Use of Inhaled Nitric Oxide in Preterm vs Term/Near-Term Neonates With Pulmonary Hypertension: Results of the PaTTerN Registry Study

Leif Nelin, MD[1]; John P. Kinsella, MD[2]; Sherry E. Courtney, MD[3]; Eugenia K. Pallotto, MD, MSCE[4]; Eva Tarau, MD[5]; Jim L. Potenziano, PhD[5]

[1]The Research Institute at Nationwide Children's Hospital, Ohio State University, Columbus, OH; [2]University of Colorado School of Medicine/Children's Hospital Colorado, Aurora, CO; [3]Arkansas Children's Hospital Research Institute, University of Arkansas for Medical Sciences/Arkansas Children's Hospital, Little Rock, AR; [4]Levine Children's Hospital, Charlotte, NC; [5]Mallinckrodt Pharmaceuticals, Bedminster, NJ

Background

- Inhaled nitric oxide (iNO) is a selective pulmonary vasodilator[1,2] that improves oxygenation and reduces the need for extracorporeal membrane oxygenation (ECMO) in neonates >34 weeks of gestational age (GA) who have pulmonary hypertension (PH) associated with hypoxic respiratory failure (HRF)[3-6]
  - Efficacy of iNO in preterm (PT) neonates with HRF/PH has not been definitively established[7,8]
  - Studies conducted to evaluate the efficacy of iNO in PT infants for prevention or treatment of bronchopulmonary dysplasia (BPD) and severe acute respiratory failure have shown mixed results[9-11]
- Current guidelines/consensus recommendations conclude there is insufficient evidence available to recommend routine use of iNO in PT infants.[10,12,13] Nevertheless, off-label use in PT neonates with HRF/PH is common
  - Placebo-controlled trials in PT neonates are unlikely, due to ethical considerations
- Observational data on iNO use from a large Japanese study of both PT and term/near-term (TNT; ≥34 weeks' GA) neonates with PH (N=1114) showed that iNO improved oxygenation as effectively in the PT group as in the TNT group without a negative impact on survival[14,15]
  - The Japanese registry study design was also used in the PaTTerN registry study (NCT03132428), which evaluated the use of iNO in PT versus TNT neonates in the United States with HRF-associated PH

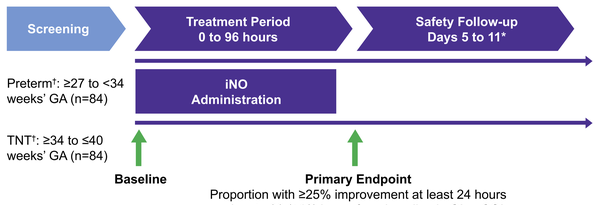
Objective

- To evaluate whether there is a difference in the degree of improvement in oxygenation between PT and TNT neonates with HRF/PH during and up to 96 hours of iNO administration, based on at least a 25% decrease in oxygenation index (OI) or surrogate OI (SOI; in nontintubated neonates)

Methods

- A multicenter, observational, prospectively defined, retrospective study of patient data in the United States. An overview of the study design is shown in **Figure 1**

Figure 1. The PaTTerN Study Design



*Safety data were obtained during iNO administration up to 96 hours and up to 7 days later (for a total of up to 11 days) or to hospital discharge, whichever came first. †Neonates aged 1 to 7 days with PH.
GA, gestational age; iNO, inhaled nitric oxide; OI, oxygenation index; PaTTerN, Premature and Term-Near-Term Neonates With Pulmonary Hypertension Receiving Inhaled Nitric Oxide; SOI, surrogate oxygenation index; TNT, term/near-term.

- PT neonates born at ≥27 weeks to <34 weeks of GA or TNT neonates born at ≥34 to ≤40 weeks of GA were included in the study
  - Patients had to be treated with iNO after birth to 7 days of age for a minimum treatment period of at least 24 hours and up to 96 (±12) hours as part of routine clinical practice in a Level III or higher NICU
  - Diagnosis of PH had to be confirmed by echocardiogram or differential saturation gradient of ≥10%
- Neonates at risk for imminent death within 24 hours of birth and those who had received ECMO and/or had other clinical complications were excluded
- Neonates in each age group were stratified by severity of PH (ie, mild, OI <16 or SOI <10; moderate, OI 16–25 or SOI 10–15; or severe, OI >25 or SOI >15 or progression to mechanical ventilation)
- The primary efficacy outcome measure is the number of neonates in the PT and TNT groups with ≥25% decrease in OI or SOI compared with baseline
  - Secondary efficacy measures included ≥25% decrease in OI/SOI in each severity subgroup; time to ≥25% decrease in OI/SOI; and effect of demographic parameters on achievement of ≥25% decrease in OI/SOI
- Adverse events of special interest included intracranial hemorrhage, air leaks of any type, necrotizing enterocolitis, intestinal perforation, pulmonary hemorrhage, retinopathy of prematurity, and sepsis
- Data were analyzed using the Farrington-Manning score test for noninferiority, based on data observed in the Japanese registry study
  - The 95% CI for the difference in proportions of PT and TNT patients with ≥25% decrease in OI/SOI must have had a lower bound greater than -0.1452 to achieve significance for noninferiority

