Dose-Response Relationship of Oral Treprostinil for Secondary Endpoints in the FREEDOM-EV Study

RJ White, MD, PhD[1]; E Grünig, MD[2]; C Jerjes-Sanchez, MD, FCCP[3]; GM Bohns Meyer, MD[4]; T Pulido, MD[5]; P Sepulveda, MD[6]; KY Wang, MD[7]; CQ Deng, PhD[8]; R Grover, MD[8]; D Solum, PhD[8]; A Ousmanou, PharmD[8]; VF Tapson, MD, FCCP[9]

[1]University of Rochester Medical Center, Rochester, NY; [2]University Hospital Heidelberg, Heidelberg, Germany; [3]Unidad De Investigación Clinica en Medicina, Monterrey, Mexico; [4]Moinhos De Vento Hospital, Porto Alegre, Brazil; [5]Ignacio Chávez National Heart Institute, Mexico City, Mexico; [6]Pontificia Universidad Católica de Chile, Santiago, Chile;[7]Taichung Veterans General Hospital, Taichung, Taiwan; [8]United Therapeutics Corporation, Research Triangle Park, NC; [9]Cedar Sinai, Los Angeles, CA

BACKGROUND

- FREEDOM-EV was a global, event driven, placebo-controlled study; 690 participants with pulmonary arterial hypertension (PAH) were randomized (346 oral treprostinil, 344 placebo). All participants were on background oral monotherapy (endothelin receptor antagonist [ERA], phosphodiesterase type 5 inhibitor [PDE-5i], or soluble guanylate cyclase stimulator [sGC]). Dosing was individualized in 0.125-mg or 0.25-mg increments three times daily (TID) to a maximum allowable dose of 12 mg TID.
- Primary efficacy endpoint was time to the first adjudicated morbidity/mortality event (the composite of all-cause death, hospitalization due to PAH and/or right heart failure, initiation of inhaled or infused prostacyclin, disease progression, and unsatisfactory long-term clinical response).
- Oral treprostinil decreased the risk of adjudicated clinical worsening compared to placebo in FREEDOM-EV (HR 0.74; 95% CI 0.56,0.97; P=0.0391), a difference driven by a reduced incidence of disease progression with oral treprostinil.[1]
- Previously presented post-hoc analyses of treprostinil clinical data provide evidence of the treprostinil dose-response relationship; increased treprostinil dose is associated with improvements in 6-minute walk distance (6MWD), Borg dyspnea score, and hospitalization outcomes.[2,3,4] In the long-term, open-label FREEDOM-EXT study, dose-related effects on 6MWD were seen in those who remained on therapy at 1 year (N=569).[5]

OBJECTIVES

- This pre-specified analysis hypothesized that changes in N-terminal pro-brain natriuretic peptide (NT-proBNP), World Health Organization Functional Class (FC), Borg dyspnea score, and 6MWD would be dose-dependent, with those achieving ≥3mg TID having better functional outcomes at Week 24.

METHODS

- Results are compared for participants achieving an oral treprostinil dose <3 or ≥3 mg TID at Week 24 vs a common placebo group.
- Adverse events that had occurred by Week 24 were included.
- Missing data were imputed as previously described.

RESULTS

- Baseline characteristics were similar (Table 1). At Week 12, 34% of participants assigned to oral treprostinil reached ≥3 mg TID. By Week 24, 63% of participants assigned to oral treprostinil reached ≥3 mg TID. Median doses were 2.5 and 3.6 mg TID at Week 12 and 24, respectively.

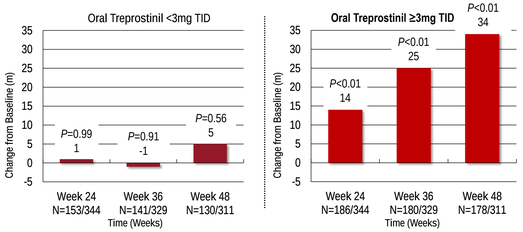
Table 1. Baseline Demographics by Dose Subgroup at Week 24

