Sotatercept improves right ventricular – pulmonary arterial coupling and right ventricular function in the PULSAR study

A Phase 2, double-blind, placebo controlled, randomized study to compare the efficacy and safety of sotatercept versus placebo when added to standard of care for the treatment of pulmonary arterial hypertension (PAH)


University of Michigan, Ann Arbor, MI; GWMFA, George Washington University, Washington DC; Acceleron Pharma, Cambridge, MA; Imperial College London, London, UK.
Disclosures

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

Dr. McLaughlin reports grants and personal fees from Acceleron, Actelion, Bayer, Gossamer, and United Therapeutics; personal fees from Altavant, Caremark, CiVi Biopharma and Neuroderm and grants from Reata Pharm. and SonoVie, outside the presented work
Right ventricular dysfunction in PAH

- Right ventricular dysfunction is a central feature of PAH and the main factor affecting prognosis\(^1\)
- Energy transfer between ventricle contractility and arterial afterload is termed coupling. Energy transfer specifically between the right ventricle (RV) and pulmonary artery is termed right ventricle–pulmonary artery (RV–PA) coupling\(^2\)

Severe RV dilation*  
Mild/Normal RV dilation*

*Left-hand video shows short axis and right-hand shows long axis apical four chamber ECHO
ECHO: echocardiography; PAH: pulmonary arterial hypertension; RV: right ventricular; RV–PA: right ventricular–pulmonary arterial
2. Hsu S. Circ Heart Fail 2019; 12: doi.org/10.1161/CIRCHEARTFAILURE.118.005715
Echocardiographic estimation of RV–PA coupling

- RV–PA coupling can be estimated non-invasively as a ratio of TAPSE/PASP values*
- A TAPSE/PASP ratio of ≥0.31 mm/mm Hg is associated with a better prognosis and reduced risk of clinical worsening

\[ \text{PASP} = \text{TRV}^2 \times 4 + \text{RA pressure} \]

\[ \text{RV–PA coupling} = \frac{\text{TAPSE}}{\text{PASP}} \]

*The cut-off value of 0.31 mm/mm Hg for RV–PA coupling has not been validated in a large cohort

PASP: pulmonary arterial systolic pressure; RA: right atrium; RV–PA: right ventricular–pulmonary arterial; TAPSE: tricuspid annular plane systolic excursion; TRV: tricuspid regurgitation velocity

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.

**Sotatercept and the role of BMPR-II/TGF-β signaling**

- **PAH**
  - Pro-proliferative
  - Anti-proliferative

- **Sotatercept**
  - Pro-proliferative
  - Anti-proliferative

Sotatercept is an investigational product that is not approved for any use in any country.

ACTRIIA: activin receptor type 2A; ALK: activin receptor-like kinase; BMP/BMPR: bone morphogenetic protein/BMP receptor; Fc, fragment crystallizable; GDF: growth differentiation factor; PAH: pulmonary arterial hypertension; pSmad: phosphorylated Smad; TGF-β: transforming growth factor-beta.
A Phase 2, randomized, double-blind, placebo-controlled study to compare the safety and efficacy of sotatercept versus placebo when added to standard of care (SOC) for the treatment of PAH in 106 patients at 43 sites across eight countries (NCT03496207)

**Inclusion criteria**

- WHO Group 1 PAH
- WHO Functional Class II or III
- Baseline right-heart catheterization with PVR ≥5 Wood units
- Baseline 6-minute walk distance (6MWD) 150–550 m
- Stable treatment with SOC therapies including mono-, double, and triple therapies:
  - An endothelin-receptor antagonist, a phosphodiesterase 5 inhibitor, a soluble guanylate cyclase stimulator, and/or a prostacyclin (including IV)

**Randomization 3:3:4 stratified by baseline WHO FC**

**Primary treatment period (24 weeks)**

- Placebo + SOC (n=32)
- Sotatercept 0.3 mg/kg + SOC (n=32)
- Sotatercept 0.7 mg/kg + SOC (n=42)

**End of placebo-controlled treatment period (EOP)†

**Extension period (18 months)**

- Sotatercept 0.3 mg/kg + SOC
- Sotatercept 0.7 mg/kg + SOC
- Current dose + SOC

**Trial currently in open-label extension phase**

†EOP represents data obtained at the end of the placebo-controlled treatment period (24 weeks)

