Efficacy and Safety of Oral Treprostinil Monotherapy for the Treatment of Pulmonary Arterial Hypertension

A Randomized, Controlled Trial

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Background—Pulmonary arterial hypertension (PAH) is a progressive, fatal disease with no cure. Parenteral and inhaled prostacyclin analogue therapies are effective for the treatment of PAH, but complicated administration requirements can limit the use of these therapies in patients with less severe disease. This study was designed to evaluate the safety and efficacy of the oral prostacyclin analogue treprostinil diolamine as initial treatment for de novo PAH.

Methods and Results—Three hundred forty-nine patients (intent-to-treat population) not receiving endothelin receptor antagonist or phosphodiesterase type-5 inhibitor background therapy were randomized (treprostinil, n=233; placebo, n=116). The primary analysis population (modified intent-to-treat) included 228 patients (treprostinil, n=151; placebo, n=77) with access to 0.25-mg treprostinil tablets at randomization. The primary end point was change from baseline in 6-minute walk distance at week 12. Secondary end points included Borg dyspnea index, clinical worsening, and symptoms of PAH. The week 12 treatment effect for 6-minute walk distance (modified intent-to-treat population) was 23.0 m (P=0.0125). For the intent-to-treat population, 6-minute walk distance improvements were observed at peak (26.0 m; P=0.0001) and trough (17.0 m; P=0.0025) plasma study drug concentrations. Other than an improvement in the combined 6-minute walk distance/Borg dyspnea score, there were no significant changes in secondary end points. Oral treprostinil therapy was generally well tolerated; the most common adverse events (intent-to-treat) were headache (69%), nausea (39%), diarrhea (37%), and pain in jaw (25%).

Conclusions—Oral treprostinil improves exercise capacity in PAH patients not receiving other treatment. Oral treprostinil could provide a convenient, first-line prostacyclin treatment option for PAH patients not requiring more intensive therapy.

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Key Words: exercise test ■ prostacyclin analogue ■ pulmonary arterial hypertension ■ treprostinil

Pulmonary arterial hypertension (PAH) is a devastating and progressive disease of the pulmonary circulation, characterized by increasing pulmonary vascular resistance that leads to right ventricular failure and premature death.[1] Current treatment paradigms for PAH focus on 3 therapeutic classes: Endothelin receptor antagonists (ERAs), phosphodiesterase type-5 inhibitors (PDE-5Is), and prostacyclin or its analogues.[1,2] The major pharmacological actions of the prostacyclin analogues in the context of PAH include vasodilation of the pulmonary and systemic vascular beds, inhibition of platelet aggregation, and inhibition of smooth muscle cell proliferation.[3,4] Parenteral prostacyclin therapy has been shown to improve hemodynamics and exercise capacity, delay clinical worsening, and improve survival in PAH patients.[5–10] Because of the relative complexity and administration challenges of continuous intravenous or subcutaneous infusions, however, parenteral prostacyclin analogue therapy typically has been reserved for the treatment of more advanced disease.[1]

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Given the established safety and efficacy profile of approved prostacyclin analogue therapies, there has been interest in developing analogues amenable to inhaled or oral use.[1,8,11] In fact, inhaled prostacyclin analogues have emerged as attractive treatment options, especially as part of second-line combination therapies, because of their relatively low incidence of systemic side effects and relative ease of use compared with parenteral therapy.[12–17] The development of effective oral prostacyclin analogues, however, has proven more challenging. Although the initial clinical results for the first-in-class oral prostacyclin beraprost were encouraging, follow-up studies were unsuccessful, and the compound never gained regulatory approval in the United States or Europe.[18,19]

Treprostinil is a chemically stable prostacyclin analogue with demonstrated safety and efficacy when administered by intravenous, subcutaneous, or inhaled routes of administration.[7,16,20] The sodium salt of treprostinil is currently approved for the treatment of PAH for either parenteral (Remodulin) or inhaled (Tyvaso) routes of administration.[21,22] Treprostinil diolamine (UT-15C; also referred to as treprostinil diethanolamine) is a treprostinil salt amenable to oral administration. In the bloodstream, both treprostinil sodium and treprostinil diolamine rapidly dissociate to the freely ionized form of treprostinil. Thus, the therapeutic use of oral treprostinil diolamine builds on the substantial clinical experience of parenteral and inhaled treprostinil sodium.

Treprostinil diolamine tablets are formulated as extended-release, osmotic tablets to support twice-daily (BID) oral administration. In pharmacokinetic studies involving PAH patients undergoing chronic, open-label therapy, treprostinil diolamine demonstrated a terminal half-life of ≈4.5 hours with a broad and sustained blood concentration for 8 to 10 hours after a single oral dose.[23] Oral treprostinil diolamine is primarily subject to CYP2C8 and, to a lesser extent, CYP2C9 metabolism and demonstrates increased bioavailability with food.[24,25] In PAH patients, an oral treprostinil dose of 3.5 mg BID produced plasma levels between 2 and 8 hours after the dose that were comparable to those seen with parenteral infusion rates of 10 to 30 $ng \cdot kg^{-1} \cdot min^{-1}$.[23] The first completed study with oral treprostinil (Oral Treprostinil in Combination With an ERA and/or a PDE-5I for the Treatment of PAH [FREEDOM-C]) failed to meet its primary end point. In that 16-week randomized, placebo-controlled study, PAH patients receiving approved background therapy (ERA, PDE-5I, or both) treated with oral treprostinil therapy had a nonsignificant increase in 6-minute walk distance (6MWD) of 11 m (P=0.07).[26] However, FREEDOM-C patients were initiated on study drug at a starting dose of oral treprostinil (1 mg BID) that was later linked to poor tolerability and a relatively high rate of discontinuations because of adverse events (AEs). Lower-strength tablets (0.25 and 0.5 mg) were subsequently developed with a goal of improving tolerability and ease of dose titrations. The present study (Oral Treprostinil as Monotherapy for the Treatment of PAH [FREEDOM-M]), therefore, was designed to assess the safety and efficacy of oral treprostinil therapy in de novo PAH patients who were not concurrently receiving approved PAH therapy.

