CHEST

Original Research

PULMONARY VASCULAR DISEASE

Oral Treprostinil for the Treatment of Pulmonary Arterial Hypertension in Patients Receiving Background Endothelin Receptor Antagonist and Phosphodiesterase Type 5 Inhibitor Therapy (The FREEDOM-C2 Study)

A Randomized Controlled Trial

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Background: **Treprostinil is a stable prostacyclin analog approved for the treatment of pulmonary arterial hypertension (PAH) as parenteral or inhaled therapy. Treprostinil diolamine, a sustained-release oral formulation of treprostinil, was studied to determine whether it could provide a more convenient prostacyclin treatment option for patients with less severe PAH. The objective of this study was to evaluate the efficacy and safety of oral treprostinil in patients with PAH receiving stable background endothelin receptor antagonist (ERA), phosphodiesterase type 5 inhibitor (PDE-5I) therapy, or both.**

Methods: **A 16-week, multicenter, double-blind, placebo-controlled study in 310 patients with PAH compared bid administration of oral treprostinil (n = 157) with placebo (n = 153). The primary end point was change in 6-min walk distance at week 16. Secondary efficacy end points were World Health Organization functional class, Borg dyspnea score, dyspnea-fatigue index, signs and symptoms of PAH, and clinical worsening.**

Results: **One hundred thirty-two patients (84%) receiving oral treprostinil and 138 (90%) receiving placebo completed the study. The mean ± SD dose of oral treprostinil at week 16 was 3.1 ± 1.9 mg bid. The Hodges-Lehmann placebo-corrected median difference in 6MWD at week 16 was 10.0 m (95% CI, −2 to 22 m; *P* = .089). There were no significant changes in secondary end points. The most common adverse events associated with oral treprostinil were headache (71%), diarrhea (55%), nausea (46%), flushing (35%), and jaw pain (25%).**

Conclusions: **The addition of oral treprostinil to background ERA and PDE-5I therapy did not result in a statistically significant improvement in exercise capacity. Side effects were common but tolerated by most subjects.**

Trial registry: **ClinicalTrials.gov; No.: NCT00887978; URL: www.clinicaltrials.gov**

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Abbreviations: 6MWD = 6-min walk distance; 6MWT = 6-min walk test; ERA = endothelin receptor antagonist; FPAH = familial pulmonary arterial hypertension; H-L = Hodges-Lehmann; IPAH = idiopathic pulmonary arterial hypertension; NP-ANCOVA = nonparametric analysis of covariance; PAH = pulmonary arterial hypertension; PDE-5I = phosphodiesterase type 5 inhibitor

Pulmonary arterial hypertension (PAH) is a progressive and fatal disease characterized by increasing pulmonary vascular resistance that leads to right ventricular failure and premature death.[1] Current treatment of PAH targets one or more of three central biologic pathways involved in the pathogenesis of the disease: prostacyclin, nitric oxide, and endothelin.[1,2] Prostacyclin analogs promote vasodilation of the pulmonary

and systemic vascular beds, inhibit the proliferation of vascular smooth muscle cells, and inhibit platelet aggregation.[3-5]

Treprostinil (Remodulin [subcutaneous or IV delivery] or Tyvaso [inhaled delivery]) is a stable prostacyclin analog approved for the treatment of PAH.[6-8] Treprostinil diolamine (also referred to as treprostinil diethanolamine or UT-15C) is a treprostinil salt formulated as an extended-release osmotic tablet to support bid oral administration. In patients with PAH, treprostinil diolamine has a terminal half-life of about 4.5 h.[9] In 44 patients with PAH receiving this drug for 4 weeks at a stable dose for at least 5 days, sustained plasma concentrations over about 12 h after a single oral dose were shown to be similar to those seen with parenteral treprostinil.[9,10]

