Corporate Update

May 2018
Tenax Therapeutics

Specialty pharmaceutical company focused on search, development, and commercialization of drugs that address diseases with high unmet medical need

• **Product - Levosimendan**
  • Calcium Sensitizer/K-ATP Channel Activator
  • Approved in 60+ countries
  • >1.4 million patients treated to date
  • US & Canadian rights

• **Levosimendan Clinical Development - Pulmonary Hypertension**
  • WHO Group 2- pulmonary hypertension associated with heart failure with preserved ejection fraction (PH-HFpEF)
  • Initiate Phase 2 Trial in Q3 2018

• **Ongoing search for assets and collaborations**
Levosimendan Clinical Development Strategy in Pulmonary Hypertension, WHO-Group 2

• Leverage positive levosimendan clinical study data
  • Positive levosimendan Phase 2 pulmonary hypertension study data
  • Positive levosimendan right heart failure data

• **Focus development in PH-HFpEF** (Pulmonary Hypertension in patients with Heart Failure and Preserved Ejection Fraction)
  • High unmet medical need
  • Large patient population with no approved drugs

• **Capitalize on PH-HFpEF advisors’ expertise and advocacy**
  • Validate clinical development strategy with PH-HFpEF experts
PH-HFpEF Development Plan Validated by World Recognized Experts in Pulmonary Hypertension and HFpEF

Stuart Rich, M.D.
Professor of Medicine
Northwestern University Feinberg School of Medicine
Director, Pulmonary Vascular Disease Program
Bluhm Cardiovascular Institute
Previous FDA Cardio-Renal Advisory Committee Member
Recognized Global Pulmonary Hypertension Expert

Daniel Burkhoff MD, PhD
Director Heart Failure, Hemodynamics and MCS Research at the Cardiovascular Research Foundation
Adjunct Associate Professor of Medicine, Columbia University

Sanjiv Shah, MD, FAHA, FACC, FASE
Professor of Medicine
Director, T1 Center for Cardiovascular Therapeutics
Director, Northwestern HFpEF Program
Division of Cardiology, Dept of Medicine
Northwestern University Feinberg School of Medicine
Rationale for Development of Levosimendan in PH-HFpEF

• PH-HFpEF is an area of high unmet medical need
  • High mortality (up to 50% at 5 years)
  • Poor quality of life (poor exercise capacity)
  • No approved therapies in PH-HFpEF

• Commercially attractive market
  • Large potential market - Estimated PH-HFpEF prevalence in the US >1,500,000
  • High value chronic therapy that addresses a large unmet need

• Mechanistic rationale for Levosimendan in PH-HFpEF
  • Including mechanisms directed at right heart failure

• Existing preliminary positive Phase 2 clinical data in Pulmonary Hypertension

• Efficient and timely Phase 2 trial is planned

• IV Levosimendan exclusivity as NCE
Global Pulmonary Hypertension Pharmaceutical Market
> $5 Billion in 2016

- Actelion-J&J, $2.0B
- United Therapeutics, $1.5B
- Pfizer, $285M
- Gilead, $819M
- Bayer, $279M

Based on publicly reported sales from company annual reports
Pulmonary Hypertension WHO Classification
Levosimendan Development Focused on Group 2

Global Pulmonary Hypertension Product Sales -2016 Allocated by WHO Group Approved Indication

- **Group 1 Approved Products**: $4,905,000
- **Group 2 Approved Products**: $0
- **Group 3 Approved Products**: $0
- **Group 4 Approved Products**: $279,400
- **Group 5 Approved Products**: $0

