Sotatercept PULSAR Phase 2 PAH Webinar
March 28, 2018
Acceleron Forward-Looking Statements

THIS PRESENTATION CONTAINS FORWARD-LOOKING STATEMENTS ABOUT THE COMPANY’S STRATEGY, FUTURE PLANS and prospects, including statements regarding the development of the Company's compounds, the timeline for clinical development and regulatory approval of the Company’s compounds and the expected timing for reporting of data from ongoing clinical trials. The words “anticipate,” “believe,” “could,” “estimate,” “expect,” “goal,” “intend,” “may,” “plan,” “potential,” “project,” “should,” “target,” “will,” “would,” and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words.

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THE FORWARD-LOOKING STATEMENTS CONTAINED IN THIS PRESENTATION ARE BASED ON MANAGEMENT’S CURRENT views, plans, estimates, assumptions and projections with respect to future events, and the Company does not undertake and specifically disclaims any obligation to update any forward-looking statements.
## PAH Webinar Agenda

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<td>John Quisel, Ph.D., J.D. SVP, Corporate Development</td>
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### Q&A SESSION
Aaron Waxman, M.D., Ph.D.

Director, Pulmonary Vascular Disease Program
Brigham and Women’s Hospital;
Associate Professor of Medicine at Harvard Medical School
Background and Center Information

- **Current Position:**
  - Associate Professor of Medicine, Divisions of Pulmonary and Critical Care Medicine and Cardiology, Harvard Medical School
  - Executive Director, Center for Pulmonary Heart Disease
  - Director, Pulmonary Vascular Disease Program

- **Experience:**
  - Member of numerous steering committees for the development of therapies in pulmonary hypertension
  - NIH and foundation funded research program
  - >130 peer reviewed publications

- **Treatment Center:**
  - Brigham and Women’s Pulmonary Vascular Disease Program
    - Largest and only accredited pulmonary vascular program in the region
    - NIH-NHLBI PVDomics Center
    - 8 Physicians, 2 PA’s, 2 Physiologists, and 4 Clinical Research Coordinators
    - 1200 patient biorepository, and more than 15 clinical trials
Components of Pulmonary Vascular Remodeling

Inflammatory Cells

Proliferation

Hypertrophy

Differentiation

Normal Pulmonary Circulation: Low Resistance & Pressure
PAH: High Resistance & Pressure $\rightarrow$ Right Heart Strain

- Progressive pulmonary vessel obstruction and constriction
- Pulmonary vessels reduced in function and patency
- Unremitting progression of right heart strain $\rightarrow$ heart failure
- Death from heart failure or abrupt rhythm disturbance
- Current therapies try to relax existing open vessels
  - No curative therapy
5th World Symposium on PH:
Hemodynamic Definition of PH/PAH

**PH**
Mean PAP ≥25 mm Hg at rest during RHC

**PAH**
Mean PAP ≥25 mm Hg plus
PAWP ≤15 mm Hg plus
PVR >3 Wood units

RHC: right heart catheterization
PAP: pulmonary arterial pressure
PAWP: pulmonary artery wedge pressure
PVR: pulmonary vascular resistance
PAH NYHA Functional Class

I. No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath).

II. Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath).

III. Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea.

IV. Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.
Historic Median Survival and Drug Approvals

Median Survival

3 years

Modest improvement in survival despite 20 years and 13 approved products

5 years

Vasodilator Pathways

sGC = soluble guanylate cyclase stimulator / Prost = prostacyclin
PDE5 = phosphodiesterase type 5 inhibitor / ERA = endothelin receptor antagonist

1995

IV Epoprostenol

1995

SC Treprostinil

2001

Bosentan

2001

Inhaled Iloprost

2002

PDE5 Sildenafil

2004

PDE5 IV Sildenafil

2005

Prost IV Treprostinil

2007

ERA Ambrisentan

2009

PDE5 Tadalafil

2013

PROST Selexipag

2015

PROST Riociguat

sGCs

ERA

Prost

Prost

PDE5

PDE5

sGCs

Prost

ERA
Standard of Care Mechanistic Pathways: Vasodilation

Early Combination Therapy is the Current Approach

Sequential Combination

Drug 1

Drugs 1 + 2

Drugs 1 + 2 + 3

Early Combination

2 or 3 Drugs Right Away

50% of newly diagnosed patients

Survival Remains Poor

REVEAL previously diagnosed patients: N=2039

No. at Risk:
Full cohort 2039 1826 1616 1430 1262 1120

MEDIAN SURVIVAL ~5 YEARS

Survival (%)
Interesting New Therapy Classes in Development

- **Elastase inhibition**
  - Neutrophil elastase levels elevated in PAH
  - Elastase inhibition associated with anti-inflammatory and anti-remodeling effects in pulmonary vasculature

