Randomized Study of Adding Inhaled Iloprost to Existing Bosentan in Pulmonary Arterial Hypertension

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Rationale: **Small, open-label studies suggest that combinations of existing therapies may be effective for pulmonary arterial hypertension (PAH).**

Objective: **To evaluate the safety and efficacy of adding inhaled iloprost, a prostacyclin analog, to the endothelin receptor antagonist bosentan in patients with PAH.**

Methods: **In a randomized, multicenter, double-blind trial, inhaled iloprost (5 μg) or placebo was added to stable monotherapy with bosentan for 12 wk. Efficacy endpoints included change from baseline in 6-min-walk distance (6-MWD), modified New York Heart Association (NYHA) functional class, hemodynamic parameters, and time to clinical worsening.**

Measurements and Main Results: **A total of 67 patients with PAH (55% idiopathic PAH, 45% associated PAH, 94% NYHA class III, and mean baseline 6-MWD of 335 m) were randomized. At Week 12, patients receiving iloprost had a mean increase in 6-MWD of 30 m ($p = 0.001$); placebo patients had a mean 6-MWD increase of 4 m ($p = 0.69$), with a placebo-adjusted difference of +26 m ($p = 0.051$). NYHA status improved by one class in 34% of iloprost versus 6% of placebo patients ($p = 0.002$). Iloprost delayed the time to clinical worsening ($p = 0.0219$). Improvements were noted in postinhalation placebo-adjusted change in mean pulmonary artery pressure (−8 mm Hg; $p < 0.001$) and pulmonary vascular resistance (−254 dyn · s · cm^{-5}; $p < 0.001$). Combination therapy was well tolerated.**

Conclusions: **Within the limitations of a relatively small sample size, results of this study demonstrate that the addition of inhaled iloprost in patients with PAH with reduced exercise capacity on bosentan monotherapy is safe and efficacious.**

Keywords: bosentan; iloprost; pulmonary arterial hypertension

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Very few controlled data regarding combination therapy for pulmonary arterial hypertension are available.

What This Study Adds to the Field

This study demonstrates the safety and efficacy of the addition of iloprost in patients with pulmonary arterial hypertension who remain symptomatic while on bosentan.

The past decade has witnessed significant advances in the treatment of pulmonary arterial hypertension (PAH). Based on known pathobiological mechanisms of action, three classes of drugs have been extensively studied for treatment of PAH: prostanoids (epoprostenol, treprostinil, iloprost), endothelin receptor antagonists (bosentan, sitaxsentan, ambrisentan), and phosphodiesterase inhibitors (sildenafil) (1).

Intravenous epoprostenol improves symptoms, exercise capacity, hemodynamics, and survival in patients with PAH (2–5). However, the cumbersome continuous intravenous delivery system carries the risks of sepsis, embolic phenomenon, and exacerbation due to infusion interruption; these issues have served as the impetus for developing alternative approaches. Two alternative modes of delivery for prostanoids have been developed: the subcutaneous route for treprostinil and the inhaled route for iloprost (6–10). In a randomized, placebo-controlled study (Aerosolized Iloprost Randomized [AIR] study), inhaled iloprost was demonstrated to be efficacious therapy for PAH based on a combined endpoint of improvement in modified New York Heart Association (NYHA) functional class, 10% or greater improvement in 6-min-walk distance (6-MWD), and absence of clinical deterioration or death after 12 wk of therapy (8). Randomized, placebo-controlled trials with the oral dual–endothelin receptor antagonist bosentan have demonstrated improvements in symptoms, exercise capacity, hemodynamics, and the time to clinical worsening in patients with PAH (11, 12). A long-term observational study has suggested that first-line therapy with bosentan, followed by other therapies if needed, improves survival in patients with idiopathic PAH (IPAH) (13). A large, randomized, placebo-controlled trial with the oral phosphodiesterase inhibitor sildenafil has also demonstrated improvements in symptoms, exercise capacity, and hemodynamics (14). Although all three classes of therapy improve important efficacy endpoints, monotherapy rarely results in a normalization of exercise capacity or hemodynamics. As in other conditions with multiple pathogenic pathways, combination therapy targeting several of these pathways may produce greater benefit in patients with PAH.

In clinical practice, bosentan is often used for initial therapy due to its ease of administration. For patients who remain impaired but for whom continuous intravenous or subcutaneous prostanoid therapy, in the opinion of the physician or the patient, is not yet indicated, the addition of inhaled iloprost to bosentan is a potentially attractive clinical option. In this study (STEP study [Safety and pilot efficacy Trial in combination with bosentan for Evaluation in Pulmonary arterial hypertension]), we assessed the safety and efficacy of the addition of either inhaled iloprost or placebo in patients with PAH receiving therapy with bosentan.

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METHODS

Selection of Patients

Between June 2004 and October 2004, we enrolled patients aged 10 to 80 yr with symptomatic PAH receiving bosentan for 4 mo or more. Entry requirements included a 6-MWD of 100–425 m, resting mean pulmonary artery pressure greater than 25 mm Hg, pulmonary capillary wedge pressure less than 15 mm Hg, and pulmonary vascular resistance of 240 dyn · s · cm^{-5} or greater. Patients with thromboembolic disease, untreated obstructive sleep apnea, portal hypertension, chronic liver disease or renal insufficiency, left-sided or unrepaired congenital heart disease, or substantial obstructive ($FEV_1/FVC < 50\%$ predicted) or restrictive (total lung capacity $< 60\%$ predicted) lung disease were excluded. Concurrent anticoagulants, vasodilators, diuretics, cardiac glycosides, or supplemental oxygen were allowed; phosphodiesterase inhibitors or other prostanoids were not. The protocol was approved by the ethics review boards at all participating institutions, and all patients provided written, informed consent.

