Clinical Pharmacokinetic Performance of a Ralinepag Extended-Release (XR) Tablet

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BACKGROUND and AIMS

Rationale for Development of the XR Formulation

- Ralinepag is an oral, potent, and selective prostacyclin receptor agonist in development for treating pulmonary arterial hypertension[1]
- In preclinical studies, ralinepag was 6–8-fold more potent than the active metabolite of selexipag (MRE-269)[2]
- In a Phase 2 trial, a ralinepag immediate release (IR) capsule formulation, given twice daily (bid) significantly reduced pulmonary vascular resistance (PVR) in patients with PAH on single- or dual-background therapy
- The pharmacokinetic (PK) performance of a ralinepag XR tablet, designed to allow more-convenient once-daily (qd) dosing while maintaining a desired minimal steady-state peak-to-trough ratio (≤2), is presented here

Approximating Exposure of Continuous Intravenous or Subcutaneous Infusion Should Enhance Oral IP Receptor Agonist Response

- Low peak-to-trough plasma fluctuation is key to minimizing maximum plasma concentration (C_{max})-related tolerability issues, and potential drug effect loss during trough plasma concentrations (C_{trough})
- Compared with a terminal half-life, the effective half-life better describes drug loss rate across a dose interval (with longer values producing lower drug concentration fluctuation across a dosing interval)
- For minimal peak-to-trough plasma fluctuation, the effective half-life needs to exceed (or at least match) the drug dosing interval
- The effective half-life is both drug and formulation dependent (it differs for IR vs XR drug formulations), whereas the terminal half-life is only drug dependent (it is the same for IR and XR drug formulations) (Table 1)

Table 1. Selective IP Receptor Agonists for PAH

Only Ralinepag Oral Formulations Have Effective Half-Lives Exceeding Drug Dosing Interval			
Oral Agent	**Dose Interval**	**Effective $t_{½}$**	**Terminal $t_{½}$**
Ralinepag XR Tablet	qd (q24h)	28-29 h[2]	~24 h[2]
Ralinepag IR Capsule	bid (q12h)	16-17.5 h[2]	~24 h[2]
Selexipag Tablet	bid (q12h)	3-4 h[5] (active metabolite)	6.2-13.5 h[5] (active metabolite)

bid, twice daily; q8h, every 8 hours; q12h, every 12 hours; q24h, every 24 hours; qd, once daily; $t_{½}$, terminal phase half-life; tid, three times daily.

Effective Half-Life ($t_{½eff}$) Equation[3]

$t_{½eff}=\tau*\ln 2/\ln[Rac/(Rac-1)]$

where Rac is the drug accumulation index, calculated from $Rac=\frac{AUC_{0-\tau}\text{ (steady state)}}{AUC_{0-\tau}\text{ (single dose)}}$, and τ is the dose interval

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 over 4 sequential treatment periods: 30 mcg IR capsule, then 60, 120, and 180 mcg doses of an XR tablet
- Cohort 2 (n=12) subjects took single oral doses of selexipag in the fasted state over 3 sequential treatment periods: 200, 400, and 600 mcg IR tablets

Study 2:

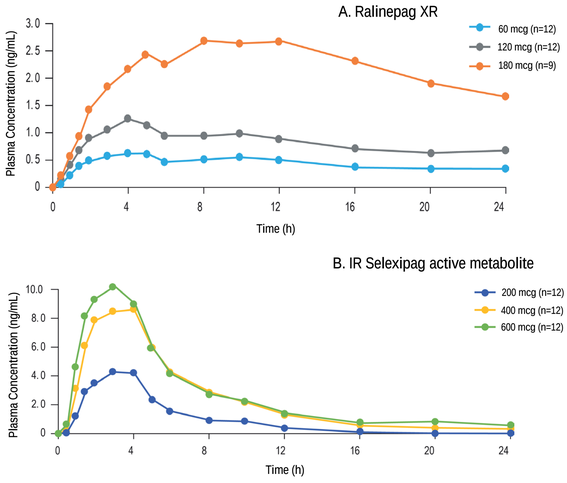
- Fasted (cohort 1, n=19) or fed (cohort 2, n=18) subjects received ralinepag XR in a dose-escalation paradigm over 25 days (dosing started at 60 mcg qd and was slowly titrated by 60-mcg dose increments every 5 days up to 300 mcg qd, depending on individual subject tolerability)

