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Addition of Inhaled Treprostinil to Oral Therapy for Pulmonary Arterial Hypertension

A Randomized Controlled Clinical Trial

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Objectives This study assessed the efficacy and safety of inhaled treprostinil in pulmonary arterial hypertension (PAH) patients receiving therapy with either bosentan or sildenafil.

Background There is no cure for PAH, despite effective treatments, and outcomes remain suboptimal. The addition of inhaled treprostinil, a long-acting prostacyclin analog, might be a safe and effective treatment addition to other PAH-specific oral therapies.

Methods Two hundred thirty-five PAH patients with New York Heart Association (NYHA) functional class III (98%) or IV symptoms and a 6-min walk distance (6MWD) of 200 to 450 m while treated with bosentan (70%) or sildenafil were randomized to inhaled treprostinil (up to 54 μg) or inhaled placebo 4 times daily. The primary end point was peak 6MWD at 12 weeks. Secondary end points included time to clinical worsening, Borg Dyspnea Score, NYHA functional class, 12-week trough 6MWD, 6-week peak 6MWD, quality of life, and PAH signs and symptoms. The biomarker N-terminal pro-brain natriuretic peptide (NT-proBNP) was assessed.

Results Twenty-three patients withdrew from the study prematurely (13 treprostinil, 10 placebo). The Hodges-Lehmann between-treatment median difference in change from baseline in peak 6MWD was 19 m at week 6 ($p = 0.0001$) and 20 m at week 12 ($p = 0.0004$). Hodges-Lehmann between-treatment median difference in change from baseline in trough 6MWD at week 12 was 14 m ($p = 0.0066$). Quality of life measures and NT-proBNP improved on active therapy. There were no improvements in other secondary end points, including time to clinical worsening, Borg Dyspnea Score, NYHA functional class, and PAH signs and symptoms. Inhaled treprostinil was safe and well-tolerated.

Conclusions This trial demonstrates that, among PAH patients who remain symptomatic on bosentan or sildenafil, inhaled treprostinil improves exercise capacity and quality of life and is safe and well-tolerated. (TRIUMPH I: Double Blind Placebo Controlled Clinical Investigation Into the Efficacy and Tolerability of Inhaled Treprostinil Sodium in Patients With Severe Pulmonary Arterial Hypertension; NCT00147199) (J Am Coll Cardiol 2010;55:1915–22)

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Abbreviations and Acronyms

6MWD = 6-min walk distance

CI = confidence interval

eCMH = extended Cochran-Mantel-Haenszel

H-L = Hodges-Lehmann

MLWHF = Minnesota Living with Heart Failure

NT-proBNP = N-terminal pro-brain natriuretic peptide

NYHA = New York Heart Association

PAH = pulmonary arterial hypertension

WRS = Wilcoxon rank sum

Over the past 15 years, agents from 3 therapeutic classes have been investigated and are now widely used for the treatment of pulmonary arterial hypertension (PAH), a rare disease characterized by progressive elevation in pulmonary artery pressure, pulmonary vascular resistance, and ultimately, right ventricular failure (1,2). Prostacyclins (epoprostenol, treprostinil, and iloprost), endothelin receptor antagonists (bosentan, ambrisentan, and sitaxsentan), and phosphodiesterase inhibitors (sildenafil, tadalafil) have been evaluated in PAH patients, on the basis of known pathobiological mechanisms of action, and have demonstrated improvements in symptoms, exercise tolerance, and in some studies, hemodynamic status, over the short term (3–9). There is no cure for PAH, despite these treatment options, and longer-term outcomes in PAH have been suboptimal. The concept of combining agents targeting different pathways in an attempt to improve outcomes is an area of active investigation, given the availability of agents from 3 distinct therapeutic categories. To date, 4 randomized placebo-controlled trials of combination therapy are completed, with mixed results (10–13).