Study Design

Eligible patients were assigned to add either iloprost inhalation (dose, 5 μg; Ventavis; CoTherix, Inc., South San Francisco, CA) or placebo to existing therapy with oral bosentan (dose, 125 mg twice daily; Tracleer; Actelion, Allschwil, Switzerland) in a double-blind, 12-wk study. Randomization was communicated to sites using a blinded interactive voice response system, and was stratified and blocked according to etiology: IPAH or associated PAH (APAH; i.e., collagen vascular disease, repaired congenital heart disease, HIV infection, or anorexigen use). The study drug was inhaled six to nine times daily while awake using the Prodose AAD device (Profile Therapeutics PLC, West Sussex, UK). An open-label extension phase of 1-yr duration followed the double-blind phase. An independent data safety monitoring board reviewed safety data.

Outcome Measures

Exercise capacity was assessed using the unencouraged 6-MWD, performed preinhalation at baseline, postinhalation (at 30 ± 15 min) at Weeks 4 and 8, and at both time points at Week 12, with the two tests separated by at least 2 h and the temporal sequence randomized (i.e., whether pre- or postinhalation). NYHA functional class and postinhalation Borg dyspnea score were also assessed at baseline and Weeks 4, 8, and 12. Hemodynamic parameters were measured by right-heart catheterization at baseline and Week 12, both pre- and postinhalation (15 min).

Statistical Analysis

Neither *a priori* assumptions of treatment effect nor formal power calculations were used to estimate the sample size for this phase 2 study. Efficacy and safety analyses included all randomized patients who received at least one dose of study drug; efficacy analyses also required at least one postbaseline outcome data. One patient, randomized to receive placebo but mistakenly receiving iloprost, was analyzed with placebo for efficacy (intention-to-treat) and with iloprost for safety (per-protocol). Two iloprost patients were without postbaseline outcome data, thus leaving 32 iloprost and 33 placebo patients in the efficacy analysis.

Treatment differences were compared using analysis of covariance: rank analysis for change from baseline in 6-MWD (with ranked baseline 6-MWD as a covariate) and parametric analysis for Borg dyspnea score and hemodynamic parameters. Analyses of within-group changes used the Wilcoxon signed-rank test. Analyses of change in NYHA class used the Cochran-Mantel-Haenszel test, stratified by baseline class (improved, no change, worse). Time to clinical worsening, assessed by Kaplan-Meier methodology using the log-rank test, was prospectively defined as the occurrence of PAH-related death, hospitalization or early study discontinuation due to worsening PAH, initiation of new PAH-specific therapy, lung transplantation, or atrial septostomy. A *post hoc* exploratory analysis of clinical response used previously specified criteria (8) that required all of the following: greater than 10% increase in 6-MWD, improvement in NYHA class, and absence of clinical deterioration or death at 12 wk. Missing data for Week 12 efficacy assessments were imputed using the last-observation-carried-forward method. Safety was assessed by reported adverse events and serial laboratory measurements (complete blood count, urinalysis, and blood chemistries). Missing safety data were not imputed.

RESULTS

Study Population

Table 1 displays the baseline demographic, functional class, and 6-MWD data for all randomized patients. There were no notable differences among the treatment groups in any demographic or baseline characteristics. The mean (SD) baseline 6-MWD of the study group overall was 335 (67) m, with the majority (94%) of patients classified as NYHA class III (indicating a moderate severity of functional and exercise limitation). Approximately half (55%) had IPAH; 45% had PAH associated with a variety of conditions, including scleroderma, other connective tissue diseases, HIV infection, repaired congenital heart disease, and anorexigen use. Hemodynamic parameters were typical of patients with advanced PAH.

The mean (SD) duration of prior therapy with bosentan was similar in the two groups: 17.6 (10.7) mo for iloprost patients and 18.8 (10.8) mo for placebo patients.

Treatment Exposure and Measurement of Treatment Compliance

Sixty-seven patients were randomized into the trial, of whom 34 were assigned to receive inhaled iloprost and 33 were assigned to receive placebo (Figure 1). The mean number of study drug inhalations per day was 5.6 in the iloprost group and 5.7 in the placebo group. The mean total daily dose of study drug was 26.8 μg (range, 2.5–32.4 μg) in the iloprost group and 27.8 μg (range, 11.6–33.3 μg) in the placebo group.