Methods

Study Design

This was a 12-week international, multicenter (online-only Data Supplement Table I), randomized (2:1 oral treprostinil:placebo), double-blind, placebo-controlled study designed to evaluate the efficacy and safety of oral treprostinil in patients with PAH not currently receiving therapy (ERA, PDE-5I, or prostacyclin) for the treatment of PAH (www.clinicaltrials.gov; NCT00325403). The study was sponsored by United Therapeutics and conducted according to Good Clinical Practice principles. All study procedures were approved by an independent institutional review board, and written informed consent was obtained from all patients before screening.

Patient Population

Eligible patients were 12 to 75 years of age with idiopathic or hereditary PAH (including PAH associated with appetite suppressant/toxin use), PAH associated with repaired congenital systemic-to-pulmonary shunts (repaired ≥5 years), or PAH associated with collagen vascular disease or HIV. Patients were ineligible if they had received ERA, PDE-5I, or prostacyclin therapy within 30 days of baseline or if they had evidence of significant left-sided heart disease or parenchymal lung disease. Baseline 6MWD was required to be between 100 and 450 m. Patients were required to be optimally treated with conventional PAH therapies (eg, anticoagulants, oral vasodilators, oxygen, digoxin) with no additions, discontinuations, or dose changes <14 days before baseline (excluding changes to anticoagulants and diuretic dose adjustments).

Study End Points

The primary end point was the effect of oral treprostinil on exercise capacity compared with placebo, as measured by the change in 6MWD from baseline to week 12. Secondary end points included Borg dyspnea score; combined 6MWD/Borg dyspnea score (for detailed methods, see Hiremath et al[10]); dyspnea-fatigue index; World Health Organization (WHO) functional class; symptoms of PAH; clinical worsening; and safety (AEs, clinical laboratory parameters, and ECG findings). Clinical worsening was defined as one of the following: Cardiovascular death, transplantation, atrial septostomy, or clinical deterioration. Clinical deterioration was defined as the initiation of new, approved PAH-specific therapy (ERA, PDE-5I, or prostacyclin) plus either hospitalization for decompensated PAH or a ≥20% decrease in 6MWD from baseline combined with worsening WHO functional class.

Study Drug

Study drug was provided as extended-release oral tablets in 0.125, 0.25, 0.5, and 1 mg strengths. Study drug was originally initiated at 1.0 mg BID; however, on the basis of tolerability issues identified in the FREEDOM-C study,[26] the study protocol was later amended to lower the starting dose to 0.5 mg BID and eventually 0.25 mg BID. Study drug was administered every 12±2 hours with dose escalation of an additional 0.25 to 0.5 mg BID every 3 days and a maximum possible dose of 12 mg BID. Patients unable to tolerate the 0.25-mg dose or requiring an intermediate dose were allowed to use the 0.125-mg tablet once this strength was made available later in the study. Because of evidence of increased bioavailability with food,[25] the study protocol recommended that all doses of study medication be ingested within ≈10 minutes after breakfast/dinner, with each meal consisting of ≥500 calories.

Study Assessments

Baseline, week 4, week 8, and week 12 assessments included vital signs, exercise capacity (including 6MWD and Borg dyspnea score), clinical worsening, dyspnea-fatigue index, WHO functional class, and symptoms of PAH. Exercise capacity was also assessed at week 11. On the basis of prior pharmacokinetic analyses,[23] exercise capacity was assessed at estimated peak (3–6 hours after morning administration [weeks 4, 8, and 12]) and trough (8–13 hours after last dose [week 11]) plasma concentrations of treprostinil. Clinical laboratory parameters were assessed at baseline, week 8, and week 12; 12-lead ECG was conducted at baseline and week 12; and clinical worsening assessment and AEs were recorded throughout the 12-week study period.

Open-Label Extension

Patients who continued taking the study drug and completed all assessments during the 12-week treatment phase were eligible to be enrolled in an open-label extension trial. Additionally, placebo patients who experienced clinical worsening and were withdrawn from study drug before week 12 were also eligible for the open-label study if they had completed all study assessments through week 12.

Statistical Analysis

The primary analysis population or modified intent-to-treat (mITT) population was the population of patients with access to the 0.25-mg strength tablet at the time of randomization. The intent-to-treat (ITT) population (as well as the safety population) was defined as all randomized patients. The per-protocol population was defined as randomized patients who completed at least the week 8 assessments or discontinued study drug because of documented clinical deterioration or nonaccidental death, excluding major protocol violations. Study power calculations were originally performed for a sample size of ≈150 patients. Subsequent protocol amendments reduced the starting dose of study drug to 0.25 mg BID and increased the sample size to ≈315 patients, including ≈195 patients with access to 0.25-mg oral treprostinil tablets at the time of randomization. A sample size of ≈195 patients provided 90% power at a significance level of $P<0.01$ (2-sided hypothesis) to detect a 45-m between-treatment difference in 6MWD change from baseline at week 12 assuming a standard deviation (SD) of 75 m. With these assumptions, an overall sample size of 349 patients provided a power of 99%. For the primary end point, nonparametric ANCOVA was used to assess the difference between active drug and placebo in 6MWD change from baseline to week 12, with adjustment for baseline 6MWD. Treatment effect (magnitude of change in 6MWD) was estimated with the Hodges-Lehmann median difference between treatment groups. For the primary end point, missing values and values after discontinuation of study/study drug were handled by use of imputation of ranks for nonparametric inferential analyses and imputation of analogous 6MWD values for descriptive statistics. The lowest rank or value corresponding to the worst overall relative change was assigned for death within 12 weeks; discontinuation because of clinical deterioration, transplantation, or atrial septostomy; and for patients too ill to perform a 6-minute walk test. The last rank carried forward or last observation carried forward was assigned to patients who withdrew prematurely from the study or study drug for other reasons or who did not perform the 6-minute walk test for any reason not mentioned above (eg, missed visit), provided that the patient performed at least 1 postbaseline 6-minute walk test. Otherwise, the mean placebo rank or value corresponding to the geometric mean relative change for the placebo group was assigned.

Secondary end points were tested in the following order: Trough 6MWD (week 11), time to clinical worsening, combined 6MWD and Borg, 6MWD at week 8, WHO functional class at week 12, Borg score at week 12, dyspnea-fatigue at week 12, 6MWD at week 4, symptoms of PAH at week 12. Formal testing was terminated as soon as any probability value was >0.05. Descriptive statistics were used to evaluate safety end points; AEs were summarized for the ITT (safety) and mITT populations. Other safety end points (vital signs, ECGs, and laboratory parameters) were summarized with the ITT (safety) population. Data are presented as mean±SD or range, median (95% confidence interval [CI]), or percentage. Statistical significance was considered to be 2-sided $P<0.05$; statistical analysis was performed with SAS software, version 9.2 (SAS Institute Inc, Cary, NC).

