Inhaled sodium nitrite in pulmonary hypertension associated with heart failure with preserved ejection fraction

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Disclosure

- Research grant from Aires Pharmaceuticals, a wholly owned subsidiary of Savara Inc. (formerly Mast Therapeutics)
Nitric Oxide

\[ \text{N}::\text{O} \]
Endothelium

Shear Stress

ACH

NOS

L-arginine → L-citrulline

NO

guanylyl cyclase (inactive) → guanylyl cyclase (active)

cGMP → GTP

Relaxation
Limitations for eNOS dependent NO signaling

- Endocrine activity limited by short half-life of NO in blood (Half life of < 2 milliseconds because NO scavenged by hemoglobin)
- Lack of intrinsic mechanism for hypoxic response (eNOS requires a molecule of oxygen to form NO)
- NO synthase is uncoupled and fails to generate NO with inflammatory and oxidant stress in disease
Nitrite salt: NaNO$_2$, KNO$_2$, HNO$_2$
Two parallel systems for NO generation in mammals
Nitrite therapeutics?
Nitrite Therapeutics

- Gastric mucosal protection
- Gastric host defense antibacterial effects
- Cerebral vasospasm
- Pulmonary hypertension
- Ischemia reperfusion:
  - heart
  - liver
  - solid organ transplantation
Nitrite therapeutics for PH (Group 1 and 2 disease)?
Clinical Development of Nitrite for PH

- One and 12-month rat and canine toxicology studies show only methemoglobinemia at very high doses
- Dose escalation phase IA studies complete in normal volunteers
- Safe dosing to 95 mg on background sildenafil in normal volunteers and five Group I PAH patients
- Phase I-II dose finding safety trial in 40 countries closed for data analysis
- Phase II catheterization study supported by NHLBI PO1 and MAST Therapeutics
Ongoing Phase II Acute Hemodynamic Study

- 43 enrolled (ClinicalTrials.gov NCT01431313)
  - 20 Group 1 (enrollment closed)
  - 17 Group 2 (of 20 planned)
  - 6 Group 3 (of 10 planned)

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
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<tbody>
<tr>
<td>MPAP (mm Hg)</td>
<td>≥ 25</td>
<td>≥ 25</td>
<td>≥ 25</td>
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<tr>
<td>PCWP (mm Hg)</td>
<td>≤ 15</td>
<td>&gt; 15</td>
<td>≤ 15</td>
</tr>
<tr>
<td>TPG (mm Hg)</td>
<td>−</td>
<td>&gt; 12</td>
<td>−</td>
</tr>
<tr>
<td>PVR (Woods units)</td>
<td>−</td>
<td>−</td>
<td>≥ 3</td>
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Acute Hemodynamic Effects of Inhaled Nitrite in Pulmonary Hypertension due to Left Heart Disease (HFpEF)

- Baseline 1 Hemodynamics!
- iNO 40 ppm x 10 min!
- Baseline 2 Hemodynamics!
- iNO off x 10 min!
- Nitrite Dose 1 Inhaled (45 mg)!
- 15 min
- 30 min
- 45 min
- 60 min
- Hemodynamics Post-Dose 1
- Nitrite Dose 2 Inhaled (90mg)!
- 15 min
- 30 min
- 45 min
- 60 min
- Hemodynamics Post-Dose 2

PH-HFpEF

**PH Group 1 (PAH)**


<table>
<thead>
<tr>
<th>mPAP (mm Hg)</th>
<th>Cardiac Index (L/Min/m²)</th>
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<tbody>
<tr>
<td>Baseline 1</td>
<td>iNO</td>
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<tr>
<td>10</td>
<td>20</td>
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<table>
<thead>
<tr>
<th>Right Atrial Pressure (mm Hg)</th>
<th>PCWP (mm Hg)</th>
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<tbody>
<tr>
<td>Baseline 1</td>
<td>iNO</td>
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<thead>
<tr>
<th>PVR (Woods units)</th>
<th>PA Compliance (mL/mm Hg)</th>
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<tr>
<td>Baseline 1</td>
<td>iNO</td>
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<td>10</td>
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PH Group 3 (Lung Dz)

Acute Hemodynamic Effects of Inhaled Nitrite in Pulmonary Hypertension due to Left Heart Disease (HFpEF)

Resistance-Compliance (RC) Curve

Inhaled Sodium nitrite improves exercise hemodynamics and ventricular performance in HFpEF

- Inhaled sodium nitrite (90mg) vs placebo (n=13 per group)
- Decrease PCWP, RA, mPAP at rest and with exercise
- Increase resting PA Compliance

Physiology of improved exercise capacity with nitrite in PH-HFpEF

- NO → Rest Venous Normoxia
- NO → Exercise Venous Hypoxia

- NO2 → RV Filling Pressures
- NO2 → LV Filling Pressures

- RV Filling Pressures → Exercise Capacity
- LV Filling Pressures → Exercise Capacity
- PA Pressures → Exercise Capacity

- PA Compliance

- Skeletal Muscle Metabolism*

Development of Nebulized Inhaled Nitrite

• Squeezable plastic ampule kit consisting of 80 mg/ml phosphate buffered Sodium Nitrite has been developed

• Nebulized 3-4 times a day with the Philips I-neb
  – Portable, rechargeable
  – Monitors compliance
Currently Enrolling Studies

**INDIE-HFpEF**

*Inorganic Nitrite Delivery to Improve Exercise Capacity in HFpEF*

Heart Failure Network (US)

- Multicenter Study, goal n=100, blinded placebo controlled, 4 week crossover
- ClinicalTrials.gov #NCT02742129
- HFpEF (clinical or RHC or BNP or echo evidence)
- Primary Endpoint: Peak VO$_2$ after 4 weeks treatment with inhaled nitrite
**INABLE-HF: Inorganic Nitrite to Amplify the Benefits and toLerability of Exercise training**
Barry A. Borlaug, MD
Mayo Clinic

- Single Center Study
- ClinicalTrials.gov #NCT02713126
- HFpEF (clinical or RHC or BNP or echo evidence) and HF is primary limit to activity
- **Primary Endpoint**: Peak $\text{VO}_2$ after 4 weeks treatment with inhaled nitrite
Conclusions

- Nitrite is potent hypoxic vasodilator at physiological concentrations.
- In studies to date, nitrite appears safe and tolerable.
- In PH-HFpEF, inhaled nitrite acutely lowers filling pressures, pulmonary pressures, mediated by a primary physiological effect of increasing pulmonary vascular compliance.
- Phase 2 studies are underway to assess the effects of chronic therapy on exercise capacity and/or hemodynamics.
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