

# Addition of Sildenafil to Long-Term Intravenous Epoprostenol Therapy in Patients with Pulmonary Arterial Hypertension

## A Randomized Trial

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**Background:** Oral sildenafil and intravenous epoprostenol have independently been shown to be effective in patients with pulmonary arterial hypertension.

**Objective:** To investigate the effect of adding oral sildenafil to long-term intravenous epoprostenol in patients with pulmonary arterial hypertension.

**Design:** A 16-week, double-blind, placebo-controlled, parallel-group study.

**Setting:** Multinational study at 41 centers in 11 countries from 3 July 2003 to 27 January 2006.

**Patients:** 267 patients with pulmonary arterial hypertension (idiopathic, associated anorexigen use or connective tissue disease, or corrected congenital heart disease) who were receiving long-term intravenous epoprostenol therapy.

**Intervention:** Patients were randomly assigned to receive placebo or sildenafil, 20 mg three times daily, titrated to 40 mg and 80 mg three times daily, as tolerated, at 4-week intervals. Of 265 patients who received treatment, 256 (97%) patients (123 in the placebo group and 133 in the sildenafil group) completed the study.

**Measurements:** Change from baseline in exercise capacity measured by 6-minute walk distance (primary end point) and hemodynamic measurements, time to clinical worsening, and Borg dyspnea score (secondary end points).

**Results:** A placebo-adjusted increase of 28.8 meters (95% CI, 13.9 to 43.8 meters) in the 6-minute walk distance occurred in patients in the sildenafil group; these improvements were most prominent among patients with baseline distances of 325 meters or more. Relative to epoprostenol monotherapy, addition of sildenafil resulted in a greater change in mean pulmonary arterial pressure by  $-3.8$  mm Hg (CI,  $-5.6$  to  $-2.1$  mm Hg); cardiac output by 0.9

L/min (CI, 0.5 to 1.2 L/min); and longer time to clinical worsening, with a smaller proportion of patients experiencing a worsening event in the sildenafil group (0.062) than in the placebo group (0.195) by week 16 ( $P = 0.002$ ). Health-related quality of life also improved in patients who received combined therapy compared with those who received epoprostenol monotherapy. There was no effect on the Borg dyspnea score. Of the side effects generally associated with sildenafil treatment, the most commonly reported in the placebo and sildenafil groups, respectively, were headache (34% and 57%; difference, 23 percentage points [CI, 12 to 35 percentage points]), dyspepsia (2% and 16%; difference, 13 percentage points [CI, 7 to 20 percentage points]), pain in extremity (18% and 25%; difference, 8 percentage points [CI,  $-2$  to 18 percentage points]), and nausea (18% and 25%; difference, 8 percentage points [CI,  $-2$  to 18 percentage points]).

**Limitations:** The study excluded patients with pulmonary arterial hypertension associated with other causes. There was an imbalance in missing data between groups, with 8 placebo recipients having no postbaseline walk assessment compared with 1 sildenafil recipient. These patients were excluded from the analysis.

**Conclusion:** In some patients with pulmonary arterial hypertension, the addition of sildenafil to long-term intravenous epoprostenol therapy improves exercise capacity, hemodynamic measurements, time to clinical worsening, and quality of life, but not Borg dyspnea score. Increased rates of headache and dyspepsia occurred with the addition of sildenafil.

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**P**ulmonary arterial hypertension is a rare, debilitating disease characterized by progressive elevation of pulmonary arterial pressure and pulmonary vascular resistance that leads to right ventricular failure and death (1, 2). Because there is no cure for the disease, the primary goal of disease management is to alleviate symptoms and prolong survival (3–5). Current therapies include prostacyclins and analogues, endothelin receptor antagonists, and phosphodiesterase inhibitors (5). Despite advances in the past 2 decades, treatment with single agents remains far from satisfactory (3, 4, 6–8). Therefore, combination therapies using drugs with different mechanisms of action expected to have additive or synergistic effects have been considered (9–11).

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**Context**

Can combination therapy improve outcomes in patients with pulmonary arterial hypertension?

**Contribution**

In this multicenter trial, 267 patients with pulmonary arterial hypertension who had been receiving intravenous epoprostenol for at least 3 months were randomly assigned to oral sildenafil or placebo for 16 weeks. Compared with placebo, sildenafil improved exercise capacity and hemodynamic measurements, lengthened time to clinical worsening, and caused more headaches and dyspepsia.

**Caution**

Although patients with lower baseline walking capacity showed improved survival, patients with better baseline walking capacity had the most benefit in exercise capacity.

**Implication**

Adding sildenafil to epoprostenol therapy may improve some outcomes for certain patients with pulmonary arterial hypertension.

—The Editors

Many combination therapies have been evaluated almost exclusively in open-label, uncontrolled investigations (12–23). Two randomized, placebo-controlled trials have been published (17, 23). In 1 study, patients who received bosentan and intravenous epoprostenol were compared with those who received intravenous epoprostenol alone (17); in the other, patients who received long-term oral bosentan therapy also received additional inhaled iloprost or placebo (23). These studies demonstrated improvements in exercise capacity (14–16, 23), hemodynamic measurements (12–15, 23), and reversal of deterioration associated with monotherapy (16). We investigated the safety and efficacy of adding oral sildenafil to long-term intravenous epoprostenol treatment. To our knowledge, this is the first comprehensive clinical trial about combination therapy for the treatment of pulmonary arterial hypertension.

**METHODS****Design**

This 16-week, multinational, randomized, double-blind, placebo-controlled, parallel-group study was conducted between 3 July 2003 and 27 January 2006, including follow-up. Screening occurred between 1 and 21 days before the start of study treatment, followed by a baseline visit (day 1), with measurements at weeks 4, 8, 12, and 16. Patients who completed the study and those requiring a change in epoprostenol dose because of clinical deterioration (that is, completed all week-16 evaluations and received at least 4 weeks of treatment) were eligible for an open-label follow-up study. Local institutional review

boards or independent ethics committees approved the protocol, and written informed consent was obtained from all patients.

**Setting and Participants**

A total of 46 centers in 11 countries were involved in this study (United States, 26; Canada, 6; France, 3; Netherlands, 2; Spain, 2; United Kingdom, 2; Belgium, 1; Czech Republic, 1; Denmark, 1; Israel, 1; and Italy, 1). All sites were academic centers or hospitals, and specialists cared for all patients. We included patients who were at least 18 years of age (16 years of age in the United States) and had received a diagnosis of pulmonary arterial hypertension (idiopathic, familial, associated with anorexigen use or connective tissue disease, or occurring after surgical repair of congenital systemic-to-pulmonary shunts done at least 5 years earlier). Patients had to have received long-term intravenous epoprostenol (Flolan, GlaxoSmithKline, Research Triangle Park, North Carolina) therapy for at least 3 months, with a stable dose for at least 4 weeks before randomization. We excluded patients with a 6-minute walk distance less than 100 meters or greater than 450 meters or those whose 6-minute walk distance was affected by conditions other than pulmonary arterial hypertension. We excluded patients who had a change in epoprostenol dose within 4 weeks before receiving the randomly assigned drug and those receiving bosentan, nitrates, or nitric oxide donor drugs. We also excluded patients with pulmonary arterial hypertension secondary to causes other than those listed, patients with cardiovascular disease, patients with retinopathy or chronic obstructive pulmonary disease and severe impairment of hepatic function, and pregnant or lactating women.

