

## BOSENTAN THERAPY FOR PULMONARY ARTERIAL HYPERTENSION

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FOR THE BOSENTAN RANDOMIZED TRIAL OF ENDOTHELIN ANTAGONIST THERAPY STUDY GROUP

## ABSTRACT

**Background** Endothelin-1 is a potent vasoconstrictor and smooth-muscle mitogen. In a preliminary study, the orally administered dual endothelin-receptor antagonist bosentan improved exercise capacity and cardiopulmonary hemodynamics in patients with pulmonary arterial hypertension. The present trial investigated the effect of bosentan on exercise capacity in a larger number of patients and compared two doses.

**Methods** In this double-blind, placebo-controlled study, we randomly assigned 213 patients with pulmonary arterial hypertension (primary or associated with connective-tissue disease) to receive placebo or to receive 62.5 mg of bosentan twice daily for 4 weeks followed by either of two doses of bosentan (125 or 250 mg twice daily) for a minimum of 12 weeks. The primary end point was the degree of change in exercise capacity. Secondary end points included the change in the Borg dyspnea index, the change in the World Health Organization (WHO) functional class, and the time to clinical worsening.

**Results** At week 16, patients treated with bosentan had an improved six-minute walking distance; the mean difference between the placebo group and the combined bosentan groups was 44 m (95 percent confidence interval, 21 to 67;  $P < 0.001$ ). Bosentan also improved the Borg dyspnea index and WHO functional class and increased the time to clinical worsening.

**Conclusions** The endothelin-receptor antagonist bosentan is beneficial in patients with pulmonary arterial hypertension and is well tolerated at a dose of 125 mg twice daily. Endothelin-receptor antagonism with oral bosentan is an effective approach to therapy for pulmonary arterial hypertension. (N Engl J Med 2002;346:896-903.)

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**P**ULMONARY arterial hypertension is a debilitating disease characterized by an increase in pulmonary vascular resistance leading to right ventricular failure and death.<sup>1</sup> Pulmonary arterial hypertension with no apparent cause is termed primary pulmonary hypertension. Pulmonary arterial hypertension can also develop in up to 50 percent of patients with scleroderma.<sup>2,3</sup> The limited oral treatment options include long-term anticoagulant therapy<sup>4,5</sup> and therapy with calcium-channel

blockers; the latter improve survival in a limited number of patients.<sup>5</sup> Beneficial effects have been reported with continuous intravenous infusion of epoprostenol (prostacyclin), but this treatment has drawbacks.<sup>6,7</sup> The efficacy of epoprostenol analogues that can be inhaled (e.g., iloprost<sup>8</sup>) or administered orally (e.g., beraprost<sup>9</sup>) remains to be confirmed.

There is increasing evidence that endothelin-1 has a pathogenic role in pulmonary arterial hypertension<sup>10</sup> and that blockade of endothelin receptors may be beneficial.<sup>11</sup> Endothelin-1 is a potent endogenous vasoconstrictor and smooth-muscle mitogen that is overexpressed in the plasma and lung tissue of patients with primary pulmonary hypertension<sup>12,13</sup> and scleroderma.<sup>14</sup> Its actions are mediated by two receptors, ET<sub>A</sub> and ET<sub>B</sub>. In a previous 12-week trial involving patients with pulmonary arterial hypertension (either primary or associated with scleroderma) who were in World Health Organization (WHO) functional class III (defined as having symptoms with mild exertion), bosentan, an oral antagonist of both endothelin receptors, improved exercise capacity and cardiopulmonary hemodynamics and was well tolerated at a dose of 125 mg twice daily.<sup>15</sup> The objectives of the current Bosentan Randomized Trial of Endothelin Antagonist Therapy (BREATHE-1) were to investigate the effect of bosentan on exercise capacity in a larger number of patients with pulmonary arterial hypertension (including patients in WHO functional class IV [defined as having symptoms at rest]) and to compare two doses (125 and 250 mg twice daily).

