Two-Year Outcomes of a Randomized Controlled Trial of Inhaled Nitric Oxide in Premature Infants

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ABSTRACT

BACKGROUND AND OBJECTIVES: The European Union Nitric Oxide trial was designed to assess the potential benefits of inhaled nitric oxide (iNO) compared with placebo in infants with respiratory failure. This follow-up study evaluated respiratory, neurodevelopmental, and other outcomes for infants entered into the European Union Nitric Oxide trial to age 2 years.

METHODS: In a multicenter, randomized, double-blind study, preterm infants born at <29 weeks' gestation with moderate respiratory failure were allocated to receive iNO (5 ppm) or placebo for 7 to 21 days. Subjects underwent assessments at 1 and 2 years corrected for prematurity.

RESULTS: At 36 weeks’ postmenstrual age, 696 of 792 infants were alive; 4 in the iNO arm subsequently died before age 2 years compared with 7 in the control arm. We evaluated 95% of the survivors at 12 months and 90% at 2 years. In the iNO arm, 244 of 363 (67.2%) infants had survived without disability at age 2 years compared with 270 of 374 (72.2%) who received placebo (P = .094). Mean (SD) cognitive composite scores (Bayley Scales of Infant and Toddler Development, third edition) were 94 (13) in the iNO group and 95 (14) in the placebo group; in the iNO group, 19% scored <85 and 9.5% developed cerebral palsy compared with 13.3% and 9%, respectively. There were no significant differences in hospitalizations overall or due to respiratory illness in use of home oxygen therapy or respiratory medications, in growth, or in other health outcomes.

CONCLUSIONS: At 2 years of age, low-dose (5 ppm) iNO started early (<24 hours after birth) for a median of 20 days did not affect neurodevelopmental or other health outcomes.

WHAT’S KNOWN ON THIS SUBJECT: Bronchopulmonary dysplasia is associated with increased long-term neurodevelopmental and respiratory morbidity. Inhaled nitric oxide given to reduce morbidity in very preterm infants does not reduce the prevalence of bronchopulmonary dysplasia and has uncertain effects on long-term outcome.

WHAT THIS STUDY ADDS: Inhaled nitric oxide (5 ppm) given early in the course of respiratory illness in infants born before 29 weeks of gestation is not associated with changes in developmental or respiratory outcomes at 2 years of age corrected for prematurity.

KEY WORDS

inhaled nitric oxide, premature infants, growth, developmental outcomes, randomized controlled trial

ABBREVIATIONS

Bayley-III—Bayley Scales of Infant and Toddler Development, third edition
BPD—bronchopulmonary dysplasia
EUNO—European Union Nitric Oxide
GMFCS—Gross Motor Function Classification System for Cerebral Palsy
iNO—inhaled nitric oxide
ROP—retinopathy of prematurity

(Continued on last page)
Despite improvements in survival for very preterm infants over the past 20 years, a high proportion of survivors are found to have a wide range of neurodevelopmental and respiratory impairments at follow-up. Bronchopulmonary dysplasia (BPD) remains an important neonatal morbidity and is a marker for an increased risk of long-term neurocognitive and respiratory impairment such as chronic airways obstruction. Of recent strategies to reduce the prevalence of BPD, inhaled nitric oxide (iNO) has been identified as a potential intervention to reduce respiratory complications and, hence, neurodevelopmental problems associated with preterm birth. However, in contrast to the potential benefit in improving neurodevelopmental outcomes demonstrated in 1 relatively small trial, larger trials have failed to demonstrate differences in outcome. All trials have used different regimens of iNO administration and different entry criteria.

The European Union Nitric Oxide (EUNO) trial was a multicenter, randomized, double-blind study designed to assess the potential benefits of iNO compared with placebo in the first 24 hours in infants with mild respiratory failure who were born at between 24 and 28 completed weeks of gestation. There was no benefit in terms of survival without BPD or prescribed secondary outcomes. Despite the lack of benefit for neonatal morbidity, iNO may affect lung or brain development. Such long-term effects have been suggested by experimental studies showing an early protective effect of iNO on lung and brain development. Thus, the goal of the current study was to evaluate neurodevelopmental, respiratory, and other outcomes in survivors of this cohort at 1 and 2 years of age.

