
Article:
Lachant, D., Raina, A., Krishnan, M. et al. (2026) Efficacy and safety of oral treprostinil in patients with pulmonary arterial hypertension on background monotherapy or dual therapy. Advances in Therapy. ISSN: 0741-238X

https://doi.org/10.1007/s12325-026-03497-4

Adv Ther
https://doi.org/10.1007/s12325-026-03497-4

ORIGINAL RESEARCH

Efficacy and Safety of Oral Treprostinil in Patients with Pulmonary Arterial Hypertension on Background Monotherapy or Dual Therapy

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Received: December 9, 2025 / Accepted: January 8, 2026

ABSTRACT

***Introduction*:** Pulmonary arterial hypertension (PAH) is a progressive, often fatal disease characterized by an elevation in pulmonary arterial pressure and pulmonary vascular resistance (PVR). Oral treprostinil is indicated for the treatment of PAH and has been shown to delay disease progression and to improve exercise capacity.

***Methods*:** The purpose of this report is to examine and summarize the data on the use of oral treprostinil in patients already on dual therapy with an endothelin receptor antagonist (ERA) and phosphodiesterase type-5 inhibitor (PDE-5i), using data from the FREEDOM-C study, FREEDOM-C2 study, and a retrospective chart review.

***Results*:** In this analysis, background monotherapy versus dual therapy did not have an impact

Prior Presentation: Portions of the data in this analysis were presented as posters at the European Society of Cardiology Congress, Barcelona, Spain (August 26–29, 2022) and the European Respiratory Society International Congress, Barcelona, Spain (September 4–6, 2022).

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Published online: 02 February 2026

on clinical parameters (6-min walk distance). Additionally, the number of background therapies did not have an impact on the dose of oral treprostinil achieved at week 16 or measures typically used to assess clinical efficacy in patients with PAH (change in 6MWD at week 16 and NT-proBNP).
Conclusion: Oral treprostinil is a safe and efficacious treatment option and has been shown to further improve clinical parameters and risk status in patients with PAH on background dual therapy.
Trial registry: ClinicalTrials.gov identifier, NCT00325442 and NCT00887978.

Keywords: Pulmonary hypertension; Treprostinil; Prostacyclin; REVEAL Lite 2; FREEDOM-C; FREEDOM-C2; Retrospective chart review

Key Summary Points

Why carry out this study?
Pulmonary arterial hypertension (PAH) is a progressive, often fatal disease characterized by an elevation in pulmonary arterial pressure and pulmonary vascular resistance (PVR). Oral treprostinil is indicated for the treatment of PAH and has been shown to delay disease progression and to improve exercise capacity.
Though often prescribed concurrently, limited guidance exists on the use of oral treprostinil with a combination of an ERA and PDE-5i.
The purpose of this report is to examine and summarize the data on the use of oral treprostinil in patients already on dual therapy with an ERA and PDE-5i, using data from the FREEDOM-C study, FREEDOM-C2 study, and a retrospective chart review.
What was learned from this study?
In this analysis, background monotherapy versus dual therapy did not have an impact on clinical parameters (6-min walk distance).
Additionally, the number of background therapies did not have an impact on the dose of oral treprostinil achieved at week 16 or measures typically used to assess clinical efficacy in patients with PAH (change in 6MWD at week 16 and NT-proBNP).
Oral treprostinil is a safe and efficacious treatment option and has been shown to further improve clinical parameters and risk status in patients with PAH on background dual therapy.

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INTRODUCTION

Pulmonary arterial hypertension (PAH) is a progressive disorder characterized by a vasculopathy that results in sustained elevation of pulmonary arterial pressure (PAP) and pulmonary vascular resistance (PVR), ultimately leading to right ventricular (RV) failure and death [1]. RV failure is the most common cause of death in patients with PAH, and RV function is a major determinant of morbidity and mortality in this patient population.

Oral treprostinil is indicated for the treatment of PAH and has been shown to delay disease progression and to improve exercise capacity [2]. The follow-up FREEDOM-EV study, associated substudies, and post hoc analyses have demonstrated the clinical benefits of oral treprostinil, including a reduction in the risk of clinical worsening, improvements in hemodynamic parameters, and improvements in risk status [3–5].

The AMBITION trial, which compared initial background monotherapy with [endothelin receptor agonist (ERA) ambrisentan and phosphodiesterase type 5 inhibitor (PDE-5i)] tadalafil alone vs combination in patients, showed initial dual therapy was superior [1]. Similarly, the combination of macitentan and tadalafil has shown safety and efficacy. In previous studies

and analyses, 24%–48% of participants were on dual background therapy (Table 1). Combination therapy with an ERA and PDE-5i has subsequently become the first-line standard of care for patients with PAH regardless of risk status with low and intermediate risk [1].

The FREEDOM studies were completed or ongoing before combination therapy became the standard of care, so most patients were on background monotherapy at the time of enrollment in the studies. Forty percent of the patients enrolled in FREEDOM-C2 were on dual therapy. Additionally, a panel of experts recommended the use of oral treprostinil in dual background patients as a third agent, and real-world evidence from claims databases shows frequent use of oral treprostinil in patients with PAH on dual background therapy [6–9].

The purpose of this report is to examine and summarize the data on the use of oral treprostinil in patients already on dual therapy with an ERA and PDE-5i. This is a novel analysis of data from the randomized, placebo-controlled FREEDOM-C and FREEDOM-C2 trials, which compare the efficacy and safety of oral treprostinil between participants on background monotherapy versus dual therapy. Additionally, real-world data from a recent retrospective chart review were used to observe longitudinal changes in risk status for patients with PAH taking oral treprostinil on background therapy at baseline.

METHODS

FREEDOM-C and FREEDOM-C2 Analysis of Background Monotherapy versus Dual Therapy

FREEDOM-C (clinicaltrials.gov identifier: NCT00325442) and FREEDOM-C2 (NCT00887978) were both randomized, placebo-controlled, double-blinded, international, multicenter studies investigating the use of oral treprostinil in participants on background monotherapy or dual therapy [10, 11]. Trial protocols were approved by the institutional review board at each participating site. Trials were conducted in accordance with Good Clinical Practice guidelines, and all participants provided written informed consent to participate.

The primary endpoint of FREEDOM-C and FREEDOM-C2 was change in 6-min walk distance (6MWD) at week 16 compared with baseline. A previous publication combined FREEDOM-C and FREEDOM-C2 and found a statistically significant treatment effect and oral treprostinil dose-dependent response but did not stratify analyses between background monotherapy and dual therapy participants [12]. Here, data from FREEDOM-C and FREEDOM-C2 were combined and stratified by background therapy to assess the treatment effect in both cohorts (Fig. 1A).

Participants ($n=331$) who received oral treprostinil in FREEDOM-C and FREEDOM-C2 were grouped into oral treprostinil dose tertiles based on their dose at week 16 [low-dose ≤ 2 mg twice a day (BID), mid-dose > 2 mg to ≤ 3.5 mg BID, and high-dose > 3.5 mg BID] and were stratified by background therapy. Participants were grouped into tertiles as a means of evenly binning results for comparison purposes. Participants given placebo ($n=329$) were classified as a separate dose group of 0 mg and were stratified by background therapy. Baseline characteristics of these populations are reported in Table 2.

