

ORIGINAL ARTICLE

Macitentan and Morbidity and Mortality in Pulmonary Arterial Hypertension

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ABSTRACT

BACKGROUND

Current therapies for pulmonary arterial hypertension have been adopted on the basis of short-term trials with exercise capacity as the primary end point. We assessed the efficacy of macitentan, a new dual endothelin-receptor antagonist, using a primary end point of morbidity and mortality in a long-term trial.

METHODS

We randomly assigned patients with symptomatic pulmonary arterial hypertension to receive placebo once daily, macitentan at a once-daily dose of 3 mg, or macitentan at a once-daily dose of 10 mg. Stable use of oral or inhaled therapy for pulmonary arterial hypertension, other than endothelin-receptor antagonists, was allowed at study entry. The primary end point was the time from the initiation of treatment to the first occurrence of a composite end point of death, atrial septostomy, lung transplantation, initiation of treatment with intravenous or subcutaneous prostanoids, or worsening of pulmonary arterial hypertension.

RESULTS

A total of 250 patients were randomly assigned to placebo, 250 to the 3-mg macitentan dose, and 242 to the 10-mg macitentan dose. The primary end point occurred in 46.4%, 38.0%, and 31.4% of the patients in these groups, respectively. The hazard ratio for the 3-mg macitentan dose as compared with placebo was 0.70 (97.5% confidence interval [CI], 0.52 to 0.96; $P=0.01$), and the hazard ratio for the 10-mg macitentan dose as compared with placebo was 0.55 (97.5% CI, 0.39 to 0.76; $P<0.001$). Worsening of pulmonary arterial hypertension was the most frequent primary end-point event. The effect of macitentan on this end point was observed regardless of whether the patient was receiving therapy for pulmonary arterial hypertension at baseline. Adverse events more frequently associated with macitentan than with placebo were headache, nasopharyngitis, and anemia.

CONCLUSIONS

Macitentan significantly reduced morbidity and mortality among patients with pulmonary arterial hypertension in this event-driven study. (Funded by Actelion Pharmaceuticals; SERAPHIN ClinicalTrials.gov number, NCT00660179.)

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*The complete list of investigators and committee members for the Study with an Endothelin Receptor Antagonist in Pulmonary Arterial Hypertension to Improve Clinical Outcome (SERAPHIN) trial is provided in the Supplementary Appendix, available at NEJM.org.

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PULMONARY ARTERIAL HYPERTENSION, A severe disease characterized by a sustained elevation of pulmonary vascular resistance, ultimately leads to right heart failure and death.¹ Disease progression occurs despite the availability of drugs that are specific for the disorder.² Endothelin-receptor antagonists, phosphodiesterase type 5 inhibitors, and prostacyclin and its analogues have been approved for the treatment of pulmonary arterial hypertension and adopted clinically on the basis of short-term trials (12 to 16 weeks) that have shown improvements in exercise capacity as measured by the distance walked in 6 minutes.³⁻¹⁰ However, current guidelines suggest that the primary end point in phase 3 trials of new treatments for pulmonary arterial hypertension should be morbidity and mortality.¹¹⁻¹³

The dual endothelin-receptor antagonist macitentan was developed by modifying the structure of bosentan to increase efficacy and safety.¹⁴ Macitentan is characterized by sustained receptor binding and enhanced tissue penetration.^{15,16} In the Study with an Endothelin Receptor Antagonist in Pulmonary Arterial Hypertension to Improve Clinical Outcome (SERAPHIN), we investigated whether long-term treatment with macitentan reduces morbidity and mortality among patients with pulmonary arterial hypertension.

METHODS

STUDY DESIGN

We conducted SERAPHIN as a multicenter, double-blind, randomized, placebo-controlled, event-driven, phase 3 trial. The study sponsor, Actelion Pharmaceuticals, designed the study and conducted all the statistical analyses. The institutional review board or independent ethics committee at each participating institution approved the protocol. The statistical plan was reviewed by two independent academic statisticians. The members of the steering committee were involved in the study design, reviewed the protocol, and provided guidance on the study conduct. An independent data and safety monitoring board reviewed all safety data in an unblinded fashion at regular intervals. All the authors had access to the data, contributed to data interpretation, contributed to writing the manuscript, reviewed and approved the final version, and made the decision to submit the manuscript for publication.

Assistance in writing the manuscript was provided by a professional medical writer paid by the sponsor. All the academic authors vouch for the accuracy and completeness of the data and analyses and for the fidelity of this report to the trial protocol, which is available with the full text of this article at NEJM.org.

SELECTION OF PATIENTS

Patients 12 years of age or older who had idiopathic or heritable pulmonary arterial hypertension or pulmonary arterial hypertension related to connective-tissue disease, repaired congenital systemic-to-pulmonary shunts, human immunodeficiency virus infection, or drug use or toxin exposure were eligible for inclusion in the trial. Confirmation of pulmonary arterial hypertension with the use of right heart catheterization was required. Patients were also required to have a 6-minute walk distance of 50 m or more and to be in class II, III, or IV according to the World Health Organization (WHO) functional classification (an adaptation of the New York Heart Association functional classification). Concomitant treatment with oral phosphodiesterase type 5 inhibitors, oral or inhaled prostanoids, calcium-channel blockers, or L-arginine was allowed, provided that the patient had been receiving a stable dose for at least 3 months before randomization. Patients receiving intravenous or subcutaneous prostanoids were excluded.

