patients receiving ambrisentan compared with placebo ($P=0.036$); in ARIES-2, similar trends were observed but were not statistically significant ($P=0.117$). For the ARIES-1 and

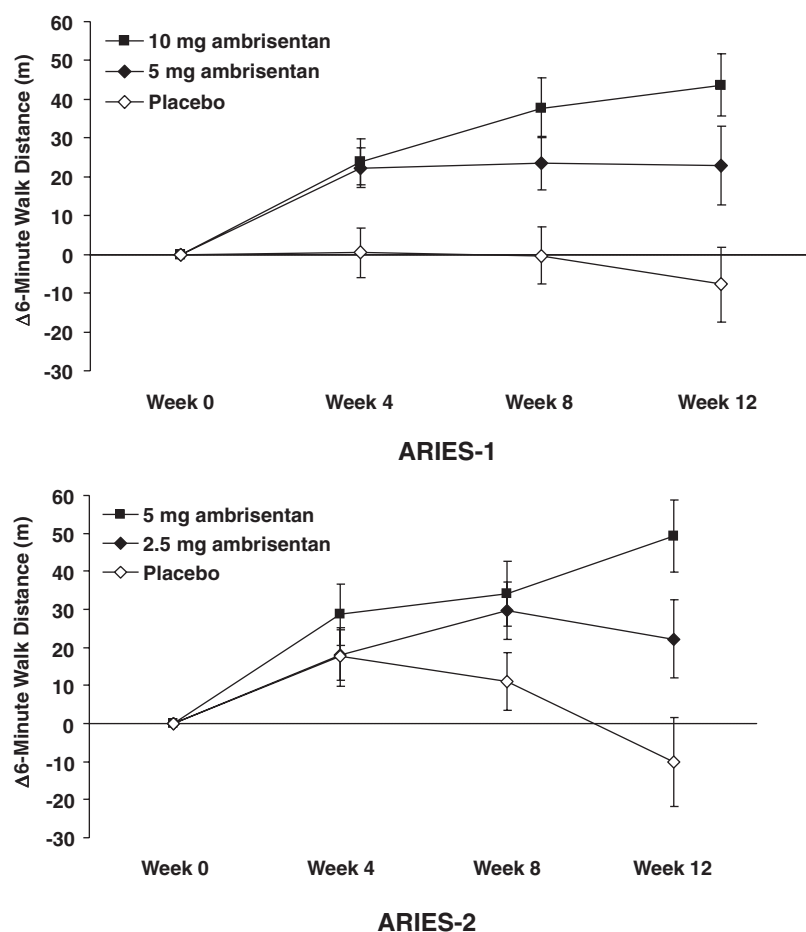


Figure 2. Mean \pm SE changes from baseline in the 6-minute walk distance at week 12 in the placebo and ambrisentan groups of ARIES-1 and ARIES-2. Comparisons of individual ambrisentan dose groups with placebo for change in 6-minute walk distance were analyzed by use of a Wilcoxon test with stratification by cause. For ARIES-1, $P=0.008$, 5 mg ambrisentan once daily vs placebo; $P<0.001$, 10 mg ambrisentan once daily vs placebo. For ARIES-2, $P=0.022$, 2.5 mg ambrisentan once daily vs placebo; $P<0.001$, 5 mg ambrisentan once daily vs placebo. A total of 201 patients in ARIES-1 and 192 patients in ARIES-2 were included in these intention-to-treat analyses.

ARIES-2 combined 5-mg group, the distribution of WHO functional class improved from baseline to week 12 compared with the combined placebo group ($P=0.025$). In both studies, the treatment effects observed were due primarily to less WHO functional class deterioration in patients receiving ambrisentan compared with patients receiving placebo (ARIES-1, 3.0% and 16.4%, respectively; ARIES-2, 3.9% and 18.5%, respectively).

