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 from equivalent viral infections 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

Market Size

- AIT estimates US market size to be **>$2 B** and projects global market to be similar size to the US market with no competition
- AIT's goal would be to reduce length of hospitalization in infants
- Elderly population trials to follow infants

(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

WILEY

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

Data from both Pilot Bronchiolitis trials demonstrated a significant reduction in LOS

2018 Trial Design and Baseline Characteristics

- Randomized 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 methemoglobinemia) and Tolerability
- Treatment was five 30 minute sessions per day not to exceed 25 treatments
- All inhalations delivered by air/oxygen blender ±NO via a simple mask with a minimum FiO2 of 21%

DATA PRESENTED AT THE SEPTEMBER 2018 EUROPEAN RESPIRATORY SOCIETY (ERS)

Characteristic		Std Treatment (N=34, Mean±SD)	NO + Std (N=33, Mean±SD)
Gender		21 M, 13 F	20 M, 13 F
Age (weeks)		16.72 ± 11.66	16.39 ± 11.7
Weight (Kg)		5.88 ± 1.81	5.82 ± 1.79
Gestation Week		38.17 ± 1.82	38.25 ± 1.81
mTal Clinical Score		8.49 ± 1.02	8.45 ± 1.02
Vital Signs	Temp.	37.37 ± 0.84	37.38 ± 0.85
	BP (Sys/Dia)	101.0/58.0	101.0/57.6
	Heart Rate	148.5 ± 21.33	148.37 ± 21.24
	Resp. Rate	56.85 ± 11.21	57.31 ± 11.08
	% SpO_2 (Room Air)	88.54 ± 4.04	88.69 ± 3.98

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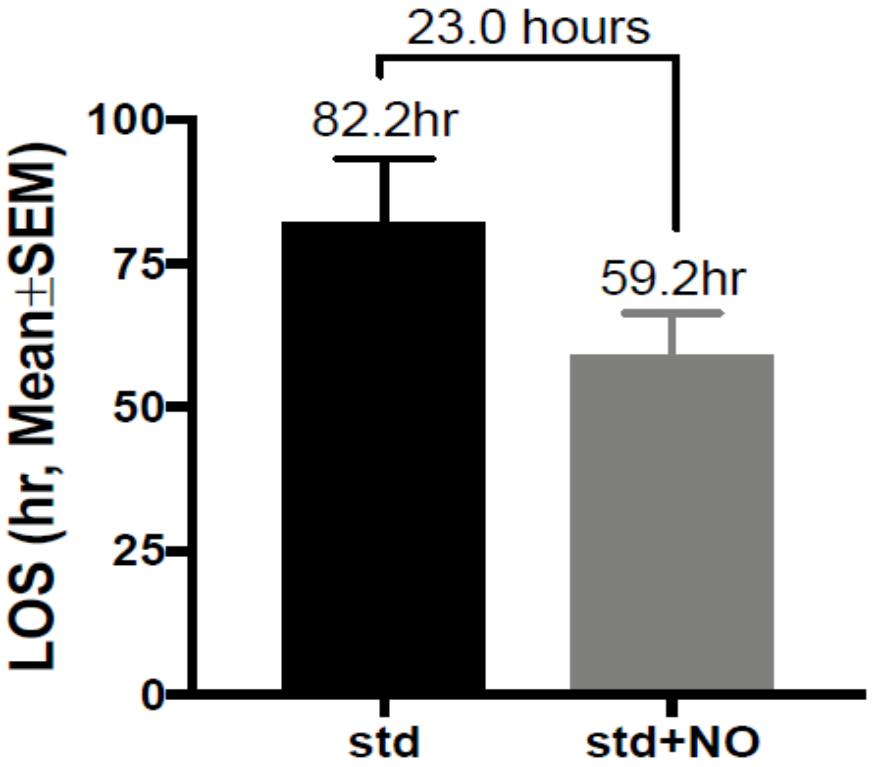
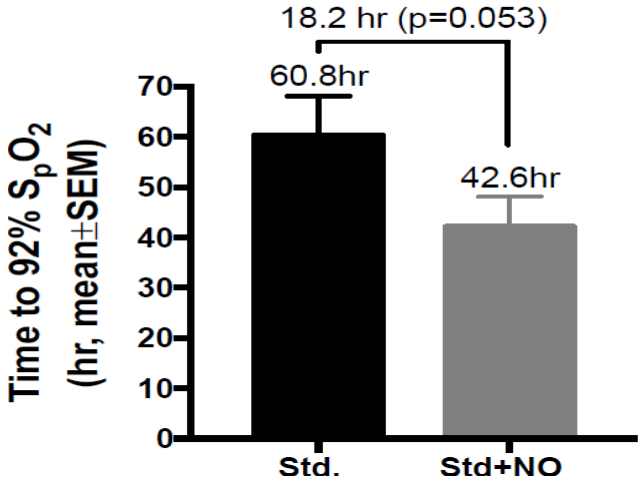
2018 Trial Results Presented at ERS 2018

Hospital length of Stay



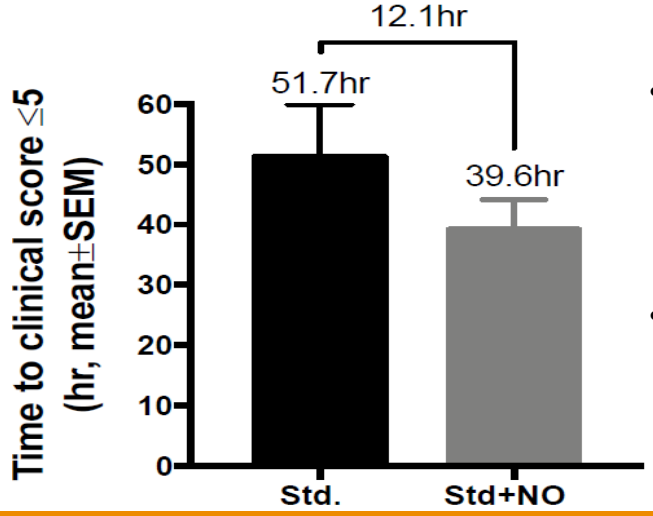
- Primary endpoint of LOS calculated from enrollment to time of hospital discharge
- Welch's t-test: p=0.085 – study was not powered for statistical significance

Oxygen Saturation



- Secondary endpoint of time to oxygen saturation of ≥92% calculated from enrollment
- Welch's t-test: p=0.053

mTal Clinial Score



- Secondary endpoint of time to modified Tal composite score of ≤5 calculated from enrollment
- Welch's t-test: p=0.20

Pivotal Study to Begin in the US in 4Q19 and Complete in 2Q20