Original Research Article

Pulmonary Circulation

Long-term study of oral treprostinil to treat pulmonary arterial hypertension: dosing, tolerability, and pharmacokinetics

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Abstract

Oral treprostinil may be an option for low- and intermediate-risk patients with pulmonary arterial hypertension, a rare lung vascular disease. This open-label extension study collected data on participants who completed previously reported, placebo-controlled oral treprostinil studies. Eligible participants had completed the prospective parent studies and took increasing doses of oral treprostinil twice daily; some later transitioned to three times daily dosing. Investigators measured 6-minute walk distance at Month 12 as the sole efficacy measure but collected adverse events throughout the study. A single center measured pharmacokinetics in 13 subjects who changed dosing from twice daily to three times daily. Eight hundred and ninety-four participants enrolled and 71% completed one year of therapy, with a median total daily dose of 7 mg and a median 6-minute walk distance increase of 22 m (interquartile range, −14 to 67 m). Subjects achieving higher doses had larger increases in 6-minute walk distance; 42% of participants completed three years of therapy. Adverse events were typical for prostacyclin class therapy, but prostacyclin-type adverse events may have been better tolerated with three times daily dosing in 105 participants. In 13 participants transitioned to three times daily dosing with pharmacokinetic measurements before and after, trough drug levels were higher with three times daily dosing. Oral treprostinil is associated with modest but durable, dose-responsive effects on exercise tolerance for those who remained on therapy at one year in this prospective, uncontrolled study. Three times daily dosing was associated with higher trough levels and better tolerability. The recently completed Freedom-EV study will provide further insights into the utility of oral treprostinil (https://clinicaltrials.gov/show/NCT01560624).

Keywords

oral treprostinil, prostacyclin analogue, pulmonary arterial hypertension, 6-minute walk distance, dose–response

Date received: 18 February 2019; accepted: 7 July 2019

Pulmonary Circulation 2020; 10(4) 1–9
DOI: 10.1177/2045894019866335

Introduction

Pulmonary arterial hypertension (PAH) is a rare but progressive and often fatal lung vascular disease. Treatment options have expanded greatly in the past 20 years,[1] and the recently completed study of initial combination therapy[2] was an important step toward transforming PAH into a

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chronic but manageable disease. Parenteral epoprostenol was the first effective treatment in controlled studies,[3] and parenteral prostanoids are still favored for the highest risk patients.[4] Unfortunately, while parenteral treprostinil and epoprostenol are quite effective, the delivery systems are problematic. Intravenous therapy is associated with rare but important risks, e.g. bloodstream infection and thrombosis.[5,6] Subcutaneous treprostinil therapy usually causes site pain, which can be severe and require narcotic analgesics (8% discontinuation rate in registration study).[7,8] Fully implantable pumps offer a new and important, but still complex, treatment option.[9]

An effective, oral prostanoid has long been a goal of PAH drug development and might improve patient acceptance of prostacyclin class therapy. Immediate-release beraprost was the first oral prostanoid studied rigorously,[10] but it never achieved FDA or EMEA regulatory approval. Short-term studies of an oral, extended-release tablet formulation of treprostinil have been previously reported.[11–13] Most recently, selexipag, a novel prodrug whose metabolite activates the IP receptor, delayed a composite disease progression endpoint in a large, successful global registration study.[14]

While short-term studies for twice daily (BID) oral treprostinil were disappointing, more recent data suggest that the oral tablet administered three times daily (TID) can substitute for parenteral treprostinil in carefully selected patients.[15] Additionally, a post hoc, aggregate analysis of the two registration studies demonstrated a benefit regardless of the analytic strategy; there was also a clear dose–response for exercise tolerance.[16] Here, we report 12-month walk data in the prospective observation of 569 oral treprostinil research participants. We measured detailed adverse events (AEs) in a subset of participants who transitioned from BID to TID dosing with the hypothesis that TID drug dosing might be better tolerated than BID dosing.