Median (IQR) changes in 6MWD from baseline to weeks 4, 8, 12, and 16 were analyzed for background monotherapy and dual therapy participants. Percent change in 6MWD from baseline to week 16 was plotted against dose at week 16. No data imputation was implemented.

Exposure-response analyses were conducted using a multivariate linear regression model to assess the relationship between oral treprostinil dose at week 16 and the percent change in 6MWD from baseline to week 16, adjusting for the number of background PAH therapies. Comparisons of changes in 6MWD at week 16 between background monotherapy and dual therapy within each dose group were performed using a two-sample *t*-test or nonparametric Wilcoxon rank-sum test. Comparisons of dose groups within each background therapy category were performed by nonparametric Kruskal-Wallis test and Dunn's test for pairwise comparisons of 6MWD change at week 16.

Table 1 Patients treated with oral treprostinil on background dual therapy in completed and ongoing clinical trials

Study	Description of study	Duration of study	Primary endpoints	Population	Total number of participants	Number of participants on dual background therapy	Citation
FREEDOM-C [10]	International, multicenter, randomized, double-blind, placebo-controlled, safety and efficacy study of oral treprostinil in combination with an ERA and/or a PDE-5i	16 weeks	Change in 6MWD at week 16	Prostacyclin-naïve patients with PAH on stable background PAH therapy	$N = 350$	$N = 156$ (45%) at baseline	Tapson et al., 2012
FREEDOM-C2 [11]	International, multicenter, randomized, double-blind, placebo-controlled, safety and efficacy study of oral treprostinil in combination with an ERA and/or a PDE-5i	16 weeks	Change in 6MWD at week 16	Prostacyclin-naïve patients with PAH	$N = 310$	$N = 125$ (40%) at baseline	Tapson et al., 2013

Table 1 continued

Study	Description of study	Duration of study	Primary endpoints	Population	Total number of participants	Number of participants on dual background therapy	Citation
FREEDOM-EXT [3]	International, multicenter, open-label extension study (participants formerly in FREEDOM-M, FREEDOM-C, FREEDOM-C2, and Phase 2 studies)	Open-label extension	Time to first clinical worsening event	Patients with PAH	*N* = 894	*N* = 251 (28%) at baseline	White et al., 2020
TDE-PH-205 [23]	Multicenter, open-label, tolerability and safety study of adult participants with stable PAH who transitioned from continuous IV/SC treprostinil to oral treprostinil	24 weeks	6MWD, hemodynamic variables, quality of life, and treatment satisfaction	Hemodynamically stable patients with PAH transitioning to parenteral treprostinil	*N* = 33	*N* = 9 (27%) at baseline	Chakinala et al., 2017

Table 1 continued

Study	Description of study	Duration of study	Primary endpoints	Population	Total number of participants	Number of participants on dual background therapy	Citation
EXPEDITE [20, 21]	Multicenter, open-label, uncontrolled, Phase 4 study of SC/IV treprostinil induction followed by oral treprostinil optimization in participants with PAH	16 weeks	Total daily dose of oral treprostinil at week 16	Prostacyclin-naïve patients with PAH undergoing rapid induction	*N* = 29	*N* = 12 (41%) at baseline	Kingrey et al., 2023 Miller et al., 2023
FREEDOM-EV OLE [24]	International, multicenter, open-label extension study of oral treprostinil in those who participated in FREEDOM-EV	Open-label extension	6MWD, WHO FC, NT-proBNP	Participants who experienced a CWE during FREEDOM-EV or closure of original study	*N* = 212	*N* = 50 (24%) added therapy	Elwing et al., 2022
ADAPT	Real-world registry of patients with PAH newly initiated on oral treprostinil	Up to 18 months	6MWD, WHO FC, AEs, titration and dosing schedules, quality of life	Real-world patients receiving commercial oral treprostinil	*N* = 181	*N* = 86 (48%) at baseline	Data on file

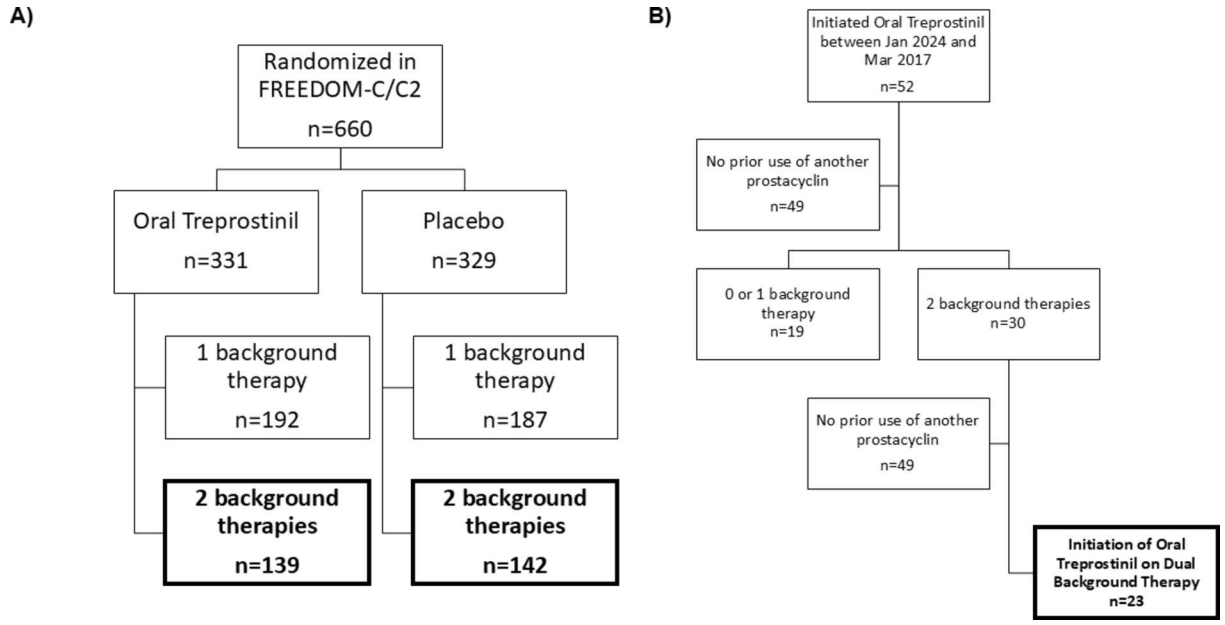

Fig. 1 Patient disposition. **A** Combined FREEDOM-C and FREEDOM-C2 analysis. **B** Retrospective chart review analysis

The Jonckheere-Terpstra test was used to assess the linear trend for 6MWD improvement with higher doses of oral treprostinil.

Participants were separated into subgroups by background therapy and change in 6MWD using 30 meters as a threshold. The percentage of participants between the two groups was calculated for weeks 4, 8, 12, and 16. Mean total daily dose was recorded for each of the subgroups.

Adverse events (AEs) were reported between treatment groups and were stratified by number of background therapies. All statistical calculations were completed using SAS version 9.4 or higher (Cary, NC).