## METHODS

## Selection of Patients

We enrolled patients who had symptomatic, severe pulmonary arterial hypertension (WHO functional class<sup>16</sup> III or IV) despite

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treatment with anticoagulant drugs, vasodilators, diuretics, cardiac glycosides, or supplemental oxygen. Pulmonary arterial hypertension was either primary or associated with connective-tissue disease (scleroderma or systemic lupus erythematosus). For ethical reasons, eligible patients in class IV were also required to have a sufficiently stable clinical status to enable them to participate in a placebo-controlled trial. The inclusion criteria were a base-line six-minute walking distance between 150 and 450 m, a resting mean pulmonary-artery pressure greater than 25 mm Hg, a pulmonary-capillary wedge pressure of less than 15 mm Hg, and pulmonary vascular resistance greater than 240 dyn·sec·cm<sup>-5</sup>. Patients were excluded if they had started or stopped any therapy for pulmonary arterial hypertension within one month before screening or if they had received or had been scheduled to receive long-term treatment with epoprostenol within three months before screening. To avoid potential drug interactions, patients were also excluded if they were receiving glyburide (glibenclamide) or cyclosporine.

The study was conducted according to the provisions of the Helsinki Declaration of 1975, as revised in 1983, and in adherence to local guidelines for good clinical practice. The local ethics review committees approved the protocol, and written informed consent was obtained from all patients.

### Study Design

The study was designed as a double-blind, randomized, placebo-controlled trial and was conducted in 27 centers in Europe, North America, Israel, and Australia. All 213 patients were randomly assigned to receive placebo or 62.5 mg of bosentan (Tracleer, Actelion, Allschwil, Switzerland) twice daily for 4 weeks, followed by 125 or 250 mg of bosentan twice daily for 12 weeks. All patients then continued to take study medication in a double-blind manner until the end of the study, which was defined as the day the last enrolled patient completed the assessment at week 16. All patients completed period 1 (16 weeks), but only those randomized within the first 2 months participated in period 2, which was designed to collect data on efficacy and safety prospectively for an additional 12 weeks of double-blind treatment. At the end of the study, all patients were eligible to enter an open-label study of bosentan.

### Outcome Measures

During period 1, patients were evaluated on an outpatient basis after 4, 8, 12, and 16 weeks of therapy. The primary efficacy measure was the change from base line to week 16 in exercise capacity, indicated by the distance a patient could walk in six minutes.<sup>17</sup> The secondary measures of efficacy were the change from base line to week 16 in the Borg dyspnea index (a measure of perceived breathlessness on a scale of 0 to 10, with higher values indicating more severe dyspnea),<sup>18</sup> the change from base line to week 16 in WHO functional class (a modification of the New York Heart Association class, with higher classes indicating more severe disease), and the time from randomization to clinical worsening (defined as the combined end point of death, lung transplantation, hospitalization for pulmonary hypertension, lack of clinical improvement or worsening leading to discontinuation, need for epoprostenol therapy, or atrial septostomy). Safety was assessed on the basis of recorded adverse events, laboratory measures, and electrocardiography. If increases in liver aminotransferase levels were to a value between five and eight times the upper limit of normal, the dose of the study drug was halved. If increases in liver aminotransferases were to a value greater than eight times the upper limit of normal, treatment was discontinued. During period 2, the patients were evaluated for efficacy and safety on an outpatient basis at 22 and 28 weeks of therapy.

### Statistical Analysis

The data were retained and analyzed by the sponsor, Actelion. All authors had full access to the data and had complete independ-

ence during the preparation of the manuscript. The null hypothesis of the study was that there would be no difference between patients receiving bosentan (both dosage groups combined) and those receiving placebo in the distributions of the changes from base line in exercise capacity. The required sample of 50 patients in each of the three groups (the two bosentan groups and the placebo group) was estimated with the goal of rejecting the null hypothesis if the means of the distributions, with equal standard deviations of 75 m, differed by at least 45 m according to the Mann-Whitney U test, with a type I error of 0.05 (two-sided) and 90 percent power.

Any data missing at the week 16 assessment were derived by using predefined replacement rules with the purpose of minimizing bias. For patients who discontinued the study medication because of clinical worsening, the values recorded at the time of discontinuation was used; patients for whom no value was recorded (including patients who died) were assigned the worst possible value (0 m). For all other patients without a week 16 assessment, the last six-minute walking distance, score on the Borg dyspnea index, and WHO functional class were used as week 16 values.