**METHODS**

**Subjects and Study Design**

The details of the original study, including patient population, inclusion/exclusion criteria, randomization and masking, and study intervention, have been reported. In brief, this was a multicenter, double-blind study conducted in infants born between 24 and 28 completed weeks of gestation with moderate respiratory illness. The primary end point was survival without BPD at 36 weeks’ postmenstrual age. Eight hundred infants were allocated to either treatment with iNO (5 ppm) or placebo for a mean duration of 16 days of therapy (target of 7–21 days dependent on clinician discretion). In the neonatal study, 65% (258 of 395) of infants treated with iNO were alive without BPD at 36 weeks’ postmenstrual age compared with 66% (262 of 400) in the placebo group ($P = .04$).

Surviving infants were evaluated at 1 and 2 years of age corrected for prematurity. Contact was maintained with subjects through regular letters and/or phone calls according to each center’s policy. Deaths after discharge from the hospital were reported to the study center to prevent inadvertent contact with parents. At both time points, parents and assessors completed questionnaires to record population demographics, overall hospitalization since the initial discharge, hospitalization for respiratory illness (as per parental statement), and use of concomitant therapies, home oxygen, or respiratory medications. The results of physical examination and growth variables were also recorded; growth variables were related to the US Centers for Disease Control and Prevention growth charts. Developmental disabilities were classified as severe, moderate, or minimal/no disability. "Severe disability" included any of the following: presence of cerebral palsy with a GMFCS ≥3; a Bayley-III cognitive composite score <70; no useful hearing, even with aids; no communication by speech or other method; and no useful vision (blind). "Moderate disability" included cerebral palsy with a GMFCS of 2; a Bayley-III cognitive composite score of 70 to <85; some hearing, with loss not corrected by aids; formal systemized method of speech; and able to see light or gross movement only. "Minimal/no disability" was deemed present in the absence of any of the findings described above. Where a formal Bayley-III evaluation was not performed, developmental attainment was estimated from clinical assessment into severe, moderate, or other categories.

**Statistical Analysis**

The goal of this outcome study was to assess the longer-term safety of iNO and development was evaluated by using the cognitive scale of the Bayley Scales of Infant and Toddler Development, third edition (Bayley-III). Language scales were not used because validation has not been performed in the majority of European languages. All Bayley-III examiners were trained in test administration and interpretation by instructors from the University of Nottingham, United Kingdom, and were blinded to treatment assignment. All examiners were subsequently assessed to ensure interrater reliability (≥90% agreement with the trainer in item scores) before commencing assessments. Other impairments were determined by using a structured interview with published definitions. The presence, severity, and need for intervention for retinopathy of prematurity (ROP) were assessed retrospectively at the 2-year follow-up.

Developmental disabilities were classified as severe, moderate, or minimal/no disability. "Severe disability" included any of the following: presence of cerebral palsy with a GMFCS ≥3; a Bayley-III cognitive composite score <70; no useful hearing, even with aids; no communication by speech or other method; and no useful vision (blind). "Moderate disability" included cerebral palsy with a GMFCS of 2; a Bayley-III cognitive composite score of 70 to <85; some hearing, with loss not corrected by aids; formal systemized method of speech; and able to see light or gross movement only. "Minimal/no disability" was deemed present in the absence of any of the findings described above. Where a formal Bayley-III evaluation was not performed, developmental attainment was estimated from clinical assessment into severe, moderate, or other categories.
to determine respiratory outcomes at 1 year of age corrected for prematurity and survival, without moderate or severe neurodevelopmental impairment at 2 years of age corrected for prematurity. The sample size was determined by the original study. Outcome data were summarized with descriptive statistics (number of observations, mean and SD, median, and minimum and maximum) for continuous response variables and with frequency and percentage for categorical response variables.

Wilcoxon rank-sum test and Fisher’s exact test were used in the analyses. All statistical tests were 2-sided at a significance level of 0.05 without adjustment for multiplicity. Data were double-entered into a validated Oracle Clinical database (version 4.5.0; Oracle Inc., Redwood Shores, CA); missing data were not imputed. All data management and statistical analyses were performed at INO Therapeutics LLC/Ikaria, Inc (Hampton, NJ), by using SAS Proprietary Software, release 9.1 (SAS Institute, Cary, NC).

Ethics
The study was approved by the appropriate regulatory authority in each country and at each institution by the local research ethics committee. Consent for participation was obtained from parents according to local requirements before the initial randomization.

RESULTS

Of the 800 infants enrolled into the study, 696 were alive at 36 weeks’ postmenstrual age and age 2 years corrected for prematurity: 4 of 395 (1.0%) in the iNO-treated group and 7 of 397 (1.8%) in the placebo group. Of these, 9 deaths occurred before hospital discharge. Subsequently, 1 infant died of pneumonia (iNO arm) and 1 of sudden infant death syndrome (placebo arm).