Treprostinil is a tricyclic benzindene prostacyclin analog, with pharmacologic actions similar to those of epoprostenol. It is stable at room temperature and has an elimination half-life of 4.6 h (14). In a randomized, placebo-controlled trial, treprostinil administered subcutaneously improved exercise capacity and hemodynamic status in PAH patients (4). Two small investigator-initiated open label studies have suggested clinical benefit with treprostinil administered intravenously (15,16). Although clinically effective, subcutaneous and intravenous administration of treprostinil might be associated with adverse effects including infusion site pain and blood stream infections, respectively (17,18).

Initial open label studies with inhaled treprostinil have demonstrated favorable effects in terms of exercise capacity and hemodynamic status (19,20). In this study (TRIUMPH [TReprostinil Sodium Inhalation Used in the Management of Pulmonary Arterial Hypertension]), we assessed the efficacy and safety of inhaled treprostinil or placebo in PAH patients receiving therapy with either bosentan or sildenafil.

Methods

This was a 12-week, randomized, placebo-controlled, double-blind, multicenter study in patients with PAH who were receiving a stable dose of bosentan or sildenafil for 3 months before study initiation. The study was sponsored by United Therapeutics Corporation. Following institutional review board approval at each participating institution, all patients provided written informed consent before any study-related assessments.

Eligible patients were between the ages of 18 and 75 years with a confirmed diagnosis of idiopathic or familial PAH or PAH associated with collagen vascular disease, human immunodeficiency virus infection, or anorexigen use. Patients were New York Heart Association (NYHA) functional class III or IV severity with a baseline 6-min walk distance (6MWD) between 200 and 450 m and were receiving bosentan 125 mg daily or any prescribed dose of sildenafil, ≥20 mg tid, for at least 3 months before study entry. Additionally, women of child-bearing potential were required to practice an acceptable method of birth control.

Patients were considered ineligible for study participation if they: were pregnant or nursing; were diagnosed with any acute or chronic illness other than those associated with PAH (collagen vascular disease, human immunodeficiency virus, or anorexigen use); had received any investigational medications, prostanoids, or phosphodiesterase inhibitors other than sildenafil within 30 days; or had changed or discontinued any PAH medication within 3 months.

Before randomization, patients were trained on proper nebulizer technique with the OPTINEB device (Nebu-Tec, Elsenfeld, Germany). Patients were randomized (1 of 1) to receive either inhaled treprostinil sodium or placebo 4 times daily in combination with bosentan or sildenafil. At the discretion of the study investigator, patients initiated therapy at 3 breaths (18 μg)/inhalation. If clinically tolerated, the dosing was to be increased over the first 2 weeks to reach a maximum of 9 breaths (54 μg) at each of the 4 daily doses. Patients were contacted by study personnel via telephone to assess patient tolerance to study drug, adverse events, and to up-titrate study drug dosing as tolerated.

Baseline, Week 6, and Week 12 assessments included physical exam including PAH signs and symptoms and vital signs, NYHA functional classification, 6MWD, Borg Dyspnea score (immediately after 6MWD), and clinical laboratory parameters including: urine pregnancy screening, blood chemistries, hematology, coagulation times, and N-terminal pro-brain natriuretic peptide (NT-proBNP). Additionally, at baseline and week 12, the following assessments were conducted: complete medical history including concomitant medications, pulmonary function tests, chest radiography, and completion of the Minnesota Living with Heart Failure (MLWHF) questionnaire. Adverse events were obtained throughout the study.

The primary end point was 6MWD measured at peak, defined as within 10 to 60 min after treprostinil inhalation at week 12. Secondary end points included time to clinical worsening, defined as death, transplantation, hospital stay due to worsening PAH, or initiation of additional approved PAH-specific therapy, Borg Dyspnea Score, NYHA functional class, trough 6 MWD at week 12 (obtained at least 4 h after study drug administration), peak 6MWD at Week 6, quality of life as measured by the MLWHF question-

naire, and PAH signs and symptoms. The NT-pro BNP was included as an ancillary assessment. All 6MWD assessments were planned at 3 to 5 h after bosentan dosing or 30 to 120 min after sildenafil dosing.