To date, oral treprostinil for the treatment of PAH has been evaluated in two randomized placebo-controlled studies.[11,12] In FREEDOM-C (Oral Treprostinil in Combination With an Endothelin Receptor Antagonist [ERA] and/or Phosphodiesterase-5 Inhibitor [PDE-5I] for the Treatment of Pulmonary Arterial Hypertension), oral treprostinil therapy in combination with background ERA and PDE-5I therapy did not improve 6-min walk distance (6MWD).[11] Study drug dosing in FREEDOM-C, with an initial dose of 1 mg bid, was associated with frequent adverse events and a relatively high rate of discontinuation.[11] FREEDOM-M evaluated the efficacy and safety of oral treprostinil monotherapy.[12] Because of the tolerability issues seen in FREEDOM-C, the FREEDOM-M primary analysis population included only patients with access to 0.25 mg tablets at randomization. For this patient population, oral treprostinil treatment significantly improved 6MWD.[12] These data indicate that although there is evidence for a therapeutic benefit of oral treprostinil, the dosing for these initial studies, in particular FREEDOM-C, was suboptimal. Therefore, FREEDOM-C2 evaluated the efficacy and safety of oral treprostinil when initiated at 0.25 mg bid in patients with PAH receiving background therapy of ERA, PDE-5I, or both.

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Materials and Methods

Patient Population

Eligible patients were aged 18 to 75 years with idiopathic PAH (IPAH) (including PAH associated with appetite suppressant or toxin use), familial PAH (FPAH), or PAH associated with congenital heart disease (repaired congenital systemic-to-pulmonary shunts for ≥ 5 years); connective tissue disease; or HIV. Diagnosis of PAH required a mean pulmonary arterial pressure of > 25 mm Hg, pulmonary capillary wedge pressure or left ventricular end-diastolic pressure of ≤ 15 mm Hg, pulmonary vascular resistance of > 3 Wood units, and the absence of unrepaired congenital heart disease. Patients were required to have received ERA or PDE-5I therapy for ≥ 90 days with a stable dose for ≥ 30 days before baseline and throughout the duration of the study. Baseline 6MWD was required to be between 150 and 425 m. Patients were considered ineligible if they were pregnant or nursing or had left-sided heart disease or significant parenchymal lung disease. The latter was defined as a total lung capacity of < 60% predicted. If total lung capacity was between 60% and 70% predicted, a high-resolution CT scan had to be performed to rule out diffuse interstitial fibrosis or alveolitis. Furthermore, the FEV_1/FVC ratio could not be < 50%. Patients could not be receiving any investigational medication or had changed or discontinued any PAH medication within 14 days. The protocol was approved by institutional review boards at all participating study centers (e-Table 1), and all patients provided written informed consent.

Study Design

FREEDOM-C2 was an international, multicenter, randomized, double-blind, placebo-controlled, 16-week study. Patients were randomized (1:1) to oral treprostinil or placebo and stratified by background therapy (ERA, PDE-5I, or both) and baseline 6MWD (≤ 350 or > 350 m). The study drug was provided as 0.25-, 0.5-, and 1-mg tablets. During the study, 0.125-mg tablets were made available to all regions except China. The study drug was initiated at 0.25 mg bid (every 12 ± 1 h), with dose escalation of an additional 0.25 mg bid every 3 days if clinically indicated. After the first 4 weeks, dose escalations could include increments of either 0.25 or 0.5 mg bid every 3 days. No dose changes were allowed for 5 days before the week 16 visit. The study drug was administered immediately after (about 10 min) breakfast and dinner, with each meal containing at least 500 calories. After completion of all study assessments, eligible patients were able to enter an open-label extension study.

Study End Points

The primary end point was the placebo-corrected change in 6MWD from baseline to week 16. Secondary end points were clinical worsening, Borg dyspnea score, combined walk distance and Borg score, N-terminal pro-brain natriuretic peptide level, World Health Organization functional classification, the Cambridge Pulmonary Hypertension Outcome Review, signs and symptoms

of PAH, and safety. Clinical worsening was defined as death, transplantation, or atrial septostomy; hospitalization as a result of right-side heart failure; a decrease in 6MWD of ≥ 20% from baseline (or too ill to walk) and the addition of an inhaled prostacyclin analog, ERA, or PDE-5I; or initiation of parenteral prostacyclin therapy for the treatment of PAH. Patients were assessed at baseline and weeks 4, 8, 12, and 16. Safety evaluations included assessment of adverse events throughout the study; assessment of laboratory samples for the determination of hematology, chemistry, and urinalysis at baseline and weeks 8 and 16; and ECG and physical examinations at baseline and week 16. Vital signs were also measured at each clinic visit.