6MWD: six-minute walk distance; ECHO: echocardiography; FC: functional class; IV: intravenous; NT-proBNP: N-terminal pro-brain natriuretic peptide; PAH: pulmonary arterial hypertension; PVR: pulmonary vascular resistance; SOC: standard of care; TAPSE: tricuspid annular plane systolic excursion; TGF-β: transforming growth factor beta; WHO: World Health Organization

A Phase 2, randomized, double-blind, placebo-controlled study to compare the safety and efficacy of sotatercept versus placebo when added to standard of care (SOC) for the treatment of PAH in 106 patients at 43 sites across eight countries (NCT03496207)

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### Primary endpoint
- Change in PVR from baseline to week 24

### Key secondary endpoints
- Change from baseline to week 24 in 6MWD, NT-proBNP, and TAPSE

### Key exploratory endpoints
- Change from baseline to week 24 in TGF-β ligands and other PAH biomarkers, and ECHO parameters

### Topline results
Results presented at the American Thoracic Society 2020 congress demonstrated improvements in:
- PVR (34% overall reduction)
- 6MWD
- NT-proBNP
- Pulmonary arterial pressure

Sotatercept was generally well tolerated and safety findings were consistent with other patient populations

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6MWD: six-minute walk distance; ECHO: echocardiography; FC: functional class; IV: intravenous; NT-proBNP: N-terminal pro-brain natriuretic peptide; PAH: pulmonary arterial hypertension; PVR: pulmonary vascular resistance; SOC: standard of care; TAPSE: tricuspid annular plane systolic excursion; TGF-β: transforming growth factor beta; WHO: World Health Organization

Methods

- Echocardiography was performed by the local lab at each site and centrally read.
- Calculation of RV-PA coupling is dependent on paired results for three parameters (TRV, RAP, TAPSE) at baseline and at EOP†.
- Data analyses on the remaining patients is ongoing.
- Unavailable values were not imputed for the echocardiography parameters.

Primary analysis data cut-off date 14 January 2020

†EOP represents data obtained at the end of the placebo-controlled treatment period (24 weeks).
*Nine patients discontinued before End of Period.

EOP: End of placebo-controlled treatment period; RAP: right atrial pressure; RVEDA: right ventricular end-diastolic area; RVESA: right ventricular end-systolic area; RVFAC: right ventricular fractional area change; RV—PA: right ventricular – pulmonary artery; SOC: standard of care; TAPSE: tricuspid annular plane systolic excursion; TRV: tricuspid regurgitation velocity.

Table and diagram showing patient distribution and analysis for RV—PA coupling.
### PULSAR study: Baseline characteristics (1/2)

<table>
<thead>
<tr>
<th></th>
<th>Placebo n=32</th>
<th>Sotatercept 0.3 mg/kg n=32</th>
<th>Sotatercept 0.7 mg/kg n=42</th>
<th>Total n=106</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Female, n (%)</strong></td>
<td>26 (81)</td>
<td>29 (91)</td>
<td>37 (88)</td>
<td>92 (87)</td>
</tr>
<tr>
<td><strong>Age, mean (range), years</strong></td>
<td>46 (21–71)</td>
<td>48.5 (23–80)</td>
<td>48.5 (19–77)</td>
<td>48 (19–80)</td>
</tr>
<tr>
<td><strong>Time since diagnosis, mean (range), years</strong></td>
<td>7.2 (0.3–22)</td>
<td>7.6 (0.7–26)</td>
<td>6.2 (0.8–24)</td>
<td>7.4 (0.3–26)</td>
</tr>
</tbody>
</table>

**PAH classification, n (%)**

<table>
<thead>
<tr>
<th>Classification</th>
<th>Placebo n=32</th>
<th>Sotatercept 0.3 mg/kg n=32</th>
<th>Sotatercept 0.7 mg/kg n=42</th>
<th>Total n=106</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic</td>
<td>19 (59)</td>
<td>13 (41)</td>
<td>29 (69)</td>
<td>61 (58)</td>
</tr>
<tr>
<td>Heritable</td>
<td>7 (22)</td>
<td>5 (16)</td>
<td>5 (12)</td>
<td>17 (16)</td>
</tr>
<tr>
<td>Associated with connective-tissue disease</td>
<td>3 (9)</td>
<td>9 (28)</td>
<td>6 (14)</td>
<td>18 (17)</td>
</tr>
<tr>
<td>Drug or toxin-induced</td>
<td>1 (3)</td>
<td>4 (13)</td>
<td>2 (5)</td>
<td>7 (7)</td>
</tr>
<tr>
<td>Associated with corrected congenital shunts</td>
<td>2 (6)</td>
<td>1 (3)</td>
<td>0 (0)</td>
<td>3 (3)</td>
</tr>
</tbody>
</table>