Excludes potential off-label uses
**PH-HFpEF Unmet Need**

Approved WHO Group 1 Drugs are **not Approved or Effective in** Group 2 Patients

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Pulmonary Hypertension WHO Group 1 (PAH)</th>
<th>Pulmonary Hypertension WHO Group 2 (HFpEF)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDE5 Inhibitors</td>
<td>FDA Approved</td>
<td>Efficacy not established</td>
</tr>
<tr>
<td>Endothelin Receptor Antagonists</td>
<td>FDA Approved</td>
<td>Efficacy not established</td>
</tr>
<tr>
<td>Soluble Guanylate Cyclase Stimulators</td>
<td>FDA Approved</td>
<td>Efficacy not established</td>
</tr>
<tr>
<td>Prostacyclins (IV/SC/Inhaled/Oral)</td>
<td>FDA Approved</td>
<td>Efficacy not established</td>
</tr>
</tbody>
</table>
PH-HFpEF Patients have Poor Outcomes

PH-HFpEF + RV Dysfunction is Associated with Highest Mortality

PH-HFpEF with Right Heart Dysfunction (RHD): Large Target Market with Very High Needs

Estimates based on
Mechanistic Rationale for Levosimendan in PH-HFpEF – More than just a Vasodilator

**Problem**
- Right Heart
  - RV Failure
- Pulmonary Vasculature
  - Increased Pulmonary Congestion & Pressure
- Left Heart
  - Poor LV Relaxation and Reduced Cardiac Output

**Levosimendan MOA**
- Ca Sensitizer
- K-ATP Channel

**Potential Benefits**
- Inotropic & Lusitropic Effects to **Improve RV Function**
- Pulmonary Vasodilation to **Reduce PA Pressure/RV Afterload**
- Inotropic & Lusitropic Effects to **Improve LV Function**
Increasing Number of Scientific Publications on Levosimendan in Pulmonary Hypertension

**Clinical Studies**


**Preclinical Studies**

Results from a Multicenter, Randomized, Placebo Controlled, Pilot Study of Levosimendan in Pulmonary Hypertension Patients

Kleber et al Patient Demographics

<table>
<thead>
<tr>
<th></th>
<th>Levosimendan (n = 18)</th>
<th>Placebo (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>62 ± 11</td>
<td>58 ± 12</td>
</tr>
<tr>
<td>Sex, M/F</td>
<td>9/9</td>
<td>8/2</td>
</tr>
<tr>
<td>Etiology of pulmonary hypertension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary arterial hypertension</td>
<td>7 (39)</td>
<td>4 (40)</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Portal hypertension</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Congenital systemic to pulmonary shunts</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Pulmonary venous hypertension due to left-sided heart disease</td>
<td>10 (56)</td>
<td>4 (40)</td>
</tr>
<tr>
<td>Pulmonary hypertension due to chronic thrombotic and/or embolic disease</td>
<td>1 (5)</td>
<td>2 (20)</td>
</tr>
<tr>
<td>Signs of right heart failure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jugular venous distension</td>
<td>12 (67)</td>
<td>7 (70)</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>14 (78)</td>
<td>8 (80)</td>
</tr>
<tr>
<td>Known response to vasodilator testing</td>
<td>18 (100)</td>
<td>10 (100)</td>
</tr>
<tr>
<td>Systemic hemodynamics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>121 ± 23</td>
<td>116 ± 15</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>72 ± 10</td>
<td>75 ± 12</td>
</tr>
<tr>
<td>Heart rate</td>
<td>75 ± 18</td>
<td>70 ± 13</td>
</tr>
<tr>
<td>New York Heart Association class</td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>15 (83)</td>
<td>9 (90)</td>
</tr>
<tr>
<td>IV</td>
<td>3 (17)</td>
<td>1 (10)</td>
</tr>
<tr>
<td>mRAP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>12 ± 5.9 (n = 15)</td>
<td>14 ± 4.9 (n = 9)</td>
</tr>
<tr>
<td>Range</td>
<td>5.29</td>
<td>7.24</td>
</tr>
<tr>
<td>Use of vasoactive medicine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diuretics</td>
<td>15 (83)</td>
<td>8 (80)</td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitor/AT2-blocker</td>
<td>14 (78)</td>
<td>6 (60)</td>
</tr>
<tr>
<td>β-Blocker</td>
<td>10 (56)</td>
<td>7 (70)</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td>6 (33)</td>
<td>4 (40)</td>
</tr>
<tr>
<td>Bosentan</td>
<td>3 (17)</td>
<td>2 (20)</td>
</tr>
</tbody>
</table>

Values are mean ± SD or n (%). Medication is expressed as the number of patients taking the drug (%).