Statistics. This study had 90% power to detect a 35-m difference (75-m SD) between treatment groups in peak 6MWD change from Baseline at week 12 with at least 200 patients enrolled with power calculations in PASS software (Microsoft, Redmond, Washington) and a nonparametric (Mann-Whitney) adjustment to a 2-sample *t* test. This assumed SD was somewhat larger than that estimated from the trial data (66.8 m), suggesting that the true power is >90%. For 6MWD variables including peak and trough, a nonparametric analysis of covariance was performed on all randomized patients. The effect of inhaled treprostinil versus placebo on 6MWD was tested with nonparametric analysis of covariance within the framework of extended Cochran-Mantel-Haenszel (eCMH) test (21,22). Specifically, a Cochran-Mantel-Haenszel mean score test was used on the standardized ranks of the residuals from an ordinary least squares regression with change in 6MWD at week 12 as a linear function of etiology (as a categorical variable) and baseline 6MWD (as a continuous variable). Etiology and baseline 6MWD were chosen as covariates for this analysis, due to their demonstrated prognostic power in various previously conducted PAH trials. For confirmatory purposes, the effect of inhaled treprostinil versus placebo on 6MWD was further tested with the Wilcoxon rank sum (WRS) test. The median difference between treatment groups was determined by the Hodges-Lehmann (H-L) between-treatment median difference. Imputation was used for missing data with worst rank for death, addition of PAH therapy during the trial or discontinuation due to disease progression, last rank carried forward for other missing values if a post-baseline assessment was performed, or the mean of placebo ranks if there was no post-baseline assessment.

All secondary variables was evaluated by comparing the difference between baseline and week 12. The difference between treatment groups for baseline and secondary variables was evaluated with either a chi-square test (for dichotomous data) or WRS test (for ordinal or continuous data).

The safety of inhaled treprostinil was evaluated by comparing adverse experiences in the 2 treatment groups with regard to frequency, intensity, seriousness, and causality. Changes in hematology, clinical chemistries, coagulation, chest radiography, lung function tests, and vital signs from baseline were also assessed between treatment groups.

Results

Demographic data. Two hundred thirty-five patients with a mean age of 54 years (range 18 to 75 years) were enrolled at 31 centers between June 2005 and July 2007. Patient demographic data are described in Table 1. Of the 235 patients, 115 were randomized to treprostinil and 120 were randomized to placebo (Fig. 1). Twenty-three patients withdrew from the study prematurely, 13 (9 bosentan, 4 sildenafil) in the treprostinil group and 10 (8 bosentan, 2 sildenafil) in the placebo group. The mean dose of study drug was 50 ± 10 μg in the inhaled treprostinil group and 52 ± 7 μg in the inhaled placebo group.

Efficacy outcomes. 6-MIN WALK. The 6MWD results are presented in Figures 2 and 3. The peak 6MWD within-treatment median changes from baseline were 21.6 m (interquartile range: −8.0 to 54.0 m) and 3.0 m (interquartile range: −26.0 to 31.5 m) for inhaled treprostinil and placebo groups, respectively, with an H-L between-treatment median difference of 20 m at week 12 (95% confidence interval [CI]: 8.0 to 32.8, p[eCMH] = 0.0004, p[WRS] = 0.0016). The H-L between-treatment median difference in change in peak 6MWD was 19 m (95% CI: 8.5 to 28.3, p[eCMH] = 0.0001, p[WRS] = 0.0004) at Week 6, and for the change in trough 6MWD it was 14 m (95% CI: 4 to 24.8, p[eCMH] = 0.0066, p[WRS] = 0.0040) at week 12. Patients in the lowest quartile for baseline 6MWD (204 to 302 m, n = 59) had the greatest treatment effect in change in 6MWD by week 12, with an H-L between-treatment median difference of 49 m (95% CI: 23.7 to 78.2, p[eCMH] = 0.0003, p[WRS] = 0.0007). As demonstrated in Figure 3, 60 patients receiving inhaled treprostinil (52%) experienced an improved 6MWD of 20 m or greater, with 36 patients (31%) improving by at least 50 m. Patients receiving background bosentan therapy experienced an H-L between-treatment median difference in change in peak 6MWD of 22 m (95% CI: 10.0 to 34.0, p[eCMH] = 0.0001, p[WRS] = 0.0004) and 25 m (95% CI: 10.2 to 40.0) p[eCMH] = 0.0002, p[WRS] = 0.0009) at weeks 6 and 12, respectively. Patients taking sildenafil background therapy had an H-L between-treatment median difference

