RSV (Bronchiolitis) Overview

- Common lower respiratory tract infection and leading cause of infant hospitalization
- Significant impact on the elderly with 180k hospitalizations per year in the US*
- No drugs approved for the treatment of RSV patients
- Standard of care in the hospital is oxygen and hydration

* From CDC RSV working group - http://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2016-06/rsv-01-karron.pdf

Completed RSV Phase 2 Trial

Trial Design

- Randomized, Prospective, Double-blind
- 43 patients (age: 2-12 months) with bronchiolitis (mainly RSV)
- N=21: 160 ppm NO + O_2 5x/day for 30 minutes up to 5 days
- N=22: Supportive Care (O_2 & hydration)
- 3 follow up visits at 2, 3 & 4 weeks post discharge

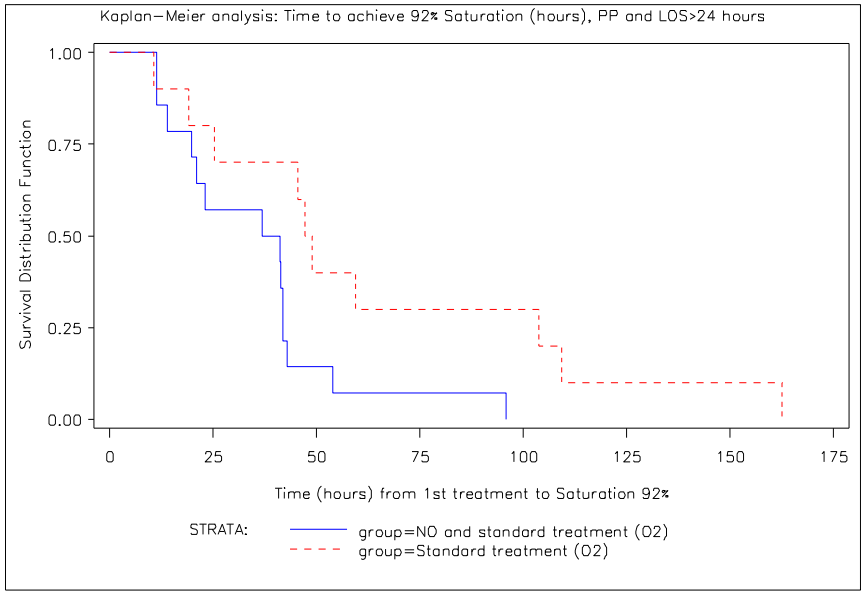
Trial Highlights

- 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)

RSV Phase 2: Time to Achieve Normal Oxygenation

Time to normal oxygen saturation

(Per Protocol, N=24, minimum of one day of hospitalization)



P-value 0.0275

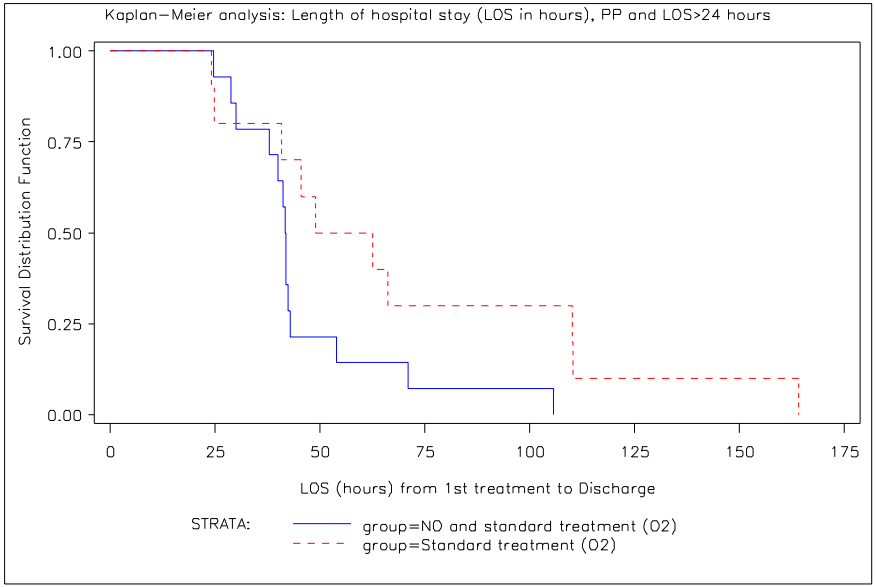
- Time to normal oxygen saturation was 80% faster with Nitric Oxide compared with standard treatment
- Mean time to oxygenation was 35hr in the Nitric Oxide group compared to 63hr in the control
- No treatment related SAEs

Data presented in oral session at ATS 2015

RSV Phase 2: Hospitalization Time

Decrease in Hospitalization time

(Per Protocol, N=24, minimum of one day of hospitalization)



P-value 0.0587

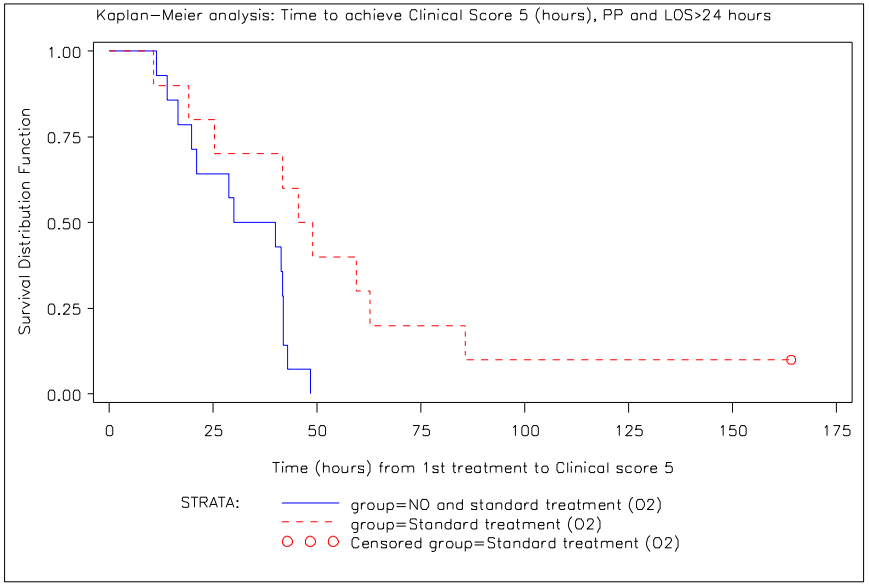
- ~34% reduction in time of hospitalization a validated FDA end point
- On average patients stayed one day less in the hospital with Nitric Oxide treatment compare to standard treatment

Data presented in oral session at ATS 2015

RSV 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)



P-value 0.0125

- 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

RSV Trial Composite End Point

Modified-Tal Scoring System

Score	Resp Rate	Wheeze	S_pO_2	Acute Respiratory Muscle Utilization
0	<30	None	>95	None (no chest in-drawing, i.e., absence of lower part of the chest moves in or retracts when inhalation occurs)
1	30-45	Terminal Expiration Only	94-95	presence of mild intercostal in-drawing (just visible), no head bobbing or tracheal tug
2	46-60	Entire expiration and inspiration with stethoscope only	90-93	moderate amount of intercostal in-drawing, no head bobbing or tracheal tug
3	>60	Entire expiration and inspiration without stethoscope only	<89	moderate or marked intercostal in-drawing with presence of head bobbing or tracheal tug

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 (O_2 + 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_pO_2 of ≥92%
- SE: Safety (specifically methaemoglobinemia and NO_2 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