Methods

Study design

The study (TDE-PH-304, FREEDOM-EXT, NCT01027949) was an open-label extension offering enrollment to eligible participants who completed Phase 2 (TDE-PH-202, NCT # 01104870; TDE-PH-203, NCT # 01477333; TDE-PH-205, NCT # 01588405) or Phase 3 studies (TDE-PH-301 (Freedom-C), NCT00325442; TDE-PH-308 (Freedom-C2), NCT00887978; or TDE-PH-302 (Freedom-M), NCT00325403) with oral treprostinil (Supplemental Table S1).[11–13] All study procedures were approved by an independent institutional review board before investigators obtained written informed consent from each participant. We collected data from 16 January 2007 to 1 September 2015. In order to make meaningful comparisons, the visit labeled "Baseline" was prior to oral treprostinil exposure; for those assigned to active drug, this was the first day of the parent study, and for those initially assigned placebo, Baseline was the final visit of the parent study. Study visits focused on dosing and safety were conducted at Months 6, 12, and yearly thereafter until subject discontinuation. Clinical laboratory parameters, study drug dosing, AEs, and concomitant PAH medications were assessed at each visit, but for efficacy, we measured 6-minute walk distance (6MWD; 3–6 h after previous dose) and Borg dyspnea score only at the Month 12 visit. No other assessments of treatment efficacy (functional class, brain natriuretic peptide) were measured, and 6MWD was not assessed at any other time points. Participants assigned active drug in the parent study continued titrating the dose; participants initially assigned placebo began oral treprostinil dosing in the extension study at 0.25 mg BID (every 12 ± 1 h). In March 2013 (seven years after study initiation), investigators learned that TID dosing was associated with better tolerability and higher doses;[15] hence, Amendment 5 allowed TID dosing. Additional information about AEs was collected for 105 participants who switched from BID to TID dosing under that Amendment. Investigator and subject impression of change were assessed for the eight most common prostacyclin-associated AEs four weeks after transition to TID dosing. Additionally, a single-center sub-study was conducted to evaluate PK and compare the AEs in 13 (of the total 105 participants) transitioning from BID to TID dosing. PK sampling occurred over a 12 h period during BID dosing and then over a 12 h period after transition to TID dosing (see Supplement). All studies were carried out in accordance with Good Clinical Practice Guidelines and the Declaration of Helsinki.

Statistical analysis

We summarized all data and present p-values for descriptive purposes only; we planned no formal hypothesis testing. Change in 6MWD is presented as median (interquartile range (IQR)). Those participants who discontinued prior to Month 12 were excluded from 6MWD analyses (observed case analysis). We assessed study discontinuation with a Kaplan–Meier curve. PK parameters were derived using noncompartmental methods and WinNonlin® Phoenix version 6.3 (Pharsight, St Louis, MO, see Supplement). We present geometric mean values for PK parameters and semi-log concentration–time curves.

Results

Subject disposition

Of 1112 subjects previously enrolled in qualifying oral treprostinil studies, 894 (80%) entered the open-label extension. As of 1 September 2015, 121 subjects outside the United States (US) were still using investigational oral treprostinil (US subjects desiring to continue drug began using commercial oral treprostinil (Orenitram®, United

Therapeutics, Research Triangle Park, NC)). Of 894 enrolled participants, 627 (70%) had dosing data at Month 12 (Fig. 1); however, change from Baseline in 6MWD results was only available for 569 participants. The most common reasons for study discontinuation prior to Month 12 are shown in Figure 1 and included AE (36%), death (21%), and progression of PAH (22%). Baseline subject characteristics are included in Table 1; the mean age was 48 ± 15 years, and participants were predominantly female (78%). Most subjects had idiopathic or heritable PAH (68%). The mean Baseline 6MWD was 351 ± 83 m, and mean time since diagnosis was 2.8 ± 4 years. At Baseline, 294 (33%) subjects were treatment-naïve, 349 (39%) were on a single background PAH therapy, and 251 (28%) were using combination endothelin receptor antagonist (ERA) and phosphodiesterase type 5 inhibitor (mostly but not exclusively bosentan + sildenafil) therapy.

Exposure

As of 1 September 2015, 894 subjects in the open-label study had taken oral treprostinil for a total of 2378 patient-years. Median exposure was 111 weeks (maximum 445 weeks). Drop-outs occurred early and continued throughout the observation, but 638 (71%), 498 (56%), and 375 (42%) participants were still taking drug at one, two, and three years, respectively (Fig. 2). For participants who continued in the study, average doses (divided BID) increased very modestly over time; the median total daily doses (TDD) were 7 mg (IQR, 4–10.5; n = 627), 8 mg (IQR, 4.5–12; n = 489), and 8.25 mg (IQR, 5–13; n = 369) at one, two, and three years, respectively. During the study, 367 (41%) subjects began at least one new PAH therapy.