Table 1 Patient Demographic Data

Characteristic	Inhaled TRE (n = 115)	Placebo (n = 120)	p Value
Age, yrs	55 (20–75)	52 (18–75)	0.056
Male/female	22/93	22/98	0.88
PAH etiology			
IPAH or familial	64 (56)	67 (56)	0.60
CVD	40 (35)	37 (31)	
Other	11 (9)	16 (13)	
Background PAH therapy			
Bosentan	77 (67)	88 (73)	0.29
Sildenafil	38 (33)	32 (27)	
Time on background therapy, weeks			
Bosentan	99 ± 79	90 ± 75	0.62
Sildenafil	65 ± 60	77 ± 69	0.44
Baseline NYHA III/IV	112/3	118/2	0.62
Baseline 6MWD, m	346 ± 63	351 ± 69	0.50

Values are mean (range), n, n (%), or mean ± SD.

6MWD = 6-min walk distance; CVD = collagen vascular disease; IPAH = idiopathic pulmonary arterial hypertension; NYHA = New York Heart Association functional class; PAH = pulmonary arterial hypertension; TRE = treprostinil.

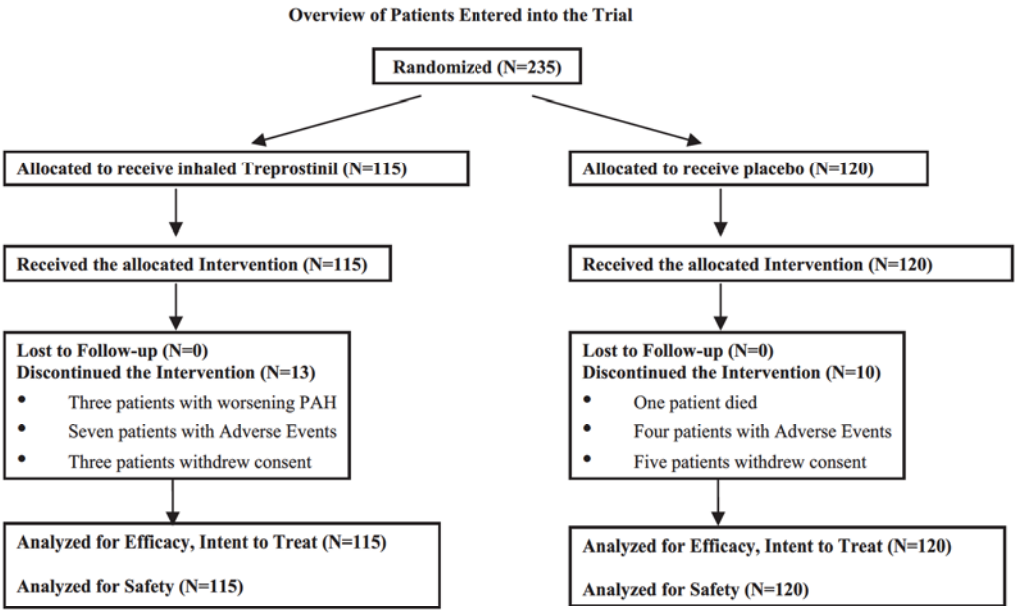

Figure 1 Patient Disposition

A total of 235 patients were randomized into the study—115 to treprostinil and 120 to placebo. All randomized patients received investigational treprostinil/placebo. There were 13 premature discontinuations in the treprostinil group and 10 in the placebo group. PAH = pulmonary arterial hypertension.

in change in peak 6MWD at weeks 6 and 12 of 11 and 9 m, respectively (p = NS).