TABLE 1. DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Parameter	Iloprost (*n = 34*)	Placebo (*n = 33*)	Total (*n = 67*)
Age, yr			
Mean (SD)	51 (14)	49 (15)	50 (14)
Range	15–77	10–72	10–77
Sex, n (%)			
Male	7 (21%)	7 (21%)	14 (21%)
Female	27 (79%)	26 (79%)	53 (79%)
Race, n (%)			
White	29 (85%)	25 (76%)	54 (81%)
African American	0	1 (3%)	1 (1.5%)
Hispanic	5 (15%)	4 (12%)	9 (13%)
Native American	0	2 (6%)	2 (3%)
Asian	0	1 (3%)	1 (1.5%)
NYHA class, n (%)			
Class II	0	1 (3%)	1 (1.5%)
Class III	35 (97%)	30 (91%)	63 (94%)
Class IV	1 (3%)	2 (6%)	3 (4.5%)
6-MWD, m			
Mean (SD)	331 (64)	340 (73)	335 (67)
Range	185–420	110–420	110–420
Primary diagnosis, n (%)			
IPAH	176 (50%)	20 (61%)	37 (55%)
APAH	17 (50%)	13 (39%)	30 (45%)
Pulmonary hemodynamics, mean (SD)			
mPAP, mm Hg	51 (11)	52 (13)	52 (12)
PVR, dynes · s · cm^{-5}	815 (381)	783 (378)	799 (381)
CO, L/min	4.74 (1.51)	4.61 (1.08)	4.67 (1.31)

Definition of abbreviations: 6-MWD = 6-min-walk distance; APAH = associated pulmonary arterial hypertension; CO = cardiac output; IPAH = idiopathic pulmonary arterial hypertension; mPAP = mean pulmonary artery pressure; NYHA = New York Heart Association; PVR = pulmonary vascular resistance.

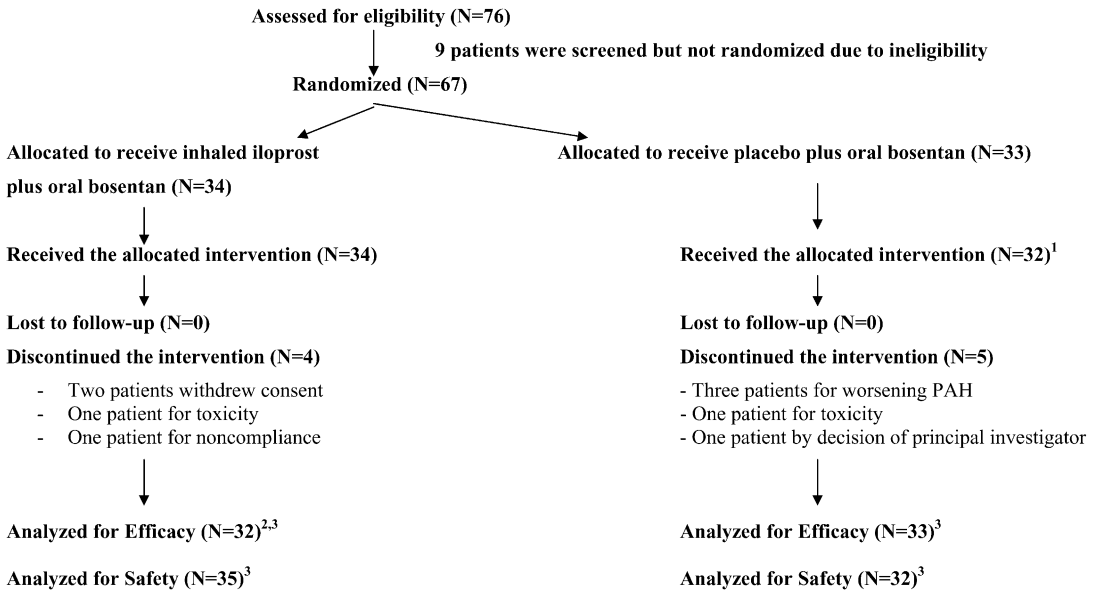

Figure 1. Overview of patients entered into the trial. [1]One patient allocated to placebo mistakenly received iloprost; [2]two patients were without post-baseline efficacy data; [3]the patient allocated to placebo who received iloprost is analyzed as a placebo patient in the efficacy analysis (intention-to-treat) and as an iloprost patient in the safety analysis (per protocol). PAH = pulmonary arterial hypertension.

The majority of patients (93.8% in the iloprost group and 93.9% in the placebo group) were compliant with study drug therapy. No patient discontinued or reduced the dose of bosentan during the study.

Assessment of Efficacy

6-MWD/Borg dyspnea index. At 12 wk, the postinhalation mean increase in 6-MWD from baseline was 30 m in iloprost patients ($p = 0.001$) versus 4 m in placebo patients ($p = 0.69$), with a placebo-adjusted difference of 26 m ($p = 0.051$; Figure 2, Table 2). The iloprost-associated improvement in 6-MWD was similar for patients with IPAH and patients with APAH, with a placebo-adjusted mean increase of 25 and 30 m, respectively. The preinhalation change from baseline in mean 6-MWD at 12 wk was 29 m ($p = 0.007$) in the iloprost group and 11 m ($p = 0.45$) in the placebo group, with a placebo-adjusted difference of 19 m ($p = 0.14$). The Borg dyspnea score at Week 12 improved in the iloprost group compared with baseline (-0.5, $p = 0.031$), although the treatment effect compared with placebo was not significant ($p = 0.16$).