Efficacy and survival

Overall median (IQR) change in 6MWD from Baseline to Month 12 was 22 (−14 to 67) meters; this was the observed case analysis in the 569 participants who completed Month 12 and had measures at Baseline and Month 12. Median (IQR) change in 6MWD from Baseline to Month 12 was 30 (−11 to 77) meters and 18 (−19 to 62) meters for subjects enrolled from the FREEDOM-M study and FREEDOM-C/C2 studies, respectively (Fig. 3(a)). At Month 12, 106 participants had initiated at least one new oral PAH therapy in addition to oral treprostinil, and 61 of these subjects are included in the 6MWD analysis. For those subjects who added one or more approved oral PAH therapies, median (IQR) change in 6MWD from Baseline to Month 12 was 10 (−32 to 45) meters as compared to 24 (−13 to 71) meters in

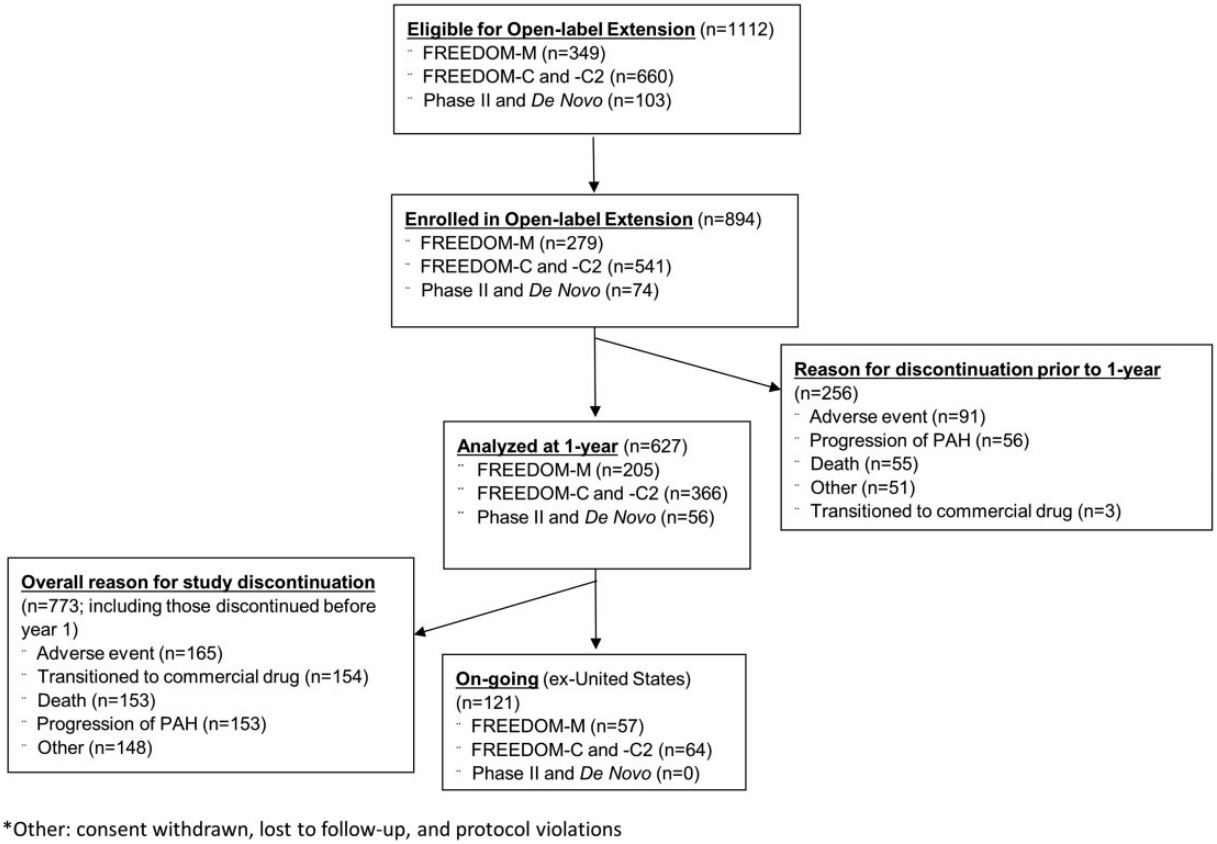


Fig. 1. CONSORT diagram depicting subject participation in the open-label extension. Two de novo subjects previously withdrawn from study FREEDOM-C due to drug supply shortage enrolled directly in the open-label extension.

Table 1. Baseline characteristics.