Neurodevelopmental Assessments
Bayley-III assessments were conducted in 260 of 306 subjects in the iNO group and in 272 of 324 subjects in the placebo group (Table 2). Mean (SD) cognitive composite scores were similar in the 2 groups: 93.5 (12.7) in the iNO group compared with 95.1 (13.5) in the control arm (difference in means: −1.6 points; P = .11). Estimates or assessments were not recorded for 12 and 19 children in the iNO and placebo groups, respectively, and these children were lost to follow-up. No significant linear association between treatment arm and overall cognitive disability was found (Table 3); the relative risk for a score <85 for subjects receiving iNO was 1.36 (P = .068).

There were no significant differences in the frequency of cerebral palsy between the iNO and placebo groups, or in seizure disorder, hearing communication, or vision deficits (Table 4). Using retrospective data collection, the proportion with ROP was similar in the iNO group compared with placebo, as was the proportion requiring treatment of ROP.

Based on a composite of the neurodevelopmental assessments performed at the 2-year follow-up, the majority of subjects in either treatment group had minimal or no neurodisabilities (Table 5). Of those iNO-treated subjects seen in follow-up, 244 of 306 (79.7%) had minimal or no disabilities compared with 270 of 324 (83.3%) in the placebo group (P = .29). The frequencies of both severe and moderate neurodisabilities were similar between the 2 treatment groups.

Survival Without Neurodevelopmental Disability
In the iNO arm, 244 of 363 (67.2%) evaluable infants survived without severe or moderate disability at 2 years compared with 270 of 374 (72.4%) infants in the placebo group (P = .092). Evaluable subjects excluded those who received no treatment (4 in each group) and those lost to follow-up before year 2 (Fig 1).

Hospitalization
The overall number and frequency of hospitalizations in the first and second years were comparable between the 2 groups (Table 6). In particular, hospitalization rates due to respiratory illness were similar between the treatment groups. In the second year compared with the first year, there was an overall decrease in hospitalization for respiratory problems for both treatment groups.

Growth and Other Outcomes
Overall weight and length increased between the 1- and 2-year follow-up, but there were no significant differences between the 2 treatment groups (Table 7). The iNO group had a statistically smaller mean head circumference at 1 year (P = .03). Mean respiratory rates, blood pressures, and pulse rates were comparable between the 2 treatment groups at the 1- and 2-year follow-up (data not shown). Oxygen saturation levels measured in room air, evaluated at 1 year only, were also similar between
the treatment groups (97.4% ± 2.1% and 97.3% ± 2.1% in the iNO and placebo groups, respectively).

**Use of Concomitant Medications and Therapies**

The 2 most common medications used in ≥10% of subjects in both treatment groups taken at the 1-year follow-up were related to respiratory problems. Of subjects taking respiratory medications during the first year, 28 of 322 (8.7%) in the iNO group versus 37 of 339 (10.9%) in the placebo group (\(P = .34\)) were taking respiratory medications classified as relievers (ipratropium, albuterol, terbutaline, salmeterol), and 34 of 322 (10.6%) in the iNO group versus 45 of 339 (13.3%) in the placebo group (\(P = .28\)) were taking respiratory medications classified as preventers (beclamethasone, budesonide, fluticasone). The proportions of subjects reporting coughing or wheezing were comparable between the 2 treatment groups (data not shown).

**DISCUSSION**

The EUINO Study was designed to test the hypothesis that low-dose iNO was safe and effective for the prevention of BPD in preterm infants with respiratory failure shortly after birth. iNO appears to have been safe and well tolerated because there were no significant differences in growth, disabilities, or
TABLE 1 Demographic and Baseline Characteristics: 1- and 2-Year Follow-up

