SPECTRA and Beyond: Signs of Disease Modification?

Aaron B Waxman, MD, PhD

Director, Pulmonary Vascular Disease Program
Brigham and Women’s Hospital, Cardiovascular Medicine, Pulmonary and Critical Care
Disclosures

Financial relationships with relevant commercial interests for three years preceding this presentation:
• Acceleron Pharma

Sotatercept is an investigational product that is not approved for any use in any country
Sotatercept and the role of BMPR-II/TGF-β signaling

- Sotatercept is a novel, first-in-class fusion protein comprising the extracellular domain of human activin receptor type IIA linked to the Fc domain of human immunoglobulin G1.
- Sotatercept is proposed to act by rebalancing signaling between pro- and anti-proliferative pathways, thereby reversing the characteristic vascular remodeling seen in PAH.

PAH

**Pro-proliferative**

- Activins/GDFs
- ALK4/5/7
- ACTRIIA/B
- BMPs
- pSmad1/5/8

**Anti-proliferative**

- Gremlin-1
- Noggin

**Sotatercept**

**Pro-proliferative**

- Activins/GDFs
- ALK4/5/7
- ACTRIIA/B

**Anti-proliferative**

- Gremlin-1
- Noggin

Sotatercept is a novel, first-in-class fusion protein comprising the extracellular domain of human activin receptor type IIA linked to the Fc domain of human immunoglobulin G1. It is proposed to act by rebalancing signaling between pro- and anti-proliferative pathways, thereby reversing the characteristic vascular remodeling seen in PAH. Sotatercept is an investigational product that is not approved for any use in any country.
A Phase 2a Single-Arm, Open-Label, Multicenter Exploratory Study to Assess the Effects of Sotatercept for the Treatment of PAH in up to 25 patients at 4 sites across the USA

SPECTRA study design

- WHO PH Group I (PAH)
  - Idiopathic or heritable
  - Drug- or toxin-induced
  - CTD-associated
  - STP shunt-associated
- PAH WHO Functional Class III
- Right heart catheterization with PVR ≥ 4 Wood units
- 6-minute-walk distance 100 -550 m
- Hgb ≤ 16 g/dL
- Stable combination PAH therapy

Open-label treatment period (24 weeks)

- Cycle 1: Sotatercept 0.3 mg/kg + SOC n=25

Extension period (18 months)

- Sotatercept 0.7 mg/kg + SOC

Post-treatment follow-up (8 weeks)

- Follow-up visits for safety at 4 and 8 weeks post last dose

CTD: connective-tissue disease; Hgb: hemoglobin; iCPET: invasive cardiopulmonary exercise testing; PAH: pulmonary arterial hypertension; PH: pulmonary hypertension; PVR: pulmonary vascular resistance; SOC: standard of care; WHO: World Health Organization

SPECTRA study: iCPET assessments

• Primary endpoint: Change from baseline in peak oxygen uptake (VO₂ max) at 24 weeks

• Secondary endpoints from iCPET measured as change from baseline at 24 weeks:
  • Ventilatory efficiency (VE/VCO₂ slope)
  • Cardiac index (L/min/m²)
  • Mean pulmonary artery pressure, (mPAP, mmHg)
  • Arteriovenous O₂ content difference (Ca-vO₂)
  • VE/VCO₂ slope (ventilatory efficiency, “dead space” assessment)
  • VO₂ at AT (O₂ consumption at anaerobic threshold)
How do we perform iCPET?

iCPET: invasive cardiopulmonary exercise testing; RA: right atrium; VO₂: peak oxygen uptake