Results

Patient disposition is summarized in Figure 1. Three hundred forty-nine patients (oral treprostinil, n=233; placebo, n=116) were randomized (ITT population); all patients received at least 1 dose of study drug. The mITT population consisted of 228 patients (oral treprostinil, n=151; placebo, n=77) who had access to the 0.25-mg study drug tablet at time of randomization and received at least 1 dose of study drug. For the mITT population, the mean±SD dose BID of study drug achieved in the oral treprostinil treatment group for patients completing the weeks 4, 8, and 12 assessments was 2.3±1.3, 3.2±1.9, and 3.4±1.9 mg, respectively (Figure 2).

Baseline Characteristics and Patient Disposition

For the mITT population, the mean age was 39.4 years (range, 12–73 years; Table 1). The majority of patients were Asian (71%) and female (73%), with a diagnosis of idiopathic or hereditary PAH (75%; see online-only Data Supplement Table II for patient randomization by geographic region). Patients were predominantly classified as being in WHO functional class III (66%), and the mean baseline 6MWD was 330 m. Most patients were recently (<1 year; 86%) diagnosed with PAH. Patient demographics were similar for the ITT population (Table 1). Of the 228 patients in the mITT population, 125 patients taking oral treprostinil (83%) and 66 taking placebo (86%) completed the study (Figure 1). Twenty-six patients taking oral treprostinil (17%) and 11 taking placebo (14%) prematurely discontinued study drug for reasons that included clinical deterioration (oral treprostinil, 4 [3%]; placebo, 2 [3%]), AEs (oral treprostinil, 6 [4%]; placebo, 2 [3%]), or death (oral treprostinil, 8 [5%]; placebo, 5 [6%]). After completion of the 12-week treatment phase, 188 patients (83%) enrolled in the open-label extension study. Patient disposition was similar for the ITT population, with the exception that for the oral treprostinil treatment group, there tended to be more premature discontinuations of study drug because of AE in the ITT population than in the mITT population (ITT population, 23 [10%]; mITT population, 6 [4%]).

Efficacy Outcomes

Six-Minute Walk Distance

Median baseline 6MWD values for the mITT population were similar between treatment groups (oral treprostinil, 350 m; placebo, 339 m). At week 12, 6MWD was significantly improved from baseline for the oral treprostinil group, with a median Hodges-Lehmann treatment effect of 23.0 m (95% CI, 4–41 m; $P=0.0125$). The 6MWD change from baseline at week 8 was also significantly improved (17.0 m; 95% CI, 1–33 m; $P=0.0307$). Although improvements in 6MWD were noted at week 4 (12.0 m; 95% CI, 0–24 m; $P=0.0518$) and week 11 (13.0 m; 95% CI, −2 to 33; $P=0.0653$), these changes were not statistically significant (Figure 2). The median change from baseline for the placebo treatment group was remarkably stable over the 12-week study period (range, −5 to 0 m). For the ITT population, the change from baseline in 6MWD at week 12 was 26.0 m (95% CI, 10–41 m; $P=0.0001$). Significant improvements were also noted for week 4 (14.0 m; 95% CI, 4–25 m; $P=0.0025$), week 8 (20.0 m; 95% CI, 7–34 m; $P=0.0008$), and the week 11 trough measurement (17.0 m; 95% CI, 3–33 m; $P=0.0025$). For the mITT population, the significance of the primary efficacy results at week 12 were confirmed if no imputation was performed for missing data (24.0 m; 95% CI, 5–41 m; $P=0.0052$), with last observation carried forward imputation for all missing data (22.0 m; 95% CI, 6–38 m; $P=0.0028$), and with the per-protocol analysis population (23.0 m; 95% CI, 4–41 m; $P=0.0105$).