Primary analysis data cut-off date 14 January 2020
PAH: pulmonary arterial hypertension
## PULSAR study: Baseline characteristics (2/2)

<table>
<thead>
<tr>
<th></th>
<th>Placebo n=32</th>
<th>Sotatercept 0.3 mg/kg n=32</th>
<th>Sotatercept 0.7 mg/kg n=42</th>
<th>Total n=106</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>WHO functional class, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>17 (53)</td>
<td>15 (47)</td>
<td>24 (57)</td>
<td>56 (53)</td>
</tr>
<tr>
<td>III</td>
<td>15 (47)</td>
<td>17 (53)</td>
<td>18 (43)</td>
<td>50 (47)</td>
</tr>
<tr>
<td><strong>Standard-of-care PAH therapy, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parenteral prostacyclin</td>
<td>10 (31)</td>
<td>11 (34)</td>
<td>18 (43)</td>
<td>39 (37)</td>
</tr>
<tr>
<td>Monotherapy</td>
<td>3 (9)</td>
<td>3 (9)</td>
<td>4 (10)</td>
<td>10 (9)</td>
</tr>
<tr>
<td>Double therapy</td>
<td>12 (38)</td>
<td>11 (34)</td>
<td>14 (33)</td>
<td>37 (35)</td>
</tr>
<tr>
<td>Triple therapy</td>
<td>17 (53)</td>
<td>18 (56)</td>
<td>24 (57)</td>
<td>59 (56)</td>
</tr>
<tr>
<td><strong>Pulmonary vascular resistance, dyn·s/cm^5</strong></td>
<td>797 ± 57.0</td>
<td>789 ± 50.8</td>
<td>756 ± 63.5</td>
<td>779 ± 33.9</td>
</tr>
<tr>
<td><strong>6-minute walk distance, m</strong></td>
<td>409 ± 11.3</td>
<td>386 ± 15.7</td>
<td>398 ± 14.1</td>
<td>398 ± 8.1</td>
</tr>
<tr>
<td><strong>NT-proBNP, pg/mL</strong></td>
<td>870 ± 214.5</td>
<td>999 ± 227.6</td>
<td>871 ± 248.2</td>
<td>908 ± 135.4</td>
</tr>
</tbody>
</table>

Primary analysis data cut-off date 14 January 2020
Mean ± standard error unless otherwise noted
NT-proBNP: amino-terminal brain natriuretic propeptide; PAH: pulmonary arterial hypertension; WHO: World Health Organization
PULSAR results: Invasive hemodynamics (n=102)

Primary analysis data cut-off date 14 January 2020
Bar graphs represent mean ± standard deviation
†EOP represents data obtained at the end of the placebo-controlled treatment period (24 weeks)
CO: cardiac output; EOP: end of placebo-controlled treatment period; mPAP: mean pulmonary arterial pressure; mPAWP: mean pulmonary arterial wedge pressure; PVR: pulmonary vascular resistance; SOC: standard of care
PULSAR results: Echocardiography (n=94)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Placebo + SOC</th>
<th>Sotatercept 0.3 mg/kg + SOC</th>
<th>Sotatercept 0.7 mg/kg + SOC</th>
</tr>
</thead>
<tbody>
<tr>
<td>RVEDA (cm²)</td>
<td>−0.00 (0.68)</td>
<td>−2.5 (0.66)</td>
<td>−2.5 (−4.4, −0.55)</td>
</tr>
<tr>
<td>RVESA (cm²)</td>
<td>−0.50 (0.63)</td>
<td>−3.1 (0.61)</td>
<td>−2.6 (−4.3, −0.83)</td>
</tr>
<tr>
<td>RVFAC (%)</td>
<td>1.9 (1.2)</td>
<td>5.0 (1.1)</td>
<td>3.1 (−0.13, 6.4)</td>
</tr>
</tbody>
</table>