Quality of Life

In ARIES-2, the SF-36 Health Survey Physical Functioning scale significantly improved ($P=0.005$) in the combined ambrisentan group (3.41 ± 6.96) compared with the placebo group (-0.20 ± 7.14); improvements in this parameter also were noted in the individual 2.5-mg ($P=0.005$) and 5-mg ($P=0.040$) dose groups. Furthermore, improvements were observed in several other SF-36 scales, including Role-Physical, Vitality, Role-Emotional, and General Health. In ARIES-1, similar trends were observed without statistical significance.

Borg Dyspnea Score

An improvement in Borg dyspnea score was observed at week 12 for the combined ambrisentan group compared with placebo in ARIES-1 (-0.6 ; 95% CI, -1.2 to 0.0 ; $P=0.017$) and ARIES-2 (-1.1 ; 95% CI, -1.8 to -0.4 ; $P=0.019$). Improvements in Borg dyspnea score compared with placebo

also were noted for the 10-mg group in ARIES-1 (-0.9 ; 95% CI, -1.6 to -0.2 ; $P=0.002$), for the 2.5-mg (-1.0 ; 95% CI, -1.9 to -0.2 ; $P=0.046$) and 5-mg (-1.2 ; 95% CI, -2.0 to -0.4 ; $P=0.040$) groups in ARIES-2, and for the combined 5-mg group (-0.7 ; 95% CI, -1.3 to -0.2 ; $P=0.031$) from both studies.

Plasma B-Type Natriuretic Peptide

In both studies, B-type natriuretic peptide plasma concentrations were similar at baseline in the placebo and ambrisentan groups (Figure 4). At week 12, plasma B-type natriuretic peptide concentrations increased slightly from baseline by 9% (ARIES-1) and 13% (ARIES-2) in the placebo groups. In contrast, plasma B-type natriuretic peptide concentrations decreased from baseline in the 5-mg (30%) and 10-mg (45%) groups in ARIES-1 and in the 2.5-mg (29%) and 5-mg (30%) groups in ARIES-2 (each $P<0.003$; Figure 4).

Long-Term Treatment

Of the 361 patients who entered into the long-term extension study (Figure 1), 43 discontinued before completing 48 weeks of treatment (14 died). The 43 patients who discontinued had had more severe disease at baseline, as evidenced by a lower baseline 6-minute walk distance, a higher baseline Borg dyspnea index, and a higher baseline WHO functional class.

Table 2. Incidence of Clinical Worsening and of Most Frequent Adverse Events in the Placebo and Ambrisentan Groups in ARIES-1 and ARIES-2

Event	ARIES-1, n (%)			ARIES-2, n (%)		
	Placebo (n=67)	5 mg Ambrisentan (n=67)	10 mg Ambrisentan (n=67)	Placebo (n=65)	2.5 mg Ambrisentan (n=64)	5 mg Ambrisentan (n=63)
Clinical worsening*†	6 (9)	3 (4)‡	3 (4)‡	14 (22)	3 (5)§	3 (5)
Death	2 (3)	1 (1)	1 (1)	3 (5)	2 (3)	0 (0)
Hospitalization for PAH	2 (3)	2 (3)	2 (3)	9 (14)	3 (5)	2 (3)
Withdrawal because of other PAH treatment	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Early escape¶	4 (6)	0 (0)	2 (3)	7 (11)	2 (3)	1 (2)
Adverse event#						
Peripheral edema	7 (10.4)	18 (26.9)	19 (28.4)	7 (10.8)	2 (3.1)	6 (9.5)
Nasal congestion	2 (3.0)	4 (6.0)	7 (10.4)	0 (0.0)	1 (1.6)	3 (4.8)
Sinusitis	0 (0.0)	3 (4.5)	3 (4.5)	0 (0.0)	1 (1.6)	1 (1.6)
Flushing	0 (0.0)	2 (3.0)	1 (1.5)	1 (1.5)	4 (6.3)	3 (4.8)
Nasopharyngitis	1 (1.5)	5 (7.5)	2 (3.0)	0 (0.0)	0 (0.0)	2 (3.2)
Abdominal pain	1 (1.5)	2 (3.0)	2 (3.0)	0 (0.0)	2 (3.1)	2 (3.2)
Constipation	1 (1.5)	3 (4.5)	4 (6.0)	1 (1.5)	2 (3.1)	1 (1.6)
Palpitations	2 (3.0)	0 (0.0)	3 (4.5)	1 (1.5)	4 (6.3)	5 (7.9)
Dyspnea	2 (3.0)	4 (6.0)	3 (4.5)	2 (3.1)	1 (1.6)	3 (4.8)
Headache	14 (20.9)	12 (17.9)	13 (19.4)	4 (6.2)	5 (7.8)	18 (12.7)

