Patient Population and Study Design

- This Phase 2 study enrolled 61 adults with stable functional class (FC) II–IV, Group 1 PAH, and 6MWD of 100–500 m

Methods

- Ralinepag is a next-generation, oral, selective and potent prostacyclin receptor agonist with a high binding affinity (Kd) of 3.4 nM for the human prostacyclin receptor in development for pulmonary arterial hypertension (PAH)1,2

- In a Phase 2 study, ralinepag significantly improved pulmonary vascular resistance (PVR) compared with placebo in patients on monotherapy (35%) or dual (65%) background therapy

- The tolerability and adverse event profile in this study was consistent with the known side effects of prostacyclin receptor agonists

Rationale

- There is evidence of a dose-response relationship for some drugs targeting the prostacyclin receptor; however, the relationship between drug plasma levels and hemodynamic parameters is unknown

- Prostacyclin receptor therapies are typically initiated at low doses and up-titrated slowly until an effective and well-tolerated maintenance dose is achieved

- Understanding the relationship between plasma levels and clinical response helps to define optimal dose levels

Study Aim

- This post hoc analysis of the Phase 2 study evaluated whether ralinepag plasma levels correlated with improvements in functional and hemodynamic parameters, and/or serum biomarkers, including 6MWD, 8-minute walk distance (6MWD), and B-type natriuretic peptide (BNP)

Patient Population and Study Design

- This Phase 2 study enrolled 61 adults with stable functional class (FC) II–IV, Group 1 PAH, and 6MWD of 100–500 m

- Patients were randomly assigned to receive ralinepag or placebo in a 6-week maximum-tolerated titration phase followed by a 13-week maintenance phase

- Right heart catheterization was performed at baseline (BL) and at Week 22 as per protocol, 4 hours post dose

- All patients were receiving at least one background PAH treatment

- PK sampling was performed at both trough and 4-hour-post-dose levels throughout the study; Only 4-hour levels were used for the plasma level correlations in this poster

- The relationships between plasma levels and efficacy measures were done by linear regression analysis

Results

Patient Characteristics

- Baseline characteristics of the study population are shown in Table 1

Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All Patients</th>
<th>Ralinepag (n=40)</th>
<th>Placebo (n=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (mean)</td>
<td>51 (18, 73)</td>
<td>46 (18, 66)</td>
<td>56 (24, 73)</td>
</tr>
<tr>
<td>Sex, %</td>
<td>53 (91)</td>
<td>33 (81)</td>
<td>20 (68)</td>
</tr>
<tr>
<td>Race, %</td>
<td>Asian 57 (92)</td>
<td>38 (92)</td>
<td>19 (73)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>BMI, kg/m² (mean)</td>
<td>27 (22)</td>
<td>26 (21)</td>
<td>28 (23)</td>
</tr>
<tr>
<td>6MWD, m (mean)</td>
<td>548 (486)</td>
<td>577 (476)</td>
<td>520 (486)</td>
</tr>
</tbody>
</table>

Lesion classification, n (%)

- Acute rejection 30 (50)
- Chronic rejection 21 (35)
- Acute cellular rejection 8 (13)
- Chronic cellular rejection 5 (8)
- Sclerosis 10 (17)
- Intimal fibrosis 11 (18)
- Others 6 (10)
- Unknown 1 (2)

Histology, n (%)

- Monotherapy 55 (91)
- Combination therapy 16 (26)

Background Pharmacy, n (%)

- Monotherapy 52 (87)
- Combination therapy 9 (15)

Table 1. Baseline Characteristics

Ralinepag Dosing

- Ralinepag total daily maintenance doses were as high as 0.6 mg, and the most common dose was 0.4 mg (Figure 2A)

- Scatter plot of Cmax and the last ralinepag dose level is seen in Figure 2B

Primary Endpoint: Absolute Change in PVR

- PVR decreased by 163.9 dyn·s·cm–5 from BL to Week 22 in patients receiving ralinepag, compared with an increase in PVR of 0.7 dyn·s·cm–5 in patients receiving placebo (P=0.02 (Figure 3)

Figure 3. Ralinepag Change in PVR

Plasma Level Correlations

- There was a significant correlation between ralinepag plasma levels and improvements in functional and hemodynamic parameters

Secondary Endpoint: Ralinepag Safety and Tolerability

- The most common adverse events were as expected for prostacyclin receptor agonists and included headaches, nausea, diarrhea, jaw pain, and flushing

Summary and Conclusions

- Ralinepag is a next-generation, oral, selective and potent prostacyclin receptor agonist in development for PAH

- Ralinepag significantly reduced PVR compared with placebo in patients with FC II–IV Group 1 PAH on single or dual background therapy

- This post hoc analysis of the Phase 2 study revealed that efficacy better correlated with ralinepag plasma levels than with ralinepag dosing

- This is the first study demonstrating a correlation between plasma levels of an oral drug targeting the prostacyclin receptor and hemodynamic parameters, potentially improving the clinical management of optimal dosing

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Disclosures

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References