Statistical analyses were completed according to the intention to treat. The changes in six-minute walking distance, Borg dyspnea index, and WHO functional class are reported as means and changes from base line or as proportions of patients, with the corresponding standard errors or 95 percent confidence intervals for the combined bosentan groups and for the placebo group. The change in walking distance was to be analyzed in subgroups defined by demographic and prognostic variables. The time from randomization to clinical worsening was analyzed by the log-rank test, and Kaplan-Meier estimates of the proportions of patients with treatment failures were calculated. All reported P values are two-sided.

## RESULTS

Two hundred thirteen patients were included in the study: 144 received bosentan (74 patients were assigned to 125 mg and 70 patients to 250 mg), and 69 received placebo. Forty-eight patients continued to receive double-blind treatment in period 2. The mean duration of treatment was 129 days in each bosentan group and 124 days in the placebo group. No instance of breaking of the treatment code occurred before the week 16 assessments; only three such breaks occurred during period 2 (up to 28 weeks).

### Base-Line Characteristics

The placebo and bosentan groups were well matched with respect to demographic and base-line characteristics (Table 1). In each group, primary pulmonary hypertension was more common than pulmonary arterial hypertension associated with connective-tissue disease, and more patients were female. As a consequence of the requirement for a stable base-line status, few patients in class IV were included in the study. All groups were similar in terms of concomitant medications and duration of the disease before the trial (time since diagnosis).

### Exercise Capacity

After 16 weeks of treatment, the distance walked in six minutes was increased by 36 m in the combined bosentan groups, whereas a deterioration of 8 m occurred in the placebo group, a mean difference of 44 m (95 percent confidence interval, 21 to

**TABLE 1.** DEMOGRAPHIC AND CLINICAL CHARACTERISTICS AT BASE LINE IN THE PLACEBO AND BOSENTAN GROUPS.\*

CHARACTERISTIC	PLACEBO (N=69)	BOSENTAN GROUPS COMBINED (N=144)	125 mg OF BOSENTAN (N=74)	250 mg OF BOSENTAN (N=70)
Sex — no. (%)				
Male	15 (22)	30 (21)	17 (23)	13 (19)
Female	54 (78)	114 (79)	57 (77)	57 (81)
Age — yr				
Mean	47.2±16.2	48.7±15.8	50.4±15.9	47.0±15.6
Range	12–80	13–80	15–79	13–80
Weight — kg	73.7±18.3	71.0±19.6	71.6±21.2	70.5±17.8
Race — no. (%)				
White	59 (86)	111 (77)	57 (77)	54 (77)
Other	10 (14)	33 (23)	17 (23)	16 (23)
Cause of pulmonary arterial hypertension — no. (%)				
Primary	48 (70)	102 (71)	57 (77)	45 (64)
Associated with scleroderma	14 (20)	33 (23)	13 (18)	20 (29)
Systemic lupus erythematosus	7 (10)	9 (6)	4 (5)	5 (7)
Previous or concomitant treatment — no. (%)				
Antithrombotic agents	50 (72)	101 (70)	51 (69)	50 (71)
Diuretics	32 (46)	79 (55)	40 (54)	39 (56)
Calcium-channel blockers	36 (52)	64 (44)	33 (45)	31 (44)
Supplemental oxygen at screening visit	23 (33)	41 (28)	19 (26)	22 (31)
Time since diagnosis — mo	28±48	30±35	30±33	30±38
6-min walking distance — m	344±76	330±74	326±73	333±75
Dyspnea score (Borg index)	3.8±2.0	3.6±2.0	3.3±2.2	3.8±1.9
WHO functional class — no. (%)				
III	65 (94)	130 (90)	68 (92)	62 (89)
IV	4 (6)	14 (10)	6 (8)	8 (11)
Cardiac index — liters/min/m <sup>2</sup> †	2.4±0.7	2.4±0.8	2.5±0.8	2.2±0.8
Pulmonary vascular resistance — dyn·sec·cm <sup>-5</sup> ‡	880±540	1014±678	884±412	1167±875
Pulmonary-artery pressure — mm Hg	53±17	55±16	53±14	57±17
Pulmonary-capillary wedge pressure — mm Hg§	9.2±4.1	9.2±3.9	9.7±4.1	8.7±3.6
Right atrial pressure — mm Hg¶	8.9±5.1	9.8±5.9	9.7±5.4	9.9±6.5

\*The groups shown represent the intention-to-treat population. Plus-minus values are means ±SD. Differences between the placebo and bosentan groups were nonsignificant by Fisher's exact test and Student's t-test. WHO denotes World Health Organization.