*All patients receiving study medication.

†More than 1 event occurred in some patients experiencing events.

‡ $P > 0.05$ vs placebo (log-rank test).

§ $P = 0.005$ vs placebo (log-rank test).

|| $P = 0.008$ vs placebo (log-rank test).

¶Early escape was defined by the presence of ≥ 2 of the following criteria: (1) a decrease of at least 20% in the 6-minute walk distance, (2) an increase of ≥ 1 WHO functional class, (3) worsening right ventricular failure (as indicated by increased jugular venous pressure, new/worsening hepatomegaly, ascites, or peripheral edema), (4) rapidly progressing hepatic or renal failure, and (5) refractory systolic hypotension (systolic blood pressure < 85 mm Hg).

#Adverse events in patients receiving ambrisentan (all doses combined) with an incidence $> 3\%$ and an incidence $\geq 1\%$ greater than patients receiving placebo (combined placebo). Adverse events are listed in descending order for the difference in incidence between patients receiving ambrisentan and patients receiving placebo.

A total of 298 patients were treated with ambrisentan for at least 48 weeks as of November 30, 2006. Eighteen of the 298 patients received additional treatments (prostanoids or phosphodiesterase type 5 inhibitors). An exploratory analysis was performed on the 280 patients receiving ambrisentan monotherapy after 48 weeks. For these patients, the mean change from baseline in 6-minute walk distance for this combined ambrisentan group was 40 m (95% CI, 33 to 48 m) at week 12 and 39 m (95% CI, 29 to 49 m) at week 48.

Safety

Ambrisentan was generally well tolerated (Table 2), with most adverse events being mild to moderate in intensity for all treatment groups. Peripheral edema, headache, and nasal congestion tended to be more frequent in patients treated with ambrisentan compared with placebo, but only nasal congestion appeared to increase with ambrisentan dose in both studies.

None of the 261 patients receiving ambrisentan developed serum aminotransferase concentrations > 3 times the upper limit of normal compared with 3 patients (2.3%) in the placebo groups. Moreover, mean values for alanine aminotransferase, aspartate aminotransferase, total bilirubin, and

alkaline phosphatase did not increase from baseline in the ambrisentan groups. No meaningful changes in prothrombin time, international normalized ratio, or weekly oral anticoagulant dose were observed in the ambrisentan-treated groups. Mean hemoglobin concentration changed by -0.84 ± 1.2 g/dL in patients receiving ambrisentan compared with 0.2 ± 1.0 g/dL in the placebo group, but the change was not dose dependent.

A total of 22 patients (16.7%) in the placebo groups and 25 patients (9.6%) in the combined ambrisentan group had at least 1 serious adverse event. Six patients (4.5%) died in the placebo group, and 4 patients (1.5%) died in the combined ambrisentan group; no death was judged to be causally related to study drug by the investigators.

