#12519

Safety and Pharmacokinetics of Ralinepag (APD811), a Next-generation, Selective Prostacyclin Receptor Agonist, in Healthy Adult Subjects

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Introduction

- Ralinepag is a novel, next-generation, oral, selective, potent prostacyclin (IP) receptor agonist in development for pulmonary arterial hypertension (PAH), with optimized pharmacokinetics (PK) and potent activity on pulmonary arteries, vascular smooth muscle cells, and platelets
- *In vitro* studies have determined the binding affinity of ralinepag at the human IP receptor to be ~3 nM, with an EC_{50} of 8.5 nM in the cAMP human IP receptor assay[1]

Objectives

- To investigate the safety, tolerability, and PK of ralinepag, including effect of dose titration in healthy volunteers

Methods

- Two Phase 1, randomized, double-blind, placebo-controlled studies:
  - Males or females, 18–45 years, 50–100 kg, in stable health

Single-dose Escalation Study

- Four cohorts (n=8/cohort; ralinepag n=6; placebo n=2) received ralinepag 0.03, 0.05, 0.1, or 0.2 mg in a fasted state

Multiple Ascending Dose Study

- Cohorts 1 and 2 (ralinepag n=20; placebo n=10) received ralinepag 0.05 mg once-daily (q.d.) in a fasted state, increasing every sixth day to 0.1, 0.2, 0.3, and 0.4 mg for up to 27 days
- Cohort 3 (ralinepag n=20; placebo n=5) received ralinepag 0.01 mg twice-daily (b.i.d.) in a fasted state, increasing every sixth day to 0.02, 0.03, 0.04, 0.05, and 0.07 mg for up to 30 days
- Safety parameters included adverse events (AEs), laboratory tests, vital signs, physical examinations, and electrocardiograms (ECGs)

Results

Single-dose Escalation Study

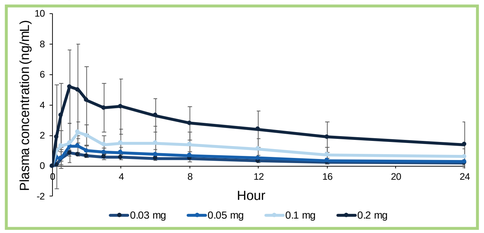
- All 32 subjects completed the study. Ralinepag was tolerated up to 0.1 mg. Dose escalation was discontinued at 0.2 mg due to treatment-emergent AEs (vomiting, headache, and nausea)
  - There were no clinically significant effects on vital signs, ECGs, or laboratory tests
- Exposure of ralinepag was dose proportional from 0.03 to 0.2 mg [**Table 1**]

Table 1. Single-dose Escalation Study: Summary of Mean Plasma PK Parameters

	Ralinepag			
	0.03 mg (n=6)	0.05 mg (n=6)	0.1 mg (n=6)	0.2 mg (n=6)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
C_{max} (ng/mL)	0.949 (0.252)	1.49 (0.32)	2.65 (0.79)	6.17 (2.68)
AUC_{last} (ng·h/mL)	15.9 (7.8)	21.5 (9.9)	41.2 (25.8)	101 (62)
AUC_{inf} (ng·h/mL)	17.3 (8.0)	22.8 (10.4)	42.6 (26.1)	103 (63)
t_{max} (hr)*	1.0 (0.5–8.0)	1.25 (0.5–1.5)	1.5 (0.5–6.0)	1.25 (0.25–4.0)
$t_{1/2}$ (hr)	20.5 (5.6)	20.7 (8.6)	23.2 (5.8)	26.4 (22.9)
CL/F (L/hr)	2.41 (1.39)	3.11 (2.75)	3.32 (1.93)	2.45 (1.72)
V_z/F (L)	62.6 (22.4)	70.4 (22.9)	98.3 (41.4)	72.9 (42.0)

*t_{max} = median (min–max). AUC = area under the plasma concentration-time curve; CL/F = apparent clearance; C_{max} = maximum plasma concentration; PK = pharmacokinetics; $t_{1/2z}$ = elimination half-life; t_{max} = time of maximum plasma concentration; V_z/F = apparent volume of distribution

Figure 1. Single-dose Escalation Study: Mean (±SD) Plasma Concentration (ng/mL) of Ralinepag 0.03, 0.05, 0.1 and 0.2 mg



- Time to maximum plasma concentration, terminal half-life, apparent volume of distribution, and clearance of ralinepag were consistent across doses [**Table 1**]
  - The plasma concentration time profile of ralinepag 0.03, 0.05, 0.1 and 0.2 mg is shown in **Figure 1**