- **Interleukin-6 (IL6) inhibition**
  - Pro-inflammatory cytokine IL6 elevated in serum and lungs of PAH patients
  - IL6-directed therapy inhibits proliferation of both smooth muscle and endothelial cells in pulmonary arterioles

- **TGF-beta (BMP-BMPR2 signaling)**
  - BMP signaling pathway is critical for maintaining pulmonary vasculature in all forms of PAH
Mutations in BMPR2 gene (encodes BMP type II receptor) cause ~75%\(^1\) of heritable PAH cases.

A majority of PAH patients without BMPR2 mutations show reduced BMPR2 expression\(^2\)

- Reduced BMP signaling likely plays a major role in all forms of PAH.

Patients with mutations in ACVRL1 and Endoglin may develop heritable PAH identical to BMPR2-PAH.

1 Based on % of PAH patients of each type at time of enrollment in US REVEAL registry (Benza et al. Circulation 122, 2010)

Key Takeaways

- PAH is a devastating disease
- Current therapies have positively impacted QoL and survival
  - Vasodilators (relax blood vessels)
- Unmet medical need is high as survival remains poor
- Critical need for therapies that modify disease pathogenesis
- BMP/BMPR2 signaling defect underlies both idiopathic and familial forms of PAH
Sotatercept
John Quisel, Ph.D., J.D.
SVP, Corporate Development
Normal BMP/BMPR2 Pathway Signaling

BMP Ligands

ALK1

BMPRII

Endothelial Cell

SMAD 1/5/8

Normal Pathway Signaling

Vessel Muscularization Balanced

Normal Artery

18
Deficient BMP/BMPR2 Pathway Signaling

Pathway Deficiency Causes:
1. BMP Deficiency
2. BMPR2 Mutation
3. Activin/TGF-beta Overexpression

Pathway Mutation/Reduced/Deficient Signaling

Vessel Muscularization ↑
Sotatercept Background

Activin Ligand Trap

- Restores BMP signaling pathway
- ~400 patients of clinical experience
- Subcutaneous injection every three weeks
Sotatercept Restores BMP Signaling Defect

- Normal BMP Signaling
- Deficient BMP Signaling
- Sotatercept Restores BMP Signaling

BMP Deficiency + Sotatercept

RLU

-50%
Sotatercept Blocked the Development of Vessel Muscularization / Pulmonary Vascular Remodeling

**Pulmonary Arterioles (10-50 µm, N=100) Classification (%)**

<table>
<thead>
<tr>
<th>Test Compound</th>
<th>Vehicle</th>
<th>Sildenafil</th>
<th>Sotatercept¹</th>
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<tbody>
<tr>
<td>% of Completely Muscularized Vessels</td>
<td>72.5%</td>
<td>67.4%</td>
<td>29.3%</td>
</tr>
</tbody>
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**Sugen hypoxia, lung histology (αSMA/elastin staining, 10X magnification)**
Sotatercept Prevented the Increase in Pulmonary Arterial Pressure

**SUGEN HYPOXIA**

**Pulmonary Circulation**

<table>
<thead>
<tr>
<th>MOLECULES</th>
<th>% Reduction in Mean Pulmonary Arterial Pressure (PAP)</th>
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<tbody>
<tr>
<td>Macitentan² (ERA)</td>
<td>-36%</td>
</tr>
<tr>
<td>Sildenafil (PDE5)³</td>
<td>-22%</td>
</tr>
<tr>
<td>Beraprost NP₁ (prostacyclin)</td>
<td>-27%</td>
</tr>
<tr>
<td>Sotatercept²⁴</td>
<td>-51%</td>
</tr>
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</table>

1 Akagi et al J Cardiovasc Pharmacol 2016; 67; 290-298.
3 RAP-011 and Sildenafil were tested in same study
Sotatercept Blocked the Development of Right Heart Failure

**Right Heart Failure**

<table>
<thead>
<tr>
<th>Weight Ratio</th>
<th>Normal</th>
<th>Vehicle</th>
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<tbody>
<tr>
<td>RV / LV+S^4</td>
<td>0.288</td>
<td>0.607</td>
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</table>

- **Sotatercept**: -54%
- **Sildenafil (PDE5)**: -10%
- **Macitentan**: -31%
- **Beraprost Na**: -32%