**Randomization and Interventions**

We used a central, computer-generated pseudo-random code (by using random, permuted blocks within strata) to assign patients to treatment groups across all centers. Eligible patients were randomly assigned to receive sildenafil or placebo in a 1:1 ratio. The randomization was stratified by the baseline 6-minute walk distance (<325 meters or ≥325 meters) and cause (idiopathic pulmonary arterial hypertension or pulmonary arterial hypertension due to other causes). When a baseline walk measurement was not available, participants were stratified on the screening walk, which was used as the baseline walk for assessing efficacy. We broke blinding codes only in emergency situations for patient safety.

Patients receiving background long-term intravenous epoprostenol therapy (3 to 181 ng per kg of body weight per minute) had previously had their therapy maximized by using a clinically standard pattern of practice, that is, starting therapy at 2 ng/kg/min and increasing the dose by 2 ng/kg/min every 15 minutes until side effects intervened. We made transient (<14 days) changes in epoprostenol doses (±10%) as required for inadequate therapeutic response. We made permanent increases in epoprostenol

doses in response to clinical worsening. We randomly assigned patients to receive sildenafil (Revatio, Pfizer Laboratories, New York, New York) or placebo. We added study medication to the background therapy. Before entry into the study, patients must have received epoprostenol for at least 3 months, received the “optimal” dose (no further benefit with increase in dose) with no change for at least 4 weeks, and been stable for right heart catheterization before receiving the randomly assigned drug. The mean duration of epoprostenol treatment before study entry was 2.91 years for the placebo group and 2.75 years for the sildenafil group. Patients were allowed up to 4 transient epoprostenol dose changes within 10% of the baseline dose. If clinical deterioration warranted a permanent change in epoprostenol dose, the patient was withdrawn from randomized study treatment. The investigator measured all changes in dosing.

Patients in the sildenafil group received sildenafil, 20 mg three times daily, for the first 4 weeks. Per protocol, at week 4, the dosage was titrated to 40 mg three times daily for the next 4 weeks and, at week 8, to 80 mg three times daily for the last 8 weeks. The patients in the placebo group had dummy dose escalations at weeks 4 and 8. If the dose of study medication was not tolerated, the patient was permitted to down-titrate once, and then received the lower dose for the duration of the study.

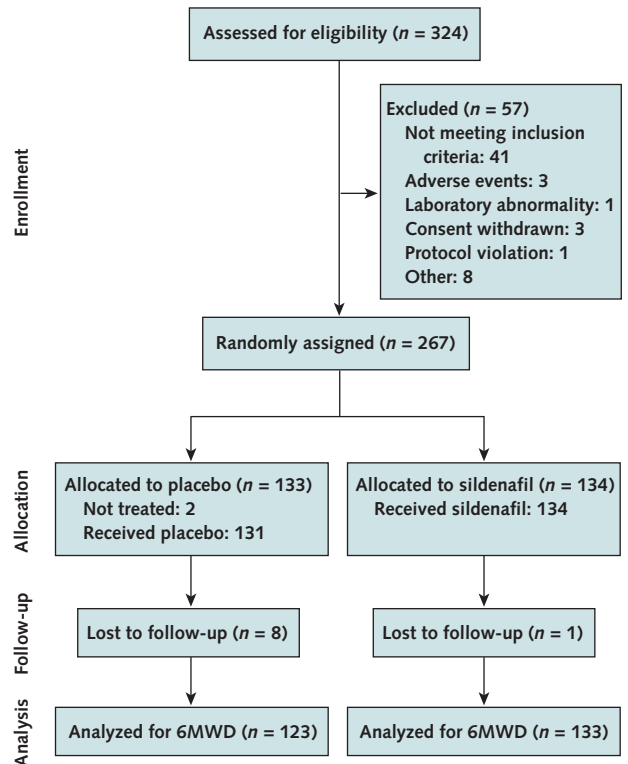
### Measurements and Outcomes

The investigators were responsible for keeping records of study drug, for accurately completing and signing the case report forms, and for all measurements. Trained clinical research associates measured all outcomes, and supervising investigators evaluated and confirmed them for accuracy. The primary outcome measure was change in exercise capacity measured by 6-minute walk distance at week 16 (24). Additional prespecified outcome measures included hemodynamic measurements, time to clinical worsening (defined as death, lung transplantation, hospitalization due to pulmonary arterial hypertension, initiation of bosentan therapy, or change in epoprostenol dose of >10% due to clinical deterioration), and Borg dyspnea score as self-assessed by patients after completing the 6-minute walk test. We analyzed treatment effects for the secondary end points sequentially only if a statistically significant effect was seen for the primary outcome. Patients recorded their health-related quality-of-life assessments by using the Short Form-36 questionnaire, version 1 (25) (score range, 0 to 100). Positive changes indicated improvement.

### Follow-up Procedures

The investigators assessed and recorded adverse events and their severity throughout the study. All patients were followed for safety 30 to 40 days after the last dose of sildenafil and 6 months and 1 year after treatment discontinuation or end of study. Patients had physical examinations, and we recorded symptoms of pulmonary

Figure 1. Study flow diagram.



6MWD = 6-minute walk distance.

hypertension, adverse events, concomitant medication, and epoprostenol dose. A urine pregnancy test was done when appropriate. We had no preplanned formal safety-related rules for discontinuation.

We asked patients to return unused study medication at each visit and provided them with enough supply for treatment until the next visit. We monitored adherence by counting tablets at each visit and recorded reasons for missed doses.

The sponsor monitored the study through routine center visits. Quality assurance audits were done at 5 centers, in accordance with good clinical practice guidelines.

### Statistical Analysis

The statistical analyses were done by statisticians employed by the sponsor; a coauthor reviewed and approved the analyses. Analyses were done by using SAS release software, version 8.2 (SAS Institute, Cary, North Carolina). We assume full responsibility for the completeness and accuracy of the content of the manuscript.

