Pharmacokinetics and Efficacy of Ralinepag (APD811) in Rats and Humans

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Introduction

• Ralinepag is a novel, next-generation, oral, highly selective prostacyclin (IP) receptor agonist that has demonstrated positive findings in a Phase 2 clinical study of pulmonary arterial hypertension (PAH)
• It is a once-daily (XR) oral therapy with potential to improve clinical management of PAH

Methods

• Selectivity and potency were assessed using radioligand competition binding and functional assays (cAMP) in human prostanoid receptor-expressing cells
• Prophylactic efficacy was assessed in a rat model of monocrotaline-induced PAH, with vehicle or ralinepag 30 mg/kg twice daily (b.i.d.) delivered by oral gavage for 20 days
• Therapeutic effects in established PAH 15 days after MCT injection were assessed in the rat PAH model given vehicle or ralinepag 3060 mg/kg b.i.d. for 14 days by oral gavage
• Hemodynamic and structural evidence of PAH was determined by micropipet pressure transducer insertion into the pulmonary artery, cardiac chamber dissection, and histopathological analysis of hematoxylin/eosin-stained lung sections
• Activity in human platelets was assessed by inducing aggregation with ADP in platelet-rich plasma preincubated with ralinepag. Platelet inhibition was measured by light transmittance aggregometry

Results

Ralinepag Has Favorable Functional IP Receptor Activity In Vitro

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Binding affinity K (nM)</th>
<th>Fold selectivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>DP₁</td>
<td>2,610</td>
<td>770</td>
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<tr>
<td>EP₁</td>
<td>9,600</td>
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<tr>
<td>EP₂</td>
<td>610</td>
<td>180</td>
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<tr>
<td>EP₃</td>
<td>143</td>
<td>42</td>
</tr>
<tr>
<td>EP₄</td>
<td>678</td>
<td>200</td>
</tr>
<tr>
<td>TP</td>
<td>&gt;10,000</td>
<td>&gt;2,000</td>
</tr>
</tbody>
</table>

• In this study, we aimed to investigate the affinity, potency, and selectivity of ralinepag for human IP receptors vs selexipag (MRE-269), and pharmacological activity in rat PAH and human platelets

Conclusions

• Ralinepag is a novel, oral, selective small-molecule IP receptor agonist
• In vitro, ralinepag has demonstrated superior potency and biological effects versus MRE-269 (selexipag active metabolite)
  - High intrinsic potency at the human IP receptor
  - Robust target tissue responses
  - inhibition of platelet aggregation
• Ralinepag has an optimized pharmacokinetic profile
  - Orally bioavailable, with long half-life
  - Low peak/trough variability
  - Potential to maintain 24-hour exposure in target therapeutic range
• Ralinepag blocks progression of established PAH in rats with oral administration

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