**% Reduction in RV Hypertrophy RV/(LV+S)**

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1 Akagi et al J Cardiovasc Pharmacol 2016; 67; 290-298.
3 RAP-011 and Sildenafil were tested in same study
4 Right ventricle / left ventricle + septum
Sotatercept and PAH Highlights

- Large and expanding WW patient population with 70K patients in U.S./EU
  - 80% with functional class II and III

- Targeting genetically defined signaling pathways critical for disease (BMPR2 pathway or TGF-beta/BMP superfamily)

- Sotatercept\(^1\) outperforms standard of care in preclinical models

- Ability to combine with standard of care
PULmonary Arterial Hypertension
Phase 2 Trial of SotAteRcept
David Badesch, M.D.

Clinical Director, Pulmonary Hypertension Center at the University of Colorado Hospital; Professor of Medicine, Divisions of Pulmonary Sciences and Critical Care Medicine and Cardiology at the University of Colorado Anschutz Medical Campus
Background and Center Information

▪ Current Position:
  – Professor of Medicine, Divisions of Pulmonary Sciences and Critical Care Medicine and Cardiology, University of Colorado Anschutz Medical Campus
  – Director, Pulmonary Hypertension Program (28 years)

▪ Experience:
  – Member of numerous steering committees for the development of therapies in PAH
  – Chair, Pulmonary Circulation Assembly, American Thoracic Society
  – Chair, Scientific Leadership Council, Pulmonary Hypertension Association
  – 137 publications, 21 chapters, 25,997 citations

▪ Treatment Center:
  – University of Colorado Pulmonary Hypertension Program
    • One of the oldest and largest pulmonary hypertension programs in the world
    • 4 Physicians, 5 Clinical Research Coordinators, 4 Clinical Nurses, and 1 NP
    • Currently participating in multiple registries, biorepositories, and clinical trials
Phase 2 Key Entry Criteria

1. Adult male and female patients, age ≥ 18
2. Symptomatic pulmonary hypertension, WHO Functional Class II and III
3. WHO Diagnostic PH Group I: PAH, the following subtypes:
   - Idiopathic PAH
   - Heritable PAH
   - Drug- and toxin-induced
   - PAH associated with connective tissue disease
   - PAH associated with simple, congenital systemic-to-pulmonary shunts at least 1 year following shunt repair
4. Baseline right heart catheterization (RHC) with ≥ 5 Wood units
5. 6-minute walk distance (6MWD): 150 - 450 meters
Phase 2 Design Schema

**Primary Treatment Period**

- Placebo (PBO) plus Standard of Care (SOC) N=30
- Sotatercept 0.3 mg/kg plus SOC N=30
- Sotatercept 0.7 mg/kg plus SOC N=30

**Extension Period**

- 18 Months
- PBO participants randomized 1:1 to 0.3 mg/kg or 0.7 mg/kg sotatercept plus SOC
- Sotatercept participants continue on current dose plus SOC

**Randomization** (1:1:1)

- 6 Months
- 24-week Primary Endpoint
- Pulmonary vascular resistance (PVR) assessment

**Periods**

- Primary Treatment Period: 6 Months
- Extension Period: 18 Months
## Phase 2 Study Endpoints at 24 Weeks Versus Baseline

<table>
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<tr>
<th>Primary Endpoint</th>
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<tr>
<td>▪ Change in pulmonary vascular resistance (PVR)</td>
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<table>
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<tr>
<th>Key Secondary Endpoint</th>
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<tr>
<td>▪ Change in 6-minute walk distance</td>
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<tr>
<th>Other Secondary Endpoints</th>
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<tr>
<td>▪ Clinical worsening</td>
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<tr>
<td>▪ Change in functional class</td>
</tr>
<tr>
<td>▪ Change in quality of life (QoL)</td>
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Phase 2 Trial Design Summary

- PULSAR Phase 2 trial initiation in Q2 2018
- Enrolling 90 functional class II/III PAH patients
- Preliminary top-line results in 1H 2020
  - 6-month primary treatment period
- Long-term 18-month extension phase
PAH Webinar Q&A Session

Aaron Waxman, M.D., Ph.D. Brigham and Women’s Hospital
David Badesch, M.D. University of Colorado Hospital
John Quisel, Ph.D., J.D. SVP, Corporate Development
Habib Dable Chief Executive Officer
Matthew Sherman, M.D. Chief Medical Officer
Peter Linde, M.D. VP, Medical Research
Todd James, IRC VP, Investor Relations and Corp. Comm.