NYHA functional class. NYHA class improved in 34% (11 of 32) of iloprost patients versus 6% (2 of 33) of placebo patients at Week 12 compared with baseline ($p = 0.002$; Table 2). The proportion of patients with improvement was similar among

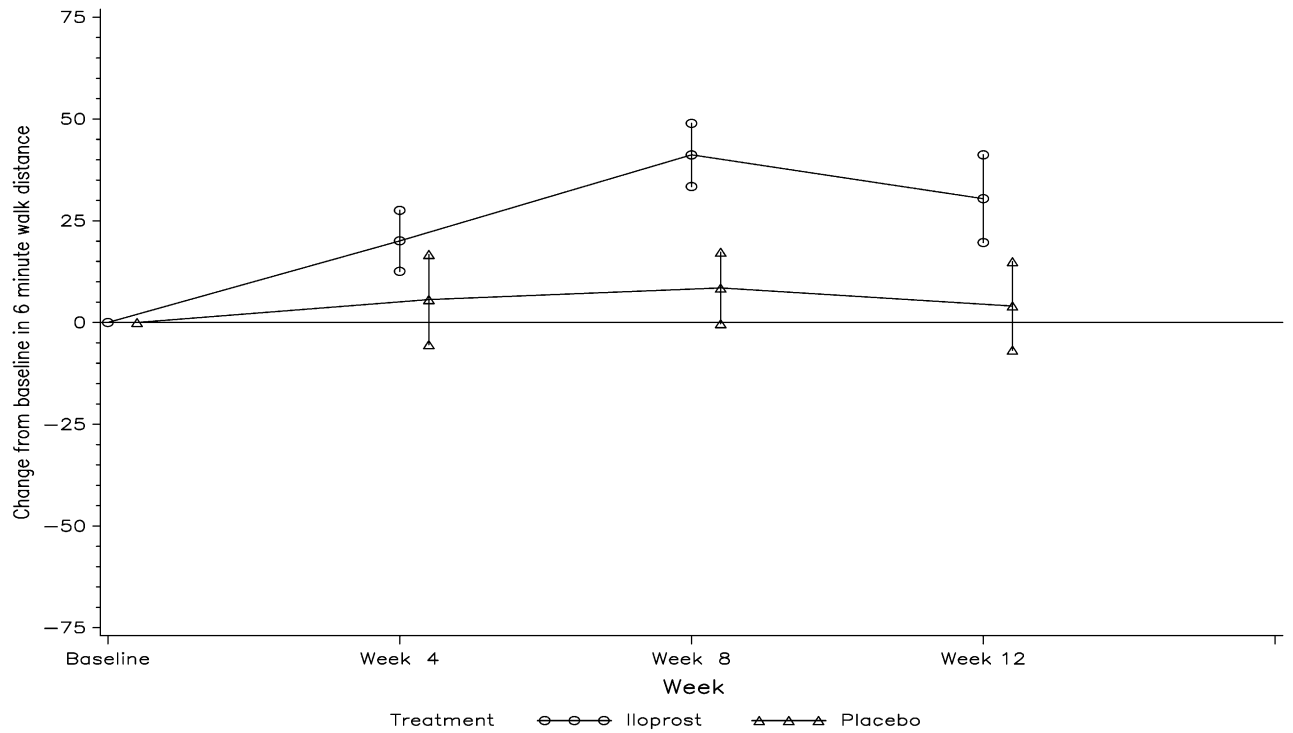

Figure 2. Change in postinhalation 6-min-walk distance. Mean (± SE) change in postinhalation 6-min-walk distance from baseline to Week 12 in the placebo and iloprost groups. $p = 0.051$ at Week 12.

TABLE 2. EFFICACY OUTCOMES

	Iloprost Group (*n* = 32)			Placebo Group (*n* = 33)			
Efficacy Variable	Baseline	Week 12	Change*	Baseline	Week 12	Change*	p Value
Change from baseline in 6-MWD							
Week 12 (postinhalation), mean (SD)	336 (61)	367 (84)	30 (60)	340 (73)	343 (99)	4 (61)	0.051
p value			0.001			0.69	
Week 12 (preinhalation), mean (SD)		365 (87)	29 (59)		358 (73)	11 (54)	0.14
p value			0.007			0.45	
Change in Borg dyspnea index							
Week 12 (postinhalation), mean (SD)	3.9 (1.7)	3.4 (1.7)	−0.5 (1.2)	3.5 (2.1)	3.6 (2.5)	0.0 (1.5)	0.16
p value			0.031			0.92	
Change from baseline in NYHA class, n (%)							
Improved by one class, n (%)			11 (34.4)			2 (6)	0.002
No change in class, n (%)			20 (62.5)			31 (91)	
Worsened by one class, n (%)			0 (0)			1 (3)	
Missing			1 (3.1)			0 (0)	
Clinical deterioration at Week 12, n (%)			0 (0.0)			5 (15.2)	0.022

Definition of abbreviations: 6-MWD = 6-min-walk distance; NYHA = New York Heart Association.

* The mean change values are derived from the mean of paired data and may not be the same as that derived by the difference in group means due to missing data.

patients with IPAH and APAH, with 6 of 16 (37.5%) and 5 of 16 (31%) iloprost patients showing improvement, respectively, compared with 1 of 20 (5%) and 1 of 13 (7.7%) placebo patients showing improvement. No patient in the iloprost group experienced deterioration in NYHA class, whereas one patient in the placebo group declined from functional class III to IV.