* According to the Venice classification.24
Change in PVR (mean ± SEM) during 24-hour infusion and 6-hour infusion at week 8

*Primary Endpoint: Change in PVR at the end of the Initial 24-hour infusion

P = 0.009*

P = 0.253

Δ PVR (%)
Change in mPAP (mean ± SEM) during 24-hour infusion and 6-hour infusion at week 8

<table>
<thead>
<tr>
<th>Time</th>
<th>Δ mPAP (%)</th>
<th>Levosimendan n=18</th>
<th>Placebo n=10</th>
<th>Levosimendan n=16</th>
<th>Placebo n=8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>20</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 0</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 8</td>
<td>-20</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

P = 0.056

P = 0.172
Levosimendan in Pulmonary Hypertension
*The Clinical Respiratory Journal* (September 2017)

**Primary endpoint-Change in WHO Functional Class**

A. Change in WHO-FC after infusion of levosimendan from basement to post-treatment. World Health Organization Function Class: WHO-FC.

**Primary Endpoint- Change in Dyspnea Scores**

B. Change in Borg dyspnoea scores from basement to post-treatment.

Phase 2 Study Design

• Double-blind study of PH-HFpEF Patients
  • PAP ≥35, PCWP ≥20, NYHA Class IIb/III, LVEF ≥40%
• 36 Evaluable patients; 25 sites; 14-18 months
• Primary Endpoint:
  • Change from baseline PCWP with bicycle exercise at Week 6
• Secondary Endpoints:
  • Change in Cardiac Index at rest and with exercise
  • Change in PVR effect at rest and with exercise
  • Change in PCWP when supine and legs elevated
  • Patient global assessment
  • Exercise duration via 6 minute walk test
  • Physician’s assessment of functional class
  • Clinical events: death and hospitalizations
Levosimendan in PH-HFpEF Phase 2 Study Design

**Open-Label Lead-In**
24 hour Infusion

Levosimendan
(0.1 µg/kg/min)

- Responders
  - n=36
- Non-Responders

**Chronic Phase (6 weeks)**
Weekly infusion through Week 5

Levosimendan
(0.075 µg/kg/min)
(n=18)

- Titration at Week 4 to 0.1 µg/kg/min

Placebo
(n=18)

Final Evaluation
Pre-IND Meeting in PH-HFpEF

- Meeting with FDA to review development of levosimendan in PH-HFpEF, March 2018
- FDA agreed nonclinical studies sufficient to support full development in PH-HFpEF
- Agreed with planned Phase 2 study design, entry criteria and endpoints
- Phase 2 study may be conducted under existing IND
- FDA acknowledged unmet medical need in PH-HFpEF could support limited Phase 3 program; topic to be discussed further at End-of-Phase 2 Meeting
Summary
The Opportunity for Levosimendan in PH-HFpEF

• PH-HFpEF is an area of high unmet medical need
  • High mortality (up to 50% at 5 years)
  • Poor quality of life (poor exercise capacity)
  • No approved therapies in PH-HFpEF

• Commercially attractive market
  • Large potential market - Estimated PH-HFpEF prevalence in the US >1,500,000
  • High value chronic therapy that addresses a large unmet need

• Mechanistic rationale for Levosimendan in PH-HFpEF
  • Including mechanisms directed at right heart failure

• Existing preliminary positive Phase 2 clinical data in Pulmonary Hypertension

• Efficient and timely Phase 2 trial is planned

• IV Levosimendan exclusivity as NCE