

Ralinepag Plasma Levels Correlate With Improvements in Functional and Hemodynamic Parameters in Patients With Pulmonary Arterial Hypertension

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Aim: Ralinepag, an oral, selective, and potent prostacyclin receptor agonist in development for the treatment of pulmonary arterial hypertension (PAH), has shown efficacy in patients with PAH in a randomized, double-blind Phase 2 study. Despite evidence of a dose–effect relationship for some drugs targeting the prostacyclin pathway, the relationship between drug plasma levels and efficacy is unknown. This post hoc analysis of the Phase 2 study evaluated whether ralinepag plasma levels correlated with improvements in functional and/or hemodynamic parameters, including pulmonary vascular resistance (PVR) and 6-minute walk distance (6MWD).

Methods: Adults with stable functional class II–IV PAH and 6MWD of 100–500 m, on background approved single or dual oral PAH treatment, were randomized 2:1 to receive ralinepag (n=40) or placebo (n=21) for 9 weeks of titration, then 13 weeks of maintenance. Treatment was initiated at 10 µg twice daily (bid) and titrated weekly to maximum tolerated dose, up to 300 µg bid. Ralinepag plasma levels were measured 4 hours post-dose at Weeks 9, 10, 14, 18, and 22. Right heart catheterization was performed at Baseline and Week 22. Efficacy was assessed as percent change in functional and hemodynamic parameters from Baseline to Week 22. Correlation coefficients between mean plasma levels of ralinepag and percent change in efficacy parameters were evaluated.

Results: Ralinepag plasma levels correlated with ralinepag dose. Over the study period, there was a significant correlation between ralinepag plasma levels and improvements in PVR and 6MWD (Table).

| Parameter | Slope (% Change per ng/mL) | 95% Confidence Interval | R ² (Pearson) | P-Value |
|-----------|----------------------------------|-------------------------|-----------------------------|---------|
| 6MWD | 2.49 | 0.45 to 4.53 | 0.10 | 0.018 |
| PVR | −4.34 | −6.77 to −1.71 | 0.18 | 0.0015 |

Conclusion: In patients with PAH, ralinepag plasma levels correlated with ralinepag dose and with improvements in PVR and 6MWD, demonstrating correlation between plasma levels of a prostacyclin pathway oral drug and hemodynamic/functional parameters.