A total of 41 patients in both studies discontinued prematurely during the 12-week treatment period: 21 patients (15.9%) receiving placebo and 20 patients (7.6%) receiving ambrisentan. Of the patients receiving placebo, 4 (3.0%) discontinued because of adverse events (pulmonary embolism [$n=2$], worsening PAH [$n=2$]), 11 (8.3%) discontinued because of early escape, and 6 (4.5%) discontinued for other reasons (clinical status not improved [$n=1$], treatment with other PAH therapy [$n=1$], withdrawal of consent [$n=2$], protocol violation [$n=1$], noncompliance [$n=1$]). Of the

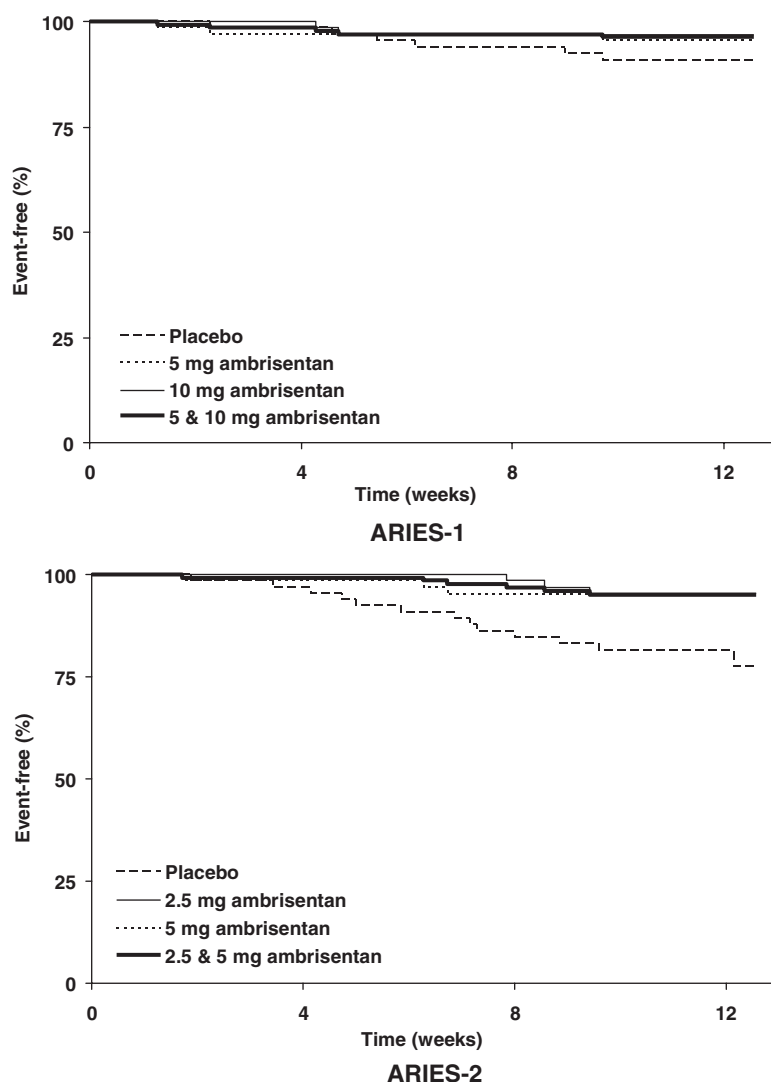


Figure 3. Kaplan-Meier estimates of the proportion of patients with clinical worsening in ARIES-1 and ARIES-2. Clinical worsening was defined by the combined end point of death, lung transplantation, hospitalization for pulmonary hypertension, atrial septostomy, study withdrawal owing to the addition of other pulmonary hypertension therapeutic agents, or study withdrawal owing to ≥ 2 of following early escape criteria: (1) a decrease of at least 20% in the 6-minute walk distance, (2) an increase of ≥ 1 WHO functional classes, (3) worsening right ventricular failure (as indicated by increased jugular venous pressure, new/worsening hepatomegaly, ascites, or peripheral edema), (4) rapidly progressing hepatic or renal failure, and (5) refractory systolic hypotension (systolic blood pressure < 85 mm Hg). $P=0.307$, $P=0.292$, and $P=0.214$, ambrisentan 5-mg, 10-mg, and 5 plus 10-mg dose groups combined, respectively, vs placebo in ARIES-1; $P=0.005$, $P=0.008$, and $P<0.001$, ambrisentan 2.5-mg, 5-mg, and 2.5 plus 5-mg dose groups combined, respectively, vs placebo in ARIES-2 (log-rank test).