Standards of care, access to specific treatments for pulmonary arterial hypertension, and management approaches vary among countries. In this international study, patients were eligible regardless of whether they were receiving background therapy for pulmonary arterial hypertension; this was specified by the protocol. Patients were closely monitored, and those who had clinical worsening were eligible to receive either the 10-mg dose of macitentan or alternative medications specific for pulmonary arterial hypertension. Written informed consent was obtained from all patients.

TRIAL PROCEDURES

Within 28 days after screening, patients were randomly assigned in a 1:1:1 ratio (with stratification according to center) to receive placebo once daily, macitentan at a once-daily dose of 3 mg, or macitentan at a once-daily dose of 10 mg. Clinical assessments (6-minute walk distance and

WHO functional class) were performed and laboratory data obtained at screening or randomization, at months 3 and 6, and every 6 months thereafter, up to and including the end of treatment. Alanine aminotransferase, aspartate aminotransferase, and hemoglobin levels were measured monthly, up to 28 days after the end of treatment. Adverse events were recorded throughout the treatment period and up to 28 days after the end of treatment. Right heart catheterization was performed in a subset of patients at month 6 (see the Supplementary Appendix, available at NEJM.org). The vital status of all patients was recorded at the end of the study (which was declared when the predefined number of primary end-point events was reached).

Patients were monitored for a primary end-point event during the double-blind treatment period. Patients who had a nonfatal primary end-point event and discontinued the double-blind treatment were eligible to receive open-label macitentan at a dose of 10 mg, as were patients who were receiving the double-blind treatment at the end of the study.

OUTCOME MEASURES

The composite primary end point was the time from the initiation of treatment to the first event related to pulmonary arterial hypertension (worsening of pulmonary arterial hypertension, initiation of treatment with intravenous or subcutaneous prostanoids, lung transplantation, or atrial septostomy) or death from any cause up to the end of treatment. Worsening of pulmonary arterial hypertension was defined by the occurrence of all three of the following: a decrease in the 6-minute walk distance of at least 15% from baseline, confirmed by a second 6-minute walk test performed on a different day within 2 weeks; worsening of symptoms of pulmonary arterial hypertension; and the need for additional treatment for pulmonary arterial hypertension. Worsening of symptoms of pulmonary arterial hypertension included at least one of the following: a change from baseline to a higher WHO functional class (or no change in patients who were in WHO functional class IV at baseline) and the appearance or worsening of signs of right heart failure that did not respond to oral diuretic therapy. An independent clinical event committee adjudicated, in a blinded fashion, all events related

to pulmonary arterial hypertension and all deaths that were reported up to the end of treatment, including whether death was due to pulmonary arterial hypertension.

Prespecified secondary end points included the change from baseline to month 6 in the 6-minute walk distance, the percentage of patients with an improvement in WHO functional class at month 6, death due to pulmonary arterial hypertension or hospitalization for pulmonary arterial hypertension up to the end of treatment, and death from any cause up to the end of treatment and up to the end of the study. Safety end points included adverse events and laboratory abnormalities.

STATISTICAL ANALYSIS

We estimated that 285 events would be needed to detect a hazard ratio for the primary end point with macitentan (at least one of the dose groups), as compared with placebo, of 0.55 over an estimated maximum study duration of 4.1 years, assuming an anticipated hazard rate of 0.43 in the placebo group, an expected 5% annual attrition rate, and an annual enrollment of 200 patients. The type I error was set at 0.005 (two-sided test) for the comparison of placebo with each dose of macitentan, with the use of Bonferroni correction to ensure an overall alpha level of 0.01, and power was set at 90%. A planned blinded reestimation of the sample size was performed 3 months before the end of the expected recruitment phase because the overall hazard rate was lower than expected, resulting in an increase in recruitment from 525 to 699 patients.

The main analyses for the primary and secondary end points were performed in the intention-to-treat population, which included all patients who had undergone randomization. The secondary end points were tested hierarchically within each dose group to control for multiple comparisons. All time-to-event end points were estimated with the Kaplan-Meier method and analyzed with the log-rank test. Data from patients without an event who stopped receiving blinded treatment were censored at the time of treatment discontinuation. Two sensitivity analyses for the primary end point were conducted to account for patients without an event who prematurely discontinued treatment; an additional sensitivity analysis for the death-related outcomes was performed to account for patients with