Results

- A total of 140 neonates (PT, n=55; TNT, n=85) were enrolled; 51% completed 96 hours of treatment (mean [SD] 7.0 [6.2] days). Baseline characteristics are summarized in **Table 1**
  - Mean (SD) duration of treatment was 8.2 (9.1) days in the PT group compared with 6.2 (2.9) days in the TNT group

Table 1. Baseline Characteristics

	Premature (N=55)	Term/Near-term (N=85)	Total (N=140)
Gestational age, mean (SD), weeks	29.41 (2.123)	37.94 (1.843)	34.59 (4.613)
Birth weight, mean (SD), grams	1323.7 (481.4)	3311.5 (797.2)	2530.6 (1193.1)
Apgar score at 5 minutes, median (min, max)*	6 (2, 9)	8 (1, 9)	7 (1, 9)

*Data were missing for 5 patients.

- A total of 50 (90.9%) PT and 75 (88.2%) TNT neonates achieved a ≥25% decrease in OI/SOI (**Table 2**)
  - Efficacy of iNO to treat HRF/PH in the PT group was noninferior to the TNT group

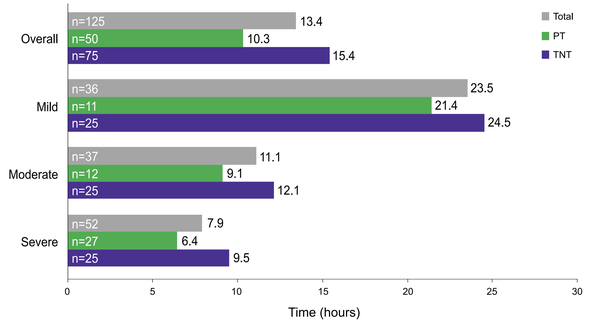
Table 2. Patients With ≥25% Improvement in Oxygenation Index/Surrogate Oxygenation Index During iNO Treatment

	Preterm Neonates (N=55)	Term/Near-Term Neonates (N=85)	Total (N=140)	Difference (95% CI)
Overall*	50/55 (90.9%)	75/85 (88.2%)	125/140 (89.3%)	0.0267 (-0.0333, 0.0868)
Mild	11/15 (73.3%)	25/31 (80.7%)	36/46 (78.3%)	-0.0731 (-0.2278, 0.0815)
Moderate	12/13 (92.3%)	25/27 (92.6%)	37/40 (92.5%)	-0.0028 (-0.1058, 0.1001)
Severe	27/27 (100%)	25/27 (92.6%)	52/54 (96.3%)	0.0741 (0.0161, 0.1321)

*Primary efficacy endpoint.
CI, confidence interval; iNO, inhaled nitric oxide.

- Mean time to achieve a ≥25% decrease in OI/SOI tended to be shorter in the PT group compared with the TNT group, but the between-group differences were not statistically significant (**Figure 2**)

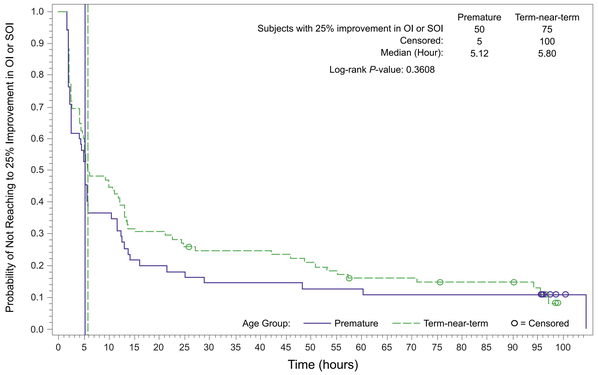
Figure 2. Mean Time to ≥25% Decrease in OI/SOI



OI, oxygenation index; PT, preterm; SOI, surrogate oxygenation index; TNT, term/near-term.

- Overall, median (95% CI) time to first occurrence of 25% improvement in OI or SOI was 5.1 (2.4, 5.9) hours in the PT group and 5.8 (4.9, 12.3) hours in the TNT group, with no statistically significant difference between the age groups (*P*=0.36) (**Figure 3**)

Figure 3. Time to First Occurrence of 25% Improvement in OI or SOI



OI, oxygenation index; SOI, surrogate oxygenation index.