The intention-to-treat sample for the study consisted of 131 patients in the placebo group and 134 patients in the sildenafil group, and 123 and 133 patients, respectively, for the primary end point (Figure 1). This sample received at least 1 dose of study medication and had baseline and postbaseline 6-minute walk assessments. We eval-

**Table 1. Baseline Patient Characteristics**

Characteristic	Placebo (n = 133)	Sildenafil (n = 134)
<b>Sex, n (%)</b>		
Men	30 (23)	24 (18)
Women	103 (77)	110 (82)
<b>Age, y</b>		
Mean (SD)	47.5 (13.2)	47.8 (12.9)
Range	18–75	20–75
<b>Ethnicity, n (%)</b>		
White	107 (80)	105 (78)
Black	7 (5)	10 (7)
Asian	7 (5)	5 (4)
Other	12 (9)	14 (10)
<b>Weight, kg</b>		
Mean (SD)	69.7 (16.2)	73.0 (19.7)
Range	40–122	38–127
<b>WHO PAH functional class, n (%)</b>		
I	2 (1.5)	1 (0.7)
II	34 (25.6)	34 (25.4)
III	87 (65.4)	88 (65.7)
IV	6 (4.5)	10 (7.5)
Missing	4 (3.0)	1 (0.7)
<b>Primary diagnosis</b>		
Idiopathic, n (%)	105 (78.9)	107 (79.9)
Mean duration (range), y	5.0 (0–37)	4.2 (0–36)
Associated with CTD		
Scleroderma, n (%)	15 (11.3)	16 (11.9)
Mean duration (range), y	4.2 (0–9)	3.0 (0–9)
SLE, n (%)	8 (6.0)	6 (4.4)
Mean duration (range), y	4.6 (2–10)	4.4 (2–7)
Other, n (%)	5 (3.8)	5 (3.7)
Mean duration (range), y	5.0 (1–13)	5.1 (3–7)
<b>Mean baseline assessments (SD)</b>		
6-minute walk distance, m	341.6 (77.3)	348.9 (71.4)
Range, m	108–450	136–450
PAP, mm Hg	51.1 (12.7)	52.2 (10.8)
Range, mm Hg	29–82	27–81
Cardiac output, L/min	5.0 (1.7)	4.5 (1.4)
PVR, dyne/sec per cm <sup>5</sup>	754.9 (367.7)	856.8 (362.9)
<b>Median epoprostenol dosage, ng/kg/min</b>		
Range, ng/kg/min	3.0–179.0	4.0–181.0

CTD = connective tissue disease; PAH = pulmonary arterial hypertension; PAP = pulmonary arterial pressure; PVR = pulmonary vascular resistance; SLE = systemic lupus erythematosus; WHO = World Health Organization.

uated the primary end point, change in 6-minute walk distance from baseline to week 16, by using a linear repeated measures longitudinal analysis (26). We found model residuals to be satisfactory on graphical inspection. When adjusted means by treatment groups are presented, they are marginal means over a balanced sample. We included the protocol-specified analysis of variance on the changes by using last-observation-carried-forward approach to impute missing week-16 values. We did sensitivity analyses when necessary. We assessed heterogeneity of the treatment effect on the primary end point with respect to cause and baseline walking distance. We used analysis of

variance to analyze the change in hemodynamic measurements from baseline to end of treatment, a stratified log-rank test to analyze time to clinical worsening, and a stratified Wilcoxon test (van Elteren) to analyze change in the Borg dyspnea score.

**Role of the Funding Source**

Pfizer, Sandwich, United Kingdom, sponsored and designed the trial and developed the protocol and the statistical analysis plan. The steering committee reviewed and approved all aspects of the study. Each investigator collected data. The sponsor managed data and monitored sites. Statisticians accessed the data only after unblinding. One coauthor (Dr. Fleming) was primarily responsible for directing, reviewing, and certifying the methodology and accuracy of the statistical analyses. All authors were equally responsible for reviewing and interpreting the data, providing input, and directing the writing of this manuscript. The sponsor did not require but provided written consent for this publication. No ghostwriters were involved in drafting or preparing this manuscript.

**RESULTS**

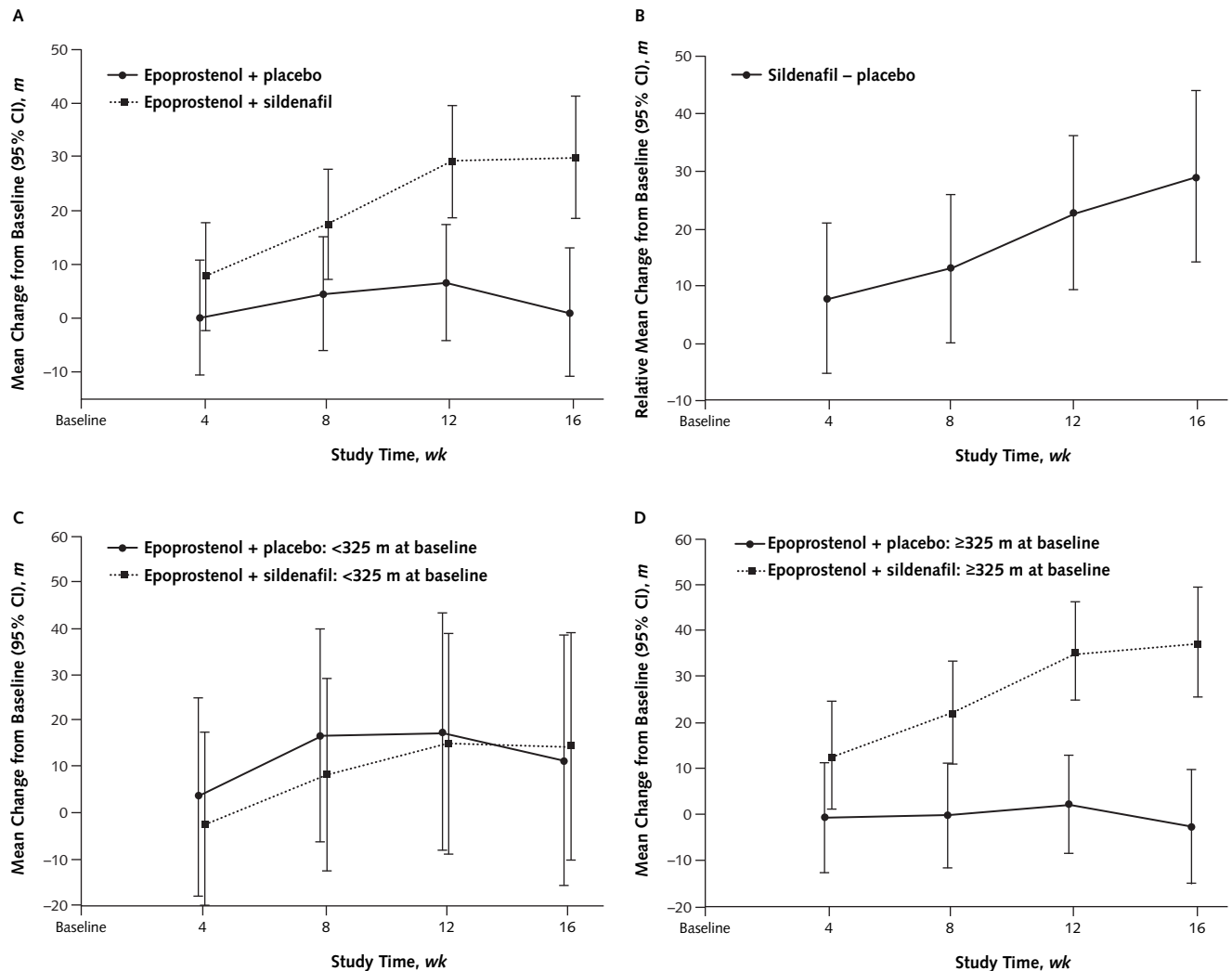
We randomly assigned 267 patients to receive sildenafil (n = 134) or placebo (n = 133; 131 were treated) (Figure 1). Baseline characteristics of the patients were similar in the 2 treatment groups (Table 1). Idiopathic pulmonary arterial hypertension was the most frequent diagnosis, and most patients (68%) had a baseline walking distance of 325 meters or more. Despite a high proportion of patients with more advanced disease, the baseline cardiac output was better than usually seen, suggesting a baseline beneficial effect of epoprostenol treatment. The median dosage of epoprostenol was similar in both groups (placebo group, 28 ng/kg/min [range, 3 to 179 ng/kg/min]; sildenafil group, 29 ng/kg/min [range, 4 to 181 ng/kg/min]). Only 1 patient in the study (in the placebo group) did not adhere to treatment. No unplanned crossovers occurred during the trial. Twenty-four patients in the placebo group required changes in epoprostenol dosing; 7 were transient, 3 were because of clinical worsening within 4 weeks, and 14 were because of clinical worsening after 4 weeks of initiation of medication. In comparison, only 11 patients in the sildenafil group required changes in epoprostenol dosing; 9 were transient, and 2 were because of clinical worsening after 4 weeks of receiving the medication.