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Placebo (N=250)	Macitentan, 3 mg (N=250)	Macitentan, 10 mg (N=242)	All Patients (N=742)
Female sex — no. (%)	184 (73.9)	187 (75.4)	194 (80.2)	565 (76.5)
Age — yr	46.7±17.03	44.5±16.26	45.5±14.99	45.6±16.13
Race or ethnic group — no. (%)†				
White	131 (52.6)	137 (55.2)	135 (55.8)	403 (54.5)
Black	8 (3.2)	5 (2.0)	6 (2.5)	19 (2.6)
Asian	71 (28.5)	69 (27.8)	65 (26.9)	205 (27.7)
Hispanic	37 (14.9)	37 (14.9)	35 (14.5)	109 (14.7)
Other	2 (0.8)	0	1 (0.4)	3 (0.4)
Time from diagnosis of PAH — yr	2.6±3.7	3.0±4.5	2.6±3.6	2.7±4.0
PAH classification — no. (%)				
Idiopathic	126 (51.0)	144 (58.3)	134 (55.6)	404 (55.0)
Heritable	3 (1.2)	8 (3.2)	2 (0.8)	13 (1.8)
Associated with connective-tissue disease	81 (32.8)	70 (28.3)	73 (30.3)	224 (30.5)
Associated with congenital shunts	26 (10.5)	15 (6.1)	21 (8.7)	62 (8.4)
Associated with HIV infection	3 (1.2)	1 (0.4)	6 (2.5)	10 (1.4)
Associated with drug use or toxin exposure	8 (3.2)	9 (3.6)	5 (2.1)	22 (3.0)
6-Min walk distance — m	352±110.6	364±95.5	363±93.2	360±100.2
WHO functional class — no. (%)‡				
I	0	0	1 (0.4)	1 (0.1)
II	129 (51.8)	138 (55.6)	120 (49.6)	387 (52.4)
III	116 (46.6)	105 (42.3)	116 (47.9)	337 (45.6)
IV	4 (1.6)	5 (2.0)	5 (2.1)	14 (1.9)
Hemodynamic variables				
Right atrial pressure — mm Hg	8.8±5.6	9.2±5.3	9.2±6.0	9.1±5.6
Pulmonary-artery pressure — mm Hg	53.1±18.1	55.1±16.7	53.5±17.6	53.9±17.5
Pulmonary-capillary wedge pressure — mm Hg	9.5±3.4	9.8±3.3	9.5±3.4	9.6±3.4
Cardiac index — liters/min/m ² of body-surface area	2.44±0.80	2.36±0.79	2.36±0.78	2.39±0.79
Pulmonary vascular resistance — dyn·sec·cm ⁻⁵	996±784.3	1044±624.2	1040±672.5	1026±696.7
Receipt of background treatment for PAH — no. (%)				
No	95 (38.2)	85 (34.3)	88 (36.4)	268 (36.3)
Yes	154 (61.8)	163 (65.7)	154 (63.6)	471 (63.7)
Phosphodiesterase type 5 inhibitor	150 (60.2)	154 (62.1)	150 (62.0)	454 (61.4)
Oral or inhaled prostanoid	7 (2.8)	18 (7.3)	15 (6.2)	40 (5.4)
Anticoagulant therapy — no. (%)	119 (47.8)	134 (54.0)	125 (51.7)	378 (51.2)

* Plus-minus values are means ±SD. There were no significant between-group differences at baseline, except regarding the use of an oral or inhaled prostanoid for the comparison between the group that received 3 mg of macitentan and the placebo group ($P<0.05$). For the categories of female sex, age, race or ethnic group, 6-minute walk distance, World Health Organization (WHO) functional class, receipt of treatment for pulmonary arterial hypertension (PAH), and receipt of anticoagulant therapy, data were missing for 1 patient in the placebo group and for 2 in the group that received 3 mg of macitentan (a total of 3 patients with missing data). For the categories of time from diagnosis of PAH and PAH classification, data were missing for 3 patients in the placebo group, for 3 in the 3-mg group, and for 1 in the group that received 10 mg of macitentan (a total of 7 patients with missing data). For right atrial pressure, pulmonary-artery pressure, pulmonary-capillary wedge pressure, cardiac index, and pulmonary vascular resistance, data were missing for 8, 8, 6, 2, and 6 patients, respectively, in the placebo group; for 3, 2, 7, 2, and 7 patients, respectively, in the 3-mg group, and for 4, 0, 7, 2, and 9 patients, respectively, in the 10-mg group (a total of 15, 10, 20, 6, and 22 patients with missing data for these respective categories). HIV denotes human immunodeficiency virus.

† Race or ethnic group was determined by the investigator.

‡ The WHO functional class ranges from I to IV, with higher numbers indicating greater functional limitations. All the trial participants who were in WHO functional class IV at baseline were enrolled in countries where epoprostenol was not available at the time of inclusion. Although only patients in WHO functional class II, III, or IV were permitted in the study according to the protocol, one patient in WHO functional class I was erroneously included.

