Abstract: **3022**

Relative bioavailability and pharmacokinetic (PK) performance of a ralinepag extended-release (XR) tablet oral formulation and the effect of food and gender in healthy human subjects

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Background/Introduction: Ralinepag is an orally available, potent and selective prostacyclin (IP) receptor agonist in development for the treatment of pulmonary arterial hypertension (PAH). Ralinepag demonstrates a longer terminal half-life (~24 h) than selexipag (≤2.5 h) and its active metabolite MRE-269 (≤13.5 h), and based on in vitro studies is more potent and efficacious than selexipag at increasing cellular cyclic adenosine monophosphate (cAMP) levels. Initial clinical studies used an immediate-release (IR) capsule. When formulated as extended-release (XR) tablet, designed to allow convenient once-daily dosing, ralinepag may be an attractive oral alternative to currently available prostacyclin analogues and IP agonists for PAH treatment.

Purpose: To compare single-dose pharmacokinetics (PK) of ralinepag IR, selexipag IR, and ralinepag XR tablet formulations, and to evaluate multiple-dose PK properties/performance of the ralinepag XR tablet formulation under fed/fasted conditions and in both genders.

Methods: Two single-center, open-label, non-randomized PK studies were conducted in healthy subjects. Study 1: cohort 1 (n=12) subjects took single oral doses of ralinepag in the fasted state given in a sequential manner over 4 treatment periods: 0.03 mg IR capsule, and then 0.06, 0.12, and 0.18 mg doses of an XR tablet. Cohort 2 (n=12) subjects took single oral doses of selexipag IR in the fasted state given sequentially over 3 treatment periods: 0.2, 0.4 and 0.6 mg IR tablets. Study 2: fasted (cohort 1; n=19) or fed (cohort 2, n=18) subjects received ralinepag XR tablet formulation in a dose-escalation sequence over 25 days (once-daily dosing started at 0.06 mg and was slowly titrated, depending on individual subject tolerability, by additional 0.06 mg dose increments every 5 days up to 0.3 mg once daily).

Results: Study 1: Dose-adjusted peak plasma exposure (Cmax/D) measures were lower, as expected, for ralinepag XR versus the IR formulation [geometric mean ratios (GMRs) ranged up to 41.2%]. Dose-adjusted total plasma exposure (AUC/D) measures were similar for both XR and IR formulations (GMRs ranged up to 97.9%). Selexipag and MRE-269 plasma PK profiles were consistent with the need for selexipag twice-daily administration. Study 2: Dose-dependent ralinepag plasma exposure measures were observed for the XR tablet formulation given once daily, with low peak–trough fluctuation and little effect of food seen across dose levels. Somewhat higher mean plasma exposure measures were observed in females versus males.

Conclusion: The ralinepag XR tablet formulation offers improved PK performance over both ralinepag and selexipag IR formulations, by providing extended drug exposure and maintaining low peak–trough fluctuation with once-daily dosing. These highly favorable and desirable PK characteristics support ralinepag XR tablet use in Phase 3 clinical studies.