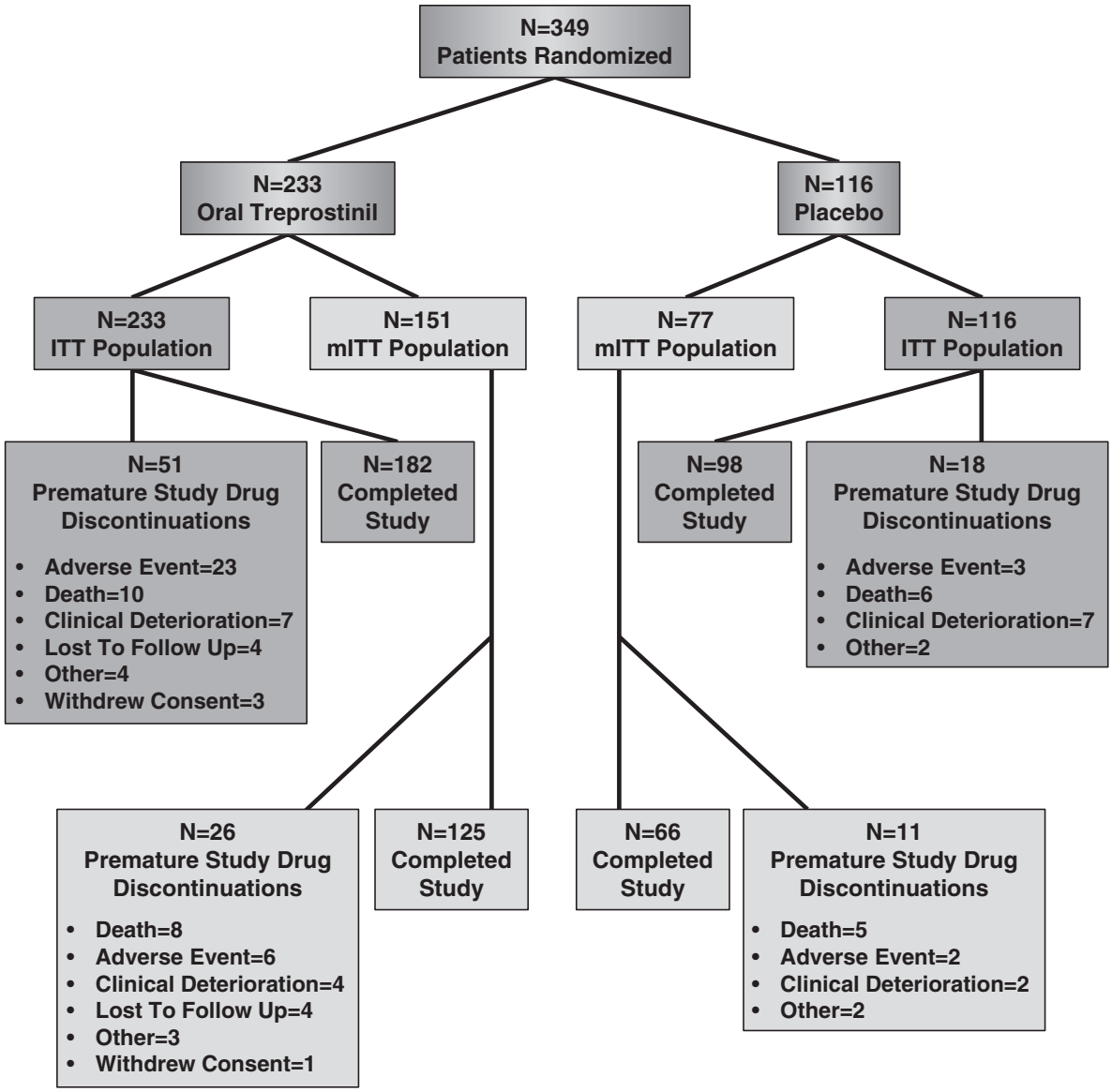

Figure 1. Patient disposition. Three hundred forty-nine patients were randomized into the study. The overall (intent-to-treat [ITT]) population consisted of all randomized patients; the modified ITT (mITT) population consisted of all patients with access to 0.25-mg oral treprostinil tablets at randomization. There were 69 premature discontinuations in the ITT population (oral treprostinil, n=51; placebo, n=18) and 37 in the mITT population (oral treprostinil, n=26; placebo, n=11). Most patients who prematurely discontinued study drug also prematurely discontinued the study before week 12 (ITT: oral treprostinil, n=32; placebo, n=12; mITT: oral treprostinil, n=20; placebo, n=9).

For the mITT population, 52% of patients taking oral treprostinil (versus 39% of patients given placebo) experienced an improvement in 6MWD of ≥20 m, and 34% (versus 23% of patients given placebo) improved by ≥50 m (Figure 3). A similar pattern was observed for the ITT population (oral treprostinil: 52% ≥20 m, 33% ≥50 m; placebo: 38% ≥20 m, 21% ≥50 m). Exploratory efficacy analyses were performed for subgroups defined by patient demographics (age, sex, and disease origin) and disease severity (baseline 6MWD and WHO functional classification). Of the covariates tested for the mITT population, the 6MWD change from baseline at week 12 was significantly improved for patients older than 41.2 years (the mean age for the overall study population), patients diagnosed with idiopathic or hereditary PAH, patients with a baseline 6MWD >350 m, and patients with WHO class III to IV symptoms at baseline (Figure 4). There were no apparent interactions between geographic region (US and Canada, India, China, or other [Mexico, Europe, and Israel]) and 6MWD treatment effect (mITT, P=0.569; ITT, P=0.802). There appeared to be an association between study drug dose and 6MWD treatment effect. As seen in Figure 2, the average dose (BID) achieved by patients completing the weeks 4, 8, and 12 assessments increased, as did the corresponding Hodges-Lehmann treatment effects, which indicates that larger treatment effects were associated with increasing study drug exposure and duration of treatment.

Secondary Outcomes

For the mITT population, there was a significant improvement in the combined 6MWD/Borg dyspnea score at week 12 (P=0.0497). For the ITT population, significant improvements in the combined 6MWD/Borg score were observed at week 4

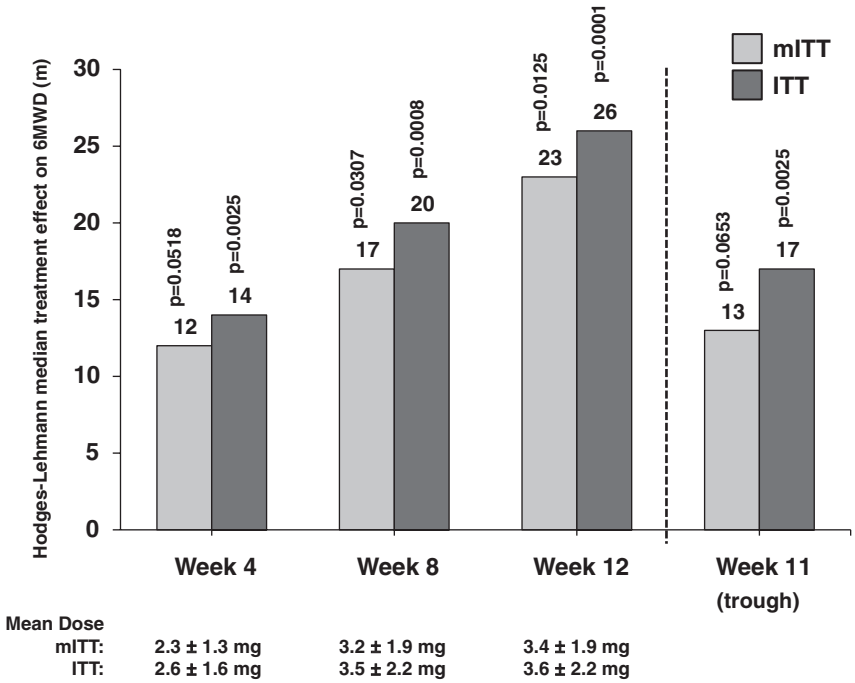

Figure 2. Change in 6-minute walk distance (6MWD). 6MWD at weeks 4, 8, and 12 was recorded at estimated peak plasma study drug concentrations; week 11 was recorded at estimated trough plasma study drug concentrations. For the modified intent-to-treat (mITT) population at week 12, there was a median treatment effect of 23 m (P=0.0125). Results presented as placebo-corrected Hodges-Lehmann between-treatment median difference for the mITT and intent-to-treat (ITT) populations. Mean±SD oral treprostinil dose (twice daily) included for completers at each study time point.

