Treatment with Oral Treprostinil Improves Hemodynamics in Participants with PAH

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Introduction: Oral treprostinil (TRE) has been shown to improve exercise capacity and delay disease progression in patients with pulmonary arterial hypertension (PAH). Its effect on hemodynamics is unknown.

Methods: FREEDOM-EV was an event-driven, Phase 3b, randomized, double-blind, placebo-controlled study. Dosing of study drug was titrated from 0.125 mg three times daily (TID) up to a maximum dose of 12 mg TID. All participants were using one approved PAH therapy at study entry, and some (n=61) consented for a hemodynamics sub-study with right-heart catheterization at Baseline and Week 24. Participants with missing or mismatched cardiac output estimates (using indirect Fick or Thermodilution methodology) at Baseline and Week 24 were excluded from the analysis (n=7). Analysis of covariance was used to measure differences with change from baseline in log-transformed data in hemodynamic parameter as the dependent variable, treatment as fixed effect, and log-transformed baseline hemodynamic parameter as a covariate.

Results: There was a 19% reduction in mean pulmonary vascular resistance (PVR) from Baseline to Week 24 in the TRE group compared to a 1% reduction in the placebo group (-134.09 vs. -9.20; p=0.0241). There was a corresponding 8% increase in cardiac output from Baseline to Week 24 n the TRE group compared to a 6% reduction in the placebo group (0.42 vs. -0.30; p=0.0051). There were no significant changes in either mean right atrial pressure (RAPm), mean pulmonary artery wedge pressure (PAWPm), or mean pulmonary artery pressure (PAPm) between the TRE and placebo groups.

Parameter	Oral treprostinil				Placebo				p-value
	n	Mean (Baseline)	Mean (Week 24)	Change from Baseline	N	Mean (Baseline)	Mean (Week 24)	Change from Baseline	
RAPm (mmHg)	34	7.68	8.00	0.32	27	7.89	6.96	-0.93	0.8173
PAPm (mmHg)	34	49.15	46.03	-3.12	27	49.37	46.96	-2.41	0.5746
PAWPm (mmHg)	34	9.97	10.71	0.74	26	9.23	8.62	-0.62	0.1154
CO (L/min)	30	5.30	5.72	0.42	24	4.82	4.52	-0.30	0.0051
PVR (dynes*sec/ cm^5)	30	720.23	586.14	-134.09	24	781.41	772.2	-9.20	0.0241

Conclusions: There was a significant reduction in PVR with an associated increase in cardiac output in the TRE group compared with the placebo group. Because there was no change in the PAPm, these data could be explained by the known pulmonary vasodilator effect of prostacyclin therapies, with or without a direct inotropic effect.