Retrospective Chart Review of Dual Background Patients with PAH

A multisite, double-blind retrospective chart review of patients with PAH treated in the US was conducted among a sample of 32 PAH-treating physicians. Eligible sites treated at least 15 patients with PAH during the index period between January 2014 to March 2017.

Patients were included in the study if they met diagnostic criteria of PAH in the 2015 ESC/ERS guidelines: [mean pulmonary arterial pressure (mPAP)] ≥ 25 mmHg, pulmonary arterial wedge pressure (PAWP) ≤ 15 mmHg, PVR > 3 Wood units, began at least one FDA-approved PAH treatment between January 2014 and March 2017, were ≥ 18 years of age at initial PAH diagnosis, had a N-terminal pro b-type natriuretic peptide test (NT-proBNP) or a brain natriuretic peptide test (BNP), had a World Health Organization Functional Class (WHO FC) assessment, and 6MWD assessments at baseline and at least one follow-up visit [13]. Patients were excluded if they had been enrolled in any PAH-related interventional clinical trial since the time of baseline assessments.

For this analysis, patients with any use of prostacyclin prior to time of baseline assessments were excluded. Patients with ongoing ERA and PDE-5i/soluble guanylate cyclase stimulator (sGC) dual background therapy prior to baseline visit and on the date of oral treprostinil initiation were identified (Fig. 1B). Baseline was defined as the most recent visit prior to oral treprostinil initiation. REVEAL Lite 2 and COMPERA 2.0 risk score calculators were used to evaluate risk categories at baseline, 0–6 months (0–6 months follow-up), and 6–12 months (6–12 months follow-up) after initiating oral treprostinil therapy [14, 15]. If patients had > 1

Table 2 Baseline characteristics of combined FREEDOM-C and FREEDOM-C2 analysis

Characteristics	Oral treprostinil ($n = 331$)		Placebo ($n = 329$)	
	Monotherapy ($n = 192$)	Dual therapy ($n = 139$)	Monotherapy ($n = 187$)	Dual therapy ($n = 142$)
Age, years, mean (SD)	51 (14)	51 (13)	50 (14)	50 (13)
Female, %	82	78	80	79
Race, %				
White	75	89	73	85
Asian	20	7	22	9
Black/African American	5	5	6	6
Etiology of PAH, %				
Idiopathic/heritable	62	71	67	65
Connective tissue	31	27	27	30
Congenital heart disease/HIV	7	2	6	6
Background PAH therapy, %				
ERA only	42	0	42	0
PDE-5i only	58	0	58	0
ERA and PDE-5i	0	100	0	100
Time since PAH diagnosis, years, mean (SD)	2.7 (3.9)	3.7 (3.3)	3.1 (4.1)	4.6 (4.2)
6MWD at baseline, meters, mean (SD)	339 (71)	338 (71)	346 (67)	336 (74)
WHO FC at baseline, %				
I	1	1	1	0
II	28	22	26	13
III	70	74	73	84
IV	1	4	1	3
NT-proBNP, pg/ml, median (IQR) (FREEDOM-C2 only)*	701 (239, 2308)	712 (327, 1540)	1,256 (208, 2777)	475 (140, 1331)

6MWD: 6-minute walk distance; BNP: brain natriuretic peptide; ERA: endothelin receptor antagonist; HIV: human immunodeficiency virus; IQR: interquartile range; NT-proBNP: N-terminal pro b-type natriuretic peptide; PAH: pulmonary arterial hypertension; PDE-5i: phosphodiesterase 5 inhibitors; SD: standard deviation; WHO FC: World Health Organization Functional Class

*In the oral treprostinil arm, there were 85 and 65 participants with available NT-proBNP levels on background monotherapy and dual therapy, respectively. In the placebo arm, 187 and 142 participants on background monotherapy and dual therapy had available NT-proBNP levels, respectively

visit during the 0–6-month follow-up or 6–12-month follow-up periods, the latest available value for each component was utilized. Patients with a visit but missing components of the REVEAL Lite 2 were assigned a value of zero for that component. For COMPERA 2.0, patient visits with any missing components (6MWD, FC, NT-proBNP/BNP) were excluded from analyses in that time period.

Ethical Approval

Trial protocols were approved by the institutional review board at each participating site. Trials were conducted in accordance with Good Clinical Practice guidelines, and all participants provided written informed consent to participate.

RESULTS

FREEDOM-C and FREEDOM-C2 Analysis of Background Monotherapy versus Dual Therapy

Baseline demographics for the combined FREEDOM-C and FREEDOM-C2 populations are shown in Table 2, stratified by background monotherapy or dual therapy. In general, patient characteristics were similar between the groups. Patients were predominantly white and female, and most patients displayed WHO FC III symptoms. The mean age was 51 years old in the oral treprostinil cohort and 50 years old in the placebo cohort. Patients in the dual background group had a longer time since PAH diagnosis than patients in the background monotherapy group.

After week 16, the median (IQR) drug dose was 2.8 (1.8, 4.0) mg BID for patients receiving background monotherapy and 2.5 (1.5, 4.0) mg BID for patients receiving dual background therapy. In oral treprostinil-treated groups of the analysis, there was a median (IQR) 6MWD change from baseline to week 16 of 16 (−8, 47) m and 14 (−16, 58) meters for patients taking background monotherapy and dual therapy, respectively. There were no statistically significant differences in these 6MWD changes comparing the background monotherapy and dual therapy groups ($p = 0.85$).

After further stratification of patients on oral treprostinil by dose tertiles, 6MWD improved steadily in patients tolerating higher doses regardless of the number of background therapies (Fig. 2). There were no significant differences in these positive 6MWD changes for any dose group at any time point (Fig. 3A, week 16 shown), suggesting that the derived benefit in 6MWD is similar for background monotherapy and dual therapy patients. There was a significant increase in 6MWD for the high-dose groups compared with the placebo for both background monotherapy and dual therapy patients (Fig. 3A).

Exposure-response analysis found a dose-dependent increase in percent change in 6MWD from baseline to week 16 corresponding to oral treprostinil dose at week 16 for both background monotherapy and dual therapy patients (Fig. 3B). Positive monotonic trends in 6MWD improvements with increasing oral treprostinil doses at week 16 were observed for background monotherapy patients (one-sided p-value = 0.0002) and dual therapy patients (one-sided p-value = 0.0242) (Fig. 3B). Exposure-response analyses found no significant interaction between the number of background PAH therapies and the last oral treprostinil dose achieved ($p = 0.69$).

In the background monotherapy, the percentage of participants with a change in 6MWD > 30 meters increased from 28% at week 4 to 46% at week 16. The mean total daily dose was 7.1 mg within this subgroup (Fig. 4A). Similarly, the percentage of participants on dual background therapy and a change in 6MWD > 30 meters increased from 26% at week 4 to 41% at week 16. The mean total daily dose for this subgroup was 7.0 mg at week 16 (Fig. 4B).