patients receiving ambrisentan, 6 (2.3%) discontinued because of adverse events (worsening PAH, worsening dyspnea, gastroenteritis, intracranial bleeding, allergic reaction, headache/face edema [$n=1$ for each]), 5 (1.9%) discontinued because of early escape, and 9 (3.4%) discontinued for other reasons (withdrawal of consent [$n=6$], protocol violation [$n=2$], lost to follow-up [$n=1$]).

Discussion

These 2 concurrent, randomized, double-blind, placebo-controlled studies demonstrate that ambrisentan improves exercise capacity, as measured by the 6-minute walk distance, in patients with PAH. The 6-minute walk distance is an independent predictor of mortality in patients with idiopathic PAH¹⁷ and has been used as the primary end point in most clinical trials in PAH.^{5,6,10,18–28}

In both studies, a 2-fold increase in ambrisentan dose was associated with a notable (20 to 27 m) increase in 6-minute walk distance, suggesting a possible dose response. The change in 6-minute walk distance appeared different for the 5-mg ambrisentan dose group in ARIES-1 (31 m) and in ARIES-2 (59 m), yet the substantial overlap of 95% CIs for

these data supports the conclusion that these results were not discordant. These studies had very similar patient populations; therefore, this difference may be due to random variability. Similar variability between studies for 6-minute walk distance also has been observed for bosentan at the same dose (70 versus 35 m).^{10,21} Nevertheless, examination of the dose response for ambrisentan should be limited to comparisons within the individual studies.

In both ARIES studies, improvements in 6-minute walk distance were observed in patients with WHO functional class II and III symptoms. This finding differs from other studies in which smaller improvements were observed in less compromised patients.^{5,10,19}

The effect of ambrisentan on exercise capacity was maintained after 48 weeks of treatment in those continuing with ambrisentan monotherapy, reinforcing the clinical significance of the exercise improvements observed in the 12-week study. Improvements were observed for most secondary end points in each of the studies, although statistical significance was more variable. This variability was not unexpected because the individual studies did not have sufficient statistical power to examine secondary end points consistently.