Statistical Methods

With a 1:1 randomization between oral treprostinil and placebo, a sample size of about 266 patients provided at least 90% power at a significance level of .05 (two-sided hypothesis) to detect a 30-m between-treatment difference in the change from baseline to week 16 in 6MWD, assuming an SD of 75 m. The primary efficacy analysis compared change in 6MWD at week 16 between treatment groups with a nonparametric analysis of covariance (NP-ANCOVA). The magnitude of the treatment effect was assessed with the median difference between treatment groups as determined by the Hodges-Lehmann (H-L) estimate. For missing primary efficacy data, the lowest rank was assigned for death within 16 weeks (excluding accidents), discontinuation because of clinical deterioration, and transplantation or atrial septostomy and for patients too ill to perform the 6-min walk test (6MWT). The mean placebo rank (for NP-ANCOVA) or value corresponding to the geometric mean relative change for the placebo group was assigned to patients who withdrew before any follow-up 6MWT. Finally, the last rank carried forward (for NP-ANCOVA) or the last observation carried forward (for summary statistics) was assigned to patients who withdrew prematurely or who did not perform the 6MWT because of any other reason not mentioned previously. Safety was evaluated by comparisons of adverse events, clinical laboratory parameters, ECG findings, and vital signs throughout the study. Descriptive statistics were used to describe all safety end points.

Results

Patient Demographics and Disposition

A total of 310 patients (oral treprostinil, 157; placebo, 153) were randomized and received the study drug between June 15, 2009, and July 22, 2011 (Fig 1). The mean age for the study population was 51 years (range, 18-76 years). Patients were primarily women (78%) with IPAH or FPAH (65%) and World Health Organization functional class III (73%) symptoms (Table 1). At baseline, 53 patients (17%) were receiving ERA therapy alone, 132 (43%) were receiving PDE-5I therapy alone, and 125 (40%) were receiving ERA and PDE-5I (Table 1).

Twenty-five patients (16%) treated with oral treprostinil and 15 (10%) with placebo prematurely discontinued the study drug for an adverse event (n = 18 [11%] and n = 5 [3%], respectively), clinical deterioration (n = 4 [3%] in both groups), and death (n = 2 [1%] and n = 3 [2%], respectively) (Fig 1). The mean ± SD maximum dose of oral treprostinil at week 16 was 3.1 ± 1.9 mg bid (range, 0.25-10.5 mg) compared with 6.1 ± 3.6 mg bid (range, 0.25-16.0 mg) in the placebo group (Table 2). After completion of the study, 122 patients (78%) receiving oral treprostinil and 138 (90%) receiving placebo enrolled in the open-label extension study.

Exercise Capacity

The H-L between-treatment median difference in 6MWD from baseline to week 16 was 10.0 m (95% CI, −2.0 to 22.0 m; $P = .089$) (Fig 2). Exploratory analyses of the 6MWD treatment effect were performed for subgroups defined by background therapy, disease etiology, and time since diagnosis (Fig 3). The placebo-corrected H-L estimates of change from baseline in 6MWD at week 16 by background therapy were as follows: ERA only (7.7 m; 95% CI, −29 to 48 m; $P = .739$), PDE-5I only (15.0 m; 95% CI, −1 to 29 m; $P = .054$), and both (4.0 m; 95% CI, −16 to 24 m; $P = .674$) (Fig 3A). The 6MWD treatment effect tended to be greater in patients with IPAH or FPAH (14.0 m, 95% CI, 0-28 m; $P = .058$) than in patients with PAH associated with connective tissue disease (−4.0 m; 95% CI, −25 to 20 m; $P = .724$) (Fig 3B). Finally, patients who received a more recent diagnosis (0-0.9 years) tended to demonstrate a larger 6MWD treatment effect (28.0 m; 95% CI, 1.0-59.0 m; $P = .059$) than patients with times since diagnosis of 0.9 to 1.7 years (10.0 m; 95% CI, −10.0 to 31.0 m; $P = .219$), 1.8 to 3.5 years (3.0 m; 95% CI, −23.0 to 28.0 m; $P = .990$), and 3.6 to 26.4 years (−2.0 m; 95% CI, −25.0 to 22.0 m; $P = .837$) (Fig 3C).