Risk status improved from baseline to follow-up in the FREEDOM-C2 group, as assessed by REVEAL Lite 2 and COMPERA 2.0 (Fig. 5). At baseline, 45% of patients were classified as high risk by REVEAL Lite 2 (Fig. 5A). The percentage of patients considered high risk decreased in subsequent follow-up visits to 36% and 33% at week 8 and week 16, respectively. The percentage of

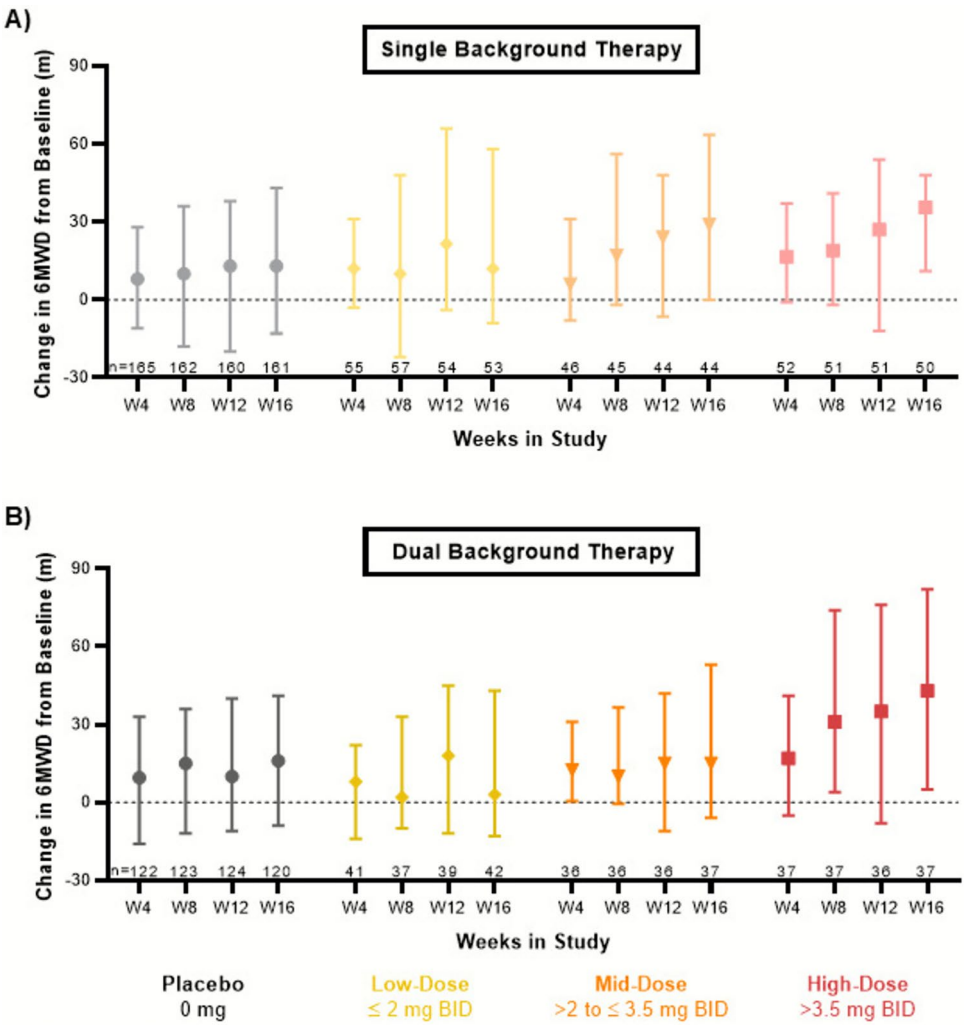

Fig. 2 Change in 6MWD from baseline to week 4, 8, 12, and 16 in the combined FREEDOM-C and FREEDOM-C2 analysis. **A** Change in 6MWD among patients on single background therapy, stratified by dose at week 16. **B** Change in 6MWD among patients on dual background therapy, stratified by dose at week 16

patients classified as low and intermediate risk increased from 30 to 39% and 25% to 28% after 16 weeks, respectively (Fig. 5A).

At baseline, 52% of patients were classified as intermediate-high risk by COMPERA 2.0 (Fig. 5B), which decreased to 30% by week 16. In general, there was improvement in risk status from baseline to week 8 and week 16. The percentage of patients considered low risk and intermediate-low risk increased from 8% to 19% and 40% to 46% after 16 weeks, respectively. Of note, no patients were considered high risk at baseline according to COMPERA 2.0. However, four patients at week 8 and five patients at week 16 were considered high risk (Fig. 5B). REVEAL Lite 2 and COMPERA 2 scores are not available for participants in the FREEDOM-C study.

AEs were more common in the oral treprostinil cohort compared with the placebo cohort (Table 3). Typical prostacyclin-related AEs in the oral treprostinil cohort were similar between background monotherapy and dual therapy patients, with dual therapy patients