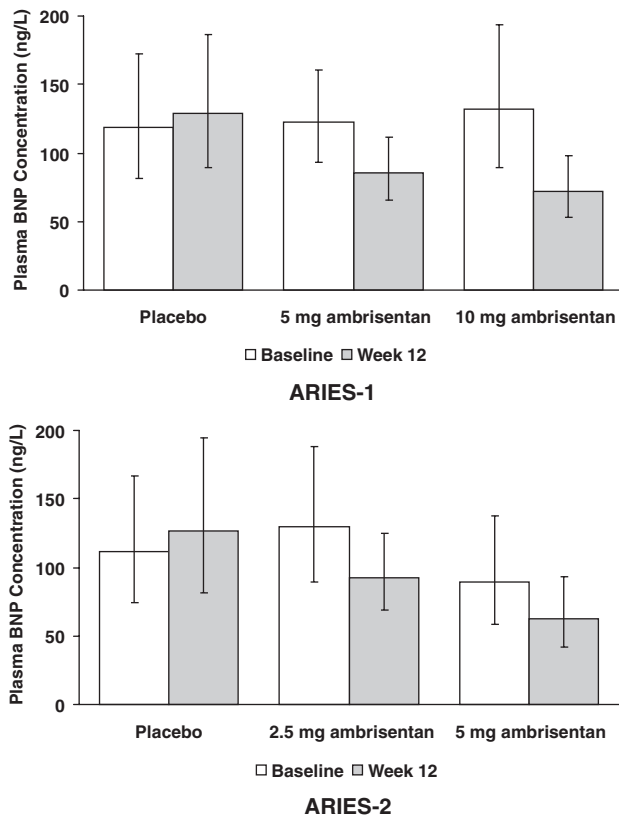


Figure 4. Geometric mean plasma B-type natriuretic peptide (BNP) concentration with 95% CIs at baseline (open bars) and week 12 (filled bars) in the placebo and ambrisentan groups in ARIES-1 and ARIES-2. With the Wilcoxon rank-sum test, $P=0.002$ and $P<0.001$, change from baseline to week 12 for ambrisentan in doses of 5 and 10 mg vs placebo once daily, respectively, in ARIES-1; $P=0.002$, $P=0.002$, change from baseline to week 12 for ambrisentan in doses of 2.5 and 5 mg, respectively, vs placebo once daily in ARIES-2. A total of 110 patients in ARIES-1 and 107 patients in ARIES-2 for whom outcome data were available were included in this analysis.

The rates of clinical worsening ranged from 4% to 5% in all ambrisentan dose groups and were reduced compared with those of the placebo groups (Table 2 and Figure 3) in both ARIES-1 and ARIES-2. However, a clear difference was observed in the overall rates of clinical worsening between the placebo groups in ARIES-1 (9%) and ARIES-2 (22%), and this may explain why statistical significance was observed in only the latter study (Table 2 and Figure 3). The difference in clinical worsening among the placebo groups of ARIES-1 and ARIES-2 was due mainly to a different rate of hospitalizations (3% and 14%, respectively). ARIES-1 and ARIES-2 patients were enrolled predominantly in North America and Europe, respectively; therefore, differences in the criteria for hospital admissions in these 2 geographic areas may be responsible in part for this discrepancy. The symptomatic improvement with ambrisentan in these studies was supported by the favorable effects on WHO functional class, Borg dyspnea score, and the SF-36 Health Survey.

Plasma B-type natriuretic peptide concentrations, which correlate with hemodynamic and right ventricular echocardiographic severity in pulmonary hypertension^{29,30} and in

particular with survival in idiopathic PAH,³¹ were significantly reduced at week 12 with each ambrisentan dose compared with placebo (Figure 4). The reduction in B-type natriuretic peptide concentrations may be related to hemodynamic improvement, as was observed in a previous phase 2 study with ambrisentan in PAH patients.¹²

All ambrisentan doses were well tolerated, with most adverse events mild to moderate in severity (Table 2). The increased frequency of nasal congestion, peripheral edema, and headache observed with ambrisentan is likely due to systemic vasodilatation. Remarkably, no elevation of serum aminotransferases concentrations greater than >3 the upper normal limits was observed in the ambrisentan-treated patients. Thus, the safety profile of ambrisentan appears to be better than that of oral bosentan and sitaxsentan, the 2 endothelin receptor antagonists currently approved for the treatment of PAH patients.

A dose-response trend was observed in the primary end point (exercise capacity) within each study, and except for nasal congestion, no apparent dose response was noted for adverse events. From these data, it appears that both the 5- and 10-mg ambrisentan doses have appropriate ratios of efficacy to safety. In the clinical setting, an up-titration to the 10-mg dose may be considered if the drug is being well tolerated at the initial 5-mg dose.

Limitations of these studies include the exclusion of certain patient populations such as patients with PAH associated with portal hypertension and congenital systemic-to-pulmonary shunts. In addition, although the long-term effect has been shown in a relatively high proportion of patients remaining on ambrisentan monotherapy for 48 weeks, these data may represent a selection of patients who respond to the drug.

Conclusions

These placebo-controlled studies demonstrate the efficacy and safety of ambrisentan in the treatment of patients with symptomatic PAH. The favorable efficacy-to-safety profile of ambrisentan may offer potential advantages over the currently approved treatment options.

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This study was sponsored by Myogen Inc (now Gilead Sciences Inc).

