Bronchiolitis (BRO) Overview

- Common lower respiratory tract infection and leading cause of infant hospitalization
- Significant impact on the elderly with >220k hospitalizations per year in the US
- No drugs approved for the treatment of BRO patients
- Standard of care in the hospital is oxygen and hydration
Market Dynamics: Bronchiolitis (BRO)

150k infant hospitalizations per year in the US for bronchiolitis*

180K elderly hospitalizations per year in the US due to RSV** implying more than 220k for bronchiolitis

AIT price will be based on reduced length of hospital stay from trials

Total US market size in excess of $2 billion

Anticipate ex-US market to be comparable to the US market

There is no competition

*Pelletier et al. Direct medical costs of hospitalizations in the United States, Pediatrics 2006
**Falsey et al. Respiratory Syncytial Virus infection in elderly and high risk adults, NEJM 2005
# Completed Bronchiolitis Phase 2 Trial

## Trial Design
- Randomized, Prospective, Double-blind
- 43 patients (age: 2-12 months) with bronchiolitis (mostly due to RSV)
- N=21: 160 ppm NO + O₂ 5x/day for 30 minutes up to 5 days
- N=22: Supportive Care (O₂ & hydration)
- 3 follow up visits at 2, 3 & 4 weeks post discharge

## Trial Highlights
- Single center at Soroka University Medical Center in Israel
- Presented at ATS 2015 in an oral session
- No treatment related SAEs
- Reduced length of hospital stay by >24hrs
- Statistical significance achieved in proposed phase III primary endpoint (Clinical Composite endpoint)

Publication Pending
Time to normal oxygen saturation
(Per Protocol, N=24, minimum of one day of hospitalization)

- Time to normal oxygen saturation was 80% faster with Nitric Oxide compared with standard treatment
- Mean time to oxygenation was 35hr in the Nitric Oxide group compared to 63hr in the control
- No treatment related SAEs

Data presented in oral session at ATS 2015
BRO Phase 2: Hospitalization Time

Decrease in Hospitalization time
(Per Protocol, N=24, minimum of one day of hospitalization)

- ~34% reduction in time of hospitalization, a validated FDA end point
- On average patients stayed one day (24 hours) less in the hospital with Nitric Oxide treatment compared to standard treatment

P-value 0.0587

Data presented in oral session at ATS 2015
BRO Phase 2: Composite End Point

Composite Clinical Score is based on Oxygenation, Respiratory Rate, Wheezing and Accessory Muscles
(Per Protocol, N=24, minimum of one day of hospitalization)

- This Composite Score is an FDA validated endpoint used in a pivotal trial for children with asthma
- Mean baseline clinical score was ~8 in both groups
- Mean Time to normal clinical score (<= 5) was 80% faster for the Nitric Oxide group

Data presented in oral session at ATS 2015
## BRO Trial Composite End Point

### Modified-Tal Scoring System

<table>
<thead>
<tr>
<th>Score</th>
<th>Resp Rate</th>
<th>Wheeze</th>
<th>$S_pO_2$</th>
<th>Acute Respiratory Muscle Utilization</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>&lt;30</td>
<td>None</td>
<td>&gt;95</td>
<td>None (no chest in-drawing, i.e., absence of lower part of the chest moves in or retracts when inhalation occurs)</td>
</tr>
<tr>
<td>1</td>
<td>30-45</td>
<td>Terminal Expiration Only</td>
<td>94-95</td>
<td>presence of mild intercostal in-drawing (just visible), no head bobbing or tracheal tug</td>
</tr>
<tr>
<td>2</td>
<td>46-60</td>
<td>Entire expiration and inspiration with stethoscope only</td>
<td>90-93</td>
<td>moderate amount of intercostal in-drawing, no head bobbing or tracheal tug</td>
</tr>
<tr>
<td>3</td>
<td>&gt;60</td>
<td>Entire expiration and inspiration without stethoscope only</td>
<td>&lt;89</td>
<td>moderate or marked intercostal in-drawing with presence of head bobbing or tracheal tug</td>
</tr>
</tbody>
</table>
Nitric Oxide for BROnchiolitis (NO-BRO) Phase 3 Trial Design

Randomized, Double Blind Trial

- Enroll 94 subjects at 3+ sites in Israel with a 1:1 randomization between 160 ppm NO + supportive care (O₂ + hydration) and supportive care alone
- Subjects will be 0-12 months old with acute bronchiolitis requiring hospitalization with at least 28 weeks of gestation
- PE (primary endpoint): the difference in hospital length of stay (discharge time based on physician decision)
- SE (secondary endpoint): the difference in time to clinical improvement based on the Modified Tal score (score ≥8 and <10 to enroll, ≤5 is goal)
- SE: the difference in time to S_pO₂ of ≥92%
- SE: Safety (specifically methaemoglobinemia and NO₂ levels) and Tolerability
- Treatment will be five 30 minute sessions per day not to exceed 25 treatments

Key Changes v. Phase 2

- Age was 2-12 months
- Gestation was a minimum of 36 weeks
- Tal score to enroll was ≥6 and ≤10
- ITT analysis was not restricted to hospitalized subjects
- Length of Stay was based upon hospital discharge, not physician decision
- Analysis included 24 subjects