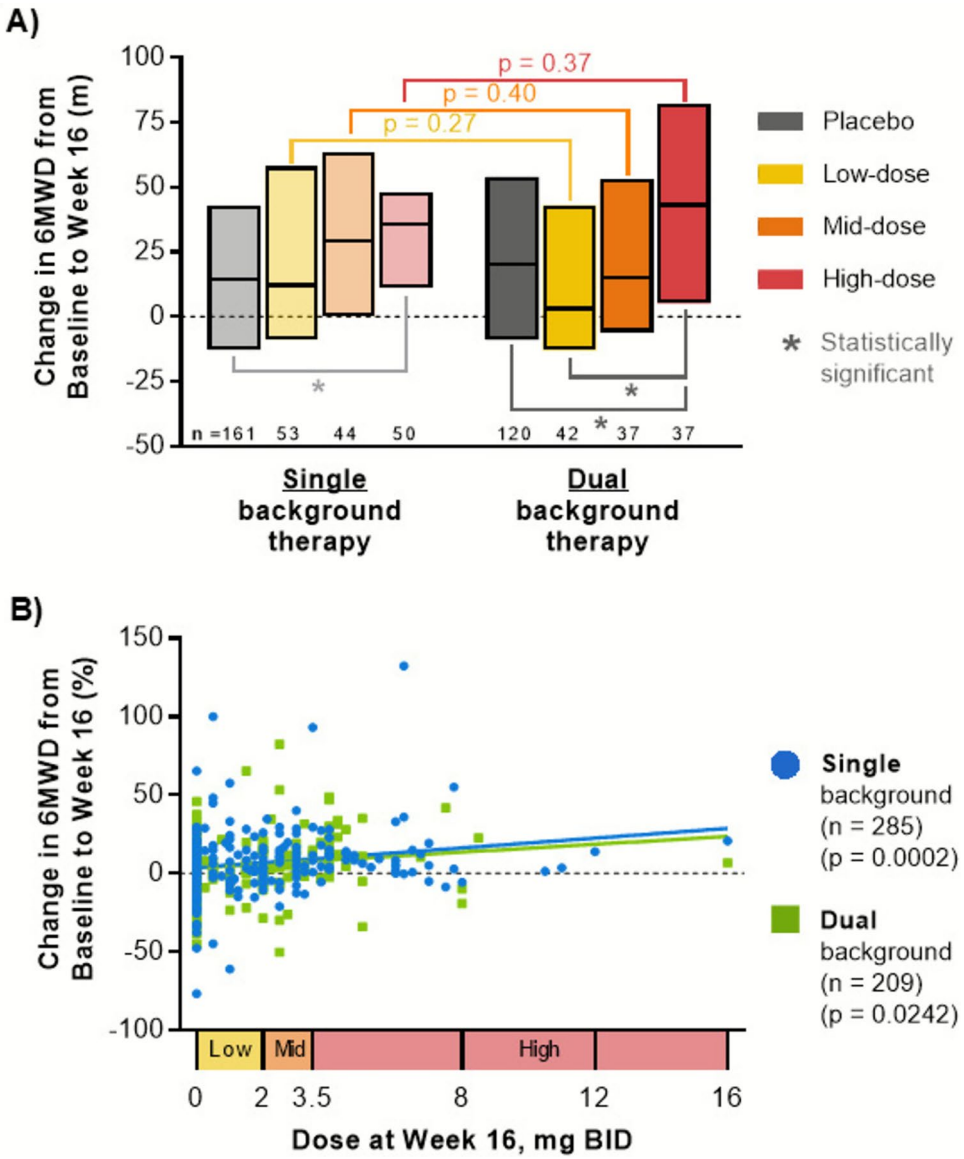

Fig. 3 Change in 6MWD from baseline to week 16 in the combined FREEDOM-C and FREEDOM-C2 analysis. **A** Comparison of single vs. dual background therapy within each dose group, with *p*-values determined by a two-sample *t*-test or nonparametric Wilcoxon rank-sum test. Comparison of dose groups within each background therapy category, with statistical significance determined by nonparametric Kruskal-Wallis test and Dunn's test for pairwise comparisons of 6MWD change at week 16. Data are presented as median and IQR. **B** Relationship between dose and percent change in 6MWD for single and dual background therapy with one-sided *p*-values testing for linear trend by Jonckheere-Terpstra

experiencing slightly more AEs (Table 3) than background monotherapy patients. The percentage of patients experiencing prostacyclin-related AEs is consistent with previously published oral treprostinil studies.

Retrospective Chart Review of Background Dual Therapy Patients with PAH

Forty-two patients starting oral treprostinil as their latest treatment between January 2014

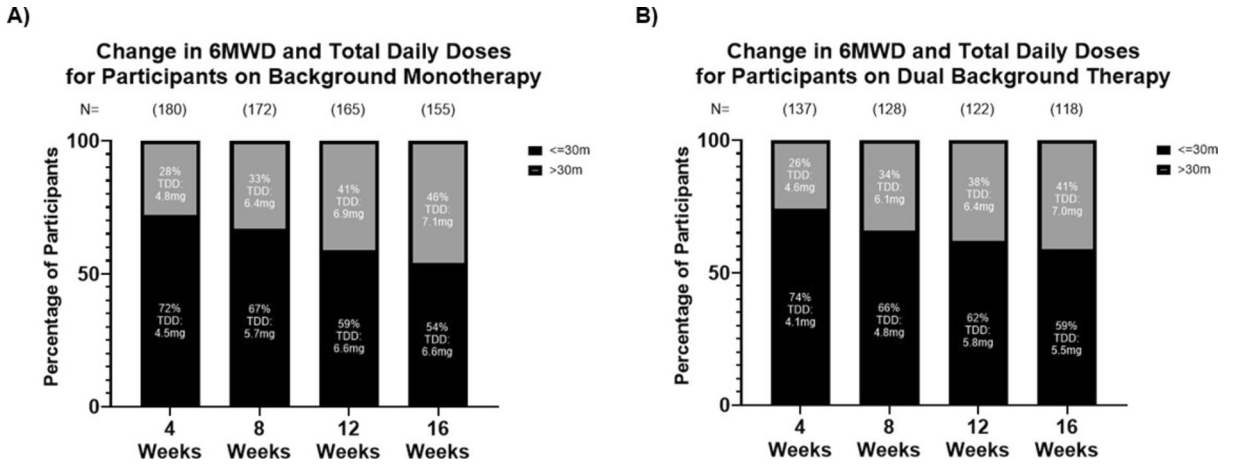

Fig. 4 Total daily doses stratified by a change in 6MWD of ≤ 30 meters or > 30 meters in the combined FREEDOM-C and FREEDOM-C2 studies. **A** Background monotherapy. **B** Dual background therapy

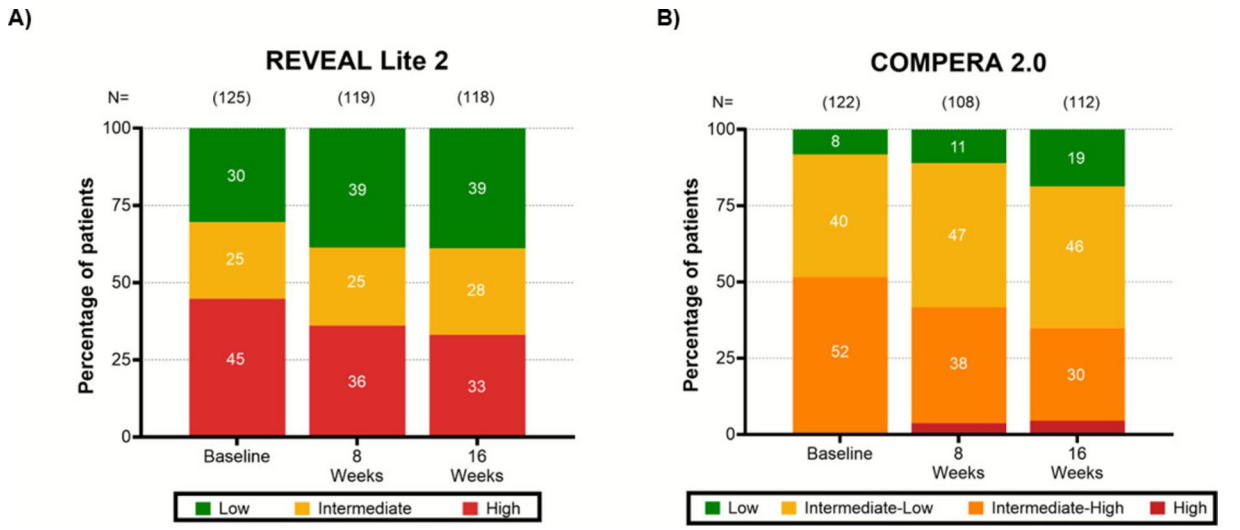

Fig. 5 Changes in risk stratification over 16 weeks in the FREEDOM-C2 studies for patients on dual background therapy. **A** REVEAL Lite 2 risk stratification. **B** COMPERA 2.0 risk stratification

and March 2017 were identified. Of these, 23 patients were on background dual PAH therapy at the time of oral treprostinil initiation, and 19 patients were on background monotherapy or no background PAH therapy. This analysis included only the subset of patients on background dual therapy at the time of oral treprostinil initiation. Baseline characteristics of patients administered background dual therapy are described in Table 4. These patients were more advanced in their disease state than the FREEDOM-C and FREEDOM-C2 populations: median time since PAH diagnosis was approximately 6 years, mean (SD) 6MWD was 141 (50) meters, and most patients were characterized as WHO FC III (Table 4).