(P=0.014), week 8 (P=0.004), and week 12 (P=0.0007). No differences in clinical worsening between treatment groups were observed for either the mITT or ITT population (Table 2).

Table 1. Baseline Characteristics

Characteristic	ITT Population		mITT Population	
	Oral Treprostinil (n=233)	Placebo (n=116)	Oral Treprostinil (n=151)	Placebo (n=77)
Age, y	40.6 (12–73)	42.5 (18–68)	37.8 (12–73)	42.5 (18–68)
Female	172 (74)	90 (78)	108 (72)	58 (75)
Race				
Asian*	110 (47)	55 (48)	108 (72)	55 (71)
White	96 (41)	47 (41)	36 (24)	20 (26)
Black	10 (4)	1 (<1)	5 (3)	1 (1)
Native American	16 (7)	12 (10)	1 (<1)	1 (1)
Not provided	1 (<1)	1 (<1)	1 (<1)	0 (0)
PAH origin/cause				
IPAH/HPAH	171 (73)	88 (76)	114 (75)	56 (73)
CVD	45 (19)	22 (19)	26 (17)	17 (22)
Repaired CHD	13 (6)	5 (4)	10 (7)	3 (4)
HIV	3 (1)	1 (<1)	1 (<1)	1 (1)
WHO functional class II/III	83/142	42/70	52/98	24/52
6MWD, m	332.3±71.6	325.2±77.1	331±65	328±71
Years since PAH diagnosis	1.0±2.7	1.0±3.1	0.7±1.9	0.8±3.5

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

CHD indicates congenital heart disease; CVD, collagen vascular disease; HPAH, hereditary pulmonary arterial hypertension; IPAH, idiopathic pulmonary arterial hypertension; ITT, intent-to-treat; mITT, modified intent-to-treat; PAH, pulmonary arterial hypertension; 6MWD, 6-minute walk distance; and WHO, World Health Organization.

*Includes patients from India (mITT, n=92) and China (mITT, n=71).

Overall, for the mITT population, 15 patients (10%) in the oral treprostinil treatment group and 8 (10%) in the placebo group experienced clinical worsening during the 12-week study period. There were no statistically significant treatment-related changes in Borg dyspnea score, WHO functional class, or symptoms of PAH observed during the study.

Safety

AEs for both the ITT and mITT populations are summarized in Table 3. For the ITT population, the most common AEs reported in the oral treprostinil treatment group were headache (69%), nausea (39%), diarrhea (37%), pain in jaw (25%) and vomiting (24%). For the ITT population, headache, nausea, diarrhea, pain in jaw, flushing, and pain in extremity were reported more frequently (P<0.05) in the oral treprostinil treatment group than in the placebo group (Table 3). The most common AEs reported in patients receiving oral treprostinil therapy (ITT) that were considered severe in intensity were headache (40%), nausea (20%), diarrhea (13%), vomiting (12%), and pain in jaw (10%). Of these, headache and pain in jaw were reported more frequently (P<0.05) in the oral treprostinil group than in the placebo group (11% and 2%, respectively). Twenty-three patients taking oral treprostinil (10%) discontinued study drug because of AEs in the ITT population. The most common prostacyclin AEs that led to study drug discontinuation among oral treprostinil patients (ITT) included headache, nausea, jaw pain, diarrhea, and vomiting. In the placebo group, 3 patients (3%) discontinued study drug because of AEs. The overall incidence and severity of AEs was similar for the mITT population, although fewer oral treprostinil patients in the mITT population prematurely discontinued study drug because of AEs (ITT, 23 [10%]; mITT, 6 [4%]).

For the ITT population, 41 patients taking oral treprostinil (18%) and 26 (22%) taking placebo experienced serious adverse events. The most commonly reported serious AEs were consistent with worsening disease and included right

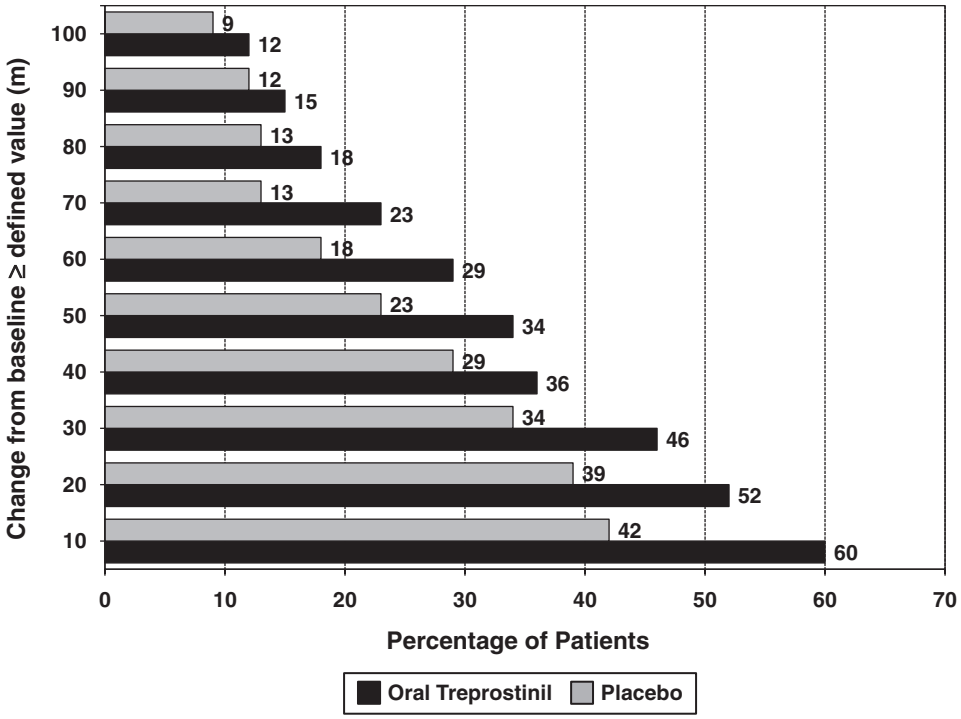

Figure 3. Improvements in 6-minute walk distance (6MWD). Distribution of the percentage of patients who achieved specific improvements in 6MWD at week 12. For example, 34% of patients in the oral treprostinil treatment group and 23% of patients in the placebo treatment group had an improvement in 6MWD of at least 50 m at week 12. Results presented for the modified intent-to-treat population.