†Data were missing for one patient receiving placebo and four receiving 125 mg of bosentan.

‡Data were missing for four patients receiving placebo, one receiving 125 mg of bosentan, and eight receiving 250 mg of bosentan.

§Data were missing for two patients receiving placebo, one receiving 125 mg of bosentan, and eight receiving 250 mg of bosentan.

¶Data were missing for two patients receiving placebo and one receiving 250 mg of bosentan.

67;  $P<0.001$ ). Although both bosentan doses induced a significant treatment effect, the placebo-corrected improvement was more pronounced for the dose of 250 mg twice daily than for the dose of 125 mg twice daily (54 m and 35 m, respectively). However, no dose-response relation for efficacy could be ascertained (Fig. 1).

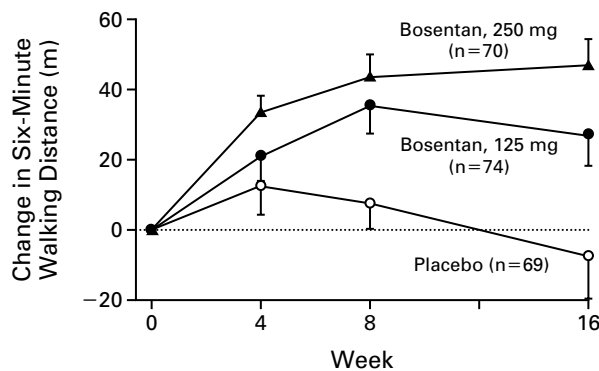
#### Robustness of the Data

The significance of the improvement in exercise capacity with bosentan was confirmed in the per protocol population (i.e., those for whom there were no

violations of the protocol;  $P<0.001$ ). It was similarly demonstrated when different approaches were adopted for the substitution of missing data: for example, when the missing walking distance for a patient who did not complete the study (because of death or worsening pulmonary arterial hypertension) was replaced by the last measured value carried forward rather than by the worst possible value ( $P<0.001$ ).

#### Subgroup Analyses

The primary efficacy measure was also assessed in different subgroups of patients (Fig. 2). An improve-



**Figure 1.** Mean ( $\pm$ SE) Change in Six-Minute Walking Distance from Base Line to Week 16 in the Placebo and Bosentan Groups.

$P < 0.01$  for the comparison between the 125-mg dose of bosentan and placebo, and  $P < 0.001$  for the comparison between the 250-mg dose and placebo by the Mann-Whitney U test. There was no significant difference between the two bosentan groups ( $P = 0.18$  by the Mann-Whitney U test).

ment in the walk-test performance of bosentan-treated patients was observed, regardless of sex, cause of disease, associated congenital heart defect, time from diagnosis, base-line walk-test performance, and base-line hemodynamic measurements. Although a similar treatment effect was evident in patients with primary pulmonary hypertension and in those with pulmonary arterial hypertension associated with scleroderma, bosentan improved the walking distance from base line in the patients with primary pulmonary hypertension (by 46 m among 102 patients in the bosentan group, as compared with a decline of 5 m among 48 patients in the placebo group), whereas it prevented deterioration in the walking distance among patients with scleroderma (an improvement of 3 m among 33 patients in the bosentan group, as compared with a decline of 40 m among 14 patients in the placebo group).

#### Borg Dyspnea Index

The changes in the Borg dyspnea index at week 16 paralleled the improvements observed in the walking test. Bosentan-treated patients had a mean decrease from base line in the Borg dyspnea index. In the group receiving 125 mg of bosentan twice daily, the index decreased from  $3.3 \pm 0.3$  to  $3.2 \pm 0.3$ , a mean change of  $-0.1 \pm 0.2$ . In the group receiving 250 mg of bosentan twice daily, the index decreased from  $3.8 \pm 0.2$  to  $3.3 \pm 0.3$ , a mean change of  $-0.6 \pm 0.2$ . In the group receiving placebo, the index increased from  $3.8 \pm 0.2$  to  $4.2 \pm 0.3$ , a mean increase of  $0.3 \pm$

0.2. The mean treatment effect was  $-0.6$  in favor of bosentan (95 percent confidence interval,  $-1.2$  to  $-0.1$ ). The placebo-corrected improvement was greater for patients receiving 250 mg ( $-0.9$ ,  $P = 0.012$  by the Mann-Whitney U test) than for those receiving 125 mg ( $-0.4$ ,  $P = 0.42$ ).