**Outcome Measures**

**Exercise Capacity**

Because 8 patients in the placebo group and 1 patient in the sildenafil group had missing data and 2 patients in the placebo group were not treated, the primary end point was evaluated in 123 and 133 patients who received sildenafil and placebo, respectively (Figure 1). The sildenafil group had a statistically significantly greater increase in the 6-minute walk distance than did the placebo group at week 16 (Figure 2). The adjusted mean change at week 16 was

Figure 2. Changes from baseline in 6-minute walk distance.



A. Change from baseline in 6-minute walk distance, by treatment group (model-adjusted estimates). B. Relative change from baseline in 6-minute walk distance (model-adjusted estimates). C. Change from baseline in 6-minute walk distance for patients with distances <325 meters at baseline, by treatment group (model-adjusted estimates). D. Change from baseline in 6-minute walk distance for patients with distances  $\geq 325$  meters at baseline, by treatment group (model-adjusted estimates).

29.8 meters for the sildenafil group and 1.0 meter for the placebo group, giving an adjusted treatment difference of 28.8 meters (95% CI, 13.9 to 43.8 meters;  $P < 0.001$ ) (Figure 2; Appendix Table, available at [www.annals.org](http://www.annals.org)). The protocol-specified last-observation-carried-forward analysis produced a relative difference of 26.0 meters (CI, 10.8 to 41.2 meters) between groups. A post hoc sensitivity analysis using a nonparametric van Elteren test, in which patients who did not have any postbaseline reading were assigned the average week-16 change for patients receiving placebo and patients who died were assigned the worst week-16 change seen among all study patients, gave an adjusted treatment difference at week 16 of 32.0 meters (CI, 20.0 to 46.0 meters). We omitted 6 participants (4 placebo recipients and 2 sildenafil recipients) from these 2

latter analyses because they had missing baseline walk distances. In the main analyses reported, we used these participants' screening walks as baseline values.

Model-adjusted treatment effects at week 16 for patients with baseline 6-minute walk distance of 325 meters or more and less than 325 meters were 39.9 meters and 3.0 meters, respectively, in favor of sildenafil (Figure 2; Appendix Figure 1, available at [www.annals.org](http://www.annals.org)). Appendix Figure 2 (available at [www.annals.org](http://www.annals.org)) shows the relationship between change in 6-minute walk distance by treatment group at week 16 and baseline walk distance as a continuous variable.

Model-adjusted treatment effects at week 16 for patients with idiopathic pulmonary arterial hypertension and pulmonary arterial hypertension associated with other

**Table 2. Incidence of Clinical Worsening Event\***

Clinical Worsening Event	Patients with Event, n (%)	
	Placebo (n = 131)	Sildenafil (n = 134)
Any reason	24 (18.3)	8 (6.0)
Death	7 (5.3)†	0 (0)
Lung transplantation	1 (0.8)	0 (0)
Hospitalization due to pulmonary arterial hypertension	11 (8.4)	8 (6.0)
Change in epoprostenol dose because of clinical deterioration	16 (12.2)	2 (1.5)
Initiation of bosentan therapy	1 (0.8)	0 (0)

\* Intention-to-treat sample.

† Patients died of acute renal failure and aggravated pulmonary hypertension on day 108; aggravated pulmonary hypertension on day 21; hemoptysis on day 33; aggravated pulmonary hypertension and cardiac and respiratory arrest on day 40; right-heart failure and acute hypotension on day 44; right-heart failure on day 24; and right-heart failure on day 9.

causes were 33.9 meters and 10.5 meters, respectively, in favor of sildenafil.

Appendix Figure 3 (available at [www.annals.org](http://www.annals.org)) shows the relationship between change in 6-minute walk distance by treatment group at week 16 and baseline epoprostenol dose.

### Hemodynamic Measurements

Compared with epoprostenol monotherapy, addition of sildenafil had a beneficial effect on hemodynamic measurements (Appendix Table, available at [www.annals.org](http://www.annals.org)). The analysis included the 6 patients with missing baseline 6-minute walk distance, for which the screening assessment was used, and was adjusted for baseline walking distance and cause. The adjusted mean change from baseline to end of treatment in mean pulmonary arterial pressure was  $-2.8$  mm Hg in the combination therapy group compared with  $1.1$  mm Hg in the placebo group, for an adjusted treatment difference of  $-3.8$  mm Hg (CI,  $-5.6$  to  $-2.1$  mm Hg). Patients receiving sildenafil plus intravenous epoprostenol, compared with those receiving intravenous epoprostenol alone, also exhibited reduced mean systemic arterial pressure ( $-3.1$  mm Hg vs.  $-0.3$  mm Hg). Similarly, these patients, compared with patients in the placebo group, had relative decreases in systemic vascular resistance ( $-160.7$  dyne/sec per  $\text{cm}^5$  vs.  $39.4$  dyne/sec per  $\text{cm}^5$ ), pulmonary vascular resistance ( $-150.6$  dyne/sec per  $\text{cm}^5$  vs.  $22.1$  dyne/sec per  $\text{cm}^5$ ), and heart rate ( $-2.6$  beats/min vs.  $1.1$  beats/min). Simultaneously, a relative average increase in cardiac output of  $0.9$  L/min (CI,  $0.5$  to  $1.2$  L/min) for patients in the sildenafil group compared with those in the placebo group occurred. Changes in pulmonary capillary wedge pressure seemed to be similar in both groups.