SECONDARY END POINTS. There was no difference in time to clinical worsening between treatment groups (Table 2). There was no change in Borg Dyspnea Score, NYHA functional classification, and PAH signs and symptoms from baseline to week 12 compared with placebo. Quality of life as assessed by the MLWHF questionnaire had an H-L between-treatment median difference of −4 in the global score (p = 0.027) and −2 in the physical score (p = 0.037), for patients receiving inhaled treprostinil.

ANCILLARY END POINT. The NT-proBNP results are presented in Figure 4. One hundred fifty-five patients provided pro-BNP results at baseline and week 12. Median baseline NT-proBNP levels were 593 pg/ml (n = 73) and 670 pg/ml (n = 82) in the treprostinil and placebo groups, respectively.

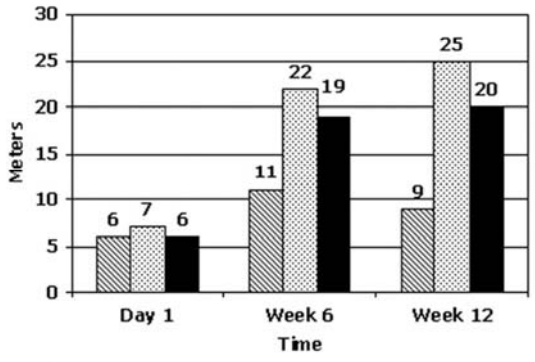

Figure 2 Change in 6MWD

Primary end point, change in peak 6-min walk distance (6MWD) for patient receiving background sildenafil **(ruled bars)**, background bosentan **(dotted bars)**, and the entire population **(solid bars)**. There was a placebo-corrected improvement of 20 m at 12 weeks in the total population. Results presented as Hodges-Lehman between-treatment median difference.

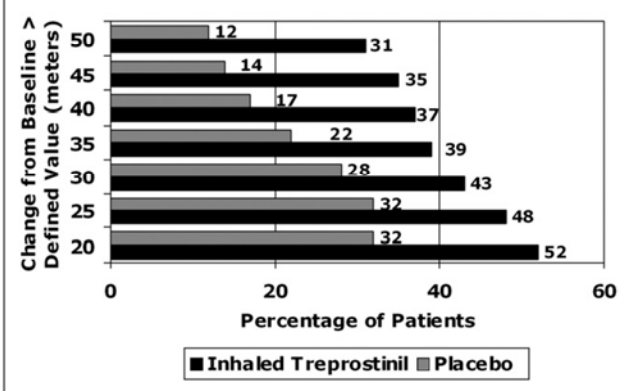

Figure 3 6MWD Improvements

Distribution of the percentage of patients who achieved specific improvements in 6-min walk distance (6MWD) at 12 weeks. For example, 31% of patients taking inhaled treprostinil and 12% of patients taking inhaled placebo had an improvement in 6MWD of >50 m at 12 weeks.

Table 2 Clinical Worsening Events

Extent of Clinical Worsening	Treatment: Inhaled TRE (n = 115)	Treatment: Placebo (n = 120)
No clinical worsening	111 (97)	114 (95)
Clinical worsening	4 (3)	6 (5)
Death	0 (0)	1 (<1)
Transplantation	0 (0)	0 (0)
PAH hospital stay	4 (3)	5 (4)
Initiation of approved PAH therapy	0 (0)	0 (0)

Values shown are n (%).
PAH = pulmonary arterial hypertension; TRE = treprostinil.

The NT-proBNP within treatment median changes from baseline were −57 pg/ml (interquartile range: −396.0 to 34.0) and 40 pg/ml (interquartile range: −93.0 to 288.0) for inhaled treprostinil and placebo group, respectively, with an H-L between-treatment median difference in change from baseline in NT-proBNP levels of −187 pg/ml (95% CI: −333 to −64.0, p = 0.0014) at week 12. The H-L between-treatment median difference in change from baseline was −159 pg/ml (95% CI: −299 to −64.0, p = 0.0003) at week 6.