#### WHO Functional Class

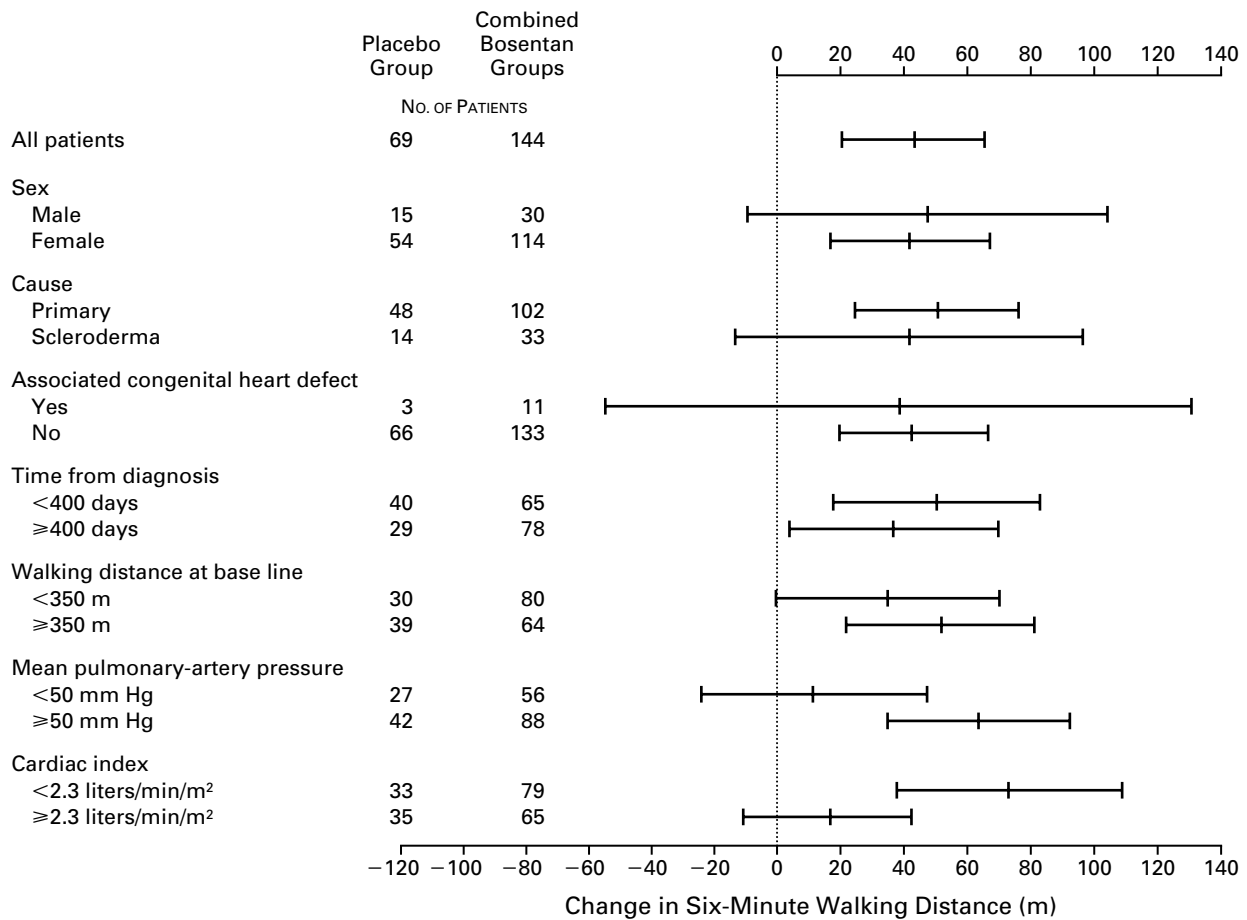
At base line, more than 90 percent of the patients were in WHO functional class III. By week 16, in the groups receiving 125 and 250 mg of bosentan, 38 percent and 34 percent of patients, respectively, had improved to class II (defined as having symptoms with moderate exertion), and 3 percent and 1 percent, respectively, had improved to class I. In contrast, among the patients receiving placebo, only 28 percent had improved to class II, and none had improved to class I (Fig. 3). Overall, 42 percent of the bosentan-treated patients and 30 percent of the placebo-treated patients were in a better functional class at week 16 than at base line, resulting in a mean treatment effect of 12 percent in favor of bosentan (95 percent confidence interval,  $-3$  to 25 percent).