Clinical worsening. During the 12-wk study, time to clinical worsening was significantly longer in iloprost-treated patients than in placebo patients ($p = 0.0219$, log-rank test; Figure 3). None of the iloprost patients met the predefined criteria for clinical worsening, compared with 5 of the 33 (15.2%) placebo patients. Of these five placebo patients, four were hospitalized for worsening PAH. The fifth patient required additional PAH-specific therapy, and thus was unblinded after 4 wk and subsequently began open-label iloprost therapy.

Composite clinical response. At Week 12, 8 of 32 (25%) iloprost patients and 0 of 33 (0%) placebo patients met the criteria for clinical response ($p = 0.002$).

Hemodynamics. From baseline to Week 12, a significant treatment effect was noted in postinhalation mean pulmonary artery pressure (−6 mm Hg for iloprost vs. +2 mm Hg for placebo, $p < 0.001$) and pulmonary vascular resistance (-164 dyn · s · cm^{-5} for iloprost vs. $+81$ dyn · s · cm^{-5} for placebo, $p = 0.007$; Table 3). Changes in hemodynamic parameters did not reach statistical significance when measured preinhalation.

Safety

The most frequently reported adverse events in the iloprost group were consistent with the known side-effect profile of prostanoids, and included headache, flushing, and jaw pain (Table 4). In addition, side effects attributable to inhalation included cough, chest pain or discomfort, pharyngolaryngeal pain, and dry mouth. In most instances, these were mild or moderate in intensity and did not require alteration of therapy. One patient in the iloprost group and two patients in the placebo group reported syncope that did not require treatment and was without sequelae. There were no clinically important changes in laboratory tests (chemistry, hematology, urinalysis), and no patient had significant liver function test elevation.

Five iloprost patients (5/35, 14%) experienced five serious adverse events and 7 of 32 (22%) placebo patients experienced 12 serious adverse events, including worsening PAH requiring hospitalization in four placebo patients. Three events were considered by the primary investigator to be related to the study drug: headache and rectal bleeding in two patients on iloprost and right-heart failure in a patient receiving placebo. Two patients discontinued study drug treatment due to adverse effects: one patient receiving iloprost, with a history of migraine headaches, discontinued due to severe global headaches; the other patient, receiving placebo, discontinued due to anemia.

DISCUSSION

The goals of PAH therapy are currently evolving. Although oral bosentan and inhaled iloprost, as well as several other therapies, are efficacious in the treatment of PAH, no therapy is a panacea. Despite significant clinical, hemodynamic, and survival improvements, many patients remain with limitations of exercise capacity on monotherapy, and others who initially improve will not realize sustained improvement and deteriorate months to years after institution of therapy. As a result, it has been suggested that well-designed trials be conducted to evaluate the role of combination or sequential therapies in PAH (15–17).

The STEP study is the largest randomized, double-blind, placebo-controlled trial completed to date that explores the use of incremental therapy for PAH. In this study, 67 patients with PAH treated with the dual–endothelin receptor antagonist bosentan for at least 4 mo were randomized to receive inhaled iloprost or placebo. The addition of inhaled iloprost to bosentan resulted in consistent improvements across a number of clinically important predefined efficacy measures. The placebo-adjusted difference in postinhalation 6-MWD at the end of the 12-wk period was 26 m ($p = 0.051$). Among iloprost patients, the similar improvement seen preinhalation (+29 m) and postinhalation (+30 m) in mean 6-MWD at Week 12 compared with baseline suggests a prolonged beneficial effect on exercise capacity separate from that seen after acute inhalation. The mean change in 6-MWD observed in placebo recipients was small and likely reflects random variation. Functional class was improved in 34% of iloprost patients and 6% of placebo patients ($p = 0.002$), the majority of whom improved from NYHA class III to class II. This is encouraging in light of two studies of long-term epoprostenol therapy that found survival was strongly correlated with NYHA functional class after 3 to 17 mo of therapy (NYHA class III/IV vs. I/II) (4, 5). Consistent with these clinical benefits, improvements were also noted in cardiopulmonary hemodynamics when