Characteristic	FREEDOM-M (n = 279)	FREEDOM-C and -C2 (n = 541)	Phase 2 and de novo (n = 74)	Overall (n = 894)
Age,[a] year (mean ± SD)	41 ± 14	50 ± 14	54 ± 14	48 ± 15
Female,[b] n (%)	202 (72%)	434 (80%)	58 (78%)	694 (78%)
Race,[c] %				
White	38%	77%	92%	66%
Asian	50%	15%	1%	25%
Black	3%	7%	4%	5%
Other	9%	2%	3%	4%
Continent, %				
North America	43%	55%	100%	55%
Asia and Israel	51%	15%	0%	25%
Europe	6%	21%	0%	15%
Australia	0%	8%	0%	5%
Etiology of PAH[d], %				
Idiopathic/Heritable	77%	66%	50%	68%
Collagen vascular disease	18%	28%	31%	25%
Other	6%	6%	16%	7%
Baseline 6MWD, m (mean ± SD)	340 ± 80	352 ± 80	389 ± 103	351 ± 83
Background PAH therapy, %				
None	98%	0%	27%	33%
ERA	0%	24%	11%	15%
PDE5-I	2%	33%	39%	24%
ERA + PDE5-I	0%	43%	23%	28%
Baseline WHO Functional Classification				
I	3%	<1%	8%	2%
II	42%	29%	35%	33%
III	56%	68%	4%	59%
IV	0%	2%	0%	1%
Missing	0%	<1%	53%	4%
Time since diagnosis, years (mean ± SD)	1.0 ± 2.9	3.7 ± 4.2	3.3 ± 3.7	2.8 ± 4.0
On-going participation, n (%)	57 (20%)	64 (12%)	0 (0%)	121 (14%)
Completed one year, n (%)	205 (73%)	366 (68%)	56 (76%)	627 (70%)
Deaths during study, n (%)	74 (27%)	86 (16%)	1 (1%)	161 (18%)
Discontinued for adverse event, n (%)	46 (16%)	112 (21%)	7 (9%)	165 (18%)

ERA: endothelin receptor antagonist; HIV: human immunodeficiency virus; PAH: pulmonary arterial hypertension; PDE5-I: phosphodiesterase type 5 inhibitor; SD: standard deviation; 6MWD: 6-minute walk distance.

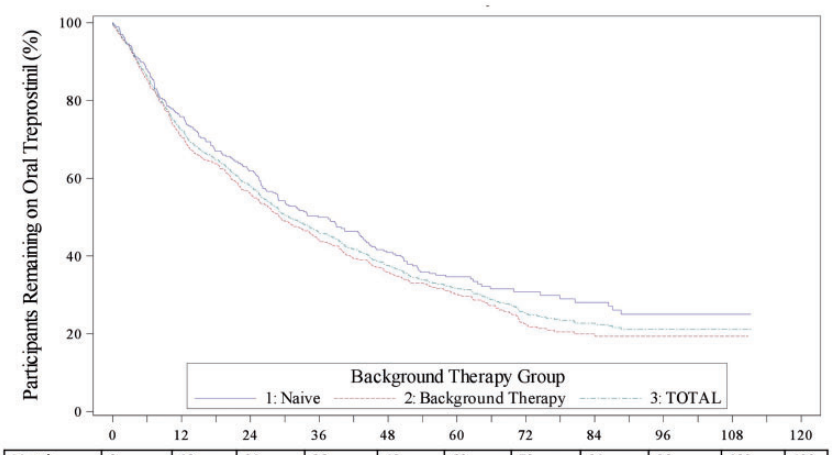
[a]Age was not available for two subjects previously enrolled in FREEDOM-C and -C2, and two subjects in Phase 2 and de novo studies.

[b]Sex was not available for two subjects previously enrolled in Phase 2 and de novo studies.

[c]Race data were not collected for two subjects in FREEDOM-M and two de novo subjects.