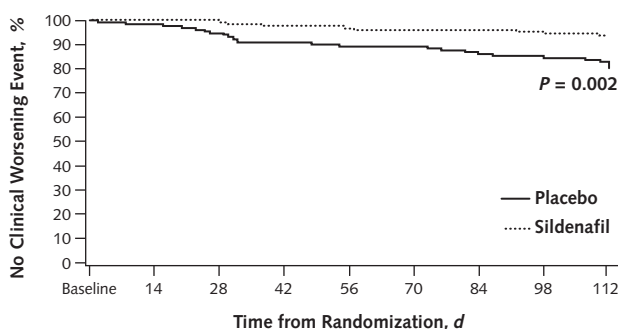
### Time to Clinical Worsening

Overall, only 8 patients treated with sildenafil had clinical worsening during the study period compared with 24 who received placebo (Table 2). The Kaplan–Meier plot (Figure 3) indicated that time to first clinical worsening event favored the sildenafil group ( $P = 0.002$ , stratified log-rank test), with a smaller proportion of patients experiencing a worsening event in the sildenafil group (0.062) than in the placebo group (0.195) by week 16. Much of this difference was attributable to a change in epoprostenol dose due to clinical worsening required by only 2 patients (none as a first event) in the sildenafil group compared with 16 patients (9 as a first event) in the placebo group, and 7 deaths (4 as a first event) recorded in the placebo group during the study period compared with none in the sildenafil group (Table 2). We did not consider any deaths as treatment related. All 7 patients had severe disease and were stratified into the group with a walk distance less than 325 meters, with a mean baseline walk distance of 182 meters (range, 108 to 238 meters), compared with 345 meters (range, 108 to 450 meters) for the study sample. Events resulting from hospitalization due to pulmonary arterial hypertension were similar between the sildenafil group ( $n = 8$ ; all first events) and the placebo group ( $n = 11$ ; 9 first events).

### Borg Dyspnea Score

Patients in both treatment groups had a median Borg dyspnea score of 3 (moderate breathlessness) at baseline, and this remained unaltered at all subsequent visits.

**Figure 3. Kaplan–Meier plot of time to clinical worsening.**



Treatment	Persons at Risk (Censored), n				
	Baseline	Day 28*	Day 56†	Day 84‡	Day 112§
Epoprostenol + placebo	131	123 (1)	116 (0)	111 (2)	70 (36)
Epoprostenol + sildenafil	134	134 (0)	128 (2)	125 (2)	78 (44)

\* The number censored between days 0 and 27.

† The number censored between days 28 and 55.

‡ The number censored between days 56 and 83.

§ The number censored between days 84 and 111.

**Table 3. Incidence of All-Cause Adverse Events\***

Adverse Event	Patients Reporting Event, n (%)†		Difference (95% CI), percentage points
	Placebo (n = 131)	Sildenafil (n = 134)	
<b>Any</b>	128 (97.7)	124 (92.5)	5 (10 to 0)
<b>Serious</b>	39 (29.8)	29 (21.6)	-8 (-19 to 2)
<b>Caused discontinuation</b>	14 (10.7)	7 (5.2)	-6 (-12 to 1)
<b>Related to sildenafil</b>			
Headache	44 (34)	76 (57)	23 (12 to 35)
Dyspepsia	3 (2)	21 (16)	13 (7 to 20)
Extremity pain	23 (18)	34 (25)	8 (-2 to 18)
Diarrhea	24 (18)	34 (25)	7 (-3 to 17)
Flushing	17 (13)	26 (19)	6 (-2 to 18)
Myalgia	3 (2)	7 (5)	3 (-2 to 8)
Blurred vision	2 (2)	6 (5)	3 (-1 to 7)
Back pain	4 (3)	6 (5)	1 (-3 to 6)
<b>Related to epoprostenol</b>			
Jaw pain	11 (8)	14 (10)	2 (-5 to 9)
Fatigue	26 (20)	27 (20)	0 (-9 to 10)
<b>Other</b>			
Nausea	23 (18)	34 (25)	8 (-2 to 18)
Edema, peripheral	9 (7)	19 (14)	7 (0 to 15)
Edema	8 (6)	17 (13)	7 (0 to 14)
Nasal congestion	3 (2)	12 (9)	7 (1 to 12)
Upper respiratory tract infection	6 (5)	14 (10)	6 (0 to 12)
Asthenia	1 (1)	7 (5)	5 (0 to 9)
Chills	0	7 (5)	5 (2 to 9)
Gastroesophageal reflux disease	1 (1)	8 (6)	5 (1 to 10)
Vomiting	13 (10)	20 (15)	5 (-3 to 13)
Arthralgia	3 (2)	9 (7)	4 (-1 to 9)
Chest pain	13 (10)	19 (14)	4 (-4 to 12)
Epistaxis	7 (5)	12 (9)	4 (-3 to 10)
Hypotension	8 (6)	12 (9)	3 (-4 to 9)
Rash	11 (8)	15 (11)	3 (-4 to 10)
Dizziness	25 (19)	28 (21)	2 (-8 to 11)
Increased international normalized ratio	4 (3)	7 (5)	2 (-3 to 7)
Pain	3 (2)	6 (5)	2 (-2 to 7)
Sinusitis	5 (4)	8 (6)	2 (-3 to 7)
Anemia	4 (3)	6 (5)	1 (-3 to 6)
Muscle spasms	4 (3)	6 (5)	1 (-3 to 6)
Palpitations	8 (6)	10 (8)	1 (-5 to 7)

\* The analysis included the intention-to-treat sample (all patients who received study medication). Some patients had >1 event.

† Adverse events given are those reported by ≥5% of patients and more frequently with sildenafil than with placebo.

## Adverse Events

Fourteen (11%) patients in the placebo group and 7 (5%) patients in the sildenafil group discontinued treatment because of adverse events (difference, -6 percentage points [CI, -12 to 1 percentage points]). One hundred twenty-eight patients in the placebo group reported 736 adverse events, compared with 124 patients in the sildenafil group who reported 960 events. The adverse events most associated with sildenafil treatment reported in the placebo group and the sildenafil group (Table 3) were headache (34% and 57%; difference, 23 percentage points [CI, 12 to 35 percentage points]), dyspepsia (2% and 16%; difference, 13 percentage points [CI, 7 to 20 percentage points]), pain in extremity (18% and 25%; difference, 8 percentage points [CI, -2 to 18 percentage points]), and nausea (18% and 25%;

difference, 8 percentage points [-2 to 18 percentage points]). Although these events occurred more in the sildenafil group, fewer patients had serious adverse events, died, or permanently discontinued study treatment in the sildenafil group than in the placebo group. Most adverse events were mild or moderate in nature. Thirty-nine (30%) patients in the placebo group and 29 (22%) patients in the sildenafil group had serious adverse events (difference, -8 percentage points [CI, -19 to 2 percentage points]). However, we considered serious adverse events to possibly be treatment related in only 2 patients in the placebo group (1 with tachycardia, worsening hypoxia, and worsening dyspnea and 1 with ascites) and 3 patients in the sildenafil group (1 with hypoxia and 2 with hypotension). One hundred thir-

ty-eight treatment-related adverse events were reported by 61 (47%) patients in the placebo group compared with 290 treatment-related events reported by 92 (69%) patients in the sildenafil group (difference, 22 percentage points [CI, 11 to 34 percentage points]).