Table 2. Primary and Secondary End Points for Events Related to Pulmonary Arterial Hypertension and Death.*

End Point	Placebo (N=250)	Macitentan, 3 mg (N=250)	Macitentan, 10 mg (N=242)	Macitentan, 3 mg, vs. Placebo		Macitentan, 10 mg, vs. Placebo		
				Hazard Ratio (97.5% CI)	P Value	Hazard Ratio (97.5% CI)	P Value	
<i>number of patients (percent)</i>								
Event related to PAH or death as the first event								
All events	116 (46.4)	95 (38.0)	76 (31.4)	0.70 (0.52–0.96)	0.01	0.55 (0.32–0.76)	<0.001	
Worsening of PAH	93 (37.2)	72 (28.8)	59 (24.4)					
Death from any cause†	17 (6.8)	21 (8.4)	16 (6.6)					
Prostanoid initiation	6 (2.4)	1 (0.4)	1 (0.4)					
Lung transplantation	0	1 (0.4)	0					
Death due to PAH or hospitalization for PAH as the first event								
All events	84 (33.6)	65 (26.0)	50 (20.7)	0.67 (0.46–0.97)	0.01	0.50 (0.34–0.75)	<0.001	
Hospitalization for PAH	79 (31.6)	56 (22.4)	45 (18.6)					
Death due to PAH‡	5 (2.0)	9 (3.6)	5 (2.1)					
Death from any cause	19 (7.6)	21 (8.4)	14 (5.8)	0.97 (0.48–1.98)	0.92	0.64 (0.29–1.42)	0.20	
Death due to PAH§	14 (5.6)	14 (5.6)	7 (2.9)	0.87 (0.37–2.04)	0.72	0.44 (0.16–1.25)	0.07	
Death from any cause by the end of the study¶	44 (17.6)	47 (18.8)	35 (14.5)	1.05 (0.65–1.67)	0.83	0.77 (0.46–1.28)	0.25	

* All end points were evaluated up to the end of the double-blind treatment period (median duration of treatment, 115 weeks), except for death from any cause up to the end of the study (median follow-up, 129 weeks). CI denotes confidence interval.

† Two patients in each of the macitentan groups had an adverse event leading to the discontinuation of treatment and died thereafter. The causes of death were hematemesis and sudden cardiac death (in one patient in the 10-mg group), cardiorespiratory failure (in one in the 10-mg group), right ventricular failure (in one in the 3-mg group), and multiorgan failure (in one in the 3-mg group). These deaths were adjudicated by the clinical event committee and, as a conservative approach, were included in the analysis of the primary end point.

‡ Data do not include patients who were hospitalized before death.

§ Data include deaths that were adjudicated by the clinical event committee to be due to PAH and that occurred during the double-blind period or deaths that occurred within 4 weeks after the end of treatment, after a confirmed worsening of PAH.

¶ The analysis included patients who were eligible to receive other treatments for PAH, including open-label macitentan at a dose of 10 mg. Data on vital status were not available at the end of the study for 27 patients (3.6%) who were lost to follow-up. The results of a sensitivity analysis for death from any cause up to the end of the study, which imputed death for 30 patients (4.0%) who had missing data on vital status at the end of the study, were consistent with the results of the main analysis (see the Supplementary Appendix).

missing data on vital status (see the Supplementary Appendix). Hazard ratios with two-sided 97.5% confidence intervals were calculated with the use of Cox regression models. Subgroup analyses were performed for the primary end point with the use of interaction tests.¹⁷

At month 6, the change from baseline in the 6-minute walk distance and the proportion of patients with an improved WHO functional class were analyzed with the use of the Wilcoxon rank-sum test and Fisher's exact test, respectively. Missing assessments were imputed with the use of either the last-observation-carried-forward method or a method that imputed data according to a worst-case scenario (see the Supplementary Appendix). Analyses of covariance with adjustment for the 6-minute walk distance at baseline were used post hoc to determine the overall treatment effect,

according to the use or nonuse of therapy for pulmonary arterial hypertension at baseline and according to the baseline WHO functional class.

RESULTS

DISPOSITION AND CHARACTERISTICS OF THE PATIENTS

Patients were enrolled at 151 centers in 39 countries between May 2008 and December 2009 (last patient visit, March 2012). A total of 742 patients were randomly assigned to receive placebo (250 patients), macitentan at a dose of 3 mg (250), or macitentan at a dose of 10 mg (242) and were included in the intention-to-treat population. Patient disposition is shown in Figure S1 in the Supplementary Appendix. Table 1 shows the demographic and clinical characteristics of the patients at baseline.

Although only patients in WHO functional class II, III, or IV were permitted in the study according to the protocol, one patient in WHO functional class I was erroneously included. One patient randomly assigned to placebo did not receive the study drug and was excluded from the safety analysis. The mean duration of study treatment was 85.3 weeks, 99.5 weeks, and 103.9 weeks for the patients receiving placebo, the 3-mg dose of macitentan, and the 10-mg dose of macitentan, respectively. A total of 94 patients (12.7%) discontinued the study drug prematurely without having a primary end-point event; data from these patients were censored at the time of treatment discontinuation in the analysis of the primary end point (Table S1 in the Supplementary Appendix).