Disclosures

Dr Galiè has served on the advisory boards of Pfizer, Actelion, Bayer-Schering, Encysive, Gilead, and Mondobiotec and has received lecture fees from Actelion and Bayer-Schering and grant support from Pfizer, Actelion, Bayer-Schering, Encysive, and Gilead. Dr Olschewski has served on the advisory boards of Gilead and United Therapeutics; he has received lecture fees from Gilead, Actelion, Bayer Schering, and Encysive; honoraria from Gilead, Actelion, Bayer Schering, and Encysive; and grant support from Actelion. Dr Oudiz has served on the advisory boards of Gilead and Actelion and has received lecture fees from Gilead, honoraria from Gilead, and grant support from Actelion and Gilead. Dr Torres has served on the advisory boards of Gilead and Actelion; he has received lecture fees from Gilead, Actelion, and Pfizer and grant support from Actelion, Gilead, and United Therapeutics. Dr Frost has served on the advisory

boards of Gilead and Actelion. She has received lecture fees from Gilead, Actelion, and Pfizer and grant support from Actelion, Gilead, Encysive, Pfizer, and United Therapeutics. Dr Ghofrani has served on the advisory boards of Pfizer, Encysive, Bayer-Schering, and Actelion. He has received lecture fees from Encysive, Actelion, Pfizer, Bayer-Schering, and Cotherix; honoraria from Pfizer, Actelion, Bayer-Schering, Encysive, and Altana; and grant support from Pfizer, Bayer-Schering, Ergonex, and Actelion. Dr Badesch has served on the advisory boards of Gilead, Actelion, Pfizer, Encysive, GSK, and United Therapeutics. He has received lecture fees from Gilead and Actelion; honoraria from Gilead, Encysive, Cotherix, and Pfizer; and grant support from Actelion, Gilead, and United Therapeutics. Dr McGoon has served on the advisory boards of Gilead and Actelion and has received grant support from Actelion, Gilead, and Medtronic. Dr McLaughlin has served on the advisory boards of Gilead, Actelion, Pfizer; she has received lecture fees from Gilead, Pfizer and Actelion and grant support from Actelion, Encysive, Pfizer, and United Therapeutics. Dr Roecker has received grant support from Gilead. Drs Gerber, Dufton, and Wiens are employees of Gilead and own Gilead stock and stock options. Dr Rubin has served on the advisory board of and received grant support from Gilead.

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CLINICAL PERSPECTIVE

Pulmonary arterial hypertension is a progressive disease characterized by an elevated pulmonary vascular resistance leading to right ventricular failure and premature death. Current therapies approved for the treatment of pulmonary arterial hypertension in North America and/or Europe include prostacyclin analogues administered by intravenous, inhaled, and subcutaneous routes; the oral endothelin receptor antagonists bosentan and sitaxsentan; and the oral phosphodiesterase type 5 inhibitor sildenafil. Although these agents are efficacious, each has safety-, tolerability-, or drug delivery–related adverse effects. The data of the Ambrisentan in Pulmonary Arterial Hypertension, Randomized, Double-Blind, Placebo-Controlled, Multicenter, Efficacy Study 1 and 2 (ARIES-1 and ARIES-2) trials show that the once-daily oral active A-selective endothelin receptor antagonist ambrisentan is effective in improving exercise capacity, functional class, and clinical outcome of patients with symptomatic pulmonary arterial hypertension. Remarkably, no elevation of serum aminotransferases concentrations >3 times the upper normal limits was observed in the ambrisentan-treated patients. The favorable efficacy-to-safety profile of ambrisentan may offer potential advantages over the currently approved treatment options.

Ambrisentan for the Treatment of Pulmonary Arterial Hypertension: Results of the Ambrisentan in Pulmonary Arterial Hypertension, Randomized, Double-Blind, Placebo-Controlled, Multicenter, Efficacy (ARIES) Study 1 and 2

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