Safety. There were no clinically significant changes in pulmonary function tests, chest radiography, or clinical laboratory parameters, including: blood chemistries, hematology, and coagulation times between treatment groups.

Seventy-five (72%) patients receiving inhaled treprostinil and 96 (87%) receiving placebo obtained the maximum dose of 9 breaths (54 μg) 4 times daily. The average time to maximum dose was approximately 3 weeks in both treatment groups.

Adverse events are summarized in Table 3. The most common adverse event was cough, which occurred in 54% of patients receiving inhaled treprostinil as compared with

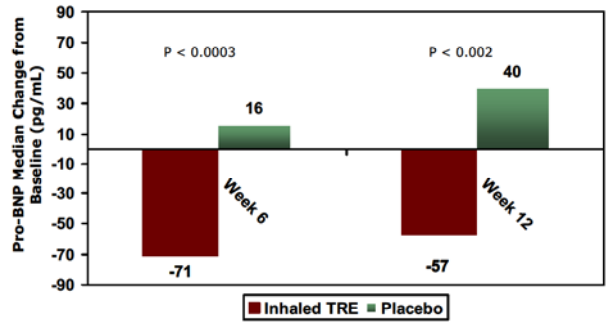

Figure 4 NT-proBNP Changes

Median change from baseline in N-terminal pro brain natriuretic peptide (NT-proBNP) at week 6 and week 12. Samples were available for 155 patients at week 12. TRE = treprostinil.

Table 3 Adverse Events Occurring in ≥10% of Patients Receiving Inhaled TRE

Adverse Events Occurring in ≥3% of TRE Patients	Treatment: Inhaled TRE (n = 115)	Treatment: Placebo (n = 120)
Cough	62 (54)	35 (29)*
Headache	47 (41)	27 (23)*
Nausea	22 (19)	13 (11)
Dizziness	20 (17)	18 (15)
Flushing	17 (15)	1 (<1)*
Throat irritation	16 (14)	10 (8)
Pharyngolaryngeal pain	13 (11)	7 (6)
Diarrhea	11 (10)	9 (8)

Values shown are n (%). *p < 0.05.
TRE = treprostinil.

29% of patients receiving placebo. There were 11 serious adverse events reported in the inhaled treprostinil group, including 3 events of worsening pulmonary hypertension, 2 events of syncope, and 1 event of each of the following: anemia, abdominal pain, diabetes mellitus, diarrhea, gastric ulcer, and right ventricular failure.

Twenty-three patients prematurely discontinued the study. In the placebo group, 1 patient died, 4 withdrew due to adverse events, and 5 patients withdrew consent; of these patients, 8 were receiving background bosentan. In the inhaled treprostinil group, 3 patients discontinued due to worsening pulmonary hypertension, 7 withdrew due to adverse events, and 3 withdrew consent; of these patients, 9 were receiving background bosentan.

Discussion

In this study, PAH patients with NYHA functional class III or IV symptoms and a 6MWD of 200 to 450 m while receiving oral monotherapy with either bosentan or sildenafil were randomized to receive either inhaled treprostinil or placebo. The primary end point of change from baseline in 6MWD at week 12 had an H-L between-treatment median difference of 20 m (p = 0.0004). Additionally, the change in 6MWD improved as early as week 6 (H-L median difference of 19 m, p = 0.0001) and was sustained at trough at week 12 (14 m, p = 0.0066). The importance of sustained effects at trough is notable, because this is the first such observation with a prostanoid given on an intermittent basis. The improvement in 6MWD was greatest in those in the lowest quartile for baseline 6MWD (49 m, p = 0.0003). This observation of greatest benefit in the most severely compromised patients studied was also made in the pivotal trial with subcutaneous treprostinil but is contrary to the recent study evaluating the addition of sildenafil in those symptomatic while receiving epoprostenol (4,12). The improvement noted in these advanced but not end-stage patients with inhaled treprostinil suggests that such patients still have capacity to improve with inhaled prostanoid therapy.

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