[d]PAH etiology was unavailable for two de novo subjects.

those whose background PAH therapy had not changed. The median (IQR) change in 6MWD from Baseline to Month 12 was 33 (−5 to 81) meters for those subjects assigned active drug in the parent study versus 9 (−28 to 47) meters for those assigned placebo (Fig. 3(b)). As a point of clarification, Baseline was designated as the first exposure to oral treprostinil, and visit windows were adjusted so that Month 12 was the same for all participants whether initially assigned placebo or active in the parent study. More frequent, early contact with participants to facilitate titration in the parent study may account for the small difference between the median (IQR) TDD in the two groups (active versus placebo), 7 (4.3–10.5) mg and 6.1 (3.5–9.5) mg, respectively. Median changes in 6MWD at Month 12 for dose tertiles 1 (≤5 mg daily), 2 (5 to ≤ 8.5 mg daily), and 3 (>8.5 mg daily) were 14 (−19 to 65; n = 203), 23 (−6 to 66;



Month	0	12	24	36	48	60	72	84	96	108	120
Naïve	294	223	180	139	112	70	37	30	14	3	0
Background Therapy	600	415	318	236	171	100	56	33	12	2	0
All	894	638	498	375	283	170	93	63	26	5	0

Fig. 2. Kaplan–Meier estimate of time to discontinuation of study in 894 oral treprostinil-treated PAH subjects. Subjects that discontinued due to initiation of commercial drug were censored. Naïve: subjects receiving oral treprostinil as initial monotherapy; Background Therapy: Sequential combination therapy with oral treprostinil in addition to ERA and/or phosphodiesterase-5 inhibitor. Treatment discontinuation tended to be more common ($p = 0.069$) for those beginning sequential combination therapy with oral treprostinil.

$n = 169$), and 31 (-17 to 75; $n = 191$) meters, respectively (Fig. 4). Borg dyspnea score did not change. Gabler et al.[17] have previously reported that a 42 m improvement in 6MWD "mediates" the protection from a clinical worsening event in a large patient level analysis of PAH registration trials. Overall, 220/569 participants with available Month 12 data achieved a 40 m improvement in walk; 83 of these were initially monotherapy trial participants while 115 were initial combination therapy participants. For the dosing tertiles, 71/203 (35%) achieved 40 m in the low dose tertile, 66/169 (39%) in the intermediate tertile, and 81/191 (42%) in the highest tertile.

Overall survival for subjects who remained in the study at one, two, and three years was 94% (confidence interval 92,95), 88% (85,90), and 82% (79, 85), respectively. At time of data lock, there were 161 (18%) reported deaths in the overall study population, with 85 (53% of deaths) attributed to disease progression. Investigators did not attribute any deaths to oral treprostinil. The death rates in Europe and the US (4.8 and 5.2 per 100 patient exposure years) were lower compared to the rest of the world (9.4).

BID to TID transition

All participants who completed Month 12 data collection were taking drug twice daily. Protocol Amendment 5 allowed participants to transition from BID to TID dosing. Most subjects reported "no change" in the top 8 most common prostacyclin-related AEs after transitioning to TID dosing; for those reporting a change, more than 80% reported that the core AEs of nausea, vomiting, diarrhea, and flushing were better after transition to TID. This group began at a mean TDD of 11.2 mg (divided BID), which was about the same four weeks later with doses divided TID. For 90 of these 105 participants who continued study participation an additional (median) 11 months, they increased to a mean TDD of 13.5 mg; for the remaining 15 participants, 8 transitioned back to BID dosing, 5 died or had PAH progression, and 2 began commercial therapy.

A single center collected PK data for 13 (of the 105) subjects before and after completing transition from BID to TID oral treprostinil, allowing up to 35 days for dose optimization on TID. Mean TDD at the first PK visit was 16 mg (on BID) compared to 20 mg at the second visit (on TID). Figure 5(a) represents the mean concentration–time profile for oral treprostinil used BID versus TID. Peak concentration (C_{max}) values were similar between the two dosing regimens (7.5 versus 7.4 ng/ml, respectively); however, trough concentration (C_{min}) values were significantly higher ($p = 0.03$, Figure 5(b)) with TID dosing. Similarly, the peak–trough fluctuation was substantially lower for TID as compared to BID dosing (143% versus 170%, respectively). The complete PK data set is available in the Supplement. Despite the increased TDD at the second visit (16 versus 20 mg daily), 12 of 13 subjects reported a net improvement of the eight most prevalent prostacyclin-related AEs. In addition, this small, single-center cohort had a median two years exposure to BID oral treprostinil at the time of transition to TID dosing; nonetheless, they quickly achieved a 23% increase in TDD before the repeat PK collection (within five weeks of the first PK collection).