*Primary analysis data cut-off date 14 January 2020*
*Bar graphs represent mean ± standard deviation*
*EOP represents data obtained at the end of the placebo-controlled treatment period (24 weeks)*
*Standard error is represented in parentheses for all LS mean values*
*CI: confidence interval; EOP: end of placebo-controlled treatment period; LS: least squares; RVEDA: right ventricular end-diastolic area; RVESA: right ventricular end-systolic area; RVFAC: right ventricular fractional area change; SOC: standard of care*
PULSAR results: Echocardiography

Primary analysis data cut-off date 14 January 2020
Bar graphs represent mean ± standard deviation
†EOP represents data obtained at the end of the placebo-controlled treatment period (24 weeks)
‡Standard error is represented in parentheses for all LS mean values
CI: confidence interval; LS: least squares; PASP: pulmonary artery systolic pressure; SOC: standard of care; TAPSE: tricuspid annular plane systolic excursion

<table>
<thead>
<tr>
<th>Endpoint, n</th>
<th>Placebo + SOC</th>
<th>Sotatercept 0.3 mg/kg + SOC</th>
<th>Sotatercept 0.7 mg/kg + SOC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LS mean, n‡</td>
<td>LS mean difference (95% CI)</td>
<td>P value</td>
</tr>
<tr>
<td>PASP (mm Hg), 54</td>
<td>4.8 (4.1), 20</td>
<td>−24.3 (4.7), 16</td>
<td>−29.1 (−41.6, −16.6)</td>
</tr>
<tr>
<td>TAPSE (mm), 91</td>
<td>−0.00 (0.05), 29</td>
<td>0.00 (0.06), 27</td>
<td>0.00 (−0.13, 0.18)</td>
</tr>
</tbody>
</table>
PULSAR results: RV–PA coupling (n=51)

Bar graphs represent mean ± standard deviation

EOP represents data obtained at the end of the placebo-controlled treatment period (24 weeks)

Standard error is represented in parentheses for all LS mean values

Cut-off values for RV–PA coupling have not been validated in a large cohort

CI: confidence interval; LS: least squares; RV–PA: right ventricular–pulmonary artery; PASP: pulmonary artery systolic pressure; SOC: standard of care; TAPSE: tricuspid annular plane systolic excursion

Primary analysis data cut-off date 14 January 2020

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Placebo + SOC (n=19)</th>
<th>Sotatercept 0.3 mg/kg + SOC (n=15)</th>
<th>Sotatercept 0.7 mg/kg + SOC (n=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LS mean</td>
<td>LS mean difference (95% CI)</td>
<td>P value</td>
</tr>
<tr>
<td>RV–PA coupling (mm/mm Hg)</td>
<td>–0.02 (0.03)</td>
<td>0.15 (0.06, 0.24)</td>
<td>0.0015</td>
</tr>
</tbody>
</table>
Conclusions

- In this limited subgroup of the PULSAR study:
  - Treatment with sotatercept was associated with statistically significant improvements in RV–PA coupling and RV function when compared with placebo.
  - Significant improvement from baseline to week 24 in both sotatercept dose groups versus placebo was observed in RV–PA coupling, RVEDA, RVESA, and PASP.
  - For RVFAC, significance was seen at the sotatercept 0.7 mg/kg dose level and was trending at the sotatercept 0.3 mg/kg dose level but did not quite reach the 0.05 significance level.
  - No changes were seen in TAPSE or in cardiac output.

- Sotatercept was generally well tolerated and safety findings were consistent with other patient populations.

- Sotatercept has the potential to be a new treatment option for PAH patients, with consistent and encouraging effects on RV–PA coupling and RV function in a post hoc analysis.

PAH: pulmonary arterial hypertension; PASP: pulmonary arterial systolic pressure; RV: right ventricular; RVEDA: right ventricular end-diastolic area; RVESA: right ventricular end-systolic area; RVFAC: right ventricular fractional area change; RV–PA: right ventricular–pulmonary artery; TAPSE: tricuspid annular plane systolic excursion.
We thank all the patients, their families, and all the PULSAR study investigators who participated in the trial:


We also thank all members of the PULSAR trial steering committee including; D. Badesch, R. De Souza, M. Hoeper, M. Humbert, I. Preston and A. Waxman

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


The authors received editorial assistance from InterComm LTD, supported by Acceleron Pharma