#### Clinical Worsening

During the course of the entire study (up to 28 weeks), bosentan significantly increased the time to clinical worsening, as compared with the time in the placebo group ( $P = 0.002$ ) (Fig. 4). In addition, each component of this end point occurred consistently more frequently in the placebo group than in either bosentan group (Table 2). There was no dose effect at any time, and the difference from placebo was significant for both doses of bosentan ( $P = 0.01$  for 125 mg twice daily, and  $P = 0.01$  for 250 mg twice daily). The difference between treatment groups in the time to clinical worsening was apparent as early as week 16. This difference was found to be significant when the data from patients who continued into period 2 were censored at the week 16 assessment ( $P = 0.004$ ).

#### Safety and Tolerability

The most frequent adverse events in both treatment groups are shown in Table 3. With the exception of abnormal hepatic function, which was more frequent in the group receiving 250 mg of bosentan than in the placebo group, the number and nature of adverse events were similar in the two bosentan groups and the placebo group. Adverse events led to premature discontinuation of the study medication in nine patients in the two bosentan groups (6 percent) and five patients in the placebo group (7 percent). The most frequent adverse events leading to withdrawal were abnormal hepatic function in the two bosentan groups (three patients for bosentan [2 percent], as compared with no patients for placebo) and



**Figure 2.** Effect of Treatment on the Six-Minute Walking Distance from Base Line to Week 16 in Various Subgroups. Bars represent 95 percent confidence intervals. Certain values could not be obtained for some patients. In some cases, very small subgroups of patients have been omitted from the analysis.

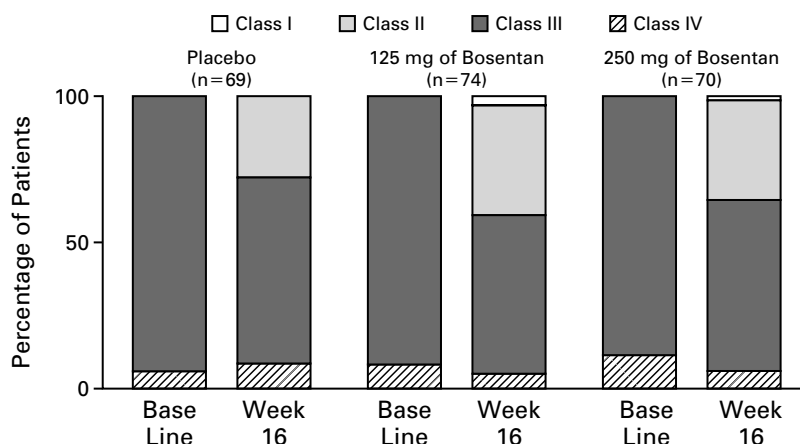
clinical worsening of symptoms of pulmonary arterial hypertension and syncope in the placebo group (four patients [6 percent] and two patients [3 percent] for placebo, as compared with two patients [1 percent] and no patients for bosentan, respectively). Abnormal hepatic function was found to be dose-dependent. Increases in hepatic aminotransferase levels to more than eight times the upper limit of normal were not observed in the placebo-treated patients but occurred in two patients in the group receiving 125 mg of bosentan twice daily (3 percent;  $P < 0.05$ ) and five patients in the group receiving 250 mg of bosentan twice daily (7 percent;  $P < 0.1$ ). Bosentan did not induce a clinically significant change in the mean heart rate ( $83 \pm 13$  bpm at base line vs.  $82 \pm 14$  bpm at end of study) or the mean arterial

pressure ( $88 \pm 13$  mm Hg at base line vs.  $85 \pm 11$  mm Hg at the end of study).