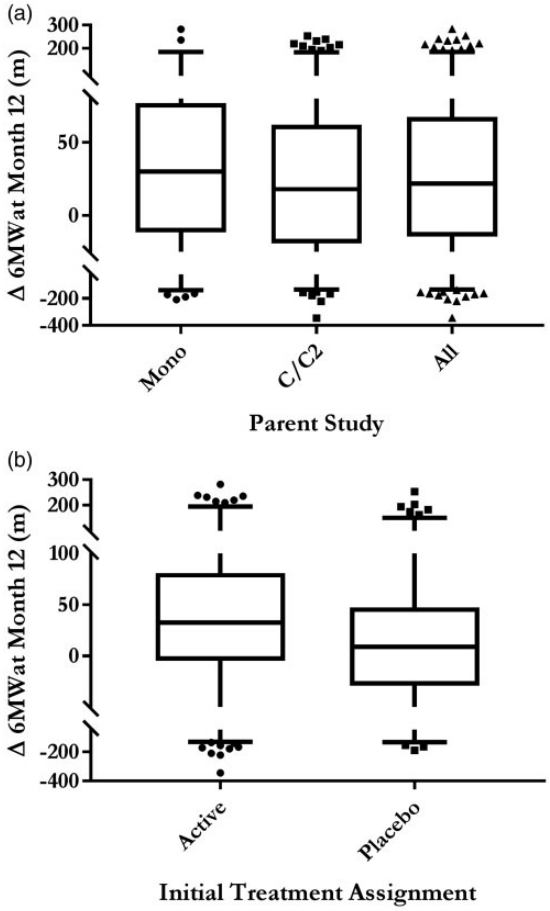


Fig. 3. (a) Box and whisker plot of the change in 6MWD for those initially participating in the Freedom-M study of initial monotherapy (n = 192) as compared to the Freedom-C and -C2 (n = 340) studies of sequential combination therapy. "All" (n = 569) also includes a small number of participants from other Phase 2 studies (see text) and (b) box and whisker plot of the change in 6MWD based on treatment assignment in parent study (active, n = 348 versus placebo, n = 221). Placebo assigned participants did not "catch up" on active therapy. Outliers by the method of Tukey are shown as individual symbols beyond whiskers.

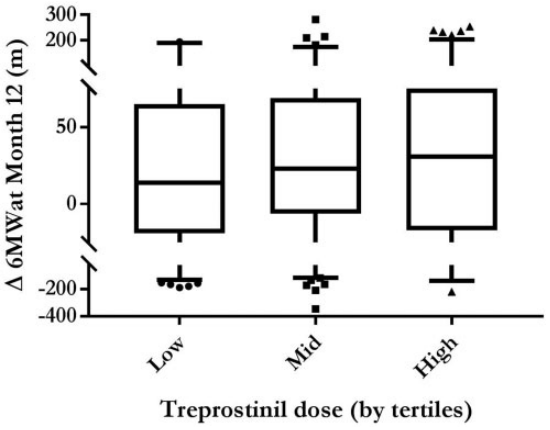


Fig. 4. Box and whisker plot of the change in 6MWD at one year. Dosing tertiles were determined by an unbiased division of subjects completing a 6-minute walk test at Month 12 into three groups of approximately equal size. The low tertile taking a TDD under or equal to 5 mg (n = 203), mid tertile taking TDD greater than 5 to less than or equal to 8.5 mg (n = 169), and high tertile taking TDD greater than 8.5 mg (n = 191). Median change in walk in the low tertile was 14 m compared with 31 m in the high tertile. Note that there are more negative outliers in the low and mid tertiles and more positive outliers in the high tertile. Outliers by the method of Tukey are shown as individual symbols beyond whiskers in both (a) and (b).

Table 2. Common adverse events occurring in subjects from time of first dose on active drug.

Event	N = 894 n (%)
Any event	890 (>99%)
Headache	696 (78%)
Diarrhea	591 (66%)
Nausea	504 (56%)
Flushing	412 (46%)
Vomiting	344 (38%)
Pain in jaw	311 (35%)
Pain in extremity	249 (28%)
Dizziness	242 (27%)
Upper respiratory tract infection	218 (24%)
Dyspnea	198 (22%)

AEs

As expected for a prostacyclin class therapy, treatment-emergent AEs were reported in more than 99% of the subjects enrolled (Table 2). The most frequent AEs included headache (78%), diarrhea (66%), nausea (56%), flushing (46%), vomiting (38%), and pain in the jaw (35%). The most frequent serious AEs were related to disease progression. Similar to the parenteral forms of treprostinil, no significant treatment-emergent trends in hematology or clinical chemistry were noted.