	Oral Treprostinil <3 mg TID N=160	Oral Treprostinil ≥3 mg TID N=186	Placebo N=344
Age at Randomization (years)			
n	160	186	344
Mean (SD)	47.8 (15.7)	43.7 (15.4)	44.8 (15.4)
Median	46.5	42	42
Age Category (years) – n (%)			
<65 years	128 (80%)	164 (88.2%)	294 (85.5%)
≥65 years	32 (20%)	22 (11.8%)	50 (14.5%)
Sex – n (%)			
Male	26 (16.3%)	45 (24.2%)	75 (21.8%)
Female	134 (83.8%)	141 (75.8%)	269 (78.2%)
Race – n (%)			
White	85 (53.1%)	102 (54.8%)	173 (50.3%)
Black or African American	3 (1.9%)	5 (2.7%)	13 (3.8%)
Asian	72 (45%)	78 (41.9%)	156 (45.3%)
Unknown	0	1 (0.5%)	2 (0.6%)
Weight at Baseline (kg)*			
Mean (SD)	67.78 (18.55)	64.59 (18.43)	68.86 (17.04)
Median	64.10	60.00	66.05
Height at Baseline (cm)*			
Mean (SD)	161.5 (8.7)	159.6 (9.6)	161.9 (8.1)
Median	160.0	159.0	162.0

*P<0.05; P-values are calculated using Kruskal-Wallis test for continuous variables.

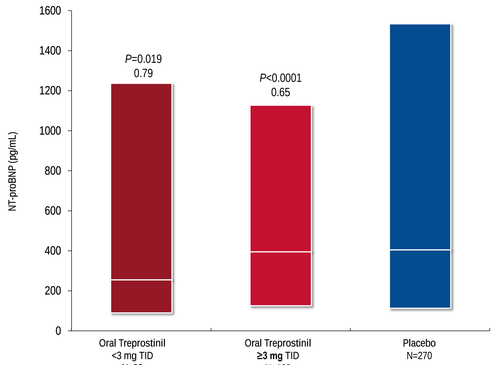
The higher dose group (≥3 mg TID group) had superior clinical responses when compared with the lower dose (<3mg TID) and placebo groups (Figures 1 to 4).

Figure 1. Change from Baseline in 6-Minute Walk Distance by Dose Subgroup at Week 24 (Hodges-Lehmann Placebo-corrected Estimates of Treatment Effect – Difference in Medians)



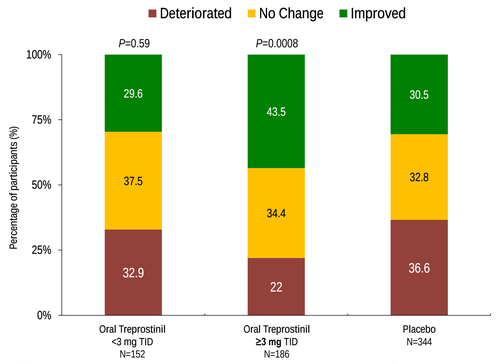
Note: for those participants who withdrew early due to death, were too ill to walk, or had no 6MWD measure due to clinical worsening event, the 6MWD is set to 0; for all other withdrawals without an assessment, LOCF is used to input. P-values are obtained from nonparametric ANCOVA adjusted for PAH background therapy and baseline 6MWD measurement. N shown are for oral treprostinil/placebo participants.

Figure 2. Change from Baseline in NT-proBNP (pg/mL) by Dose Subgroup at Week 24



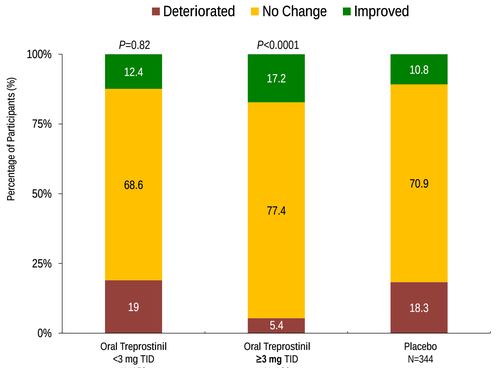
Note: Only participants with both baseline and Week 24 NT-proBNP measures are included. NT-proBNP measurements after the subject discontinued the study drug were excluded from the analyses. Each study drug dose sub-group is compared to the common placebo group. P-value and LSMean Difference are obtained from the analysis of covariance with the change from baseline in log-transformed data in NT-proBNP as the dependent variable, treatment as fixed effect, and log-transformed baseline NT-proBNP as a covariate.

Figure 3. Change from Baseline in Borg Dyspnea Score by Dose Subgroup at Week 24



Note: For those participants who withdrew early due to death, were too ill to walk, or had no Borg dyspnea measure due to clinical worsening event, the Borg score is set to worst score of 10; for all other withdrawal without Borg measurement, LOCF is used for imputation. Each study drug dose subgroup is compared to the common Placebo group. P-values are obtained from Fisher's exact test.

