Comparative receptor pharmacology, pre-clinical efficacy and pharmacokinetics of a novel, next-generation prostacyclin receptor agonist, ralinepag (APD811), in humans and rats

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Background: Ralinepag is a novel, next-generation, oral, selective, potent prostacyclin (IP) receptor agonist in development for pulmonary arterial hypertension (PAH) treatment.

Purpose: Assess ralinepag for receptor binding affinity, functional potency and selectivity for human IP receptors, and biological activity in rat PAH models and human platelets.

Methods: Binding affinity, potency and selectivity were assessed by radioligand competition binding and functional potency assays (cAMP) in human recombinant IP receptor-expressing cells and pulmonary artery (PA) smooth muscle cells. PK was assessed in male rats after intravenous (IV) and oral dosing. Prophylactic effects were assessed in monocrotaline-induced PAH in rats (vehicle or ralinepag 30mg/kg twice daily [b.i.d.] for 20 days). Biological activity was assessed in a rat PAH model (oral vehicle or ralinepag 30 and 60mg/kg b.i.d. for 14 days), and human platelets in plasma preincubated with ralinepag before induced aggregation with ADP. Comparative receptor pharmacology studies assessed the potency and efficacy of ralinepag vs existing PAH treatments, iloprost and MRE-269 (active form of selexipag).

Results: Ralinepag is a potent, selective agonist for human IP receptors, with a binding affinity of 3.4nM. Ralinepag increases cAMP levels (EC_{50}: 24nM), and has 42- to 2900-fold selectivity for IP vs prostanoid family receptors. In rats, ralinepag has oral bioavailability of 57.4% and a $t_{1/2}$ of 5.45h. Ralinepag inhibits induced PAH (reduced right ventricular weight, PA pressure and vascular remodeling), and dose-dependently prevents PAH progression. Ralinepag potently inhibits human ADP-stimulated platelet aggregation vs MRE-269 (IC_{50}: 40nM vs 288nM). All treatments have a similar binding affinity for IP receptors (Table). As % efficacy of the full agonist iloprost, ralinepag has higher maximal cAMP stimulation vs MRE-269 (67% vs 48%; Table).

Conclusions: Ralinepag is a potent, selective, efficacious agonist at human IP receptors, with preventative and therapeutic effects in PAH models. Results suggest ralinepag has greater functional potency and efficacy than MRE-269. This profile provides rationale for further investigation of ralinepag in clinical studies in PAH.

				% of maximal cAMP response		
Test System (parameter)	**Ralinepag**	**MRE-269**	**Iloprost**	**Ralinepag**	**MRE-269**	**Iloprost**
Recombinant IP Receptor Binding (Ki; nM)	3.4	3.5	3.4	NA	NA	NA
Recombinant IP Receptor cAMP (EC_{50}; nM)	24	151	3.3	67	48	100
Primary Human PA Smooth Muscle Cell cAMP (EC_{50}; nM)	24	184	2.9	65	41	100

Disclosures: JA, YS, MM and DU are employees of Arena Pharmaceuticals, Inc., San Diego, or its subsidiary and BW acted as a consultant.