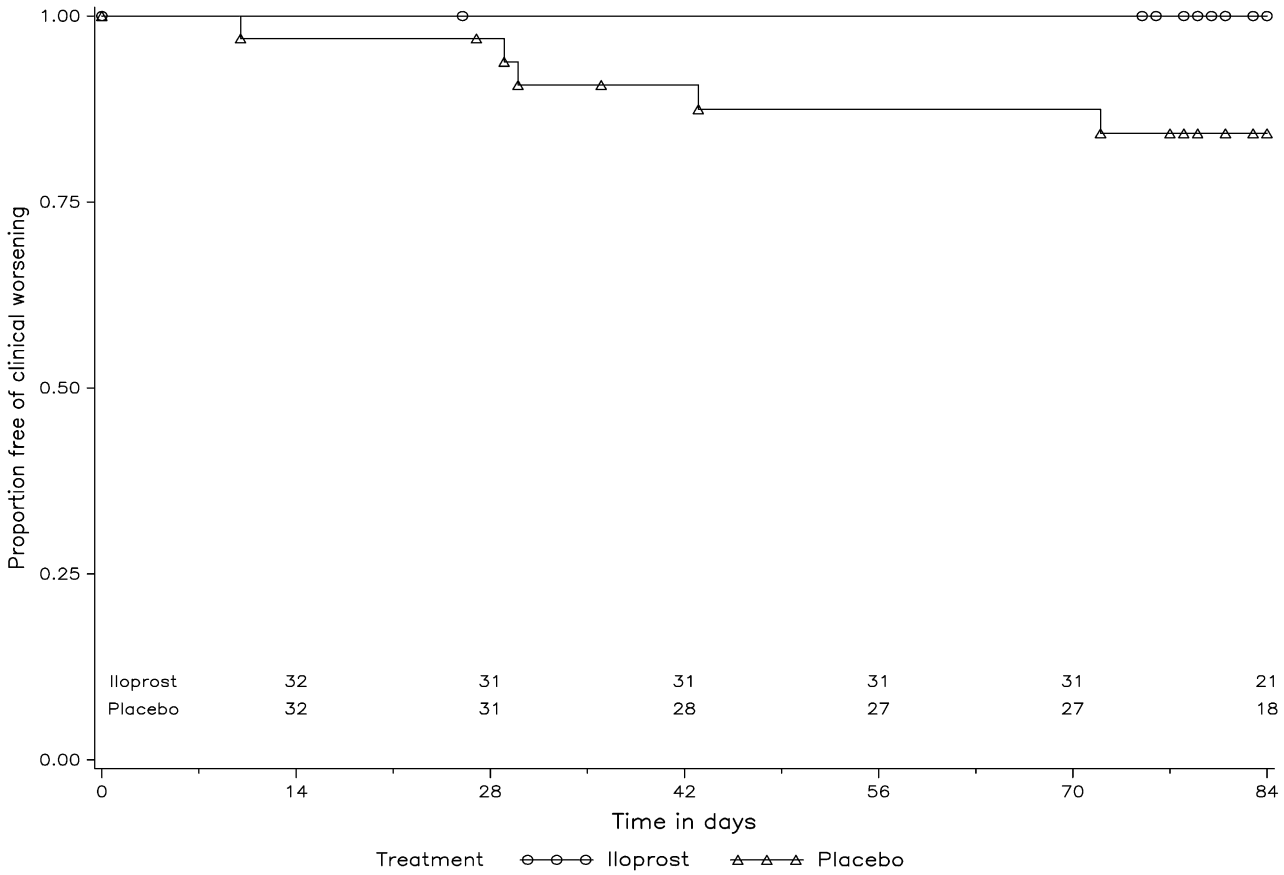

Figure 3. Time to clinical worsening. Clinical worsening was defined as follows: death due to PAH, hospitalization for worsening PAH, early discontinuation from the study due to worsening PAH, the need for new chronic PAH–specific therapy (e.g., systemic prostanoids), lung transplantation, or atrial septostomy. p = 0.0219 by the log-rank test for the comparison of the iloprost group with the placebo group at Week 12.

measured after inhalation, including mean pulmonary artery pressure, pulmonary vascular resistance, and mixed venous oxygen saturation, without adverse effects on systemic blood pressure or heart rate. In addition, improvements were also noted in the predefined endpoint of time to clinical worsening, as no patient in the iloprost group and five patients in the placebo group met this endpoint during the 12-wk study period (p = 0.02). Therefore, over the short-term, the addition of iloprost to bosentan may have a beneficial effect in modulating the progression of disease.

TABLE 3. HEMODYNAMIC PARAMETERS AT WEEK 12: PRE- AND POSTINHALATION CHANGE FROM BASELINE

	Iloprost (*n* = *29*)				Placebo (*n* = *28*)				
Measure	Baseline*	Week 12	Change	Change (%)	Baseline*	Week 12	Change	Change (%)	p Value
Week 12 Postinhalation									
mPAP, mm Hg	51 (11)	46 (13)	−6 (7)	−12.0	52 (13)	55 (16)	2 (6)	3.2	<0.0001
PVR, dyn · s · cm^{-5}	821 (389)	676 (404)	−164 (223)	−19.7	783 (378)	867 (496)	81 (267)	6.7	0.0007
mSAP, mm Hg	88 (12)	87 (13)	−1 (14)	−0.8	83 (10)	86 (11)	3 (10)	3.6	0.6094
SVR, dyn · s · cm^{-5}	1474 (452)	1330 (429)	−91 (405)	−2.1	1374 (461)	1436 (426)	10 (399)	5.1	0.04065
HR, beats/min	81 (13)	79 (12)	−3 (12)	−2.3	74 (9)	75 (10)	2 (7)	3.0	0.5369
CO, L/min	4.74 (1.52)	4.82 (1.46)	0.10 (0.99)	5.28	4.61 (1.08)	4.57 (1.30)	0.10 (0.87)	3.21	0.8235
MVO_2,%	64.7 (8.1)	64.7 (8.3)	0.4 (4.9)	0.8	62.8 (7.3)	59.5 (8.8)	−3.7 (6.8)	−5.8	0.0071
Arterial O_2,%	93.9 (5.4)	92.8 (4.6)	−1.3 (3.9)	−1.3	94.0 (4.2)	92.4 (4.2)	−1.9 (4.1)	−2.0	0.5776
Week 12 Preinhalation									
mPAP, mm Hg	51 (11)	50 (13)	−2 (9)	−2.5	52 (13)	55 (15)	2 (5)	2.8	0.0808
PVR, dyn · s · cm^{-5}	821 (389)	832 (465)	−8 (246)	0.4	783 (378)	801 (402)	15 (216)	1.1	0.7635

Definition of abbreviations: arterial O_2 = systemic arterial saturation; CO = cardiac output; HR = heart rate; mPAP = mean pulmonary artery pressure; mSAP = mean systemic arterial pressure; MVO_2 = mixed venous oxygen saturation; PVR = pulmonary vascular resistance; SVR = systemic vascular resistance.