Figure 4. Change from Baseline in WHO Functional Class by Dose Subgroup at Week 24



Note: For those participants who withdrew early due to death, were too ill to walk, or had no WHO FC measure due to clinical worsening event, the WHO FC is set to worst class of IV; for all other withdrawal without WHO FC measurement, LOCF is used for imputation. Each study drug dose subgroup is compared to the common Placebo group. P-values are obtained from Fisher's exact test.

Rate of AEs and discontinuations due to AEs were similar for both oral treprostinil groups (Table 2).

Table 2. Treatment Emergent Adverse Events by Dose Subgroup at Week 24

Preferred Term, n(%)	Oral Treprostinil <3 mg TID N=160	Oral Treprostinil ≥3 mg TID N=186	Placebo N=344
Any Event	159 (99.4%)	180 (96.8%)	302 (87.8%)
Headache	121 (75.6%)	125 (67.2%)	102 (29.7%)
Diarrhea	97 (60.6%)	116 (62.4%)	80 (23.3%)
Flushing	47 (29.4%)	80 (43.0%)	23 (6.7%)
Nausea	53 (33.1%)	67 (36.0%)	63 18.3%)
Vomiting	40 (25.0%)	58 (31.2%)	25 (7.3%)
Dizziness	34 (21.3%)	35 (18.8%)	57 (16.6%)
Pain in extremity	23 (14.4%)	30 (16.1%)	19 (5.5%)
Upper respiratory tract infection	20 (12.5%)	30 (16.1%)	43 (12.5%)
Pain in jaw	27 (16.9%)	27 (14.5%)	8 (2.3%)

Note: Adverse event threshold of >15% participants in any group by preferred term.

DISCUSSION

- Oral treprostinil is an effective prostacyclin analogue associated with typical prostacyclin-type adverse events. Participants achieving higher doses had greater clinical benefits.
- Adverse event rates were similar between the oral treprostinil groups. It is unclear whether this is because of better intrinsic tolerability or more active management of adverse events by investigators.

LIMITATIONS

- Imputation was common in this analysis, as participants had either exited the study for clinical worsening or adverse events; 19% and 15% of participants did not have Week 24 6MWD and FC measures, respectively, and values were imputed.

CONCLUSIONS

- Achieving a higher oral treprostinil dosing regimen was associated with a better clinical response at 24 weeks. Although the improvement in exercise capacity for the higher dose group (≥3 mg TID) was modest, it was coupled with a reduction in Borg dyspnea score.
- Prostacyclin-type adverse events were common but did not clearly differ between the two dosing groups. Additional investigation is warranted.
- A dose escalation plan aiming for 3 mg TID by Week 24 may be a reasonable initial oral treprostinil treatment goal for adults with PAH.

REFERENCES

1. White RJ, Sanchez Diaz CJ, Bohns Meyer GM, Pulido T, Sepulveda P, et al. Risk Scores and Risk-based Stratification of Clinical Worsening Events in Pulmonary Arterial Hypertension Participants Treated with Oral Treprostinil: FREEDOM-EV. *Am J Respir Crit Care Med*. 2019;199:A5587.
2. Ramani G, Shen E, Broderick M, Wasik A, Rao Y. Novel analysis of treprostinil dose-response relationship using weight-normalized dosing. *Am J Respir Crit Care Med*. 2018;197:A7582.
3. Ramani G, Broderick M, Classi P, Borg E, Nelsen A. Increasing Treprostinil Dose Reduces Annual Hospitalization Rates and Consequent Costs in Patients with Pulmonary Arterial Hypertension. Presented at the AMCP Nexus conference. Orlando, FL. October 22-25, 2018.
4. Broderick M, Ramani G, Borg E, Saunders A, Nelsen A. The Effect of Treprostinil Dose on Time to All Cause and Pulmonary Arterial Hypertension Related Hospitalizations. *Chest*. 2018; 154(4): S94A–S95A.
5. White RJ, Parikh K, Allen R, Feldman J, Jerjez-Sanchez C, et al. Long-term study of oral treprostinil to treat pulmonary arterial hypertension: dosing, tolerability, and pharmacokinetics. *Pulm Circ*. First published July 10, 2019.

ACKNOWLEDGEMENTS

Thank you to Jay Henson (United Therapeutics) and Erick Borg, PharmD (United Therapeutics) who provided writing and editorial support.

Take a picture for a copy of the poster handout.

Presented at European Respiratory Society International Conference | September 27-October 2, 2019 | Madrid, Spain | #19135
Disclosure: This study was sponsored by United Therapeutics Corporation.

United Therapeutics CORPORATION