### Health-Related Quality of Life and Patient Preferences

We measured health-related quality-of-life changes by using the Short Form-36 questionnaire. The mean baseline scores were similar for both groups. Compared with the placebo group, the sildenafil group showed greater adjusted improvement from baseline in physical functioning (−0.3 [CI, −4.7 to 4.1] for placebo vs. 7.8 [CI, 3.6 to 12.1] for sildenafil;  $P = 0.003$ ), physical role (3.6 [CI, −5.4 to 12.7] vs. 10.7 [CI, 2.0 to 19.4];  $P = 0.20$ ), bodily pain (0.6 [CI, −4.3 to 5.5] vs. 5.8 [CI, 1.0 to 10.6];  $P = 0.09$ ), general health (−1.4 [CI, −4.8 to 2.1] vs. 6.6 [CI, 3.3 to 9.9];  $P < 0.001$ ), vitality (0.8 [CI, −3.3 to 4.9] vs. 10.2 [CI, 6.2 to 14.2];  $P < 0.001$ ), social functioning (−2.5 [CI, −7.8 to 2.9] vs. 4.0 [CI, −1.1 to 9.2];  $P = 0.049$ ), and mental health (−3.7 [CI, −7.0 to −0.5] vs. 3.0 [CI, −0.1 to 6.2];  $P = 0.001$ ), but not in role–emotional (4.6 [CI, −4.2 to 13.5] vs. 1.8 [CI, −6.8 to 10.3];  $P = 0.60$ ).

More patients in the sildenafil group (49.2%) than in the placebo group (25.4%) indicated a definite preference for study treatment compared with their previous treatment. Similarly, more patients in the sildenafil group (67.2%) than in the placebo group (42.1%) showed a definite willingness to use the same medication again.

### DISCUSSION

Sildenafil and epoprostenol achieve vasodilation through different mechanisms (27, 28). Administered separately, each agent improves 6-minute walk distance in patients with pulmonary arterial hypertension (29, 30). The 3-year survival rate for patients receiving intravenous epoprostenol monotherapy was 63% (31, 32). Intravenous epoprostenol has been used for a decade to treat pulmonary arterial hypertension, whereas oral sildenafil is a newer drug with demonstrated efficacy for this indication without the safety concerns associated with intravenous delivery (5). Still, pulmonary arterial hypertension remains a progressive and life-threatening disease, and deterioration eventually occurs in many patients (1, 8).

Our PubMed search for English-language studies on combination therapy with sildenafil until 1 March 2007 yielded 9 articles. Although small and uncontrolled, earlier studies nevertheless demonstrated that sildenafil, in combination with other agents, was effective for treating pulmonary arterial hypertension (12–16, 18–21), particularly in reversing the decline in exercise endurance that can occur with bosentan monotherapy (16). The results of our randomized, placebo-controlled, double-blind clinical trial indicate that combination therapy is a promising avenue to increasing treatment efficacy. The side effects associated

with combination treatment of sildenafil and epoprostenol were mild to moderate (Table 3). Only 7 patients receiving both drugs discontinued treatment because of adverse events. These data suggest that the benefits of combination treatment outweigh the adverse effects.

In this study, 72% of patients had functional class III or IV pulmonary arterial hypertension at baseline. All patients enrolled in this study were receiving intravenous epoprostenol for at least 3 months and had received an optimal stable dosage for at least 30 days (range, 3 to 181 ng/kg/min), that is, not decompensating at the time of entry into the study and not receiving a higher or lower dose than might be needed. Adding oral sildenafil to this treatment regimen resulted in a relative improvement of 29 meters in exercise capacity after 16 weeks. This improvement did not occur in isolation but rather was associated with positive changes in several secondary end points, including hemodynamic measurements, time to clinical worsening, and quality of life. It should be noted that the improvement seen with combination therapy is in addition to the effect reported for patients receiving epoprostenol monotherapy (29, 30, 33, 34). Exercise capacity showed improvements in both etiologic classifications, but the effect was greater among patients who received a diagnosis of idiopathic pulmonary arterial hypertension. However, unlike the earlier trial (29), no improvement in exercise capacity was found in patients with baseline walking distance less than 325 meters, although the addition of sildenafil markedly improved hemodynamic measurements, even in this subgroup. Although Appendix Figure 3 (available at [www.annals.org](http://www.annals.org)) suggests that the effect of sildenafil is independent of the baseline epoprostenol dose, Appendix Figure 2 (available at [www.annals.org](http://www.annals.org)) suggests that the effect varies according to baseline 6-minute walk distance. The spline fit to the data shows a favorable trend for patients with a baseline distance of 325 meters or more. If patients are pooled according to whether their baseline distance is greater or less than 325 meters, then Appendix Figure 1 (available at [www.annals.org](http://www.annals.org)) suggests that sildenafil essentially has no effect on exercise capacity for patients with a baseline distance less than 325 meters and provides substantial benefit in those with a baseline distance of 325 meters or more. Of course, these subgroup analyses should be treated with great caution. These observations require independent confirmation through further clinical studies.

The addition of sildenafil treatment to stable doses of epoprostenol resulted in several hemodynamic benefits, including a modest reduction in mean pulmonary arterial pressure, an improvement in cardiac output, and a corresponding substantial reduction in calculated pulmonary vascular resistance, compared with patients who received epoprostenol alone. In addition, patients in the 2 treatment groups had identical Borg dyspnea scores at the end of week 16, indicating that, overall, patients receiving combination

treatment could walk further than those receiving epoprostenol alone and with the same degree of perceived exertion.

The Short Form-36 questionnaire showed that patients treated with combination therapy had greater improvements in quality of life than those treated with epoprostenol alone. In addition, more patients who received combination therapy preferred their new treatment over previous treatment with epoprostenol alone.

An important result obtained in this study was the increase in the time to clinical worsening events in the combination treatment group. By the end of week 16, fewer patients in the sildenafil group than in the placebo group had clinical worsening events. Epoprostenol dose adjustments were made because of clinical deterioration and may have had a dominant effect on the calculation of time to clinical worsening, because 9 of 24 (38%) patients who reported clinical worsening in the placebo group, compared with none receiving sildenafil, had this change as their first event. Although this study was not designed to assess mortality rate, the death of 7 patients in the placebo group, compared with none in the sildenafil group, suggests that combination therapy may confer a survival benefit. Although no improvement in exercise capacity was found in patients with baseline 6-minute walk distance less than 325 meters, all 7 deaths in this subgroup occurred in patients who received placebo. Hence, the exercise capacity and mortality rate data provide conflicting evidence about the effect of combination therapy in this subgroup.

Limitations of our study include the exclusion of patients with pulmonary arterial hypertension associated with other causes (that is, HIV, portal hypertension, and uncorrected congenital systemic-to-pulmonary shunts). It is important to highlight that the treatment benefits measured were seen in patients exposed to sildenafil, 80 mg three times daily, with most (79.9%) patients achieving that dose at week 8. The currently approved dose of sildenafil (20 mg) was not studied, and it would be inappropriate to extrapolate these results to this dose. The data reported here are also reflective of short-term therapy. Long-term safety and efficacy data for the combination therapy have not been obtained yet. The large imbalance in missing data between treatment groups is a further limitation of our study.