Numbers are given as mean (SD).

* Some patients contributed baseline but not Week 12 data.

TABLE 4. ADVERSE EVENTS*

Variable	No. Patients (%)	
	Iloprost Group (*n* = 35)	Placebo Group (*n* = 32)
Any adverse event	35 (100)	29 (90.6)
Headache	19 (54.3)	7 (21.9)
Cough	14 (40)	6 (18.8)
Jaw pain	10 (28.6)	3 (9.4)
Flushing	9 (25.7)	3 (9.4)
Chest pain	7 (20)	4 (12.5)
Pharyngolaryngeal pain	7 (20)	2 (6.3)
Chest discomfort	6 (17.1)	4 (12.5)
Nausea	6 (17.1)	5 (15.6)
Dizziness	5 (14.3)	8 (25.0)
Palpitations	4 (11.4)	4 (12.5)
Peripheral edema	3 (8.6)	3 (9.4)
Pain in extremity	3 (8.6)	2 (6.3)
Dry mouth	3 (8.6)	0 (0)
Fatigue	1 (2.9)	5 (15.6)
Upper respiratory tract infection	1 (2.9)	4 (12.5)
Dyspnea exacerbated	1 (2.9)	4 (12.5)
Abdominal distention	0 (0)	3 (9.4)

* Includes any adverse events reported by at least three patients in either group.

Therapy with inhaled iloprost in addition to bosentan was well tolerated, and appeared safe, with an adverse event profile typical of the prostanoid class. Side effects related to the inhaled delivery system, such as cough, while common, were mild to moderate and did not result in treatment discontinuation. Syncope, which occurred in 8% of the iloprost-treated patients in the AIR study and was characterized as severe in 5% of those patients, occurred in only one iloprost-treated patient (nonserious) in our study.

In the one other placebo-controlled combination therapy trial that has been published to date, Humbert and colleagues randomized 33 patients with PAH initiating intravenous epoprostenol to receive either bosentan or placebo (18). Improved hemodynamics, exercise capacity, and functional class were observed in both groups. Data showed a trend for a greater (though not statistically significant) improvement in all hemodynamic parameters in the combination group. However, an increased number of adverse events were observed in the combination group compared with the epoprostenol group. Although an important study, the practical implications of this study in the current day are limited because most patients with PH, with the exception of the most seriously ill, commence therapy with oral rather than intravenous agents.

Other data regarding combination therapy have been limited to small, open-label, uncontrolled case series in patients with an inadequate response (in the judgment of the investigators) to monotherapy. Hoeper and colleagues studied the effect of bosentan as add-on therapy in an open-label pilot study in 20 patients with IPAH receiving nonparenteral prostanoids (either inhaled iloprost [n = 9] or oral beraprost [n = 11]) (19). After 3 mo of combination therapy, improvements were described for 6-MWD and in cardiopulmonary exercise testing parameters. Ghofrani and colleagues described a series of 14 patients with PAH who deteriorated after initial clinical response to treatment with long-term inhaled iloprost and in whom sildenafil therapy was added (20). In this group, adjunct therapy with oral sildenafil improved the 6-MWD, functional class, and hemodynamics. Similarly, Hoeper and coworkers described the effects of combination therapy with sildenafil in a series of nine patients with IPAH in whom therapy with bosentan resulted in a transient improvement but subsequent decline in exercise tolerance (21). Combination therapy with sildenafil resulted in improvements in exercise capacity as measured by the 6-MWD and cardiopulmonary exercise testing.

Among the three classes of medications currently available, and targeted at the abnormalities in the prostacylin, endothelin, and nitric oxide pathways, bosentan has become widely used as initial therapy for the majority of patients with functional class III PAH. For those who fail to achieve the desired clinical response with bosentan monotherapy, addition of a prostanoid is considered. Although intravenous epoprostenol and subcutaneous or intravenous treprostinil are options in this situation, both have serious drawbacks, including the invasive nature of the therapy, and adverse effects, including sepsis, life-threatening infusion interruption, and infusion site pain. These detrimental effects are circumvented with delivery of iloprost by inhalation. Thus, the combination of oral bosentan and inhaled iloprost is a logical treatment option in the current era. This combination proved to be both safe and effective in the current study. Notably, syncope was infrequent with combination therapy and less severe than in the AIR study, perhaps attributable to background therapy with bosentan.

In the current study, the exact mechanism of the demonstrated benefit of adding iloprost to bosentan compared with continuing bosentan alone remains unclear. In the absence of a third study arm in which iloprost replaced bosentan rather than being added to it, we are unable to discern whether continued bosentan offered any benefit, be it additive or synergistic, to inhaled iloprost. In fact, the observed clinical benefit may have been due to iloprost alone. Although this constitutes a limitation to the interpretation of the results of the study, it mimics current clinical practice, in which therapeutic agents tend to be added successively in failing patients rather than as a replacement. Nevertheless, the formal evaluation of withdrawal of bosentan (or other failing agent) at the time of initiation of inhaled iloprost may have important clinical and economic implications, and should be considered in future such studies.