Risk status, as assessed by REVEAL Lite 2 and COMPERA 2.0, improved from baseline to follow-up (Fig. 6). At baseline, 87% of patients were classified as high risk by REVEAL Lite

Table 3 Adverse events in the oral treprostinil and placebo groups stratified by the number of background PAH therapies from combined FREEDOM-C and FREEDOM-C2 analysis

Preferred term *n* (%)	Oral treprostinil (*n* = 332)		Placebo (*n* = 328)	
	Monotherapy (*n* = 193)	Dual therapy (*n* = 139)	Monotherapy (*n* = 186)	Dual therapy (*n* = 142)
Diarrhea	107 (55)	86 (62)	52 (28)	33 (23)
Headache	151 (78)	111 (80)	75 (40)	50 (35)
Nausea	97 (50)	88 (63)	51 (27)	39 (27)
Vomiting	61 (32)	48 (35)	21 (11)	6 (4)
Pain in jaw	57 (30)	57 (41)	16 (9)	12 (8)
Flushing	73 (38)	66 (47)	27 (15)	15 (11)
Dizziness	43 (22)	17 (12)	34 (18)	7 (5)

2 (Fig. 6A), with a mean (SD) REVEAL Lite 2 score of 7.9 (0.8). At subsequent follow-up visits, the percentage of patients considered high risk decreased, while the percentage of patients in the intermediate-risk strata increased. In the 0–6 months and 6–12 months after oral treprostinil initiation, 59% and 68% of patients improved risk strata, respectively. The mean (SD) REVEAL Lite 2 risk score of this population decreased to 7.0 (1.1) and 6.5 (1.1) at 0–6 months and 6–12 months, respectively, indicating a shift from a high-risk status at baseline to an intermediate risk.

At baseline, 96% of patients were classified as intermediate-high risk by COMPERA 2.0 (Fig. 6B). Consistent with the REVEAL Lite 2 changes, there was a general improvement in risk status from baseline to 0 to 6 months to 6 to 12 months. A total of 67% of patients improved COMPERA 2.0 risk strata by 0 to 6 months, and 88% of patients improved risk strata by 6 to 12 months. Drivers of these risk status shifts were improvements in 6MWD and WHO FC. Mean (SD) baseline 6MWD was 141 (50) meters, increasing to 166 (52) and 206 (50) from 0 to 6 months and 6 to 12 months, respectively. At baseline, two (9%) patients were WHO FC II, with all other patients classified as WHO FC III. At 0 to 6 months, 13 (59%) were WHO FC II, and at 6 to 12 months, 19 (86%) were WHO FC II; all other patients were WHO FC III.

DISCUSSION

Clinician use of oral treprostinil in patients on background dual therapy has been largely driven by treatment guidelines suggesting initial use with an ERA and PDE-5i. The 7th World Symposium on Pulmonary Hypertension recommended the addition of oral treprostinil as treatment escalation in patients already on combination oral therapy who are at intermediate-low risk as determined by the COMPERA 2.0 risk score calculator. However, data on the clinical outcomes in patients receiving oral treprostinil on a background dual therapy have been limited.

There are no known mechanistic reasons for drug-drug interactions that would suggest oral treprostinil would not be efficacious or safe when taken with an ERA and PDE-5i. Clinical consensus recommends oral treprostinil with background dual therapy in low- and intermediate-risk patients. These patients have relatively stable disease and allow adequate time to titrate therapy to achieve a low-risk status. Oral treprostinil is also appropriate and should be considered for patients who refuse or are unable to manage parenteral, subcutaneous, or inhaled prostacyclin class therapy [16, 17]. These novel analyses demonstrate that patients derive similar benefits from oral treprostinil regardless of the number of background therapies.

Table 4 Baseline characteristics of patients included in the retrospective chart review

Characteristic	Background dual therapy (*n* = 23)
Age, years, mean (SD)	55 (10)
Female, *n* (%)	14 (60.9)
Etiology of PAH, *n* (%)	
Idiopathic/heritable/familial	10 (44)
Connective tissue	4 (17)
Portal hypertension	2 (9)
Congenital heart disease	1 (4)
HIV	3 (13)
Other[b]	3 (13)
Background PAH therapy, %	
None	0
ERA only	0
PDE-5i only	0
ERA and PDE-5i	23 (100)
Time since PAH diagnosis, months, median, years (IQR)	6.4 (6.1–7.98)
6MWD at baseline, meters, mean (SD)	141 (50)
WHO FC at baseline, n (%)	
I	0
II	2 (9)
III	21 (91)
NT-proBNP, pg/ml, median (IQR)[b]	263.5 (145.5–361)
BNP, pg/ml, median (IQR)[b]	125 (110–135)

6MWD: 6-minute walk distance; BID: twice a day; BNP: brain natriuretic peptide; ERA: endothelin receptor antagonist; HIV, human immunodeficiency virus; IQR: interquartile range; NT-proBNP: N-terminal pro b-type natriuretic peptide; PAH: pulmonary arterial hypertension; PDE-5i: phosphodiesterase 5 inhibitors; SD: standard deviation; WHO FC: World Health Organization Functional Class

[a]Other PAH etiologies: schistosomiasis, sarcoidosis, sleep apnea

[b]There were four participants with available NT-proBNP levels and 19 patients with available BNP levels

In this analysis, background monotherapy versus dual therapy did not have an impact on clinical parameters (6MWD). The FREEDOM-C and FREEDOM-C2 groups were similar overall, and changes in 6MWD were consistent between groups. Increasing the dose of oral treprostinil does appear to provide a dose-response effect and confer greater clinical benefit. A previous study reported a statistically robust treatment effect of oral treprostinil on 6MWD for patients taking PAH background monotherapy or dual therapies [12]. This current analysis expands

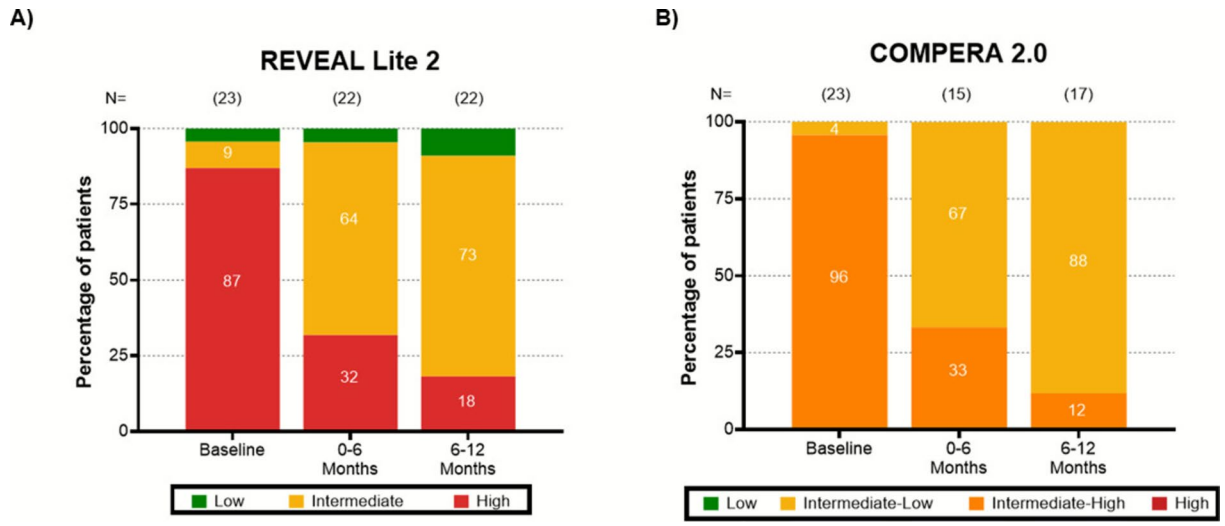

Fig. 6 Changes in risk stratification over 1 year in the retrospective chart review analysis for patients on dual background therapy. **A** REVEAL Lite 2 risk stratification. **B** COMPERA 2.0 risk stratification