Secondary End Points

No significant differences were observed for any secondary efficacy end points ($P > .05$). Eleven patients (7%) receiving oral treprostinil and 10 (7%) receiving placebo experienced clinical worsening during the study (Table 3). The most common clinical worsening event across treatment groups was death, with six deaths (4%) in the treprostinil group and four (3%) in the placebo group.

Safety

The most common adverse events reported for the oral treprostinil group were headache (71%), diarrhea (55%), nausea (46%), flushing (35%), and jaw pain (25%) (Table 4). The most common prostacyclin adverse events resulting in oral treprostinil discontinuation were headache (6%), nausea (3%), vomiting (2%), and diarrhea (2%). More patients in the oral treprostinil group prematurely discontinued the study drug because of headache (6%) compared with the placebo group (0%). Twenty-three patients (15%) in

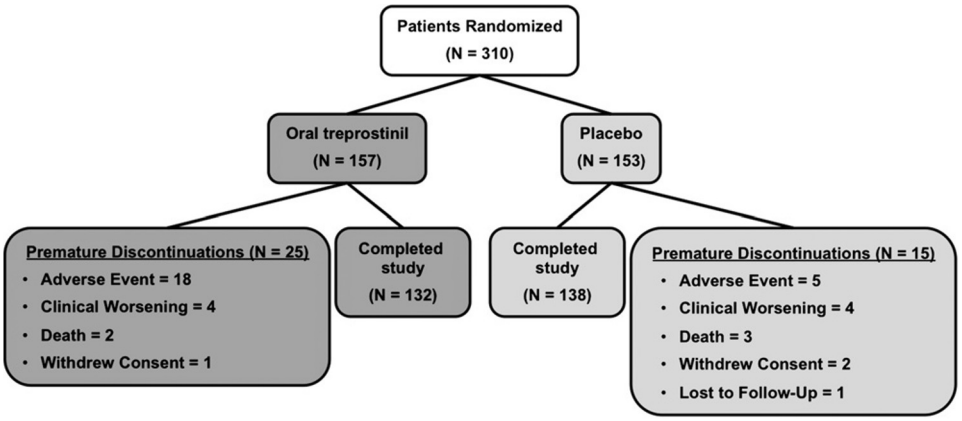

FIGURE 1. Patient flow diagram. A total of 310 patients were randomized to treatment with oral treprostinil (n = 157) or placebo (n = 153). Twenty-five patients receiving oral treprostinil and 15 receiving placebo prematurely discontinued the study drug during the 16-week study period.

both the oral treprostinil group and the placebo group experienced at least one serious adverse event. The most common serious adverse events for patients in the oral treprostinil group were right ventricular failure (3%), dyspnea (3%), lower respiratory tract infection (2%), and pulmonary hypertension (1%). Ten patients died during the 16-week study (oral treprostinil, 6 [4%]; placebo, 4 [3%]). Three deaths within the oral treprostinil group were considered possibly attributable to the study drug, with one event each of severe lung infection or respiratory failure, sudden death, and progression of disease. There were no significant treatment-related changes in physical examination findings or clinical laboratory parameters, including blood chemistry levels, hematology, or urinalysis, between groups during the 16-week study period.