Overall, these data are consistent with those from previous open-label, uncontrolled studies, in which patients were successfully treated with sildenafil in combination with other therapies (12–16, 18, 19, 21). Taken together, these results indicate that sildenafil may be used in combination with epoprostenol as part of a multiple treatment regimen to improve exercise capacity in patients with pulmonary arterial hypertension without an apparent increase in adverse events, especially in stable patients with pulmonary arterial hypertension who remain symptomatic despite long-term intravenous epoprostenol treatment. However, these results can not be extrapolated to the most common clinical setting these days (that is, start treatment

with first-line oral therapy then add intravenous epoprostenol therapy as needed). It is worth noting that no data or guidelines discuss whether to continue oral therapy in a deteriorating patient who needs to begin intravenous prostacyclin therapy.

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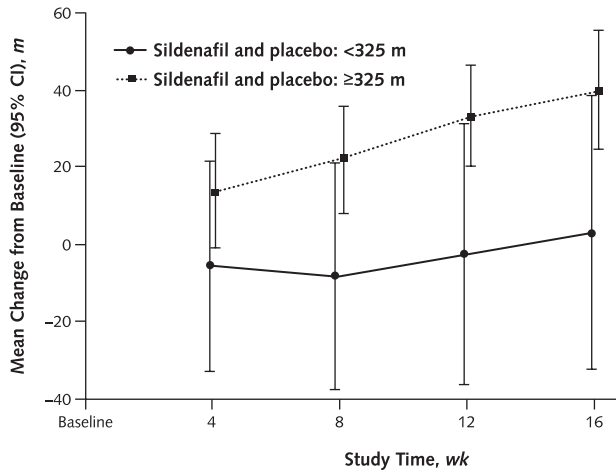
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## APPENDIX: MEMBERS OF THE PACES (PULMONARY ARTERIAL HYPERTENSION COMBINATION STUDY OF EPOPROSTENOL AND SILDENAFIL) STUDY GROUP

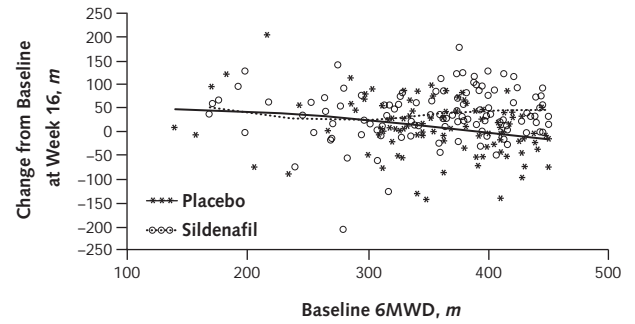
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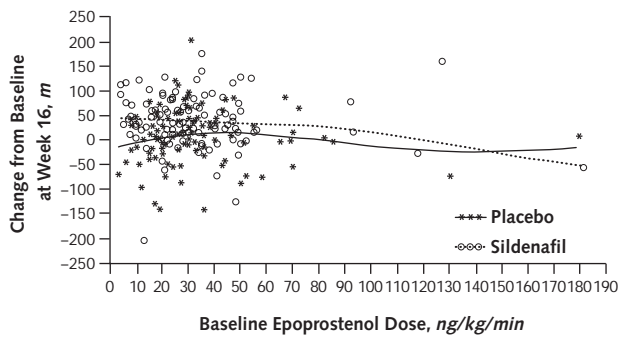
*Appendix Figure 1.* Mean change from baseline in 6-minute walk distance, stratified by baseline walk (model-adjusted estimates).



*Appendix Figure 2.* Change from baseline in 6-minute walk distance (6MWD), by baseline walk and treatment group.



*Appendix Figure 3.* Change from baseline in 6-minute walk distance, by baseline epoprostenol dose and treatment group.



Appendix Table. Mean Summary of Baseline and Changes from Baseline to End of Treatment in 6-Minute Walk Distance and Hemodynamic Measurements (95% CI)