<table>
<thead>
<tr>
<th>Variable</th>
<th>1-Year Follow-up</th>
<th>2-Year Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Inhaled Nitric Oxide (n = 322)</td>
<td>Placebo (n = 339)</td>
</tr>
<tr>
<td>Gestational age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD), wk</td>
<td>26.5 (1.3)</td>
<td>26.6 (1.3)</td>
</tr>
<tr>
<td>&lt;26 Weeks, n (%)</td>
<td>100 (31.1)</td>
<td>110 (32.4)</td>
</tr>
<tr>
<td>≥26 Weeks, n (%)</td>
<td>222 (68.9)</td>
<td>229 (67.6)</td>
</tr>
<tr>
<td>Birth weight, mean (SD), g</td>
<td>860.2 (213.8)</td>
<td>878.5 (193.0)</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>163 (50.6)</td>
<td>189 (55.8)</td>
</tr>
<tr>
<td>Female</td>
<td>159 (49.4)</td>
<td>150 (44.2)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>265 (82.3)</td>
<td>279 (82.3)</td>
</tr>
<tr>
<td>Black</td>
<td>30 (9.3)</td>
<td>39 (11.5)</td>
</tr>
<tr>
<td>Asian</td>
<td>3 (0.9)</td>
<td>2 (0.6)</td>
</tr>
<tr>
<td>Other</td>
<td>24 (7.5)</td>
<td>19 (5.6)</td>
</tr>
<tr>
<td>BPD at 36 weeks corrected age, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>79 (24.5)</td>
<td>92 (27.1)</td>
</tr>
</tbody>
</table>

* P values were calculated by using Fisher’s exact test for categorical data and Wilcoxon rank-sum test for numerical data.

TABLE 2 Bayley-III Cognitive Scores at 2-Year Follow-up

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Inhaled Nitric Oxide (n = 306)</th>
<th>Placebo (n = 324)</th>
<th>P&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scaled score, n</td>
<td>260</td>
<td>272</td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>8.7 (2.54)</td>
<td>9.0 (2.70)</td>
<td>.12</td>
</tr>
<tr>
<td>Median (range)</td>
<td>9.0 (1.0–18.0)</td>
<td>9.0 (1.0–19.0)</td>
<td></td>
</tr>
<tr>
<td>Standardized score, n</td>
<td>260</td>
<td>272</td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>93.5 (12.70)</td>
<td>95.1 (13.51)</td>
<td>.11</td>
</tr>
<tr>
<td>Median (range)</td>
<td>95.0 (55.0–140.0)</td>
<td>95.0 (55.0–145.0)</td>
<td></td>
</tr>
</tbody>
</table>

* P values were calculated by using Wilcoxon rank-sum test.

TABLE 3 Overall Cognitive Disability Outcomes at 2-Year Follow-up

<table>
<thead>
<tr>
<th>Category</th>
<th>Inhaled Nitric Oxide (n = 306)</th>
<th>Placebo (n = 324)</th>
<th>Total (N = 630)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe disability: Bayley-III &lt;70</td>
<td>7 (2.3)</td>
<td>12 (3.7)</td>
<td>19 (3.0)</td>
</tr>
<tr>
<td>Moderate disability: Bayley-III of 70 to &lt;85</td>
<td>51 (16.7)</td>
<td>31 (9.6)</td>
<td>82 (13.0)</td>
</tr>
<tr>
<td>Mild disability: Bayley-III of 85 to &lt;100</td>
<td>118 (38.6)</td>
<td>120 (37.0)</td>
<td>238 (37.8)</td>
</tr>
<tr>
<td>No disability: Bayley-III ≥100</td>
<td>118 (38.6)</td>
<td>142 (43.8)</td>
<td>260 (41.3)</td>
</tr>
<tr>
<td>Not done</td>
<td>12 (3.9)</td>
<td>19 (5.9)</td>
<td>31 (4.9)</td>
</tr>
</tbody>
</table>

Data are presented as n (%).

Rehospitalization rates in the 2 groups in evaluations at 12 months’ and 24 months’ corrected age. Neurodevelopmental outcomes were carefully assessed, and there was no significant difference in neurologic development between the treatment groups (including the incidence of cerebral palsy) or any significant difference in respiratory outcomes. The rate of follow-up was high; 95% of surviving subjects were evaluated at 1 year and 92% at 2 years. Assessments were carried out by accredited and validated assessors, all of whom had been trained by the same team to achieve >90% agreement with an independent psychologist. The demographic and baseline characteristics of the 2 treatment groups remained well matched throughout follow-up and were also closely comparable to the treatment groups as originally randomized.

Impaired neurodevelopmental outcome and BPD are common long-term complications of surviving premature infants, especially in extremely premature infants who are born at or earlier than 25 weeks’ gestation. Potential sequelae include the following: cognitive abnormalities; motor deficits; vision and hearing loss; higher risk of hospitalization for recurrent illness, including acute respiratory diseases; other infectious diseases; gastrointestinal diseases; and exacerbations of chronic respiratory conditions. These children are also more likely to have chronic medical problems including poor growth, BPD, gastroesophageal reflux, and an increased risk of sudden infant death syndrome.