and corroborates the results from this previous report in finding a treatment effect of oral treprostinil on 6MWD regardless of the number of background therapies. A lack of significant change in 6MWD was observed after selexipag in both the GRIPHON and TRACE studies [18, 19]. Despite treatment interventions investigated in these trials, patients did not experience a notable improvement in their exercise capacity as measured by the 6MWD endpoint. This finding should be considered when evaluating the overall impact of these therapies on patient functional status and quality of life.

Importantly, the number of background therapies did not have an impact on the dose of oral treprostinil achieved at week 16 or measures typically used to assess clinical efficacy in patients with PAH (change in 6MWD at week 16 and NT-proBNP). Additionally, typical prostacyclin-related AEs were similar between background monotherapy and dual therapy groups, suggesting similar tolerability profiles between the two groups. In an era of many treatment options for the management of PAH, careful shared decision making between patients and healthcare professionals should be considered. When combining multiple treatment options, AEs may arise and can be appropriately managed. There are potential benefits with each additional treatment, but shared-decision making is needed to balance the risks and benefits. Provider familiarity is needed to help manage symptoms appropriately, especially with dose titration. How much uncontrolled AE management with BID dosing influenced 6MWD results is not known. The EXPEDITE study showed that starting with parenteral treprostinil first may be an easier way to manage AE side effects while achieving a therapeutic dose [20, 21].

Increased drug exposure may increase impact on risk status. In the FREEDOM-C and FREEDOM-C2 studies, participants saw improvements in risk over time with twice daily dosing. Three times daily dosing in the retrospective chart review demonstrated greater effects in risk reduction. It is possible that higher doses may result in greater risk modification and clinical benefits, as seen in the EXPEDITE study and a post hoc analysis on the FREEDOM-EV study [20–22]. All data suggest that oral treprostinil in patients on dual background therapy decreases risk, with effects more pronounced in higher doses, suggesting a drug exposure effect. Dose-response analysis in a chronic, progressive disease that changes in severity over time requires a definitive timepoint to analyze the outcomes. Varying follow-up time makes it difficult to conduct this analysis with a fully titratable medication with variable dosing over time.

From the chart review analysis, the addition of oral treprostinil to background dual therapy improved PAH clinical parameters and risk score classification, as calculated by REVEAL Lite 2 and COMPERA 2.0, within 6 months of initiation, with additional clinical benefit seen through 12 months. This analysis provides real-world use of oral treprostinil outside of clinical trials and includes different patient types that may have a higher risk status or a more advanced form of PAH. The retrospective chart review analysis had several limitations. Generalizability may be limited by the study design, small sample size, and potential recall and/or selection bias associated with the charts chosen and the data abstracted. Although sex differences are well described in PAH, sex-specific analyses were not performed in this study because of the limited male sample size. The populations analyzed in the studies were predominately female, which is reflective of the PAH population [1]. A larger and more sex-balanced cohort would be needed to explore potential sex-based differences in these outcomes. Functional class is subjective, and assessment is potentially subject to observer bias. Dosing was administered twice daily in this study, which was increased to three times a day in subsequent studies. It is possible that a higher dosing frequency in the present study might have resulted in improved efficacy. The retrospective chart review was initially used to analyze clinician gestalt versus risk calculator scores and their impact on subsequent treatment decisions; therefore, it was a special subpopulation. This may hinder generalizability and the sample size available.

CONCLUSION

Oral treprostinil represents a safe and effective therapeutic option for patients with pulmonary arterial hypertension receiving background dual therapy. In this study, patients who achieved higher doses demonstrated further improvements in 6MWD and risk status, supporting the importance of adequate dose optimization. The development of EXPEDITE titration strategies and three-times-daily dosing regimens has facilitated the attainment of higher doses and may enhance tolerability, allowing for greater clinical benefit. These findings underscore the role of dosing strategy in maximizing the therapeutic impact of oral treprostinil and support its use as part of a comprehensive, risk-based treatment approach in PAH.

ACKNOWLEDGEMENTS

The authors thank the participants in FREEDOM-C, FREEDOM-C2, and the retrospective chart review.

Medical Writing/Editorial Assistance. The authors thank Heather Gorby, PhD (Gorby Consulting, LLC) under contract with United Therapeutics for medical writing support.

Author Contributions. D. Lachant served as the academic lead for analysis and interpretation of the data. A. Raina, M. Krishnan, N. Sood, JA. Barbera, V. Balasubramanian, D. Kiely, and J. Elwing revised the manuscript. D. Lee and B. Wu provided support on data analyses. D. Lachant, S. Hwang, S. Seaman, and M. Broderick wrote the initial draft of the manuscript. S. Hwang and S. Seaman shared leadership responsibility with D. Lachant in the analysis and interpretation of data and early revisions of the manuscript. J. Elwing and M. Broderick helped with interpretation of the statistics and their inclusion in the manuscript and revised the manuscript throughout its development. All authors approved the decision to submit the manuscript for publication.

Funding. United Therapeutics Corporation supported this study and provided funding for the journal's Rapid Service and Open Access Fees.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of Interest. D. Lachant has received consulting fees from Merck and Jansen. The University of Rochester receives research funds from United Therapeutics. A. Raina is part of the governance of the ABIM cardiovascular disease board. M. Krishnan is on the speakers bureau for Liquidia and is on the scientific advisory board/consults for United Therapeutics, Johnson & Johnson, and Liquidia. N. Sood has received consulting fees from United Therapeutics, Gossamer, Merck, and Boehringer Ingelheim, as well as honoraria from Bayer for lectures, presentations, speakers bureaus, manuscript writing or educational events. The University of California-Davis receives research funds from United Therapeutics, Gossamer, Merck, Pulmovant, and Pfizer. V. Balasubramanian is on the speakers bureau for United Therapeutics, Merck, Liquidia, and Boehringer Ingelheim; conduct research with Gossamer, Mannkind; and is a consultant for United Therapeutics. JA. Barberà has received grants or contracts from Janssen-Cilag and Merck Sharp & Dome; consulting fees from Janssen, Cilag and Merck Sharp & Dome; honoraria from Janssen, Cilag, Merck Sharp & Dome, AOP Orphan, and Ferrer International; and support for attending meetings and/or travel from Janssen, Cilag, Merck Sharp & Dome, AOP Orphan. D.G. Kiely has received grants or contracts from Janssen Pharmaceuticals, National Institute of Health Research Sheffield Biomedical Research Centre, Ferrer, and United Therapeutics; consulting fees from Janssen Pharmaceuticals, Ferrer, Altavant, MSD, United Therapeutics, Liquidia, Gossamer Bio, and Apollo; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Janssen Pharmaceuticals, Ferrer, Altavant, MSD, and United Therapeutics; support for attending meetings and/or travel from Janssen, Ferrer, MSD, and United Therapeutics; and has participated on a safety monitoring board or advisory board for Janssen, MSD, and Liquidia. DGK is also leads the UK National Audit of Pulmonary Hypertension. D. Lee, B. Wu,, S. Hwang, S. Seaman, and M. Broderick are paid employees of United Therapeutics. J. Elwing consults for United Therapeutics, Gossamer Bio, Liquida, Merck, Janssen/Actelion/Johnson&Johnson, Insmed, and Pulmovant and has received research support from United Therapeutics, Gossamer Bio, Acceleron/Merck, Pharmosa/Liquidia, Lung LLC, Pulmovant. Inhibikase, Insmed, Novartis, and NS Pharma.