Measurement or Statistic	Baseline 6-Minute Walk Distance*						All Patients†		
	<325 Meters			≥325 Meters			Placebo	Sildenafil	Difference between Groups
	Placebo	Sildenafil	Difference between Groups	Placebo	Sildenafil	Difference between Groups			
<b>6-minute walk distance, m‡</b>									
Patients, <i>n</i>	35	41	–	88	92	–	123	133	–
Baseline	260.6 (239.2 to 282.0)	264.4 (249.9 to 279.0)	–	384.3 (376.5 to 392.2)	388.9 (381.8 to 396.0)	–	349.1 (336.3 to 362.0)	350.5 (338.7 to 362.4)	–
Change from baseline	11.3 (–15.8 to 38.4)	14.3 (–10.4 to 39.0)	3.0 (–32.3 to 38.4)	–2.8 (–15.1 to 9.5)	37.1 (25.1 to 49.1)	39.9 (24.4 to 55.5)	1.0 (–10.9 to 12.9)	29.8 (18.5 to 41.2)	28.8 (13.9 to 43.8)
<b>Pulmonary arterial pressure, mm Hg</b>									
Patients, <i>n</i>	28	35	–	74	82	–	102	117	–
Baseline	50.4 (47.1 to 53.8)	47.6 (44.6 to 50.5)	–	50.4 (47.3 to 53.6)	54.6 (52.2 to 56.9)	–	50.4 (48.0 to 52.9)	52.5 (50.5 to 54.4)	–
Change from baseline	–1.2 (–3.7 to 1.4)	–0.1 (–2.4 to 2.2)	1.1 (–2.2 to 4.3)	1.5 (–0.2 to 3.3)	–4.3 (–5.9 to –2.6)	–5.8 (–7.9 to –3.7)	1.1 (–0.4 to 2.6)	–2.8 (–4.2 to –1.4)	–3.8 (–5.6 to –2.1)
<b>Mean right arterial pressure, mm Hg</b>									
Patients, <i>n</i>	28	35	–	74	82	–	102	117	–
Baseline	10.4 (8.7 to 12.1)	9.5 (7.5 to 11.6)	–	6.9 (5.9 to 8.0)	8.6 (7.6 to 9.7)	–	7.9 (7.0 to 8.8)	8.9 (7.9 to 9.9)	–
Change from baseline	1.6 (–0.2 to 3.4)	–0.4 (–2.0 to 1.2)	–1.9 (–4.2 to 0.3)	0.9 (–0.3 to 2.0)	–1.3 (–2.4 to –0.1)	–2.1 (–3.6 to –0.7)	1.2 (0.2 to 2.2)	–0.8 (–1.8 to 0.1)	–2.1 (–3.3 to –0.9)
<b>Cardiac output, L/min§</b>									
Patients, <i>n</i>	24	26	–	55	66	–	79	92	–
Baseline	4.9 (4.2 to 5.6)	4.3 (3.9 to 4.8)	–	5.2 (4.7 to 5.7)	4.6 (4.2 to 5.0)	–	5.1 (4.7 to 5.5)	4.5 (4.2 to 4.8)	–
Change from baseline	–0.4 (–0.9 to 0.1)	0.9 (0.4 to 1.4)	1.3 (0.6 to 2.0)	–0.2 (–0.5 to 0.1)	0.5 (0.1 to 0.8)	0.7 (0.3 to 1.1)	–0.2 (–0.5 to 0.1)	0.6 (0.3 to 0.9)	0.9 (0.5 to 1.2)
<b>Pulmonary capillary wedge pressure, mm Hg</b>									
Patients, <i>n</i>	27	35	–	68	80	–	95	115	–
Baseline	10.1 (8.6 to 11.7)	8.0 (6.6 to 9.3)	–	8.7 (8.0 to 9.5)	9.6 (8.7 to 10.4)	–	9.1 (8.5 to 9.8)	9.1 (8.4 to 9.8)	–
Change from baseline	0.4 (–1.8 to 2.5)	3.3 (1.4 to 5.1)	2.9 (0.2 to 5.6)	0.6 (–0.5 to 1.8)	0.1 (–1.0 to 1.2)	–0.6 (–1.9 to 0.8)	0.9 (–0.1 to 2.0)	1.4 (0.4 to 2.4)	0.5 (–0.8 to 1.7)
<b>Mean systemic arterial pressure, mm Hg</b>									
Patients, <i>n</i>	25	28	–	66	77	–	91	105	–
Baseline	86.2 (80.9 to 91.5)	85.0 (80.5 to 89.4)	–	86.6 (83.2 to 90.0)	83.9 (81.4 to 86.5)	–	86.5 (83.7 to 89.3)	84.2 (82.0 to 86.4)	–
Change from baseline	–0.5 (–5.2 to 4.2)	–4.5 (–8.8 to –0.1)	–3.9 (–9.9 to 2.1)	0.4 (–2.5 to 3.3)	–2.0 (–4.6 to 0.7)	–2.4 (–5.6 to 0.9)	–0.3 (–2.8 to 2.2)	–3.1 (–5.4 to –0.8)	–2.8 (–5.7 to 0.1)
<b>Heart rate, beats/min</b>									
Patients, <i>n</i>	28	34	–	72	81	–	100	115	–
Baseline	82.7 (77.6 to 87.7)	89.1 (84.3 to 93.8)	–	85.3 (82.6 to 88.1)	85.8 (83.3 to 88.3)	–	84.6 (82.2 to 87.0)	86.8 (84.5 to 89.0)	–
Change from baseline	1.0 (–3.1 to 5.1)	–2.2 (–5.9 to 1.5)	–3.2 (–8.4 to 2.0)	0.9 (–1.8 to 3.6)	–2.9 (–5.5 to –0.2)	–3.7 (–7.0 to –0.5)	1.1 (–1.2 to 3.4)	–2.6 (–4.7 to –0.4)	–3.6 (–6.4 to –0.9)
<b>Mixed venous oxygen saturation, %</b>									
Patients, <i>n</i>	21	32	–	70	78	–	91	110	–
Baseline	61.7 (58.7 to 64.6)	62.6 (58.8 to 66.4)	–	66.8 (64.6 to 68.9)	63.0 (61.1 to 64.9)	–	65.6 (63.8 to 67.4)	62.9 (61.2 to 64.6)	–
Change from baseline	–5.2 (–8.9 to –1.4)	1.1 (–2.0 to 4.2)	6.3 (1.6 to 11.0)	–2.3 (–4.3 to –0.3)	4.8 (2.8 to 6.7)	7.1 (4.7 to 9.5)	–3.9 (–5.7 to –2.1)	3.0 (1.4 to 4.7)	6.9 (4.8 to 9.0)
<b>Systemic vascular resistance, dyne/sec per cm<sup>5</sup>§</b>									
Patients, <i>n</i>	21	19	–	48	62	–	69	81	–
Baseline	1375.0 (1134.1 to 1615.9)	1542.4 (1369.5 to 1715.4)	–	1401.4 (1272.3 to 1530.4)	1432.9 (1323.5 to 1542.3)	–	1393.0 (1281.0 to 1506.0)	1459.0 (1367.0 to 1551.0)	–
Change from baseline	33.7 (–159.2 to 226.6)	–142.5 (–346.4 to 61.4)	–176.2 (–440.6 to 88.2)	39.1 (–80.2 to 158.4)	–167.4 (–273.3 to –61.4)	–206.5 (–336.6 to –76.3)	39.4 (–60.9 to 139.7)	–160.7 (–257.0 to –64.5)	–200.1 (–316.8 to –83.5)
<b>Systemic vascular resistance index, dyne/sec per cm<sup>5</sup>/m<sup>2</sup>§</b>									
Patients, <i>n</i>	21	19	–	48	62	–	69	81	–
Baseline	2416.4 (2022.3 to 2810.6)	2657.3 (2438.7 to 2875.9)	–	2470.2 (2258.8 to 2681.6)	2448.9 (2274.3 to 2623.4)	–	2454.0 (2270.0 to 2638.0)	2498.0 (2355.0 to 2640.0)	–
Change from baseline	54.6 (–259.0 to 368.3)	–203.9 (–535.6 to 127.7)	–258.6 (–688.6 to 171.4)	73.9 (–128.5 to 276.2)	–280.7 (–460.3 to –101.0)	–354.5 (–575.3 to –133.8)	73.4 (–94.5 to 241.2)	–258.3 (–419.3 to 97.2)	–331.6 (–526.9 to 136.4)
<b>Pulmonary vascular resistance, dyne/sec per cm<sup>5</sup>§</b>									
Patients, <i>n</i>	23	26	–	50	65	–	73	91	–
Baseline	747.3 (600.1 to 894.6)	794.6 (672.5 to 916.7)	–	696.4 (601.9 to 790.9)	872.6 (782.9 to 962.3)	–	712.0 (635.0 to 790.0)	850.0 (778.0 to 922.0)	–
Change from baseline	–7.7 (–118.0 to 102.6)	–149.2 (–255.3 to –43.1)	–141.5 (–286.8 to 3.8)	41.5 (–28.5 to 111.6)	–143.7 (–211.7 to –75.6)	–185.2 (–269.4 to –101.0)	22.1 (–37.2 to 81.4)	–150.6 (–208.1 to –93.2)	–172.7 (–245.0 to –100.5)
<b>Pulmonary vascular resistance index, dyne/sec per cm<sup>5</sup>/m<sup>2</sup>§</b>									
Patients, <i>n</i>	23	26	–	50	65	–	73	91	–
Baseline	1288.1 (1057.8 to 1518.4)	1390.9 (1195.0 to 1586.8)	–	1221.5 (1057.6 to 1385.4)	1492.7 (1352.8 to 1632.6)	–	1242.0 (1112.0 to 1373.0)	1464.0 (1351.0 to 1577.0)	–
Change from baseline	–5.9 (–196.6 to 184.8)	–253.6 (–437.1 to –70.1)	–247.7 (–498.8 to 3.5)	69.0 (–47.8 to 185.7)	–244.6 (–357.9 to –131.2)	–313.6 (–453.8 to –173.3)	39.3 (–60.7 to 139.3)	–255.4 (–352.4 to –158.4)	–294.7 (–416.6 to –172.9)

\* Values adjusted for cause.

† Values adjusted for baseline 6-minute walk distance and cause.

‡ Change from baseline at week 16 derived from repeated measures (longitudinal) analysis.

§ Patients with cardiac output measured by using the Fick technique. Patients with shunts who had cardiac output measured by thermodilution rather than the Fick technique were excluded.