Table 1—*Baseline Patient Demographics*

Parameter	Oral Treprostinil (n = 157)	Placebo (n = 153)
Age, y	51.5 (18-76)	50.4 (20-75)
Female	119 (76)	122 (80)
PAH etiology		
IPAH/FPAH	104 (66)	99 (65)
APAH		
CTD	48 (31)	49 (32)
CHD	3 (2)	1 (<1)
HIV	2 (1)	4 (3)
WHO functional class		
I	0 (0)	0 (0)
II	43 (27)	37 (24)
III	110 (71)	115 (76)
IV	3 (2)	0 (0)
6MWD, m	329.4 ± 69.2	336.8 ± 63.5
NT-proBNP, pg/mL	1,324.8 ± 1,617.0	1,604.7 ± 2,375.1
Background therapy		
PDE-5I	67 (43)	65 (42)
ERA	25 (16)	28 (18)
PDE-5I + ERA	65 (41)	60 (39)
Years since PAH diagnosis	2.6 ± 2.6	3.3 ± 4.1

Data are mean ± SD or No. (%). 6MWD = 6-min walk distance; APAH = associated pulmonary arterial hypertension; CHD = congenital heart disease; CTD = connective tissue disease; ERA = endothelin receptor antagonist; FPAH = familial pulmonary arterial hypertension; IPAH = idiopathic pulmonary arterial hypertension; NT-proBNP = N-terminal pro-brain natriuretic peptide; PAH = pulmonary arterial hypertension; PDE-5I = phosphodiesterase type 5 inhibitor; WHO = World Health Organization.

DISCUSSION

Sixteen weeks of oral treprostinil in combination with stable background therapy of ERA, PDE-5I, or both failed to improve exercise capacity in patients with PAH. There were no significant improvements in secondary end points. Although adverse events were common with oral treprostinil, it was well tolerated by most patients; the most frequent side effects were consistent with prostacyclin therapy.

For the primary end point, the change in 6MWD from baseline to week 16 was 10 m; this was not statistically significant. In FREEDOM-C and studies with other prostacyclin analogs, it appeared that there could be synergy between oral treprostinil and background PDE-5I therapy.[8,11,13,14] Although patients receiving oral treprostinil combined with background PDE-5I therapy experienced approximately twice the 6MWD treatment effect (15.0 m) as those receiving background ERA therapy (7.7 m), it cannot be proven that this finding represents true synergy. This potential effect was not demonstrated in patients receiving both ERA and PDE-5I background therapy (4.0 m). The complexities of administering three concurrent oral therapies may have perhaps limited optimal study drug dosing. It is interesting that the 6MWD treatment effect tended to be greater in patients receiving a more recent diagnosis (28 m for patients with PAH for 0-0.9 years) than in patients with a greater disease duration (−2 m for ≥ 3.6 years PAH duration). It is possible that these data reflect a survivor effect, with

Table 2—*Overview of Study Drug Dosing*

Study Visit[a]	Dose Achieved, mg bid	
	Oral Treprostinil	Placebo
Week 4 (152/152)	1.7 ± 0.9	2.3 ± 1.1
Week 8 (145/151)	2.5 ± 1.5	3.9 ± 2.1
Week 12 (141/143)	3.0 ± 1.8	5.7 ± 3.2
Week 16 (134/140)	3.1 ± 1.9	6.1 ± 3.6

Data are presented as mean ± SD.
[a]No. patients receiving oral treprostinil/placebo.

favorable responders to their current PAH therapy having less room for response to additional therapies. The patients who received intensive PAH-specific treatment for a longer period may simply be less responsive to the addition of new therapy. This concept is supported by findings that the overall 6MWD treatment effect tends to be smaller in combination trials than in monotherapy trials in treatment-naive patients.[8,15-19] A ceiling effect for 6MWD treatment response is another potential explanation.

In FREEDOM-C, oral treprostinil 1.0 mg bid was associated with poor tolerability and a relatively high rate of discontinuations related to adverse events, leading to the development of 0.25- and 0.5-mg tablets during the course of the study. For the overall FREEDOM-C study population, 25 patients (14%) receiving oral treprostinil discontinued because of adverse events. Of note, none of the patients in this group who had access to all dosage strengths (0.25-, 0.5-, and 1.0-mg tablets) at the time of randomization discontinued treatment because of an adverse event compared with patients with only access to higher-strength tablets at randomization (0.5 and 1 mg, 12%; 1 mg, 25%).[11] For FREEDOM-M, the rate of discontinuation because of adverse events was also lower for patients receiving oral treprostinil with access to 0.25-mg tablets compared with the overall study population (4% vs 10%, respectively).[12] For the current study, 18 patients (11%) receiving oral treprostinil discontinued the study drug because of adverse events.