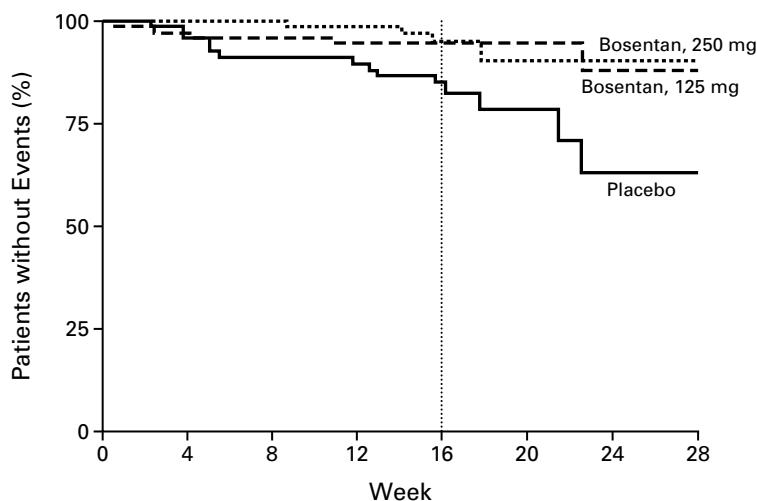
Three patients died during the study (all during period 1): two patients receiving placebo died of aggravated pulmonary arterial hypertension and one patient receiving 125 mg of bosentan twice daily died of cardiac failure. Three additional patients receiving 250 mg of bosentan twice daily died within four weeks after withdrawal from or completion of the study: two were withdrawn because of pneumonia or a worsening condition, and one died of pulmonary hemorrhage while in the open-label extension study.

#### DISCUSSION

In a preliminary study of patients with pulmonary arterial hypertension,<sup>15</sup> bosentan improved exercise



**Figure 3.** Change in World Health Organization Functional Class from Base Line to Week 16 in the Placebo and Bosentan Groups. Higher classes indicate a greater severity of disease.



No. AT RISK	0	4	8	12	16	20	24	28
Placebo	69	68	63	62	48	10	7	3
Bosentan, 125 mg	74	72	71	70	55	18	14	7
Bosentan, 250 mg	70	70	70	68	48	13	11	6

**Figure 4.** Kaplan–Meier Estimates of the Proportion of Patients with Clinical Worsening. Clinical worsening was defined by the combined end point of death, lung transplantation, hospitalization or discontinuation of the study treatment because of worsening pulmonary arterial hypertension, a need for epoprostenol therapy, or atrial septostomy.  $P < 0.05$  for the comparison of the bosentan groups with the placebo group at weeks 16 and 28 by the log-rank test. There was no significant difference between the two bosentan groups at weeks 16 and 28 ( $P = 0.87$ ).

capacity and cardiopulmonary hemodynamics. The present multicenter, randomized, placebo-controlled trial establishes the efficacy of bosentan in improving exercise capacity in a larger number of patients with pulmonary arterial hypertension. A significant improvement was shown in all subgroup analyses.

The six-minute walk test is a reliable tool for the assessment of exercise capacity in patients with pulmonary arterial hypertension. Furthermore, it is an independent predictor of mortality.<sup>19</sup> In a study of epoprostenol in patients with primary pulmonary hypertension, a treatment-related improvement of 47 m

**TABLE 2.** INCIDENCE OF CLINICAL WORSENING IN THE PLACEBO AND BOSENTAN GROUPS.\*

EVENT	PLACEBO (N=69)	BOSENTAN GROUPS		125 mg OF BOSENTAN (N=74)	P VALUE†	250 mg OF BOSENTAN (N=70)	P VALUE†
		COMBINED (N=144)	P VALUE‡				
	no. (%)			no. (%)		no. (%)	
Clinical worsening up to week 28‡	14 (20)	9 (6)	0.004	5 (7)	0.02	4 (6)	0.01
Death	2 (3)	1 (1)	0.25	1 (1)	0.61	—	0.24
Hospitalization or discontinuation for pulmonary arterial hypertension	9 (13)	6 (4)	0.02	3 (4)	0.07	3 (4)	0.08
Lack of clinical improvement leading to discontinuation	1 (1)	—	0.32	—	0.48	—	0.50
Worsening of pulmonary arterial hypertension leading to discontinuation	5 (7)	5 (3)	0.30	3 (4)	0.48	2 (3)	0.27
Receipt of prostacyclin (epoprostenol)	3 (4)	4 (3)	0.68	2 (3)	0.67	2 (3)	0.68

\*The groups shown represent the intention-to-treat population. P values for the comparison with placebo were obtained by Fisher's exact test.