Discussion

This long, prospective data collection provides useful information about oral treprostinil as a treatment option. For those who remained on therapy with an observed walk, there appeared to be a small but sustained improvement in 6MWD from Baseline out to 12 months, regardless of background PAH-specific therapy. The present analysis supports the hypothesis that improvements in exercise tolerance are dose dependent (Fig. 4) and strengthens the basis for a TID dosing scheme by directly comparing BID and TID dosing. We did not observe new safety signals.

Continuous, parenterally delivered prostacyclin was the first effective treatment for PAH,[3] and parenteral prostanoids remain the standard for high-risk patients.[4] The initial

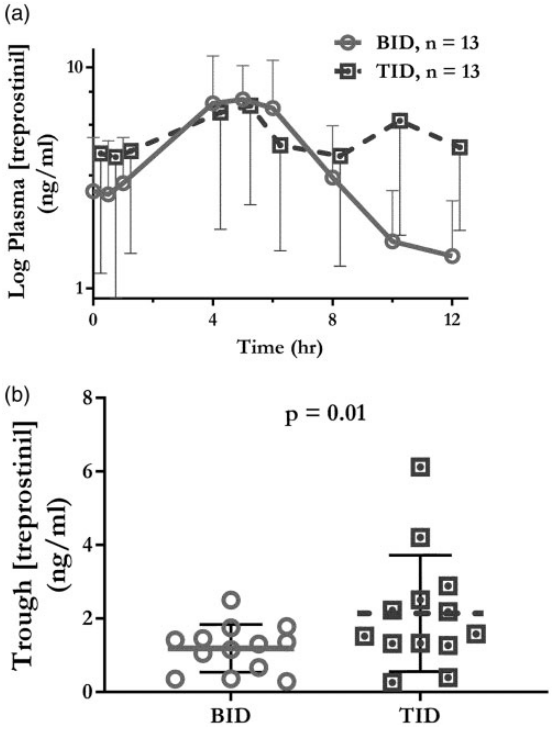


Fig. 5. (a) Log transformed mean (±SD) blood treprostinil concentration (n = 13) after the same participants took BID and TID oral treprostinil. Twelve-hour blood sampling for PK was completed during BID dosing (within 14 days prior to transitioning to TID dosing regimen) and during TID dosing (within 35 days from transition in subjects receiving a stable dose for at least 5 days). The mean morning dose prior to PK collection for BID and TID dosing regimens was 8.1 and 6.8 mg, respectively (e.g. 16 and 20 mg TDD, respectively) and (b) trough plasma concentrations rose from a mean of 1.2 ng/ml to a mean of 2.1 ng/ml (median 1.3 ng/ml versus 1.6 ng/ml). This was highly significant in a Wilcoxon matched pairs signed rank test (the conservative nonparametric analysis). BID: twice daily; TID: three times daily.

trial of oral treprostinil dosed BID demonstrated modest benefits in a 12-week study of exercise tolerance for treatment-naïve individuals.[13] Although uncontrolled and acknowledging the substantial attrition (29% at Month 12), the observed 30 m walk improvement at Month 12 is similar to that observed at Week 12, suggesting that clinically relevant benefits are maintained for those who can tolerate oral treprostinil.[18] This benefit was not attributable to other therapies; only 11% of participants with observed walks had started new PAH therapies, and they had lower 6MWDs (presumably because their disease had progressed to the point that treating investigators added additional therapy). Moreover, similar to a recently published post hoc analysis of the placebo-controlled, 16-week sequential combination data,[16] Figure 4 suggests the possibility of a dose–response in the 563 participants at Month 12 with an observed walk and dose. A reasonable proportion (39%) of these participants achieved the 40 m improvement previously associated with protection from clinical worsening.[17]

When participants used BID drug, doses were essentially unchanged between Year 2 and Year 3. This is similar to the recently published experience from Chin et al.,[19] except that those prostacyclin-experienced investigators achieved higher average TDD at two years than the global cohort reported here (9 mg at 12 months; 12 mg at 24 months). The presently reported 90 participants who switched to TID and had a follow-up visit increased their doses by an average of 27% over 11 months of observation. This is different than the individual site experience (n = 6) reported by Chin et al.,[19] for whom transition to TID dosing did not allow further dose titration. The present data and that of Chin et al.[19] agree that the drug was better tolerated with TID dosing (especially gastrointestinal AEs); it is not clear why the larger cohort reported here was able to further up-titrate oral treprostinil after the switch to TID, but it is worth noting that those six participants are included in the current report.