In addition, children born prematurely are at risk of impaired lung function that may result in reduced exercise capacity or an increase in respiratory symptoms. In a cross-sectional study in 126 children (mean age: 10 years), those with a mean gestational age of 27 weeks had reduced lung function as measured by spirometry and half the exercise capacity compared with term-born controls. In a follow-up report of a large, prospective, population-based cohort outcome study in infants born extremely premature (≤25 weeks’ gestation), 102 of 182 (56%) had impaired baseline function at 11 years of age. Experimental models suggest that alveolar development might be maintained by iNO during mechanical ventilation, resulting in early improvement of lung function. Whether this effect can be seen in humans or if this effect translates into longer-term respiratory improvement remains unknown.

The rate of premature births remains above targets set by the Healthy People 2010 initiative. In addition, among very low gestational age infants, improved survival has not affected the high rates of short- or long-term neurodevelopmental or respiratory sequelae. This, in turn, further highlights...
In the initial report, no effect was observed on the primary outcome (death or BPD) and this was confirmed by subsequent meta-analysis. The population in our study was more homogeneous regarding race (majority were white infants) and initial respiratory disease (exclusion of the most hypoxemic infants) than in previous US studies. The results seen in the current study, in which the number of followed-up subjects was the largest to date, are consistent with those observed by other investigators. For example, Watson et al published the clinical and neurologic outcomes for a group of 455 preterm infants at 1 year who had been randomly assigned to receive 5 ppm iNO or placebo, in a fashion similar to the current study, they reported no differences in survival or survival without neurodevelopmental impairment. Walsh et al reported the 2-year neurodevelopmental outcomes of 477 preterm infants who had been randomly assigned into the iNO Chronic Lung Disease Study. There were no differences in death (iNO versus placebo: 8% vs 8%), physical growth, or the composite of neurodevelopmental impairment among survivors (iNO versus placebo: 45% vs 49%), suggesting that iNO was well tolerated. In a single-center study in 138 preterm children, however, iNO therapy resulted in an improvement in neurodevelopmental outcomes at age 2 years compared with subjects receiving placebo (relative risk: 0.53; 95% confidence interval: 0.33–0.87; P = .01). This finding was primarily due to a 47% decrease in cognitive impairment risk (defined by a score of <70 on the Bayley Scales of Infant Development, second edition, index [BSID-II]). The investigators speculated that the beneficial effect of iNO was mediated through enhancement of somatic growth or by directly affecting the brain through mechanisms involving the cerebral vasculature or neuronal maturation.

The continued need for vigilance in monitoring these individuals over the long-term. Clinical trials investigating therapies in neonates should provide long-term follow-up data to identify potentially beneficial or harmful treatments. iNO is one of these treatments, as stated by the National Institutes of Health Consensus Conference in 2010. In the initial report, no effect was observed on the primary outcome (death or BPD) and this was confirmed by subsequent meta-analysis. The population in our study was more homogeneous regarding race (majority were white infants) and initial respiratory disease (exclusion of the most hypoxemic infants) than in previous US studies. The results seen in the current study, in which the number of followed-up subjects was the largest to date, are consistent with those observed by other investigators. For example, Watson et al published the clinical and neurologic outcomes for a group of 455 preterm infants at 1 year who had been randomly assigned to receive 5 ppm iNO or placebo, in a fashion similar to the current study, they reported no differences in survival or survival without neurodevelopmental impairment. Walsh et al reported the 2-year neurodevelopmental outcomes of 477 preterm infants who had been randomly assigned into the iNO Chronic Lung Disease Study. There were no differences in death (iNO versus placebo: 8% vs 8%), physical growth, or the composite of neurodevelopmental impairment among survivors (iNO versus placebo: 45% vs 49%), suggesting that iNO was well tolerated. In a single-center study in 138 preterm children, however, iNO therapy resulted in an improvement in neurodevelopmental outcomes at age 2 years compared with subjects receiving placebo (relative risk: 0.53; 95% confidence interval: 0.33–0.87; P = .01). This finding was primarily due to a 47% decrease in cognitive impairment risk (defined by a score of <70 on the Bayley Scales of Infant Development, second edition, index [BSID-II]). The investigators speculated that the beneficial effect of iNO was mediated through enhancement of somatic growth or by directly affecting the brain through mechanisms involving the cerebral vasculature or neuronal maturation.

