Clinical pharmacokinetic performance of a ralinepag extended-release tablet

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Aim: Ralinepag is an oral, selective, and potent prostacyclin receptor agonist in development for treating pulmonary arterial hypertension. Single-dose pharmacokinetic (PK) comparison of ralinepag extended-release (XR) and ralinepag/selexipag immediate-release (IR) formulations and multiple-dose PK performance of ralinepag XR under fasted/fed conditions.

Methods: Study 1: cohort 1 (n=12) – fasted healthy subjects took single ralinepag doses sequentially over 4 treatment periods: 30 mcg IR capsule and then 60, 120, and 180 mcg doses of an XR tablet. Cohort 2 (n=12) – fasted subjects took single selexipag doses sequentially over 3 treatment periods: 200, 400, and 600 mcg IR tablets. Study 2: fasted (n=19) or fed (n=18) healthy subjects received ralinepag XR tablets in a repeat dose-escalation paradigm over 25 days (starting dose 60 mcg once daily [qd], titrated by additional 60 mcg increments every 5 days up to 300 mcg qd as tolerated).

Results: Study 1: dose-adjusted peak plasma exposure (C_{max}/D) measures were lower for ralinepag XR versus IR (geometric mean ratio [GMR] range up to 41.2%). Dose-adjusted total plasma exposure (AUC/D) measures were similar for XR and IR (GMR range up to 97.9%). Selexipag and MRE-269 plasma PK profiles were consistent with the need for administration at least twice daily. Study 2: dose-dependent plasma exposure measures were observed for the ralinepag XR tablet with low steady-state peak-to-trough ratio (≤2) upon qd dosing, approximating the 'ideal' continuous IV infusion–like PK profile for agents in this drug class and minimal food effect. Females had higher mean exposure measures than males, for which such differences were not statistically significant or considered clinically meaningful.

Conclusion: The ralinepag XR tablet offers improved PK performance over both ralinepag and selexipag IR formulations, with extended exposure and low peak-to-trough ratio with qd dosing, supporting its use in the ADVANCE Phase 3 program.