Combination therapy with sotatercept analog RAP-011 is superior to sildenafil alone in severe experimental PAH and RAP-011 benefits persist after treatment cessation

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Currently Available Therapeutics:
Vasoactive Agents
Eg: Prostacyclin analogs, PDE5i, ERA,
Sotatercept analog RAP-011

Activin Ligand Trap

• Is a homodimeric fusion protein consisting of extracellular domain of human ActRIIA linked to murine immunoglobulin (Ig) G1 Fc domain

• Is proposed to act by rebalancing signaling between pro- and anti-proliferative pathways
Treatment with RAP-011 in preclinical experiments improved:

- Hemodynamics
- Right ventricular (RV) hypertrophy
- RV function
- Pulmonary vascular remodeling
Aims

1. To investigate whether RAP-011 adds therapeutic benefit when combined with sildenafil compared to sildenafil alone

2. To investigate whether benefits of RAP-011 persist after monotherapy cessation
Methods: Aim 1

**Combination Therapy Protocol**

SUGEN-Hypoxia-Normoxia (SU-Hx-Nx) PAH

- **SD Rat**
- **HUPOXIA [10% O₂]**
- **NORMOXIA [21% O₂]**

**SUS416 20 mg/kg sc.**

<table>
<thead>
<tr>
<th>Time (wks)</th>
<th>Description</th>
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<tbody>
<tr>
<td>0</td>
<td>Treatment (4 Wks)</td>
</tr>
<tr>
<td>3</td>
<td>SUS416</td>
</tr>
<tr>
<td>5</td>
<td></td>
</tr>
<tr>
<td>7</td>
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<td>9</td>
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</table>

- RAP-011 (2.5 mg/kg BIW S.C) or Sildenafil (30 mg/kg BID P.O) or both

**Cardiopulmonary Assessment by Echocardiography and Hemodynamics**
1. Combination treatment of RAP-011 with sildenafil yielded greater improvement than sildenafil alone for right ventricular systolic pressure (RVSP), total pulmonary resistance index (TPRI), and pulmonary artery acceleration time (PAAT) (**P < 0.001, ****P < 0.0001).
2. Combination treatment of RAP-011 with sildenafil yielded greater improvement than sildenafil alone for right ventricular hypertrophy (RV/LV+S), right ventricular free wall thickness (RVWT), right ventricular fractional area change (RV FAC). (**P < 0.05, **P < 0.01, ***P < 0.001, ****P < 0.0001).
3. Combination treatment of **RAP-011 with sildenafil** improved **right ventricular geometry** better than **sildenafil** alone.

<table>
<thead>
<tr>
<th>Normal</th>
<th>Vehicle</th>
<th>RAP-011</th>
<th>Sild</th>
<th>Sild + RAP-011</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before Therapy</td>
<td></td>
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<tr>
<td>After Therapy</td>
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Methods: Aim 2

Treatment Cessation Protocol

SUGEN-Hypoxia-Normoxia (SU-Hx-Nx) PAH

SD Rat

SUS416 20 mg/kg sc.

HYPOXIA [10% O₂]

NORMOXIA [21% O₂]

0 3 5 7 9 13 wks

SU5416

Treatment (4 Wks)

Treatment Withdrawal

RAP-011 (2.5 mg/kg BIW S.C)

Cardiopulmonary Assessment by Echocardiography and Hemodynamics
Results: Pulmonary Parameters

4. Benefits of RAP-011 in right ventricular systolic pressure (RVSP), total pulmonary resistance index (TPRI) and pulmonary artery acceleration time persisted after treatment cessation (**P < 0.0001).
5. Benefits of RAP-011 in **right ventricular hypertrophy** (RV/LV+S), **right ventricular free wall thickness** (RVWT), **tricuspid annular plane systolic excursion** (TAPSE) persisted after treatment cessation (*P < 0.05, ****P < 0.0001).
Conclusions

• Our results indicate that combination therapy with RAP-011 exerts larger effects than a standard vasodilator alone in severe experimental PAH.

• Benefits of RAP-011 persist 4 weeks after cessation of monotherapy in severe experimental PAH.

• This activity profile could potentially translate to clinical benefits of sotatercept either alone or as add-on to currently available therapies for PAH.
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