ventricular failure (oral treprostinil, 13 [6%]; placebo, 4 [3%]) and worsening PAH (oral treprostinil, 6 [3%]; placebo, 9 [8%]), the latter of which was reported more often in patients given placebo ($P<0.05$). A similar pattern was observed for the mITT population, with 27 treprostinil patients (18%) and 15 placebo patients (19%) experiencing serious AEs. The

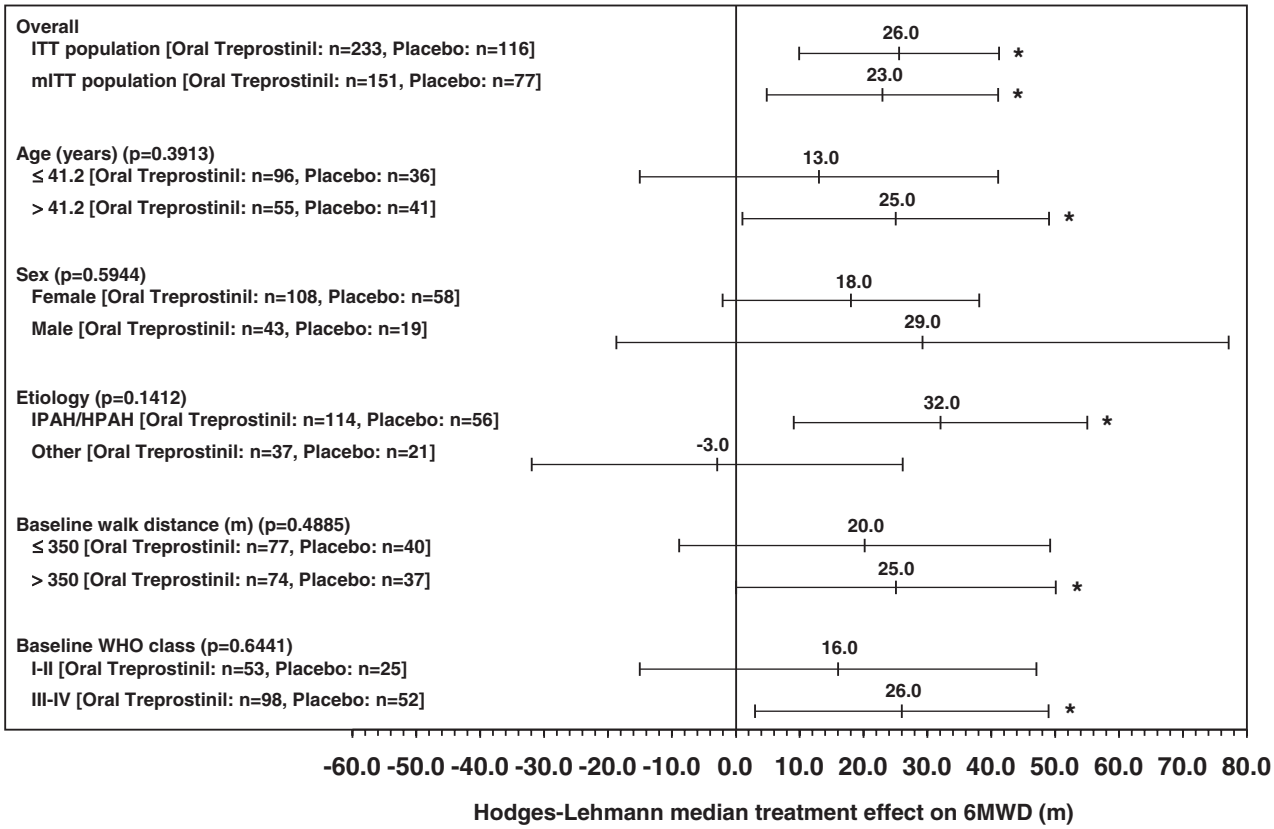

Figure 4. Change in 6-minute walk distance (6MWD) by covariates. Results presented as Hodges-Lehmann median estimate of treatment effect for the change in 6MWD at week 12 by covariate classification for the modified intent-to-treat (mITT) population. Subgroup interaction probability values provided for covariates; *$P<0.05$. HPAH indicates hereditary pulmonary arterial hypertension; IPAH, idiopathic pulmonary arterial hypertension; ITT, intent to treat; mITT, modified intent-to-treat; and WHO, World Health Organization.

most commonly reported serious AEs for the mITT population were right ventricular failure (oral treprostinil, 10 [7%]; placebo, 3 [4%]) and worsening PAH (oral treprostinil, 3 [2%]; placebo, 4 [5%]).

There were 16 deaths in the ITT population, including 10 among patients taking oral treprostinil (4%) and 6 among those given placebo (5%) (Figure 1). Additionally, 1 patient in the oral treprostinil group died after completing the week 12 visit but before enrolling in the open-label extension study. Two deaths in the oral treprostinil group were considered by the individual investigator to be possibly attributable to study drug (1 event of vasovagal syncope and 1 event of pulmonary edema). For the mITT population, there were 14 deaths, including 9 patients taking oral treprostinil (6%) and 5 taking placebo (8%). Of the 9 patients taking oral treprostinil who died, 8 (5%) died before discontinuation of study drug (Figure 1). Although there were occasional transient changes in individual laboratory parameters during the study, there were no significant treatment-related trends in laboratory parameters between treatment groups over time. Similarly, there were no significant treatment-related differences in mean vital signs or ECG parameters over the course of the study.

Discussion

Although the therapeutic benefits of inhaled and parenteral prostacyclin analogue therapies are well established, the use of these therapies is complex, and they are often challenging to administer.[8] As such, these therapies are typically reserved for use as part of a second-line, combination therapy (ie, inhaled plus ERA or PDE-5I) or for the treatment of severe disease (parenteral). An oral prostacyclin analogue would add a first-line, prostacyclin-based treatment option to the PAH therapy armamentarium and could provide a viable initial treatment option for PAH patients with less severe disease.