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Of note, the current study used the Bayley-III as a component of neurodevelopmental assessment. Investigators have suggested that this latest iteration of the Bayley scales underestimate the proportions of children with developmental delay at 2 years of age when compared with the Bayley Scales of Infant Development, second edition, particularly in low-scoring children. Thus, comparisons of developmental scores

### TABLE 4 Neurologic, Vision, Hearing, and Speech/Communication Assessments at 2-Year Follow-up

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Inhaled Nitric Oxide (n = 306)</th>
<th>Placebo (n = 324)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral palsy</td>
<td>29 (9.5)</td>
<td>29 (9.0)</td>
<td>.89</td>
</tr>
<tr>
<td>Seizures</td>
<td>3 (1.6)</td>
<td>3 (2.5)</td>
<td>.47</td>
</tr>
<tr>
<td>Other neurologic problems</td>
<td>12 (3.9)</td>
<td>17 (5.2)</td>
<td>.45</td>
</tr>
<tr>
<td>Any vision or eye defect</td>
<td>44 (14.4)</td>
<td>35 (10.8)</td>
<td>.19</td>
</tr>
</tbody>
</table>

Data are presented as n (%) unless otherwise indicated.

### TABLE 5 Overall Neurodevelopmental Disabilities at 2-Year Follow-up

<table>
<thead>
<tr>
<th>Disability</th>
<th>Inhaled Nitric Oxide (n = 306)</th>
<th>Placebo (n = 324)</th>
<th>Total (N = 630)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe</td>
<td>14 (4.6)</td>
<td>15 (4.6)</td>
<td>29 (4.6)</td>
<td>.40</td>
</tr>
<tr>
<td>Moderate</td>
<td>48 (15.7)</td>
<td>39 (12.0)</td>
<td>87 (13.8)</td>
<td></td>
</tr>
<tr>
<td>Minimal or no disability</td>
<td>244 (79.7)</td>
<td>270 (83.3)</td>
<td>514 (81.6)</td>
<td></td>
</tr>
</tbody>
</table>

Data are presented as n (%) unless otherwise indicated.

### TABLE 6 Hospitalizations During 1- and 2-Year Follow-up

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Inhaled Nitric Oxide</th>
<th>Placebo</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-Year follow-up, n</td>
<td>341</td>
<td>355</td>
<td>.32</td>
</tr>
<tr>
<td>Discharged from the hospital on supplemental oxygen, n (%)</td>
<td>28 (9.2)</td>
<td>37 (10.4)</td>
<td></td>
</tr>
<tr>
<td>Still hospitalized, n (%)</td>
<td>4 (1.2)</td>
<td>1 (0.3)</td>
<td>.20</td>
</tr>
<tr>
<td>n with available data on subsequent hospitalization</td>
<td>322</td>
<td>339</td>
<td></td>
</tr>
<tr>
<td>Hospitalized for respiratory illness, n (%)</td>
<td>153 (47.5)</td>
<td>151 (44.5)</td>
<td>.48</td>
</tr>
<tr>
<td>Number of subsequent hospitalizations, n</td>
<td>78 (24.2)</td>
<td>79 (25.3)</td>
<td>.79</td>
</tr>
<tr>
<td>Median (range), occurrences</td>
<td>2.0 (1.0–17.0)</td>
<td>1.0 (1.0–7.0)</td>
<td>.23</td>
</tr>
<tr>
<td>Duration of hospitalizations, n</td>
<td>148</td>
<td>148</td>
<td></td>
</tr>
<tr>
<td>Median (range, d)</td>
<td>9.0 (1.0–366.0)</td>
<td>8.0 (1.0–57.0)</td>
<td>.34</td>
</tr>
</tbody>
</table>

Of note, the current study used the Bayley-III as a component of neurodevelopmental assessment. Investigators have suggested that this latest iteration of the Bayley scales underestimate the proportions of children with developmental delay at 2 years of age when compared with the Bayley Scales of Infant Development, second edition, particularly in low-scoring children. Thus, comparisons of developmental scores

*P values were calculated by using Fisher’s exact test for categorical data and Wilcoxon rank-sum test for numerical data.
between the current study and those that used previous editions of this assessment tool may be difficult. Because the same tool was used for both groups of infants in this study, the results of the comparisons are valid.

CONCLUSIONS
In conclusion, iNO, as used in this study at 5 ppm started within the first 24 hours after birth in preterm infants, did not affect growth, neurologic development, or respiratory outcome up to 2 years of age. This study is ongoing through 7 years, when additional neurologic assessments will be performed.

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