VO₂ and VCO₂

CaO₂
Arterial oxygen content

CvO₂
Venous oxygen content

Incremental exercise to peak
2-min recovery
2-min unloaded cycling
Rest
1-hour post peak
## SPECTRA study: Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Total N=10</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Female, n</strong></td>
<td>6</td>
</tr>
<tr>
<td><strong>Age, median (range), years</strong></td>
<td>45 (25-66)</td>
</tr>
<tr>
<td><strong>Time since diagnosis, median (range), years</strong></td>
<td>3.2 (0.6-13.1)</td>
</tr>
<tr>
<td><strong>PAH classification, n</strong></td>
<td></td>
</tr>
<tr>
<td>Idiopathic</td>
<td>5</td>
</tr>
<tr>
<td>Associated with connective-tissue disease</td>
<td>4</td>
</tr>
<tr>
<td>Heritable</td>
<td>1</td>
</tr>
<tr>
<td><strong>Standard-of-care PAH therapy, n</strong></td>
<td></td>
</tr>
<tr>
<td>Parenteral prostacyclin</td>
<td>7</td>
</tr>
<tr>
<td>Double therapy</td>
<td>5</td>
</tr>
<tr>
<td>Triple therapy</td>
<td>5</td>
</tr>
<tr>
<td><strong>Supine resting pulmonary vascular resistance, median (range), dyn·s/cm&lt;sup&gt;5&lt;/sup&gt;</strong></td>
<td>564 (370-870)</td>
</tr>
<tr>
<td><strong>6-minute walk distance, median (range), m</strong></td>
<td>359 (254-506)</td>
</tr>
</tbody>
</table>

Data cut-off date 21 Sept 2020

PAH: pulmonary arterial hypertension
### SPECTRA study results: Supine Resting Hemodynamics

<table>
<thead>
<tr>
<th></th>
<th>Baseline (n=10)</th>
<th>Week 24/EOS# (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Pulmonary Arterial Pressure (mPAP), mmHg</td>
<td>43.4 ± 9.7</td>
<td>30.6 ± 9.7</td>
</tr>
<tr>
<td>Pulmonary Arterial Wedge Pressure (PAWP), mmHg</td>
<td>10.0 ± 4.0</td>
<td>9.1 ± 4.8</td>
</tr>
<tr>
<td>Cardiac Output (CO), L/min</td>
<td>4.7 ± 0.7</td>
<td>4.8 ± 1.4</td>
</tr>
<tr>
<td>Pulmonary Vascular Resistance (PVR), dyn·sec/cm⁵</td>
<td>576 ± 139</td>
<td>369 ± 121</td>
</tr>
</tbody>
</table>

Data cut-off date 21 Sept 2020
Mean ± SD
EOS: End of study visit, n=1, performed after 3 doses of study drug
Treatment Emergent Adverse Events (TEAE) reported:

- 9/10 patients reported at least one TEAE
  - Arthralgia, dizziness, fluid overload, gingival bleeding, hematochezia, hemoglobin increased, infusion site pain, palpitations, pyrexia, upper respiratory tract infection, weight increased

- Two SAEs reported (fluid overload, resolved; hematochezia, resolved), both considered not related to study drug and no dose interruption or reduction required.

- One discontinuation due to AE (patient felt worsening pain at Remodulin® site injection)
SPECTRA Study:
Case Report of First Patient (1/2)

- 25-year-old female, idiopathic PAH for 4.7 years, receiving tadalafil and ambrisentan for the treatment of PAH. At baseline, subject was classified as WHO FC III and 6MWD was 285.5 m.

- The subject’s medical history includes gastroesophageal reflux disease, sleep disorder, depression, endometriosis, restless leg syndrome and dust allergy.

<table>
<thead>
<tr>
<th>Resting supine hemodynamics</th>
<th>Baseline</th>
<th>Week 24</th>
<th>Week 48</th>
</tr>
</thead>
<tbody>
<tr>
<td>mPAP, mmHg</td>
<td>39</td>
<td>13</td>
<td>11</td>
</tr>
<tr>
<td>mRAP, mmHg</td>
<td>8</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>PAWP, mmHg</td>
<td>8</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>CO, L/min</td>
<td>3.73</td>
<td>4.24</td>
<td>3.42</td>
</tr>
<tr>
<td>DPG, mmHg</td>
<td>20</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>PVR, dynes-sec/cm²</td>
<td>665</td>
<td>170</td>
<td>187</td>
</tr>
</tbody>
</table>

- At 24 weeks, subject was classified as WHO FC I and 6MWD was 468.7 m (183.2 m increase from baseline).