In the present study, PAH patients not receiving other therapy (ERA or PDE-5I) were randomized to oral treprostinil or placebo for 12 weeks. Significant improvements in 6MWD were noted at week 12 for both the mITT and ITT populations and were observed by week 8 in the mITT population and week 4 in the ITT population. Importantly, 6MWD improvements were increased significantly at trough concentrations (week 11) for the ITT population and trended toward significance for the mITT population. Although there were no formal dose-response or pharmacokinetic analyses performed in the present study, there appeared to be a positive relationship between duration of treatment, dose of study drug achieved, and 6MWD treatment effect. In the present study, the average dose of oral treprostinil achieved by mITT patients who completed the week 12 assessments was 3.4 mg. Previous pharmacokinetic data suggest that PAH patients treated with this dose of oral treprostinil would exhibit clinically relevant serum treprostinil concentrations similar to those seen with parenteral infusion rates of ≈10 to 30 $ng \cdot kg^{-1} \cdot min^{-1}$ and similar to or greater than those seen with the recommended maintenance dose (54 μg 4 times a day) of inhaled treprostinil.[23,27,28]

More than half (52%) of the patients treated with oral treprostinil demonstrated at least a 20-m improvement in 6MWD at week 12, and 34% had an improvement of ≥50 m. These improvements are similar to those observed with the addition of inhaled treprostinil to background ERA or PDE-5I therapy (52% ≥20 m; 31% ≥50 m).[16] Interestingly, the improvements seen in the placebo group in the present study (39% ≥20 m; 23% ≥50 m) were actually greater than those observed for the placebo group in the inhaled treprostinil study (32% ≥20 m; 12% ≥50 m),[16] despite the fact that patients given placebo in the present study were not receiving background therapy. Together, these results further emphasize the need for placebo-controlled trials when the primary end point is 6MWD.

Oral treprostinil was generally well tolerated in the mITT population, and the incidence and severity of observed AEs were consistent with the previously observed effects of prostacyclin therapy (headache, nausea, diarrhea, flushing, and pain

Table 2. Clinical Worsening

	ITT Population		mITT Population	
Category	Oral Treprostinil (n=233)	Placebo (n=116)	Oral Treprostinil (n=151)	Placebo (n=77)
No clinical worsening	211 (91)	101 (87)	136 (90)	69 (90)
Clinical worsening	22 (9)	15 (13)	15 (10)	8 (10)
Death*	13 (6)	8 (7)	9 (6)	6 (8)
Hospitalization/new therapy†	9 (4)	5 (4)	6 (4)	1 (1)
6MWD/WHO/new therapy‡	0 (0)	2 (2)	0 (0)	1 (1)
Transplantation or atrial septostomy	0 (0)	0 (0)	0 (0)	0 (0)

Values shown as n (%).

ITT indicates intent-to-treat; mITT, modified intent-to-treat; 6MWD, 6-minute walk distance; and WHO, World Health Organization.

*Includes 1 patient (oral treprostinil) who died after discontinuing study drug.

†Hospitalization for PAH plus addition of new PAH therapy.

‡A ≥20% decrease in 6MWD with worsening WHO functional class plus addition of new PAH therapy.

Table 3. Adverse Events

	ITT Population		mITT Population	
Adverse Event	Oral Treprostinil (n=233)	Placebo (n=116)	Oral Treprostinil (n=151)	Placebo (n=77)
Any event	219 (94)	106 (91)	138 (91)	68 (88)
Headache	160 (69)	36 (31)*	95 (63)	15 (19)*
Nausea	91 (39)	25 (22)*	45 (30)	14 (18)
Diarrhea	86 (37)	21 (18)*	46 (30)	12 (16)*
Pain in jaw	59 (25)	8 (7)*	17 (11)	3 (4)
Vomiting	57 (24)	19 (16)	26 (17)	12 (16)
Flushing	50 (21)	9 (8)*	23 (15)	5 (6)
Pain in extremity	44 (19)	9 (8)*	21 (14)	6 (8)
Abdominal pain	31 (13)	9 (8)	13 (9)	4 (5)
Myalgia	24 (10)	5 (4)	6 (4)	0 (0)

Adverse events occurring in at least 10% of patients receiving oral treprostinil in the ITT population. Values (n [%]) reported for the intent-to-treat (n=349) and modified intent-to-treat (n=228) populations.

ITT indicates intent-to-treat; and mITT, modified intent-to-treat.

*$P<0.05$.

in jaw or extremity).[7,13,15,16] There was no evidence of previously unidentified, treatment-limiting, oral administration–specific AEs. It appears that the 0.25-mg BID starting dose in the mITT population was better tolerated (lower rate of discontinuation in the mITT population than in the ITT population, many of whom started on 1 mg BID). This is consistent with the higher discontinuation rate in the original FREEDOM-C trial when the starting dose was 1 mg BID.[26] Future trials will focus on a starting dose of 0.25 mg to improve drug tolerance. The lower starting dose for the mITT population did not appear to limit patient dose escalation to a clinically relevant range (3.4 mg at week 12), as demonstrated by the robust improvements in 6MWD. As mentioned above, the dose of oral treprostinil achieved by patients in the first 12 weeks of the present study has been shown to produce plasma exposures similar to those demonstrated for low-dose parenteral or the recommended dose of inhaled treprostinil delivery.[23,27,28]