Multiple Ascending Dose Study

- 26/30 subjects in Cohorts 1 and 2 and 24/25 subjects in Cohort 3 completed the study
  - The highest tolerated dose was 0.3 mg q.d. in Cohorts 1 and 2 and 0.07 mg b.i.d. in Cohort 3
  - Four subjects withdrew due to AEs (0.05 mg q.d.: vomiting, headache; 0.1 mg q.d.: nausea, headache, palpitations; 0.05 mg q.d.: atrial fibrillation [conduction abnormalities observed before drug administration]; 0.01 mg b.i.d.: non-specific ST and T wave changes on ECG)
- Severity of AEs reported are shown in **Table 2** and treatment-emergent AEs in >1 subject in any treatment group are shown in **Table 4**
- Consistent with the effect of other IP agonists, a transient increase in heart rate at peak ralinepag concentrations was observed
  - ECG analysis did not suggest a significant effect on the QT interval
- Plasma concentrations increased with increasing dose, independent of q.d. or b.i.d. administration
- The geometric mean C_{max} for ralinepag 0.03 to 0.3 mg q.d. was dose-proportional (range 2.05–17.60 ng/mL)
- Ralinepag accumulation from Day 1 to Day 5 was approximately two-fold after q.d. or b.i.d. dosing
  - Accumulation from Day 6 to Day 10 was less than two-fold after consecutive q.d. dosing [**Table 3**]
- There was no apparent association between ralinepag concentration and occurrence of AEs

Table 2. Multiple Ascending Dose Study: Summary of Treatment-emergent AEs – Number (%) Subjects in Safety Population (n=55)

	Last ralinepag dose (mg)										
	Cohorts 1 and 2 (q.d.)					Cohort 3 (b.i.d.)					
	Placebo (n=10)	0.03 (n=3)	0.05 (n=9)	0.1 (n=7)	0.3 (n=1)	Placebo (n=5)	0.02 (n=4)	0.03 (n=6)	0.04 (n=2)	0.05 (n=6)	0.07 (n=2)
Number of subjects reporting AE	9 (90)	3 (100)	9 (100)	7 (100)	1 (100)	3 (60)	4 (100)	6 (100)	2 (100)	6 (100)	1 (50)
Number of subjects reporting AE by severity											
Mild	4 (40)	0	0	0	0	0	0	0	0	0	0
Moderate	5 (50)	3 (100)	8 (88.9)	7 (100)	1 (100)	3 (60)	4 (100)	6 (100)	2 (100)	6 (100)	1 (50)
Severe	0	0	1 (11.1)	0	0	0	0	0	0	0	0
Number of subjects reporting SAE	0	0	1 (11.1)	0	0	0	0	0	0	0	0

AE = adverse event; b.i.d. = twice daily; q.d. = once daily; SAE = serious adverse event

Table 3. Multiple Ascending Dose Study: Summary of Mean (SD) PK Parameters and Accumulation Index of Ralinepag 0.1 mg q.d.

Day[a]	t_{max}[b] (h)	C_{max} (ng/mL)	AUC_{0-24} (h·ng/mL)	Accumulation index[c]	
				C_{max}	AUC_{0-24}
6	146 (1)	4.17 (1.13)	39.6 (15.9)	NA	NA
10	242 (0)	5.15 (1.48)	48.3 (19.7)	1.24 (0.15)	1.21 (0.09)

[a]Individual subjects received ralinepag 0.05 mg on Days 1–5, followed by ralinepag 0.1 mg q.d. on Days 6–10; [b]t_{max} = median (min–max); [c]Accumulation index (Day 10 exposure/Day 6 exposure)
AUC = area under the plasma concentration-time curve; C_{max} = maximum plasma concentration; NA = not applicable; PK = pharmacokinetics; q.d. = once daily; SD = standard deviation; t_{max} = time of maximum plasma concentration

Table 4. Multiple Ascending Dose Study: Number (%) of Treatment-emergent AEs Reported by >1 Subject Receiving Placebo or Ralinepag q.d. and b.i.d. (n=55)