We have previously reported low trough serum treprostinil levels in PAH research participants using oral treprostinil BID;[15,20] the present data show that in a small cohort of individuals, TID dosing produced significant increases in average trough levels with smaller peak–trough fluctuations. We speculate that the more favorable AE profile (despite a higher TDD) and, for this group of participants, the ability to increase the TDD during a relatively short period of time is related to the increased trough and the reduced peak–trough fluctuations. The recently completed Freedom-EV study required TID dosing of oral treprostinil, and based upon the present data and the parenteral–oral transition study,[15] we recommend TID dosing carefully spaced around a 24 h clock (doses every 7–8 h). This recommendation was also made in a recent consensus process.[21]

Limitations

Any open-label observation is limited by the absence of blinding, and we have no control group. Attrition was high as compared to long-term prospective observations of oral ambrisentan therapy,[22] but lower than a similarly long observation of subcutaneous treprostinil—a drug that provides substantial benefit for those who can tolerate it.[23] Prostacyclin adverse effects can be more bothersome than those for other PAH therapies, and our observed degree of intolerance is probably not surprising. Our uncontrolled, unblinded, efficacy observations are therefore applicable only to those subjects who were able to tolerate drug over a prolonged time. For comparison, a similar rate of drug intolerance (14% of participants stopped drug because of an AE) was observed during the median 98 weeks of follow-up in the pivotal selexipag study (>90% of those participants reported an AE).[14]

We should have measured exercise tolerance at 6 months and at serial visits after 12 months. In addition, N-terminal pro-brain natriuretic peptide and WHO-functional class assessment would have been prognostically significant

adjuncts to exercise tolerance, and we should have measured these as well.

In summary, the data suggest that BID oral treprostinil provides sustained, dose-responsive benefits in exercise tolerance at 12 months for those who enrolled in the open-label study and remained on therapy (56% of those who initially entered the FREEDOM registration studies). Dose increases plateaued with BID dosing, but in participants who switched to TID, subsequent dose increases were possible. Attrition due to AE typical for prostacyclin class medication was ~13% in the initial short-term studies and continued during the open-label extension, but AE may be less intense with a TID dosing strategy.[21]

Acknowledgements

The authors would like to acknowledge all investigators and study coordinators that participated in the FREEDOM-EXT study.

Conflict of interest

RJW serves as a consultant and an investigator to United Therapeutics with all funds to the institution; KP, CJ-S, LP, AK, SS, and SB serve as investigators for United Therapeutics; RA and CDV serve as consultants and investigators for United Therapeutics; JF serves as a consultant, investigator, and speaker for United Therapeutics. KG and MB are employees of United Therapeutics.

Funding

The original studies were funded by United Therapeutics.

Ethical Approval

All study procedures were approved by an independent institutional review board before investigators obtained written informed consent from each participant.

Guarantor

RJW.

Contributorship

KG and MB assembled the data tables, drafted methods section, and responded to author queries for additional data; KP, RA, JF, CJ-S, LP, AK, CDV, SS, and SB collected data and offered critical feedback; RJW collected data, drafted manuscript, directed statistical analyses, made figures, and incorporated author feedback for final submission. The sponsor, United Therapeutics, and its employees aggregated the data from global sites and did all statistical analyses as planned in the protocol and subsequently directed by the authors. RJW, KG, and MB guarantee the integrity of the work as a whole.

Clinical trial registry

FREEDOM-EXT, NCT01027949 (https://clinicaltrials.gov/show/NCT01027949); A Pharmacokinetic Substudy of the TDE-PH-304 Protocol, NCT01934582 (https://clinicaltrials.gov/show/NCT01934582); FREEDOM-C, NCT00325442 (https://clinicaltrials.gov/show/NCT00325442); FREEDOM-C2, NCT00887978 (https://clinicaltrials.gov/show/NCT00887978); A Dose Response Study of UT-15C SR in Patients with Exercise-Induced Pulmonary Hypertension: TDE-PH-202 NCT01104870 (https://clinicaltrials.gov/show/NCT01104870); Addition of UT-15C SR to Pulmonary Arterial Hypertension Patients Currently Receiving Tyvaso, NCT01477333 (https://clinicaltrials.gov/show/NCT01477333); Remodulin to Oral Treprostinil TDE-PH-205, NCT01588405 (https://clinicaltrials.gov/show/NCT01588405); FREEDOM-M, NCT00325403 (https://clinicaltrials.gov/show/NCT00325403); FREEDOM-eV, NCT01560624 (https://clinicaltrials.gov/show/NCT01560624).

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Supplemental Material

Supplemental material for this article is available online.

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