RESULTS

Study 1: Single-dose PK Profile Comparison of Ralinepag XR Versus IR Selexipag in Healthy Subjects

Prolonged plasma PK profile for ralinepag XR tablet supports qd dosing (Figure 1A), whereas the plasma PK profile for the active metabolite of selexipag is consistent with need for more frequent dosing (Figure 1B)

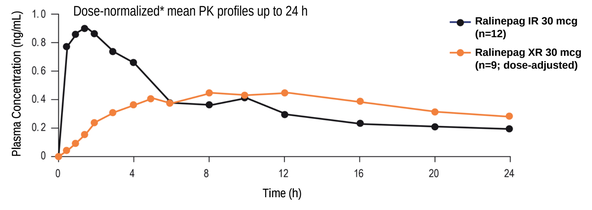
Figure 1. Ralinepag XR (A) and Selexipag (B) PK Profiles up to 24 Hours Post-dose Only



Plasma PK Profiles for Single-dose Ralinepag IR vs XR

- Ralinepag XR tablet demonstrates more favorable prolonged absorption that produces lower peak-to-trough plasma fluctuation and lower dose-normalized C_{max} (59% to 71%) compared with the IR capsule (Figure 2)
- Dose-normalized total plasma exposure (AUC) values were similar for 180 mcg XR/30 mcg IR (geometric mean ratio [GMR]=97.3%), but slightly lower at 60 and 120 mcg XR (GMR=80% and 63%)

Figure 2. Ralinepag Single-dose IR vs XR PK Profiles

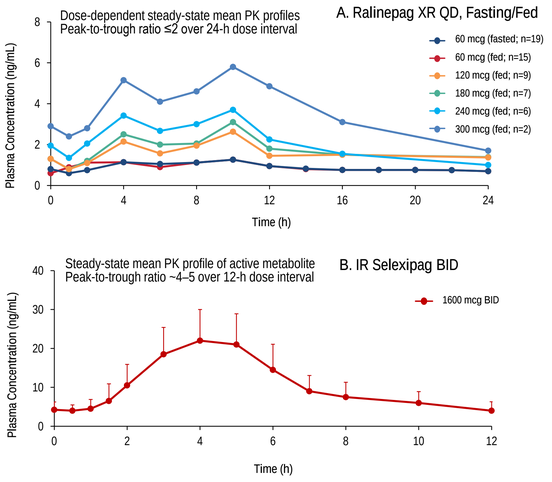


*Plasma concentration–time profiles were dose-adjusted (dose-normalized) to a common 30 mcg dose using PK data from single dosing of IR (30 mcg) and XR (180 mcg) formulations.

Study 2: Steady-state Plasma PK Profiles for Ralinepag XR vs IR Selexipag

Ralinepag XR tablet (qd) at steady state demonstrates dose-dependent plasma exposure with minimal food effect and low peak-to-trough ratio (≤2) (Figure 3A) compared with a peak-to-trough ratio of ~4–5 for the active metabolite of selexipag (bid) (Figure 3B)

Figure 3. Ralinepag XR Steady-state Fed/Fasted PK Profiles (A) and IR Selexipag Steady-state PK Profile (B)[4]



CONCLUSIONS

- To achieve minimal peak-to-trough plasma fluctuation, the effective half-life of the formulated drug, or active metabolite, needs to exceed the drug dosing interval
  - PK performance and effective half-life of ralinepag XR tablet supports qd dosing, whereas the effective half-life for the active metabolite of IR selexipag supports the need for more frequent administration
- The peak plasma exposure after a single dose of ralinepag XR is lower than that of IR
  - The relative bioavailability of ralinepag XR and IR were similar with respect to total plasma exposure
- Daily dosing of ralinepag XR tablet at steady state demonstrates:
  - Dose-dependent plasma exposure and low steady-state peak-to-trough ratio (≤2) with qd dosing, approximating the 'ideal' continuous IV infusion–like PK profile for agents in this drug class
  - Minimal observed effect of food on peak and total plasma exposure measures; thus, dosing could be done without respect to meals
- These data support the use of ralinepag XR in the ADVANCE Phase 3 program

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