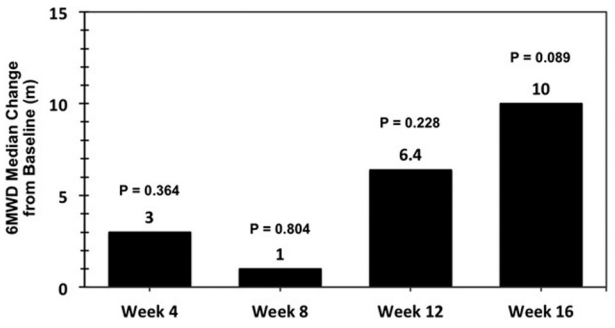

FIGURE 2. Change in 6MWD. For week 16, there was a median treatment effect of 10.0 m ($P = .089$). Data are presented as placebo-corrected Hodges-Lehmann between-treatment median differences. 6MWD = 6-min walk distance.

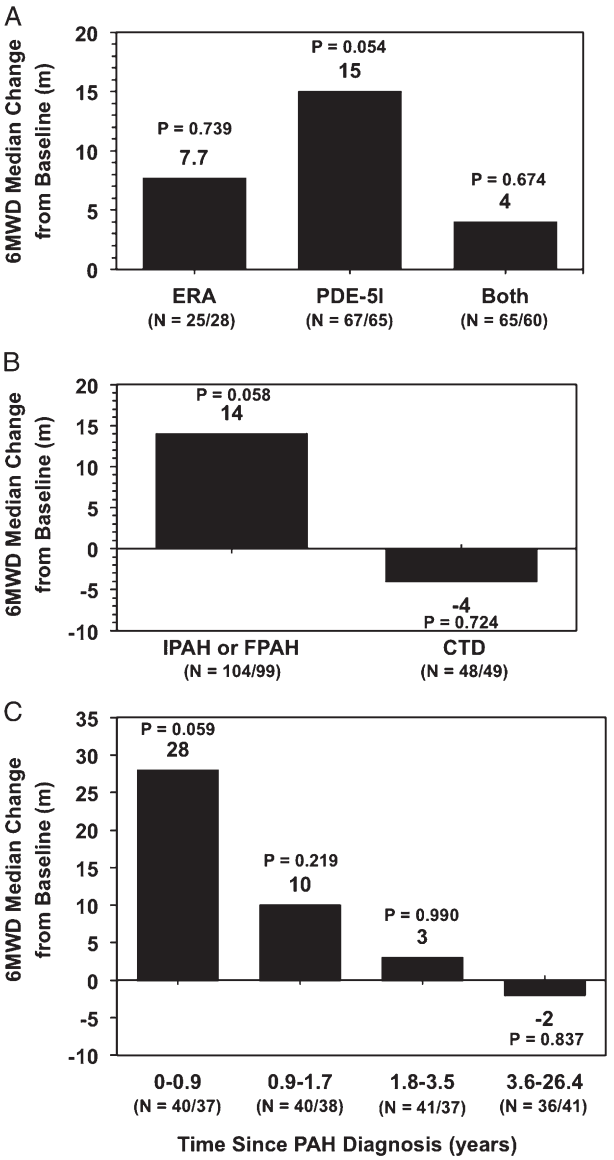

FIGURE 3. A-C, 6MWD covariates. Data are presented as the Hodges-Lehmann median estimate of treatment effect for change in 6MWD at week 16 by background ERA, PDE-5I, or both (A); PAH etiology (B); and time since PAH diagnosis (C). The sample size is presented for oral treprostinil/placebo for each covariate. CTD = connective tissue disease; ERA = endothelin receptor antagonist; FPAH = familial pulmonary arterial hypertension; IPAH = idiopathic pulmonary arterial hypertension; PAH = pulmonary arterial hypertension; PDE-5I = phosphodiesterase type 5 inhibitor. See Figure 2 legend for expansion of other abbreviation.