Ethical Approval. Trial protocols were approved by the institutional review board at each participating site. Trials were conducted in accordance with Good Clinical Practice guidelines, and all participants provided written informed consent to participate.

REFERENCES

1. Humbert M, Kovacs G, Hoeper MM, Badagliacca R, Berger RMF, Brida M, et al. ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J. 2022;43(38):3618–731.

2. Orenitram (package insert). 2023.

3. White RJ, Jerjes-Sanchez C, Bohns Meyer GM, Pulido T, Sepulveda P, Wang KY, et al. Combination Therapy with Oral Treprostinil for Pulmonary

Arterial Hypertension. A Double-Blind Placebo-controlled Clinical Trial. Am J Respir Crit Care Med. 2020;201(6):707–17.

4. Khan A, White RJ, Meyer G, Pulido Zamudio TR, Jerjes-Sanchez C, Johnson D, et al. Oral treprostinil improves pulmonary vascular compliance in pulmonary arterial hypertension. Respir Med. 2022;193:106744.

5. Benza RL, Gomberg-Maitland M, Farber HW, Vizza CD, Broderick M, Holdstock L, et al. Contemporary risk scores predict clinical worsening in pulmonary arterial hypertension - An analysis of FREEDOM-EV. J Heart Lung Transplant. 2022;41(11):1572–80.

6. Brewer J, Anguiano R, Awdish R, Coons J, Kimber A, Morrison A, et al., editors. (2021) An Expert Panel Delphi Consensus Statement on Appropriate Patient Selection and Management of Adverse Events in Patients Receiving Oral Treprostinil for the Treatment of Pulmonary Arterial Hypertension. ATS International Conference; Virtual.

7. Wu B, Morland K, Classi P, Sketch M, Nelsen A, Goyal R, et al., editors. (2021) Economic Burden of Patients with Pulmonary Arterial Hypertension Prior to Initiation of Treprostinil: A Retrospective Analysis of US Claims Data. American Thoracic Society; Virtual.

8. Dean BB, Saundankar V, Stafkey-Mailey D, Anguiano RH, Nelsen AC, Gordon K, et al. Medication adherence and healthcare costs among patients with pulmonary arterial hypertension treated with oral prostacyclins: a retrospective cohort study. Drugs. 2020;7(3):229–39.

9. Classi P, editor Outcomes and costs associated with oral treprostinil and selexipag one year into treatment: a U.S. claims database analysis in patients with pulmonary arterial hypertension. Chest; 2021.

10. Tapson VF, Torres F, Kermeen F, Keogh AM, Allen RP, Frantz RP, et al. Oral treprostinil for the treatment of pulmonary arterial hypertension in patients on background endothelin receptor antagonist and/or phosphodiesterase type 5 inhibitor therapy (the FREEDOM-C study): a randomized controlled trial. Chest. 2012;142(6):1383–90.

11. Tapson VF, Jing ZC, Xu KF, Pan L, Feldman J, Kiely DG, et al. 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. Chest. 2013;144(3):952–8.

12. White RJ, Rao Y. Novel analysis of the oral treprostinil combination therapy trial data. Am J Respir Crit Care Med. 2016;193(12):1434–6.

13. Galiè N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J. 2016;37(1):67–119.

14. Benza RL, Kanwar MK, Raina A, Scott JV, Zhao CL, Selej M, et al. Development and validation of an abridged version of the REVEAL 2.0 risk score calculator, REVEAL Lite 2, for use in patients with pulmonary arterial hypertension. Chest. 2021;159(1):337–46.

15. Hoeper MM, Pausch C, Olsson KM, Huscher D, Pittrow D, Grünig E, et al. COMPERA 2.0: a refined four-stratum risk assessment model for pulmonary arterial hypertension. Eur Respir J. 2022;60(1):2102311.

16. Rahaghi FF, Feldman JP, Allen RP, Tapson V, Safdar Z, Balasubramanian VP, et al. Recommendations for the use of oral treprostinil in clinical practice: a Delphi consensus project pulmonary circulation. Pulm Circ. 2017;7(1):167–74.

17. Brewer J, Wilson M, Coons JC, Schmit A, Whittenhall ME, Kimber A, et al. Practical management of oral treprostinil in patients with pulmonary arterial hypertension: lessons from ADAPT, EXPEDITE, and expert consensus. Respir Med. 2024;231:107734.

18. Sitbon O, Channick R, Chin KM, Frey A, Gaine S, Galiè N, et al. Selexipag for the treatment of pulmonary arterial hypertension. N Engl J Med. 2015;373(26):2522–33.

19. Howard LS, Rosenkranz S, Frantz RP, Hemnes AR, Pfister T, Hsu Schmitz SF, et al. Assessing daily life physical activity by actigraphy in pulmonary arterial hypertension: insights from the randomized controlled study with selexipag (TRACE). Chest. 2023;163(2):407–18.

20. Kingrey JF, Miller CE, Franco V, Smith JS, Zolty R, Oudiz RJ, et al. Implementing the EXPEDITE parenteral induction protocol: rapid parenteral treprostinil titration and transition to oral treprostinil. Pulm Circ. 2023;13(3):e12255.

21. Miller CE, Franco V, Smith JS, Balasubramanian V, Kingrey J, Zolty R, et al. Parenteral treprostinil induction for rapid attainment of therapeutic doses of oral treprostinil. Respir Med. 2023;218:107374.

22. White RJ, Grünig E, Jerjes-Sanchez D C, Bohns Meyer GM, Pulido T, Sepulveda P, et al. (2019) Dose-response relationship of oral treprostinil for secondary endpoints in the FREEDOM-EV study. PA5462.

23. Chakinala MM, Feldman JP, Rischard F, Mathier M, Broderick M, Leedom N, et al. Transition from parenteral to oral treprostinil in pulmonary arterial hypertension. J Heart Lung Transplant. 2017;36(2):193–201.

24. Elwing JM, F Rahaghi F, Hage A, Dv Vizza C, Grünig E, K Wang K, et al. Oral treprostinil as part of a triple-therapy regimen for pulmonary arterial hypertenion: analysis from the FREEDOM-EV open-label extension. Chest. 2022;162(4):A2363–4.