

Ralinepag Reduces Pulmonary Vascular Resistance (PVR) in a Phase 2 Study Confirming Preclinical Findings on Prostacyclin (IP) Receptors in Human Tissues

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Purpose

Ralinepag is a next-generation, selective and potent IP receptor agonist in development for pulmonary arterial hypertension (PAH). Human IP receptor binding affinity and selectivity of ralinepag were examined, and its functional receptor activation was compared to that of selexipag and iloprost on human platelets, pulmonary artery smooth muscle cells (PASMCs), and pulmonary arteries (PAs). To confirm preclinical efficacy, change in PVR was evaluated in patients with functional class (FC) II–IV group 1 PAH on disease-specific background therapy in a Phase 2 study.

Methods

Potency, selectivity, and functional assays were conducted, including cAMP accumulation as well as cell proliferation in human IP receptor–expressing Chinese hamster ovary (CHO) cells and human PASMCs from PAH patients. Human platelet responses were measured by light transmittance aggregometry. Distal PAs were mounted in a myograph and precontracted with U46619. In the Phase 2 study, adults with stable FC II–IV PAH were randomized 2:1 to receive ralinepag (n=40) or placebo (n=21) for 9 weeks of titration (up to 300 mg twice daily), then 13-week maintenance of maximum tolerated dose. Right heart catheterization was performed at baseline and at 22 weeks. The primary efficacy endpoint was change in PVR from baseline to week 22.

Results

Ralinepag has high binding affinity ($K_i = 0.003 \mu\text{M}$) and selectivity at the human IP receptor. Ralinepag, iloprost, and MRE-269 (selexipag metabolite) increased cAMP in IP receptor–expressing CHO cells; ralinepag and MRE-269 had an E_{Max} of 67% and 48% relative to iloprost. Ralinepag inhibited PASMC proliferation and human ADP-stimulated platelet aggregation more potently than MRE-269. In PAs, ralinepag caused greater relaxation than iloprost and MRE-269. The Phase 2 clinical study enrolled patients with FC II/III/IV (56%/43%/2%) PAH and mean 6-minute walk distance of 378 m. Baseline median PVR was 705 (ralinepag) and 480 (placebo) $\text{dyn}\cdot\text{s}\cdot\text{cm}^{-5}$; all patients were on background PAH treatment, with 65% (ralinepag-treated) and 48% (placebo) of patients receiving dual therapy. Ralinepag reduced median PVR by 163.9 $\text{dyn}\cdot\text{s}\cdot\text{cm}^{-5}$ from baseline, versus a 0.7 $\text{dyn}\cdot\text{s}\cdot\text{cm}^{-5}$ increase with placebo ($P=0.02$).

Conclusions

Ralinepag is a next-generation, selective and potent IP receptor agonist that elicited greater pharmacological responses in human platelets, PAs, and PASMCs than the active selexipag metabolite, MRE-269, and had a favorable vasorelaxant profile compared with iloprost. In a Phase 2 clinical study, ralinepag significantly reduced PVR vs placebo in PAH patients on background therapy, confirming preclinical findings and providing rationale for further investigation.

Clinical Implications

The Phase 2 study of ralinepag in patients on background therapy showed significant improvement in PVR, a well-established indicator of treatment benefit that correlates with long-term clinical outcomes in patients with PAH.

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