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# Treatment with Oral Treprostinil Delays Disease Progression in Participants with Pulmonary Arterial Hypertension - Results from the FREEDOM-EV Study

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**Background:** Oral treprostinil (TRE) has been shown to improve exercise capacity in patients with pulmonary arterial hypertension (PAH), but its effect on clinical outcomes was unknown.

**Methods:** In this global, event-driven study, eligible participants taking one approved oral PAH medication were randomized to TRE or placebo (PBO). Dosing was individualized and titrated from 0.125 mg three times daily (TID) up to 12 mg TID. The primary objective was to determine the effect of TRE on time to first adjudicated clinical worsening (CW) event: death, hospitalization due to worsening PAH, initiation of inhaled/infused prostacyclin, disease progression (≥ 15% decrease in six minute walk distance [6MWD] and increase in functional class [FC] or worsening heart failure), or unsatisfactory long-term clinical response (decrease in 6MWD and remained in FC III/IV for at least 24 weeks).

**Results:** 690 participants were randomized (346 TRE, 344 PBO). Participants were predominantly female and <65 years with idiopathic/heritable PAH. The median time since PAH diagnosis was 0.54 years, and the median time on background PAH therapy was 0.45 years. The majority had FC II symptoms, and the median baseline 6MWD was 405 m. Median TRE dose achieved was 2.5, 3.56, 4, and 4.75 mg TID at Weeks (W) 12, 24, 36, and 48. The majority of TRE participants (63%) achieved a dose ≥3 mg TID at W24. There were 90 and 124 CW events with TRE and PBO, respectively (HR 0.74; 95% CI 0.56-0.97; log-rank p=0.0391). Treatment difference was driven by delayed disease progression (5.5% TRE, 14.5% PBO; HR 0.39; 95% CI 0.23-0.66; log-rank p=0.0002). NT-proBNP levels were significantly improved at W24 and 36 (p<0.0001, both). Borg score (after 6MW) and FC were significantly improved at W24, 36, and 48 (p<0.05, all). 6MWD improved with TRE at W36 and W48 (Hodges-Lehmann: 13 [p=0.0094] and 21 m [p=0.0008]); there was a trend toward improvement at W24. Combined 6MWD/Borg dyspnea score was significantly improved with TRE at W24 compared to PBO (p=0.0057). 18.8% of TRE and 4.1% of PBO participants discontinued study drug prematurely due to adverse events (AEs). Prostacyclin AEs were more common with TRE. While mortality was similar at end of randomized treatment (4.9% TRE, 5.2% PBO), overall mortality at study closure was lower in those initially assigned oral TRE (11% TRE, 17.4% PBO; HR 0.63; 95% CI 0.42-0.95; Log-rank p=0.0324). Vital status was unknown for 43 TRE and 31 PBO participants; PBO participants who began open-label TRE after a CW event were included in analysis according to initial treatment assignment.

**Conclusions:** In participants taking one oral PAH medication, early, sequential combination therapy with TRE significantly delayed disease progression compared to PBO. Functional and symptomatic improvements at W24-48 help to confirm the treatment benefits of oral TRE.

*Presented at the 2019 Pulmonary Hypertension Association (PHA) Pulmonary Hypertension Professional Network (PHPN) Symposium.*