MORBIDITY AND MORTALITY

A total of 287 patients had a primary end-point event over a median treatment period of 115

weeks (Table 2): 116 patients (46.4%) in the placebo group, 95 patients (38.0%) in the group that received 3 mg of macitentan, and 76 patients (31.4%) in the group that received 10 mg of macitentan. Worsening of pulmonary arterial hypertension was the most frequent primary end-point event. The hazard ratio for the primary end point with the 3-mg dose of macitentan versus placebo was 0.70 (97.5% confidence interval [CI], 0.52 to 0.96; $P=0.01$ by the log-rank test), and the hazard ratio with the 10-mg dose of macitentan versus placebo was 0.55 (97.5% CI, 0.39 to 0.76; $P<0.001$ by the log-rank test) (Fig. 1). The results of the sensitivity analyses performed to account for premature discontinuation of treatment were consistent with those of the primary analysis (Table S2 in the Supplementary Appendix). The effect of macitentan was consistent in several exploratory subgroup analyses (Fig. S2 and S3 in the Supplementary Appendix).

The composite end point of death due to pulmonary arterial hypertension or hospitalization for pulmonary arterial hypertension occurred in 84 patients (33.6%) in the placebo group, 65 patients (26.0%) in the group that received 3 mg of macitentan, and 50 patients (20.7%) in the group that received 10 mg of macitentan (Table 2 and Fig. 2), with hospitalization accounting for most of these events. The hazard ratio with the 3-mg dose of macitentan versus placebo was 0.67 (97.5% CI, 0.46 to 0.97; $P=0.01$ by the log-rank test), and the hazard ratio with the 10-mg dose of macitentan versus placebo was 0.50 (97.5% CI, 0.34 to 0.75; $P<0.001$ by the log-rank test). Secondary end points related to death are shown in Table 2 and in Figure S4 in the Supplementary Appendix. The sensitivity analyses for death from any cause up to the end of the study, which assumed that the 30 patients (4.0%) with missing vital-status data at the end of the study had died as of the last contact, were consistent with the main analysis (Table S3 in the Supplementary Appendix).

EXERCISE CAPACITY AND FUNCTIONAL CLASS

At month 6, the 6-minute walk distance had decreased by a mean of 9.4 m in the placebo group. In contrast, the 6-minute walk distance had increased by a mean of 7.4 m in the group that received 3 mg of macitentan (treatment effect with 3-mg dose vs. placebo, 16.8 m; 97.5% CI, -2.7 to 36.4; $P=0.01$) and by a mean of 12.5 m in the group that received 10 mg of macitentan (treat-

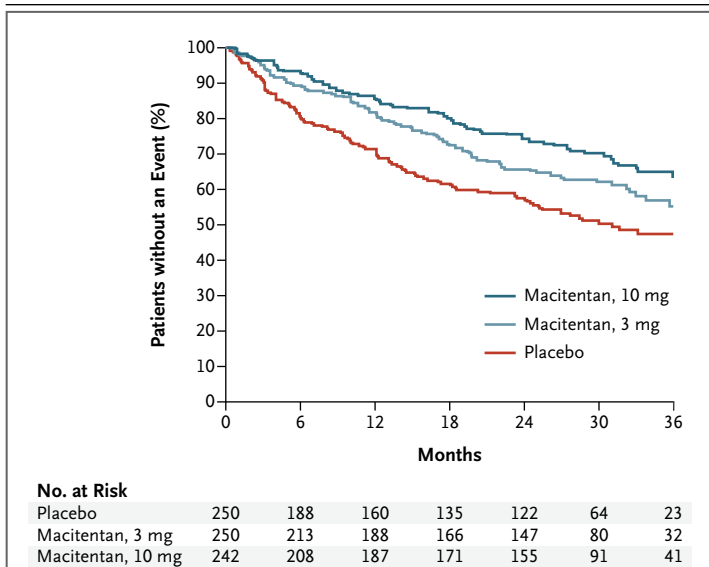


Figure 1. Effect of Macitentan on the Composite Primary End Point of a First Event Related to Pulmonary Arterial Hypertension or Death from Any Cause.

Kaplan–Meier estimates for the first event related to pulmonary arterial hypertension (worsening of pulmonary arterial hypertension, initiation of treatment with intravenous or subcutaneous prostanoids, lung transplantation, or atrial septostomy) or death from any cause show a significant treatment effect in favor of macitentan at a once-daily dose of 3 mg versus placebo (hazard ratio, 0.70; 97.5% CI, 0.52 to 0.96; $P=0.01$ by the log-rank test) and macitentan at a once-daily dose of 10 mg versus placebo (hazard ratio, 0.55; 97.5% CI, 0.39 to 0.76; $P<0.001$ by the log-rank test). The intention-to-treat analysis took into account all available data, whereas the Kaplan–Meier curve is truncated at 36 months.

ment effect with 10-mg dose vs. placebo, 22.0 m; 97.5% CI, 3.2 to 40.8; $P=0.008$). These effects were also examined according to whether or not the patient was receiving therapy for pulmonary arterial hypertension at baseline and according to the WHO functional class at baseline (Table S4 in the Supplementary Appendix). The WHO functional class improved from baseline to month 6 in 13% of the patients in the placebo group, as compared with 20% of those in the group that received 3 mg of macitentan ($P=0.04$) and 22% of those in the group that received 10 mg of macitentan ($P=0.006$).

