**Introduction**

Novel therapies that reverse remodeled pulmonary arteries, improve pulmonary hemodynamics and restore right ventricular (RV) structure and function are warranted in pulmonary arterial hypertension (PAH). Aberrant BMP/TGFβ signaling plays a prominent role in pulmonary vascular remodeling. RAP-011 (a murine analog of Sotatercept), a recombinant homodimeric fusion protein consisting of extracellular domain of human ActRIIA linked to murine immunoglobulin (Ig) G1 Fc domain, was recently shown to rebalance BMP/TGFβ signaling and attenuate early stage PAH in preclinical models. Sotatercept, a selective ligand trap for activin/GDFs, is currently being evaluated in the PULSAR Phase 2 trial in PAH.

**Hypothesis**

1. RAP-011 improves pulmonary hemodynamics in advanced stages of PAH.
2. RAP-011 improves flattening of septal wall and right ventricular geometry.
3. RAP-011 improves pulmonary vascular resistance and right ventricular structure and function.
4. RAP-011 resolves vascular remodeling.

**Methods**

Model of Severe Angio-obliterative Pulmonary Arterial Hypertension

**Results**

1. **RAP-011 improves pulmonary hemodynamics in advanced stages of PAH**

   Right Ventricular Systolic Pressure

<table>
<thead>
<tr>
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<th>SU/Hx/Nx 5-9 Wks</th>
<th>SU/Hx/Nx 9-13 Wks</th>
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<tbody>
<tr>
<td>Normal</td>
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<tr>
<td>PAH</td>
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<tr>
<td>RAP-011</td>
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<tr>
<td>Sildenafil</td>
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   *p<0.05 vs Normal
   #p<0.05 vs PAH
   @p<0.05 vs Sildenafil

2. **RAP-011 improves flattening of septal wall and right ventricular geometry**

   Early Stage

   Advanced Stage

3. **RAP-011 improves pulmonary vascular resistance and right ventricular structure and function**

   Pulmonary Vascular Resistance Index

   Right Ventricular Wall Thickness

   Right Ventricular Fractional Area Change

4. **RAP-011 resolves vascular remodeling**

   Normal

   5 Wk SU-Hx-Nx-PAH

   9 Wk SU-Hx-Nx-PAH

   Sildenafil 5-9 Wks

   RAP-011 5-9 Wks

   RAP-011 9-13 Wks

**Conclusion**

RAP-011 (Sotatercept) treatment, distinct from sildenafil, improves pulmonary hemodynamics, RV structure and cardiac function, and may provide a novel disease-modifying benefit to patients with PAH.

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