- A univariate analysis of age, severity group, disease subtype, birth weight, race, and gender for effect on achieving a 25% improvement in OI or SOI showed a significant difference for race
  - White race neonates were more likely than non-white neonates to achieve a ≥25% decrease in OI/SOI (odds ratio [95% CI], 1.69 [1.2, 2.4]; *P*=0.003)
  - The rate of achievement of ≥25% decrease in OI/SOI increased by a factor of 1.001 (95% CI, 1.0005, 1.0010; *P*<0.0001) for each unit (gram) increase of birth weight
  - There was no difference between PT and TNT in achieving a ≥25% improvement in OI/SOI (odds ratio [95% CI], 1.78 [0.9, 3.5]; *P*=0.09)
- Overall, 12 (8.6%) patients showed no response (<5% decrease in OI/SOI) and 3 (2.1%) showed partial response (≥5% to <25% decrease in OI/SOI) to iNO treatment
  - More TNT neonates than PT neonates had no response (9 [10.6%] vs 3 [5.5%], respectively)
- Overall, 17 patients experienced a total of 21 adverse events of special interest, all of which were classified as serious events (**Table 3**)
  - None of the events were considered related to study medication

Table 3. Adverse Events of Special Interest

	Preterm Neonates (N=55) No. patients (%) | No. events	Term/Near-Term Neonates (N=85) No. patients (%) | No. events
Any adverse event of special interest	13 (23.6) | 17	4 (4.7) | 4
Intracranial hemorrhage	10 (18.2) | 10	1 (1.2) | 1
Air leaks of any type	3 (5.5) | 4	2 (2.4) | 2
Necrotizing enterocolitis	1 (1.8) | 1	0 | 0
Pulmonary hemorrhage	1 (1.8) | 1	1 (1.2) | 1
Sepsis	1 (1.8) | 1	0 | 0
Death	0 | 0	0 | 0

CONCLUSIONS

- Results from this observational, noninferiority registry study testing treatment of PT vs TNT neonates with HRF/PH showed that treatment with iNO for improvement in oxygenation in PT neonates with PH was at least as effective as in TNT neonates
- 50% of treatment responders in each age group achieved a response within 6 hours after initiation of iNO treatment
- No new or unexpected safety signals associated with iNO treatment were reported
- Results from the current study are consistent with those observed in the previous Japanese registry studies

References

1. Frostell C, Fratacci MD, Wain JC, Jones R, Zapol WM. *Circulation*. 1991;83(6):2038-47. **2.** Frostell CG, Blomqvist H, Hedenstierna G, Lundberg J, Zapol WM. *Anesthesiology*. 1993;78(3):427-35. **3.** Clark RH, Kueser TJ, Walker MW, et al. *N Engl J Med*. 2000;342(7):469-74. **4.** Davidson D, Barefield ES, Kattwinkel J, et al. *Pediatrics*. 1998;101(3 Pt 1):325-34. **5.** The Neonatal Inhaled Nitric Oxide Study Group. *N Engl J Med*. 1997;336(9):597-604. **6.** INOmax [package insert]. Bedminster, NJ: INO Therapeutics; 2019. **7.** The Franco-Belgium Collaborative NO Trial Group. *Lancet*. 1999;354(9184):1066-71. **8.** Field D, Elbourne D, Truesdale A, et al. *Pediatrics*. 2005;115(4):926-36. **9.** Donohue PK, Gilmore MM, Cristofalo E, et al. *Pediatrics*. 2011;127(2):e414-e22. **10.** Kumar P. *Pediatrics*. 2014;133(1):164-70. **11.** Hoehn T, Krause MF, Buhrer C. *Klin Padiatr*. 2006;218(2):57-61. **12.** Cole FS, Alleyne C, Barks JD, et al. *Pediatrics*. 2011;127(2):363-9. **13.** Abman SH, Hansmann G, Archer SL, et al. *Circulation*. 2015;132(21):2037-99. **14.** Suzuki S, Togari H, Potenziano JL, Schreiber MD. *J Perinat Med*. 2018;46(6):657-63. **15.** Rhine WD, Suzuki S, Potenziano JL, Escalante S, Togari H. *Clin Ther*. 2019;41(5):910-9.

Acknowledgments

This study was funded by Mallinckrodt Pharmaceuticals. Medical writing and editorial support was provided by Michael D. Morren, RPh, MBA, of Peloton Advantage, LLC, an OPEN Health company, and funded by Mallinckrodt Pharmaceuticals.

Disclosures

Leif Nelin, John P. Kinsella, Sherry E. Courtney, and Eugenia K. Pallotto have no financial relationships to disclose. Eva Tarau is an employee of Mallinckrodt Pharmaceuticals and may hold stock or stock options in that company. Jim L. Potenziano is a former employee of Mallinckrodt Pharmaceuticals and holds stock in that company.

Presented at the Annual Meeting of the Pediatric Academic Societies (Virtual), April 30–May 4, 2021.