Overall, the results from the present study with respect to 6MWD are similar to those seen in placebo-controlled studies for currently approved oral therapies (both ERA and PDE-5I) that are typically used in the treatment of de novo PAH.[29–32] In contrast to prior studies with bosentan, ambrisentan, and tadalafil, however, oral treprostinil had no effect on the incidence of clinical worsening.[29,31,32] Overall, the incidence of clinical worsening in the present study was relatively low (10%), which may reflect the short duration of the study (12 weeks), the fairly large percentage of patients with WHO class II symptoms (34%), and the only moderately impaired exercise capacity across patients at baseline (mean 6MWD=330 m). Of note, the incidence of clinical worsening in the placebo group in the present study (10%) was virtually identical to that reported for the 12-week studies for ambrisentan (Ambrisentan in Pulmonary Arterial Hypertension Study 1 [ARIES-1]; 9%) and sildenafil (Sildenafil Use in Pulmonary Arterial Hypertension [SUPER]; 10%), studies that also lacked a significant treatment effect with respect to clinical worsening,[30,31] and lower than that seen in the 12-week Ambrisentan in Pulmonary Arterial Hypertension Study 2 (ARIES-2; 22%) and the longer duration BREATHE-1 study (Bosentan Randomized Trial of Endothelin Antagonist Therapy; 20% through week 28), 2 studies in which there were significant treatment effects for clinical worsening.[29,31] It is also interesting that although the overall incidence of clinical worsening in the present study was low, death was the most frequent clinical worsening event, with 8% and 6% of patients dying in the placebo and oral treprostinil groups, respectively. As a point of comparison, deaths in the placebo groups in the ARIES-1 and SUPER studies were 3% and 1%, respectively. This apparent discrepancy between incidence of clinical worsening and frequency of death may be explained in part by geographic differences between studies and the fact that the majority of patients in the present study came from countries such as China, in which advanced parenteral and organ transplant treatment options are less readily available (online-only Data Supplement Table II). Related to this, it is also important to consider potential issues about the extrapolation of the efficacy results presented here to a more Western patient population. Although the data are limited, recent analyses suggest that 6MWD treatment effects in Chinese patient populations are similar to those seen in Western populations and that survival rates for Chinese PAH patients have improved in the modern treatment era.[33–36] In general, however, comparison of efficacy results across trials is highly problematic because of differences in patient population and study design and only properly addressed in head-to-head studies such as the ongoing AMBITION trial (AMBITION: A Randomised, Multicenter Study of First-Line Ambrisentan and Tadalafil Combination Therapy in Subjects With Pulmonary Arterial Hypertension; www.clinicaltrials.gov; NCT01178073) comparing 2 first-line, oral monotherapies (ambrisentan or tadalafil) with the respective combination therapy.

Study Limitations

The conclusions drawn from the present study are limited by the relatively short duration (12 weeks), the relative lack of patients with either less severe disease (WHO functional class I or 6MWD >450 m) or more severe disease (WHO functional class IV), the relatively small numbers of nonidiopathic or nonhereditary PAH patients, and the fact that the study drug was evaluated as monotherapy only. Longer studies are required to further address end points such as clinical worsening and survival, although these studies will likely have to rely on combination therapy with an active control group given the ethical issues of conducting a long-term placebo-controlled study in the context of a progressive and fatal disease. Similarly, more head-to-head studies are needed to directly compare the efficacy of available first-line oral therapies with distinct mechanisms of action.

Conclusions

Oral treprostinil is the first oral prostacyclin analogue to meet the primary end point in a randomized, controlled trial in the PAH patient population. The results of the present study support the use of oral treprostinil as initial therapy in PAH patients with class II or III symptoms. Additional studies are needed to investigate the long-term impact of oral treprostinil therapy on PAH disease progression.

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Disclosures

Dr Jing has served as a consultant, scientific advisor, and investigator in clinical trials for Actelion, Bayer, Pfizer, and United Therapeutics. Dr Parikh has served as an investigator in clinical trials for United Therapeutics. Dr Pulido has served as a consultant, scientific advisor, and investigator in clinical trials for Actelion, Bayer, Pfizer, Gilead, Lilly, and United Therapeutics. Dr Jerjes-Sanchez has served as a consultant and scientific advisor for Pfizer and Actelion; he has also received research funding for participation in other multicenter clinical trials. Dr White has served as a paid consultant to the sponsor and

has received research funding to participate in multicenter clinical trials with this study's sponsor (United Therapeutics), Lilly/ICOS, Gilead Sciences, and Actelion; he also has investigator-initiated research support from United Therapeutics and Gilead. Dr White does not have equity interest in any pharmaceutical company, and his paid consulting activities are fully disclosed and supervised by the University of Rochester Conflict of Interest Committee. Dr Allen has served as a consultant and received speaking engagement and grant support from Gilead and United Therapeutics; he has contracts with Actelion, Bayer, and GeNO. Dr Torbicki has conducted research supported by Actelion, Bayer, and United Therapeutics; has served as a consultant for Actelion and Bayer; and has received honoraria from Actelion, Bayer, AOP, United Therapeutics, Eli Lilly, and GSK. Dr Xu has served as an investigator in clinical trials sponsored by Actelion and United Therapeutics. D. Yehle, K. Laliberte, and C. Arneson are employees of the sponsor, United Therapeutics. Dr Rubin has been a consultant and investigator for Actelion and United Therapeutics and serves on the Scientific Advisory Board for United Therapeutics.

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CLINICAL PERSPECTIVE

Pulmonary arterial hypertension (PAH) is a progressive, fatal disease characterized by increasing pulmonary vascular resistance that leads to right ventricular failure and death. In the past ≈15 years, the PAH treatment armamentarium has grown dramatically to encompass oral endothelin receptor antagonists, oral phosphodiesterase type-5 inhibitors, and parenteral/inhaled prostacyclin analogues. Despite the availability of diverse therapies, there is no cure for PAH, and long-term survival for patients remains poor. The prostacyclin analogue therapeutic class has an established history of safety and efficacy for the treatment of PAH. The therapeutic use of prostacyclin analogues, however, is currently restricted to continuous parenteral infusion or frequent inhaled administration because of the relatively short in vivo half-life of these compounds. Thus, the development of oral prostacyclin analogues is of significant clinical interest. Treprostinil is a prostacyclin analogue currently approved for the treatment of PAH for subcutaneous, intravenous, and inhaled administration. Treprostinil diolamine is a treprostinil salt formulated for oral administration. Here, we describe the safety and efficacy of oral treprostinil monotherapy for the treatment of PAH. The results of the present study support the use of oral treprostinil as an initial therapy in PAH patients with World Health Organization class II or III symptoms to improve exercise capacity. The use of a titratable prostacyclin analogue as an initial therapy will meet an unmet need in the treatment of patients with PAH.

SUPPLEMENTAL MATERIAL

Supplemental Table I. Principal Investigators and Study Sites.

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Mexico, Europe, Israel	
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Supplemental Table II. Patient Randomization by Region.

	ITT Population		mITT Population	
Region	**Oral Treprostinil** (n=233)	**Placebo** (n=116)	**Oral Treprostinil** (n=151)	**Placebo** (n=77)
US and Canada	72 (31)	33 (28)	34 (23)	19 (25)
India	57 (24)	35 (30)	57 (38)	35 (45)
China	51 (22)	20 (17)	51 (34)	20 (26)
Mexico, Europe, Israel	53 (23)	28 (24)	9 (4)	3 (4)

Values presented as n (%).

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