- At 48 weeks, subject remained WHO FC I and 6MWD was 443.7 (158.2 m increase from baseline).
# SPECTRA Study
## Case Report of First Patient (2/2) Peak Exercise Hemodynamics (iCPET)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>Week 24</th>
<th>Week 48</th>
</tr>
</thead>
<tbody>
<tr>
<td>Work, W</td>
<td>39</td>
<td>66</td>
<td>85</td>
</tr>
<tr>
<td>mPAP, mmHg</td>
<td>41</td>
<td>27</td>
<td>23</td>
</tr>
<tr>
<td>TPG, mmHg</td>
<td>37</td>
<td>25</td>
<td>22</td>
</tr>
<tr>
<td>PAWP, mmHg</td>
<td>4</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>CO, L/min</td>
<td>7.0</td>
<td>7.84</td>
<td>7.4</td>
</tr>
<tr>
<td>PVR, dynes-sec/cm$^5$</td>
<td>423</td>
<td>255</td>
<td>237</td>
</tr>
<tr>
<td>Pulmonary artery compliance, mL/mmHg</td>
<td>2.2</td>
<td>3.9</td>
<td>2.3</td>
</tr>
<tr>
<td>VO$_2$ max, mL/kg/min</td>
<td>10.7</td>
<td>17.7</td>
<td>20</td>
</tr>
<tr>
<td>VO$_2$ max, % predicted</td>
<td>33%</td>
<td>54%</td>
<td>62%</td>
</tr>
<tr>
<td>Ca-vO$_2$, mL/dL</td>
<td>9</td>
<td>10.4</td>
<td>15.3</td>
</tr>
<tr>
<td>$V_e$/VCO$_2$ slope</td>
<td>55</td>
<td>27</td>
<td>30</td>
</tr>
</tbody>
</table>

Data cut-off date 21 Sept 2020  
Ca-vO$_2$: arteriovenous O$_2$ content difference; CO: cardiac output; iCPET: invasive cardiopulmonary exercise testing; mPAP: mean pulmonary arterial pressure; PAWP: pulmonary arterial wedge pressure; PVR: pulmonary vascular resistance; TPG: transpulmonary pressure gradient; VO$_2$: oxygen consumption; $V_e$/VCO$_2$: ventilatory efficiency
The ongoing SPECTRA study has shown substantial improvements in hemodynamics as well as exercise tolerance and capacity in the limited number of subjects studied to date.

Sotatercept was generally well tolerated, consistent with the previously reported safety profile in PAH$^1$.

Additional data on sotatercept will be presented during AHA 2020:

- McLaughlin V, et al. “Sotatercept improves right ventricular – pulmonary arterial coupling and right ventricular function in the PULSAR study”, Dickinson W. Richards Memorial Lecture, Cardiopulmonary Best Abstract Award, presentation number 287
- Joshi S, et al. “Sotatercept analog RAP-011 inhibits right ventricular remodeling and restores function in a mouse model of pressure overload”, poster number MP282

We thank all the patients, their families, and all the SPECTRA study investigators who participated in the trial.

- SPECTRA study investigators: Aaron B. Waxman, MD, PhD, Franz Rischard, MD, Michael Risbano, MD, and Robert Frantz, MD.

- The study was sponsored by Acceleron Pharma, Cambridge, MA, USA

- Acceleron personnel: Jonathan Lu, Rebecca Young, Solaiappan Manimaran, Jennifer Barnes, Musa Mutyaba, Erica Davis, Atanas Atanasov, Saba Qamar, Carrie Barron, Jay Backstrom, Janethe Pena