Second Indication: Bronchiolitis (BRO) Overview

Bronchiolitis is the leading cause of hospitalization for infants worldwide [1]

Bronchiolitis Overview & Market Dynamics

- **~150,000 infant hospitalizations** per year in the US[2]
- Significant impact on the elderly with **177,000 hospitalizations** per year in the US[3]
- **No drugs approved** for the treatment of BRO patients[4]
- Standard of care in the hospital is oxygen and hydration[5]

Market Size

- AIT estimates US market size is to be over **$2 B** and projects global market to be similar size to the US market with no real competition
- AIT's goal would be to reduce length of hospitalization

(1) Scand J Trauma Resusc Emerg Med. 2014; 22: 23.; WHO
(2) Pelletier et al. Direct medical costs of hospitalizations in the United States, Pediatrics 2006
(3) CDC (due to RSV only)
(4) American Academy of Pediatrics

Completed Two Pilot Bronchiolitis Trials

Data from both Pilot Bronchiolitis trials demonstrated a significant reduction in length of hospital stay (LOS)

2014 Trial Design and Highlights

- Randomized, Prospective, Double-blind
- 43 patients (age: 2-12 months) with acute bronchiolitis (mostly due to RSV) and at least 36 weeks of gestation
- N=22: Supportive Care (O_2 & hydration)
- N=21: Supportive Care + 160 ppm NO for 30 minutes 5x/day up to 5 days
- Follow up visits 2, 3 & 4 weeks post discharge
- Single center at Soroka University Medical Center in Israel
- Data presented at ATS 2015 in an oral session
- Reduced length of hospital stay by ~24hrs in patients who stayed in the hospital for at least 24 hours
- No treatment related SAEs
- Improvements in composite endpoint (modified Tal score) and O_2 consistent with improvement in LOS

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ORIGINAL ARTICLE: RESPIRATORY INFECTIONS

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Nitric oxide inhalations in bronchiolitis: A pilot, randomized, double-blinded, controlled trial

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Abstract

Aim: The aims of this pilot study were to determine safety, tolerability (primary outcome) and efficacy (secondary outcome) of high-dose inhaled nitric oxide for the treatment of infants with moderately severe bronchiolitis.

Methods: This was a pilot, double-blinded, randomized controlled study (phase IIa). Intermittent inhalations of nitric oxide 160 ppm for 30 min or oxygen/air (control) were given 5 times/day to hospitalized infants (2–11 months) with acute bronchiolitis. Oxygen saturation, methemoglobin, and nitric dioxide (NO_2) levels and vital signs were monitored.

Results: Forty-three infants were enrolled. Baseline characteristics were comparable in both study groups. Mean clinical score, comprised of four components: respiratory rate, use of accessory muscles, wheezes and crackles, and % room-air oxygen saturation, was 7.86 (±1.1) and 8.09 (±1.2) in the NO and control groups, respectively, consistent with moderate severity. The overall frequency of adverse events was similar between the groups. Repeated nitric oxide inhalations did not result in increased inhaled NO_2 levels or cumulative effect on methemoglobin levels. Secondary outcomes of efficacy were measured by length of hospitalization (LOS) in hours: LOS did not differ between groups. However, in a post-hoc analysis of a subgroup of infants hospitalized for >24 h (n = 24), the median LOS was shorter in the nitric oxide (41.9 h) than in the control group (62.5 h) (P = 0.014).

Conclusion: Our study was unable to detect a difference in side effects using intermittent high-dose nitric-oxide inhalation or supportive treatment alone, in infants with moderate bronchiolitis. Preliminary efficacy outcomes are encouraging.

KEYWORDS
bronchiolitis, inhaled nitric oxide in bronchiolitis, nitric oxide, randomized controlled trial, respiratory syncytial virus

(1) : https://onlinelibrary.wiley.com/doi/epdf/10.1002/ppul.23905

Completed Two Pilot Bronchiolitis Trials

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2018 Trial Design

- Enrolled 67 subjects at 6 sites in Israel with a 1:1 randomization between 160 ppm NO + supportive care (O_2 + hydration) and supportive care alone
- Subjects were 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 (LOS)
- SE (secondary endpoint): time to clinical improvement using the Modified Tal score (score ≥7 and <10 to enroll, ≤ 5 is goal)
- SE: the difference in time to SpO_2 of >92%
- SE: Safety (specifically NO_2 levels and methaemoglobinemia) and Tolerability
- Treatment was five 30 minute sessions per day not to exceed 25 treatments

2018 Trial Results to Date

Hospital LOS	**ITT**		**aITT**	
Arm	NO	Ctrl	NO	Ctrl
# of Patients	33	34	32	34
Mean LOS (hrs)	66.8	84.2	60.4	81.4
NO Benefit (hrs)	17.4		**21.0**	
P-value*	0.27*		**0.11***	

*Not significant p≤0.05; Welch's t-test used
ITT = intent to treat; aITT = adjusted intent to treat

- Adjusted intent to treat (aITT) differs from the ITT via 2 protocol deviations: 1 patient removed from the NO arm due to enrollment with a feeding tube; and 1 patient LOS reduced in the control arm
- There were no serious adverse events (SAEs) related to NO therapy

Pivotal Study Targeted for 2019/2020 Winter

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