Given that all patients were initiated on the lower strength oral treprostinil 0.25 mg, it is unknown why there appeared to be a relatively higher rate of discontinuation because of adverse events in this study compared with equivalent starting dose populations in FREEDOM-C or FREEDOM-M, although differences in patient population and sample size limit direct comparisons.

The adverse event profile observed in this study was consistent with prostacyclin therapy and that seen

Table 3—*Summary of Clinical Worsening*

Category	Oral Treprostinil (n = 157)	Placebo (n = 153)
No clinical worsening	146 (93)	143 (93)
Clinical worsening	11 (7)	10 (7)
Death	6 (4)	4 (3)
Hospitalization for right-sided heart failure	4 (3)	2 (1)
≥ 20% decrease in 6MWD and additional therapy	1 (< 1)	3 (2)
Added parenteral prostacyclin	0 (0)	1 (< 1)

Data are presented as No. (%). See Table 1 legend for expansion of abbreviation.

in FREEDOM-M and FREEDOM-C.[6-8,11,12] There was no evidence of any new adverse events associated with oral treprostinil administration in combination with ERA and PDE-5I. Overall, although the adverse event profiles for oral treprostinil monotherapy compared with combination therapy with ERA, PDE-5I, or both appeared similar, the incidence of adverse events was perhaps slightly higher in the two combination studies compared with FREEDOM-M.[11,12] Additionally, the final mean dose of oral treprostinil achieved in FREEDOM-M (3.4 ± 1.9 mg bid at week 12) was slightly higher than that achieved in the current study at either week 12 (3.0 ± 1.8 mg) or week 16 (3.1 ± 1.9 mg). Together, these data suggest that slower titration of oral treprostinil may be required when administered in combination with ERA and PDE-5I.

The present study had several limitations. It is feasible that the relatively short duration of the trial limited the dose of oral treprostinil that was achieved, making it potentially difficult to demonstrate a statistically significant treatment effect. Thus, the results of this study together with those of FREEDOM-C and FREEDOM-M suggest that the appropriate clinical evaluation of oral treprostinil in combination with background ERA and PDE-5I therapy may require a longer trial to allow for doses to reach higher levels that might result in better efficacy. In addition, with a high percentage of patients receiving dual background therapy, the ability of a third agent to improve exercise capacity may be difficult in this time frame.

Table 4—*Adverse Events That Occurred in ≥ 10% of Patients Receiving Oral Treprostinil*

Adverse Event	Oral Treprostinil (n = 157)	Placebo (n = 153)
Any event	157 (100)[a]	136 (89)
Headache	112 (71)[a]	61 (40)
Diarrhea	87 (55)[a]	38 (25)
Nausea	73 (46)[a]	34 (22)
Flushing	55 (35)[a]	16 (10)
Pain in jaw	39 (25)[a]	10 (7)
Vomiting	33 (21)[a]	16 (10)
Dizziness	30 (19)[a]	15 (10)
Pain in extremity	27 (17)[a]	11 (7)
Dyspnea	25 (16)[a]	10 (7)
Fatigue	23 (15)	16 (10)
Myalgia	18 (11)	10 (7)
Upper RTI	17 (11)	13 (8)
Edema peripheral	17 (11)	10 (7)

Data are presented as No. (%). RTI = respiratory tract infection.
[a]$P < .05$ for oral treprostinil vs placebo.

Conclusions

Sixteen weeks of oral treprostinil therapy did not significantly improve 6MWD in patients with PAH receiving background therapy of ERA, PDE-5I, or both. Oral treprostinil therapy in combination with ERA and PDE-5I therapy appeared to be safe. Although side effects were common, they were tolerated by most patients. Additional studies of longer duration would be required to fully evaluate the clinical benefit of oral treprostinil therapy at higher doses in combination with ERA or PDE-5I background therapy.

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Dr Tapson: contributed to the study design; data collection, analysis, and interpretation; and drafting, critical review, and final approval of the manuscript.
Dr Jing: contributed to the data collection, analysis, and interpretation and critical review and final approval of the manuscript.
Dr Xu: contributed to the data collection, analysis, and interpretation and critical review and final approval of the manuscript.
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Additional information: The e-Table can be found in the "Supplemental Materials" area of the online article.

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