CARDIAC HEMODYNAMICS

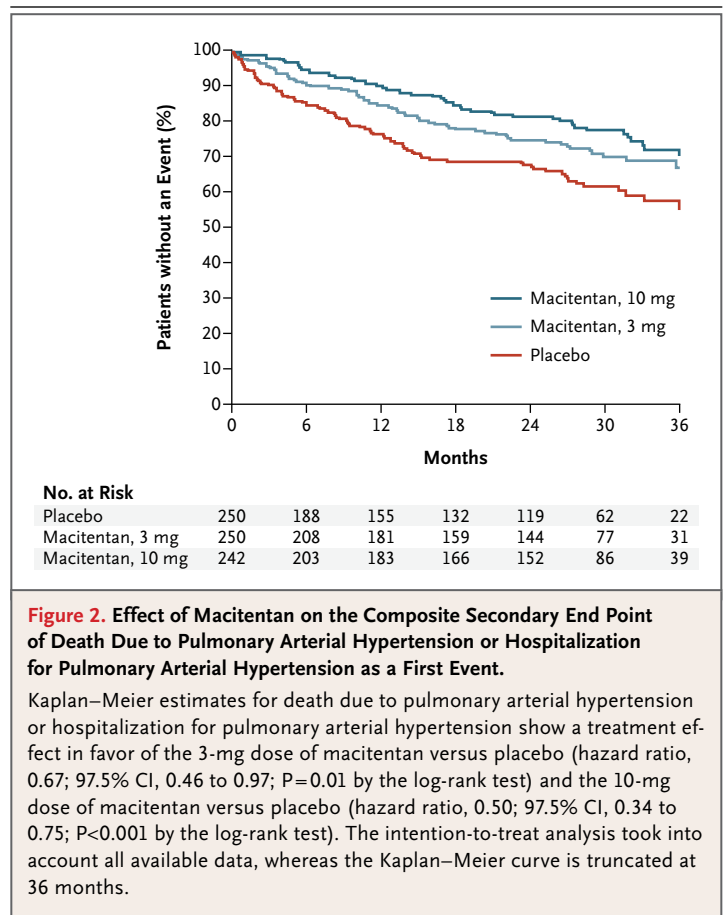
A subset of patients participated in a hemodynamic study that included right heart catheterization at baseline and month 6. Patients in both macitentan groups had significant decreases in pulmonary vascular resistance and significant increases in the cardiac index, as compared with the placebo group (Table S5 in the Supplementary Appendix).

SAFETY

The number of patients in the placebo, 3-mg macitentan, and 10-mg macitentan groups who discontinued the study drug owing to adverse events was 31 (12.4%), 34 (13.6%), and 26 (10.7%), respectively. Table 3 lists the most frequently occurring adverse events. The incidence of peripheral edema and the incidence of alanine aminotransferase or aspartate aminotransferase levels that were more than 3 times the upper limit of the normal range were similar across the three groups (Table 3). The time to the first appearance of an alanine aminotransferase or aspartate aminotransferase level that was more than 3 times the upper limit of the normal range is provided in Figure S5 in the Supplementary Appendix. As compared with patients who received placebo, higher percentages of patients in the two macitentan groups had nasopharyngitis, headache, and anemia (Table 3). Three patients, one in each group, discontinued treatment owing to anemia.

DISCUSSION

In this event-driven study, macitentan significantly reduced morbidity and mortality among patients with pulmonary arterial hypertension. Because pulmonary arterial hypertension is a



chronic life-threatening disease, data from long-term outcome studies are required to assess the effect of therapy on disease progression. Current guidelines for clinical research on pulmonary arterial hypertension support the use of these long-term outcome studies.^{11–13} SERAPHIN shows that large-scale studies of the effects of treatments for pulmonary arterial hypertension on morbidity and mortality are feasible for the assessment of the long-term effects of therapies for this disease.

The treatment effect for the primary end point was driven mainly by differences in the rates of worsening of pulmonary arterial hypertension. A significant treatment effect was also observed with respect to the composite secondary outcome of death or hospitalization related to pulmonary arterial hypertension, which was driven by lower rates of hospitalization in the macitentan groups than in the placebo group. Since pulmonary arterial hypertension is a progressive disease and clinical deterioration is likely to precede death, it