†P values are for the comparison with the placebo group.

‡More than one event occurred in some patients.

**TABLE 3.** MOST FREQUENT ADVERSE EVENTS IN THE PLACEBO AND BOSENTAN GROUPS.\*

EVENT	PLACEBO (N=69)	BOSENTAN GROUP		125 mg OF BOSENTAN (N=74)	P VALUE†	250 mg OF BOSENTAN (N=70)	P VALUE†
		COMBINED (N=144)	P VALUE‡				
	no. (%)			no. (%)		no. (%)	
Headache	13 (19)	30 (21)	0.86	14 (19)	1.00	16 (23)	0.68
Dizziness	13 (19)	16 (11)	0.14	9 (12)	0.35	7 (10)	0.15
Worsening of symptoms of pulmonary arterial hypertension	13 (19)	11 (8)	0.02	7 (9)	0.15	4 (6)	0.02
Cough	8 (12)	8 (6)	0.16	4 (5)	0.23	4 (6)	0.24
Dyspnea	7 (10)	7 (5)	0.15	2 (3)	0.09	5 (7)	0.56
Syncope	4 (6)	13 (9)	0.59	6 (8)	0.75	7 (10)	0.53
Flushing	3 (4)	13 (9)	0.28	7 (9)	0.33	6 (9)	0.49
Abnormal hepatic function	2 (3)	13 (9)	0.15	3 (4)	1.00	10 (14)	0.03

\*The groups shown represent the intention-to-treat population. P values for the comparison with placebo were obtained by Fisher's exact test.

†P values are for the comparison with the placebo group.

was associated with improved survival.<sup>6</sup> To date, consistent improvement of exercise capacity in patients with severe pulmonary arterial hypertension has been reported only in open-label studies with continuous intravenous epoprostenol,<sup>6,7</sup> the only currently approved treatment for pulmonary arterial hypertension, and more recently with the stable inhaled prostacyclin analogue, iloprost.<sup>8</sup> This result indicates the clinical relevance of the magnitude of the improvements observed in the present study. In addition,

bosentan was found to reduce significantly the risk of clinical worsening and of the occurrence of all the end points contributing to the definition of clinical worsening.

Treatment with 125 mg of bosentan twice daily was not associated with a significant increase in adverse events or with a change in their nature when compared with placebo. However, increasing the dose to 250 mg twice daily led to a greater frequency of increased aminotransferase levels. This observation is

in accord with the known dose-dependency of the incidence and severity of cases of elevated aminotransferase levels observed with bosentan treatment.<sup>20,21</sup> In our opinion, 125 mg twice daily is the clinically preferable dose.

One limitation of the present study is that patients with pulmonary arterial hypertension secondary to other diseases, such as portal hypertension or infection with the human immunodeficiency virus, were not included. In addition, the study was not designed to evaluate the long-term effects of bosentan or to demonstrate improved survival. However, bosentan significantly increased the time to clinical worsening and reduced the proportion of patients in WHO functional class IV, suggesting that it may slow the progression of disease. Nevertheless, long-term clinical experience is still needed.

In conclusion, the orally administered dual endothelin-receptor antagonist bosentan significantly improves exercise capacity and increases the time to clinical worsening in patients with severe pulmonary arterial hypertension. Our results confirm the therapeutic potential of endothelin-receptor blockade in patients with pulmonary arterial hypertension, either primary or associated with connective-tissue disease.

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**CORRECTION**

**Bosentan Therapy for Pulmonary Arterial Hypertension**

Bosentan Therapy for Pulmonary Arterial Hypertension . On page 896, the dose in the fifth line of the Methods section of the Abstract should have read, "62.5 mg of bosentan twice daily for 4 weeks," not "6.25 mg of bosentan twice daily for 4 weeks," as printed. In the original Web publication of this article, the dose was correct.