In addition to the limitations imposed by study design considered above, other limitations of this study include the relatively small numbers of patients enrolled and the relatively short (12-wk) treatment period. However, the patients enrolled in the study were typical of patients enrolled into other PAH studies and included patients with IPAH and APAH with a variety of underlying associated conditions, without imbalance between the treatment arms. Another potential limitation is that of unintentional unblinding, due to the adverse event profiles of iloprost versus placebo.

Although the strategy of initial bosentan therapy and the subsequent addition of inhaled iloprost is a rational treatment paradigm in the current era, there are limitations of this strategy. Inhaled iloprost requires administration approximately six times per day, which some patients may find inconvenient. Although mild to moderate in nature, cough occurs in 40% of patients (vs. 19% in the placebo group). The treatment effects are most prominent postinhalation and may wane over several hours. Last, one needs to consider the expense of combination therapy and the relative cost-effectiveness of treatment with two expensive medications.

Progress in the treatment of PAH has led to the availability of multiple medications from three distinct therapeutic classes. Similar to the therapeutic approach for left ventricular systolic dysfunction, combination therapy with drugs from different therapeutic classes is likely to be the foundation of PAH therapy in the future. The results from this study suggest that the addition of inhaled iloprost to oral bosentan is a safe and effective treatment approach.

Conflict of Interest Statement: V.V.M. has over the past 3 yr served as a consultant, speaker, and/or member of the advisory board for Actelion, CoTherix, Encysive, Myogen, Pfizer, and United Therapeutics. Over the past 3 yr, her institution, the University of Michigan, has received funding from Actelion, CoTherix, Encysive, Lung Rx, Pfizer, and United Therapeutics for participation in multicenter clinical trials. R.J.O. has served as a consultant for CoTherix and Myogen. He has participated in advisory boards for Actelion, Encysive, Pfizer, United Therapeutics, and GlaxoSmithKline. He has received lecture fees from Actelion, CoTherix, Encysive, and United Therapeutics. In addition, he received the following amounts for research grants as a participant in multicenter clinical trials: Actelion, $12,000; CoTherix, $23,000; Encysive, $111,000; Myogen, $74,000; Pfizer, $107,000; United Therapeutics, $15,000. A.F. has received $250,000 from Encysive, $236,000 from Myogen, $260,000 from CoTherix, and $130,000 from Pfizer as research grants for participating in multicenter clinical trials for 2003–2006, and is undertaking clinical research as part of a multicenter trial ($70,000) funded by Actelion to start in 2006. V.F.T. has in the past 3 yr received consulting fees from CoTherix. He has received speaking fees from Actelion, CoTherix, and Pfizer. He has attended advisory boards for Actelion, CoTherix, Encysive, Pfizer, and United Therapeutics. His institution has received research funds from Actelion, CoTherix, Encysive, Pfizer, Lung Rx, and United Therapeutics for participation in multicenter clinical trials. S.M. serves on the advisory board for Actelion, Encysive, and Pfizer. However, his total receipt from this activity has been less than $10,000/yr in the preceding 3 yr. He has grants pending with the industries listed: Actelion, $25,000; United Therapeutics, $20,000; Lilly, $35,000; CoTherix, $20,000. R.N.C. has served as a consultant for Actelion and CoTherix. He has served on advisory boards for Actelion, CoTherix, and Pfizer. He has received research grants from Actelion, CoTherix, Pfizer, Myogen, and Lung Rx. D.B.B. has received grant/research support from GlaxoWellcome/GlaxoSmithKline, United Therapeutics/Lung Rx, Boehringer Ingelheim, Actelion, ICOS/Texas Biotechnologies, Encysive, Pfizer, Myogen, CoTherix, Lilly/ICOS, American Lung Association, American Heart Association, National Institutes of Health, and the Scleroderma Foundation. In addition, he has served as a steering committee member, advisory board member, consultant, or speakers bureau member for GlaxoWellcome/GlaxoSmithKline, Actelion, Berlex, Astra-Merck, AstraZeneca, Myogen, Intermune, Forrest Labs, Encysive, Exhale Therpeutics/CoTherix, Pfizer, United Therapeutics, Scios, Amgen, Mondo-Biotech, ICOS, and PR Pharmaceuticals. R.J.B. serves as a scientific advisory board member for ICOS/Lilly ($5,000), Pfizer ($5,000), Actelion ($5,000), and Encysive ($5,000). She serves as a consultant to GlaxoSmithKline ($15,000), United Therapeutics ($20,000), and CoTherix ($20,000). She has received research grants for participating in multicenter clinical trials from United Therapeutics ($40,000), CoTherix ($15,000), Pfizer ($150,000), Encysive ($140,000), and Myogen ($20,000). H.H.H. was an employee of CoTherix, Inc., during the conduct of the study. L.J.R. has served as a consultant to Schering AG from 1999–2005 ($40,000) and as an investigator and consultant to CoTherix from 2004–2006 in the development of inhaled iloprost for pulmonary arterial hypertension (consultancy, $40,000; research grants to institution, $50,000).

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