Variable	Placebo (N=249)	Macitentan, 3 mg (N=250)	Macitentan, 10 mg (N=242)
Patients with ≥ 1 adverse event — no. (%)	240 (96.4)	240 (96.0)	229 (94.6)
Patients with ≥ 1 serious adverse event — no. (%)	137 (55.0)	130 (52.0)	109 (45.0)
No. of adverse events	1365	1614	1446
Adverse event — no. of patients (%) [†]			
Worsening of pulmonary arterial hypertension [‡]	87 (34.9)	75 (30.0)	53 (21.9)
Upper respiratory tract infection	33 (13.3)	50 (20.0)	37 (15.3)
Peripheral edema	45 (18.1)	40 (16.0)	44 (18.2)
Nasopharyngitis	26 (10.4)	37 (14.8)	34 (14.0)
Right ventricular failure [‡]	56 (22.5)	37 (14.8)	32 (13.2)
Headache	22 (8.8)	33 (13.2)	33 (13.6)
Anemia	8 (3.2)	22 (8.8)	32 (13.2)
Dizziness	27 (10.8)	24 (9.6)	26 (10.7)
Bronchitis	14 (5.6)	20 (8.0)	28 (11.6)
Dyspnea	22 (8.8)	26 (10.4)	18 (7.4)
Cough	30 (12.0)	20 (8.0)	21 (8.7)
Laboratory abnormality — no. of patients/total no. (%)			
Alanine aminotransferase or aspartate aminotransferase $>3\times$ ULN	11/244 (4.5)	9/247 (3.6)	8/236 (3.4)
Alanine aminotransferase or aspartate aminotransferase $>3\times$ ULN and bilirubin $>2\times$ ULN	4/237 (1.7)	5/241 (2.1)	4/230 (1.7)
Hemoglobin ≤ 8 g/dl	1/237 (0.4)	4/241 (1.7)	10/230 (4.3)

* One patient randomly assigned to receive placebo did not receive the study drug and was excluded from the safety analysis. ULN denotes upper limit of the normal range.

[†] Adverse events listed are those that occurred in more than 10% of the patients in any study group during the treatment period and up to 28 days after discontinuation of the study drug.

[‡] The majority of these events were also reported as primary end-point events.

is not surprising that death from any cause or from pulmonary arterial hypertension was rarely the first recorded event, and there was no significant difference between the active-treatment groups and the placebo group in the rates of death as components of these composite end points. When death was considered alone, there were trends toward reductions in both the rate of death from any cause and the rate of death due to pulmonary arterial hypertension with the 10-mg dose of macitentan as compared with placebo. However, the trial was not powered to show an effect on mortality alone, and these trends were not significant.

The magnitude of improvement in the 6-minute walk distance with the 10-mg dose of macitentan at month 6 was within the range of that observed in randomized studies lasting 12 to 16 weeks¹⁸⁻²¹ and in a recent observational open-label study²² in which the study drugs were added

to the therapy that the patients were already receiving for pulmonary arterial hypertension. Our post hoc examination of the 6-minute walk distance for patients in WHO functional class I or II and for those in WHO functional class III or IV at baseline showed that the treatment effects with the 10-mg dose of macitentan were similar to the results of other studies that enrolled patients in WHO functional class II²³ or WHO functional class III or IV.⁵ The 6-minute walk distance is widely used in clinical practice and studies; however, pooled analyses of randomized, controlled trials involving patients with pulmonary arterial hypertension have shown that the change in the 6-minute walk distance may not be a sufficient surrogate for the clinical outcome.^{24,25} This observation reinforces the importance of event-driven studies that use multiple indicators of disease progression.

In this study, few patients in any of the three groups had elevations in liver enzyme levels. The incidence of peripheral edema, a known safety concern with other endothelin-receptor antagonists, was similar in the placebo and macitentan groups.^{7,26} The only clinical laboratory finding of note was that decreased hemoglobin levels, a laboratory abnormality that has been reported with other endothelin-receptor antagonists,^{3,7,23} occurred more frequently with macitentan than with placebo. The incidence of headache, nasopharyngitis, and anemia was higher with macitentan than with placebo.

Our study has several limitations. Perhaps the most important is the fact that patients who discontinued blinded use of the study medication before the occurrence of a primary endpoint event were not followed for such events to the end of the trial. However, the results of the two sensitivity analyses performed to address

this issue were similar to those of the primary analysis. Second, this study did not address the efficacy of macitentan as compared with other approved oral therapies for pulmonary arterial hypertension. Whether currently approved drugs would have shown the same results, if tested in the same context, is unknown.

In conclusion, macitentan significantly reduced morbidity and mortality among patients with pulmonary arterial hypertension. Benefits were shown both for patients who had not received treatment previously and for those receiving therapy for pulmonary arterial hypertension at study entry.