System organ class / Preferred term*	Last ralinepag dose (mg)									
	Cohorts 1 and 2 (q.d.)				Cohort 3 (b.i.d.)					
	Placebo (n=10)	0.03 (n=3)	0.05 (n=9)	0.1 (n=7)	Placebo (n=5)	0.02 (n=4)	0.03 (n=6)	0.04 (n=2)	0.05 (n=6)	0.07 (n=2)
Cardiac disorders										
Palpitations	0	0	1 (11.1)	3 (42.9)	0	0	3 (50.0)	1 (50.0)	1 (16.7)	0
Eye disorders										
Ocular hyperemia	0	0	0	0	1 (20.0)	0	1 (16.7)	0	2 (33.3)	0
Gastrointestinal disorders										
Nausea	2 (20.0)	3 (100.0)	8 (88.9)	6 (85.7)	0	2 (50.0)	6 (100.0)	1 (50.0)	5 (83.3)	0
Vomiting	0	3 (100.0)	5 (55.6)	4 (57.1)	0	0	3 (50.0)	0	0	0
Constipation	4 (40.0)	1 (33.3)	2 (22.2)	3 (42.9)	1 (20.0)	0	1 (16.7)	0	0	0
Abdominal pain	1 (10.0)	1 (33.3)	4 (44.4)	1 (14.3)	1 (20.0)	0	2 (33.3)	0	2 (33.3)	0
Diarrhea	1 (10.0)	2 (66.7)	2 (22.2)	1 (14.3)	0	0	3 (50.0)	0	4 (66.7)	0
Abdominal distension	2 (20.0)	0	1 (11.1)	1 (14.3)	0	0	0	0	0	0
General disorders and administration site conditions										
Application site dermatitis	3 (30.0)	2 (66.7)	2 (22.2)	2 (28.6)	0	0	0	0	0	0
Chest discomfort	0	0	1 (11.1)	0	0	0	2 (33.3)	1 (50.0)	0	0
Feeling hot	0	0	1 (11.1)	1 (14.3)	0	0	0	0	2 (33.3)	0
Fatigue	2 (20.0)	0	1 (11.1)	1 (14.3)	0	0	1 (16.7)	0	2 (33.3)	0
Non-cardiac chest pain	0	0	2 (22.2)	0	0	0	0	0	0	0
Metabolism and nutrition disorders										
Decreased appetite	2 (20.0)	1 (33.3)	2 (22.2)	1 (14.3)	0	0	0	0	1 (16.7)	0
Musculoskeletal and connective tissue disorders										
Pain in jaw	0	2 (66.7)	7 (77.8)	4 (57.1)	1 (20.0)	2 (50.0)	4 (66.7)	2 (100.0)	5 (83.3)	0
Arthralgia	0	0	0	0	1 (20.0)	1 (25.0)	4 (66.7)	2 (100.0)	2 (33.3)	0
Myalgia	1 (10.0)	2 (66.7)	2 (22.2)	2 (28.6)	1 (20.0)	1 (25.0)	3 (50.0)	2 (100.0)	3 (50.0)	0
Back pain	0	0	1 (11.1)	0	2 (40.0)	0	1 (16.7)	0	1 (16.7)	0
Pain in extremity	1 (10.0)	0	2 (22.2)	1 (14.3)	0	0	0	0	0	0
Nervous system disorders										
Headache‡	2 (20.0)	3 (100.0)	8 (88.9)	7 (100.0)	3 (60.0)	3 (75.0)	6 (100.0)	2 (100.0)	6 (100.0)	0
Dizziness	1 (10.0)	2 (66.7)	3 (33.3)	0	1 (20.0)	2 (50.0)	3 (50.0)	0	4 (66.7)	0
Somnolence	2 (20.0)	1 (33.3)	2 (22.2)	0	1 (20.0)	0	1 (16.7)	0	1 (16.7)	0
Skin and subcutaneous tissue disorders										
Contact dermatitis	1 (10.0)	0	0	0	0	1 (25.0)	0	0	0	1 (50.0)
Vascular disorders										
Flushing‡	0	1 (33.3)	1 (33.3)	4 (57.1)	1 (20.0)	0	2 (33.3)	0	1 (16.7)	0

*Ear discomfort was reported by two subjects (40.0%) in Cohort 3 receiving placebo b.i.d.; hordeolum was reported by three subjects (33.3%) in Cohort 1 and 2 receiving ralinepag 0.05 mg q.d.; ‡One subject receiving ralinepag 0.3 mg q.d. in Cohort 1 and 2 reported headache and flushing. AE = adverse event; b.i.d. = twice daily; q.d. = once daily

Summary and Conclusions

- Ralinepag was studied in two randomized, placebo-controlled trials: a single-dose escalation study and a multiple ascending dose study
- The tolerability of ralinepag in healthy subjects varied across doses, with the observed AEs being as expected for an IP agonist
- In the single-dose escalation study, ralinepag had a long half-life, and exposure was dose-proportional
- There was no appreciable accumulation of ralinepag after consecutive dosing in the multiple dose study
- Results support progress into clinical studies evaluating ralinepag in patients with PAH

References

1. Tran T-A, et al. *J Med Chem.* 2017;60:913–27.

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Disclosures

- Disclosures: IP is principal investigator for studies sponsored by Actelion, Bayer, Eiger, Gilead, United Therapeutics (Tufts Medical Center); has received honoraria for consultancies from Actelion, Gilead; is member of the adjudication committee for Pfizer clinical trial. MM was an employee of Arena Pharmaceuticals, Inc., San Diego at the time of the study. BR, JA, CL, and RC are employees of Arena Pharmaceuticals, Inc., San Diego.

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