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APPENDIX

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REFERENCES

- Galiè N, Hoepfer MM, Humbert M, et al. Guidelines for the diagnosis and treatment of pulmonary hypertension: the Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). *Eur Heart J* 2009;30:2493-537. [Erratum, *Eur Heart J* 2011;32:926.]
- Benza RL, Miller DP, Barst RJ, Badesch DB, Frost AE, McGoon MD. An evaluation of long-term survival from time of diagnosis in pulmonary arterial hypertension from REVEAL. *Chest* 2012; 142:448-56.
- Channick RN, Simonneau G, Sitbon O, et al. Effects of the dual endothelin-receptor antagonist bosentan in patients with pulmonary hypertension: a randomised placebo-controlled study. *Lancet* 2001;358:1119-23.
- Olschewski H, Simonneau G, Galiè N, et al. Inhaled iloprost for severe pulmonary hypertension. *N Engl J Med* 2002; 347:322-9.
- Rubin LJ, Badesch DB, Barst RJ, et al. Bosentan therapy for pulmonary arterial hypertension. *N Engl J Med* 2002;346:896-903. [Erratum, *N Engl J Med* 2002;346:1258.]
- Simonneau G, Barst RJ, Galiè N, et al. Continuous subcutaneous infusion of treprostinil, a prostacyclin analog, in patients with pulmonary arterial hypertension: a double-blind, randomized, placebo-controlled trial. *Am J Respir Crit Care Med* 2002;165:800-4.
- Galiè N, Badesch BD, Oudiz R, et al. Ambrisentan therapy for pulmonary arterial hypertension. *J Am Coll Cardiol* 2005; 46:529-35.
- Galiè N, Ghofrani HA, Torbicki A, et al. Sildenafil citrate therapy for pulmonary arterial hypertension. *N Engl J Med* 2005;353:2148-57. [Erratum, *N Engl J Med* 2006;354:2400-1.]
- Galiè N, Olschewski H, Oudiz RJ. 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. *Circulation* 2008; 117:3010-9.
- Galiè N, Brundage B, Ghofrani A, et al. Tadalafil therapy for pulmonary arterial hypertension. *Circulation* 2009;119:2894-903. [Erratum, *Circulation* 2011;124(10): e279.]
- McLaughlin VV, Badesch DB, Delcroix M, et al. End points and clinical trial design in pulmonary arterial hyper-

- tension. *J Am Coll Cardiol* 2009;54:Suppl: S97-S107.
12. Committee for Medicinal Products for Human Use. Guideline on the clinical investigations of medicinal products for the treatment of pulmonary arterial hypertension. London: European Medicines Agency, 2009 (http://www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/12/WC500016686.pdf).
 13. Galiè N, Simonneau G, Barst RJ, Badesch D, Rubin L. Clinical worsening in trials of pulmonary arterial hypertension: results and implications. *Curr Opin Pulm Med* 2010;16:Suppl 1:S11-S19.
 14. Bolli MH, Boss C, Binkert C, et al. The discovery of N-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-N'-propylsulfamide (macitentan), an orally active, potent, dual endothelin receptor antagonist. *J Med Chem* 2012;55:7849-61.
 15. Iglarz M, Binkert C, Morrison K, et al. Pharmacology of macitentan, an orally active tissue-targeting dual endothelin receptor antagonist. *J Pharmacol Exp Ther* 2008;327:736-45.
 16. Gatfield J, Mueller Grandjean C, Sasse T, Clozel M, Nayler O. Slow receptor dissociation kinetics differentiate macitentan from other endothelin receptor antagonists in pulmonary arterial smooth muscle cells. *PLoS One* 2012;7(10):e47662.
 17. Cuzick J. Forest plots and the interpretation of subgroups. *Lancet* 2005;365:1308.
 18. Simonneau G, Rubin LJ, Galiè N, et al. Addition of sildenafil to long-term intravenous epoprostenol therapy in patients with pulmonary arterial hypertension: a randomized trial. *Ann Intern Med* 2008;149:521-30. [Errata, *Ann Intern Med* 2009;150:63, 151:435.]
 19. Barst RJ, Oudiz RJ, Beardsworth A, et al. Tadalafil monotherapy and as add-on to background bosentan in patients with pulmonary arterial hypertension. *J Heart Lung Transplant* 2011;30:632-43.
 20. McLaughlin VV, Oudiz RJ, Frost A, et al. Randomized study of adding inhaled iloprost to existing bosentan in pulmonary arterial hypertension. *Am J Respir Crit Care Med* 2006;174:1257-63.
 21. McLaughlin VV, Benza RL, Rubin LJ, et al. Addition of inhaled treprostinil to oral therapy for pulmonary arterial hypertension: a randomized controlled clinical trial. *J Am Coll Cardiol* 2010;55:1915-22.
 22. Badesch DB, Feldman J, Keogh A, et al. ARIES-3: ambrisentan therapy in a diverse population of patients with pulmonary hypertension. *Cardiovasc Ther* 2012;30:93-9.
 23. Galiè N, Rubin LJ, Hoeper M, et al. Treatment of patients with mildly symptomatic pulmonary arterial hypertension with bosentan (EARLY study): a double-blind, randomised controlled trial. *Lancet* 2008;371:2093-100.
 24. Gabler NB, French B, Strom BL, et al. Validation of 6-minute walk distance as a surrogate endpoint in pulmonary arterial hypertension trials. *Circulation* 2012;126:349-56.
 25. Savarese G, Paolillo S, Costanzo P, et al. Do changes of 6-minute walk distance predict clinical events in patients with pulmonary arterial hypertension? A meta-analysis of 22 randomized trials. *J Am Coll Cardiol* 2012;60:1192-201.
 26. Humbert M, Barst RJ, Robbins IM, et al. Combination of bosentan with epoprostenol in pulmonary arterial hypertension: BREATHE-2. *Eur Respir J* 2004;24:353-9.

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