6.0.4.13.1 Comparison of defined safety parameters up to 28 days (cont)

No individual has NO_2 levels >5.0 ppm. Subject 03-59003 had levels >3.0 on several occasions during I-NO therapy, with a peak of 3.3 after 11.6 hours. The infant was discharged with both reactive airways disease and broncho-pulmonary dysplasia.

2. Incidence of intraventricular hemorrhage and seizures

Inverventricular hemorrhage was detected in 12% of the infants (1/8 with available data).

Seizures occurred in 3/14 (21%) of the infants.

The relationship of these adverse events to the administration of I-NO is difficult to establish with these small numbers. The overall NDA database includes these subjects, and will address this issue in sections 8.1 and 8.2 below.

3. Laboratory evaluations

These will be included in the analysis of lab values in section 8.1.

4. Incidence and relationship of all adverse events and specific adverse events to I-NO

These will be included in the analysis of lab values in section 8.1.

Of the other adverse events noted by the investigators, the following adverse events which occurred will be noted here, and included in section 8.3 as well.

1. Asthma

Asthma was identified in the INO-03 trial. Subject 03-59001 received I-NO 5 ppm for 73 hours, and developed asthma 1 week after starting I-NO. The infant did not receive ECMO, HFOV, or HFJV, but required supplemental O_2 at the time of discharge as well as bronchodilator therapy. Long-term follow-up is not available.

2. Air leak syndrome/pneumothoraces

28% (4/14) of the subjects in the INO-03 trial had experienced a pneumothorax at the end of 28 days.

Table 6.0.4.13.1.1 Listing of pneumothoraces in the INO-03 trial[a].

Subject group	Duration of I-NO therapy	Notes
I-NO 5 ppm		
03-57003	120 hours	No ECMO, HFOV/HFJV
03-59004	32 hours	No ECMO, HFOV/HFJV
I-NO 20 ppm		
03-58001	16 hours	ECMO
03-59002	168 hours	No ECMO, HFOV/HFJV Required O_2 at 28 days, BPD

a. Data from NDA volumes 2.30 and 2.31.

3. PPHN Sequelae

The percentage of each group which had one of the PPHN sequelae is listed below.

6.0.4.13.1 Comparison of defined safety parameters up to 28 days (cont)

Details of these adverse events will be included in section 8.1 and 8.2.

Table 6.0.4.13.1.2 Comparison of the rates of specific safety parameters from INO-03.[a] Note that not all subjects have data for a given parameter.

Changes in safety endpoints	I-NO 5 ppm	I-NO 20 ppm	I-N0 80 ppm	Combined I-NO
Incidence of methemoglobinemia >5%	0/4 (0%)	0/8 (0%)	1/2 (50%)	1/14 (7%)
Incidence of elevated NO_2 level (>5 ppm)[a]	0/4 (0%)	0/8 (0%)	0/2 (0%)	0/14 (0%)
Incidence of seizures	0/4 (0%)	3/7 (43%)	0/2 (0%0	3/14 (21%)
Incidence of air leak syndrome[c]	2/4 (50%)	2/8 (25%)	0/2 (0%)	4/14 (28%)
Incidence of bronchopulmonary dysplasia[d]	0/4 (0%)	1/7 (14%)	1/2 (50%)	2/14 (14%)
Subjects requiring O_2 at 28 days	0/4 (0%)	1/7 (14%)	1/2 (50%)	2/14 (14%)
Subjects with reactive airways disease at 28 days	0/4 (0%)	1/7 (14%)	1/2 (50%)	2/14 (14%)
Incidence of sensorineural hearing loss[e]	0/4 (0%)	2/8 (25%)	1/2 (50%	3/14 (21%)
Intracranial abnormalities detected by ultrasound, CT or MRI scan				
Abnormality on cranial ultrasound[b]	0/3 (0%)	1/4 (25%)	0/1 (0%)	1/8(12%)
Interventricular hemorrhage	0/3 (0%)	1/4 (25%)	0/1 (0%)	1/8(12%)
Intracranial infarct detected by CAT scan or MRI	0/3 (0%)	1/4 (25%)	0/1 (0%)	1/8(12%)

a. Occupational health guidelines have set an eight hour maximum exposure limit at 5 ppm for nitrogen dioxide (NO_2)(76).

b. Only those infants who had a normal cranial ultrasound at the start of the trial and an ultrasound at the end of the trial are included.

c. Air leak syndrome includes the occurrence of any one of the following: interstitial emphysema; pneumomediastinum; pneumopericardium; and pneumothorax. In this trial, the only abnormality noted was pneumothorax.

d. Bronchopulmonary dysplasia defined as: use of supplemental O_2 at 28 days of life in the presence of an abnormal CXR, or the use of bronchodilators suggesting severe reactive airway disease on discharge.

e. Sensorineural hearing loss was detected using brain stem auditory evoked responses (BAER).

4. Subject deaths: no subject deaths occurred in the INO-03 trial

6.0.4.14 INO-03 Efficacy summary

The primary intent of the INO-03 study was to collect further safety data. This, coupled with the absence of a control group, and the small number of subjects entered into the trial, limit the information regarding efficacy in this trial.

Fifty-seven % of the subjects in the INO-03 trial met one of the four primary PPHN endpoints. This compares with 56% of the control subjects, and 50% of the I-NO group in the INO-01/ -02 trial.

None of the infants in the INO-03 trial died, compared with 2% of the control group in the INO-01/ -02 trial, and 8% of the I-NO group in the INO-01/ -02 trial.

Twenty-one % of the subjects in the INO-03 trial received ECMO, compared with 39% of the control subjects in the INO-01/ -02 trial, and 29% of the I-NO group in the INO-01/ -02 trial.

Overall, the infants in the INO-03 trial had similar incidence rates for the primary endpoints to those seen in the INO-01/ -02 trial.

6.0.4.15 INO-03 Safety summary

No deaths, and no unanticipated adverse events were identified in this small study.

The safety data from this study (summarized in Table 6.0.4.13.1.2) will be incorporated into the overall safety database in sections 8.1 and 8.2 below.

6.0.4.16 INO-03 Reviewer's Summary

1. While efficacy was not specifically part of the proposal for this trial, the subjects were transferred to ECMO at rates similar to those of the subjects in the larger trials.

2. No adverse events were seen which did not also occur in the other, larger, trials. The small numbers of subjects preclude the use of statistics to analyze the safety data, but the safety information agreed in large part with the other trials. The rates of occurrence for specific adverse events were tabulated, and will be incorporated into the larger, overall Safety Review in sections 8.1 and 8.2.

7.0 Integrated Review of Efficacy

There are three aspects of the determination of efficacy for I-NO: meeting pre-specified primary endpoints; demonstrating physiological effect; and demonstrating clinical benefit. The latter two aspects of efficacy were included in the secondary and exploratory endpoints of the three trials. A summary of the primary and secondary endpoints of the NINOS, INOSG and INO-01/ -02 trials is below.

7.0.1 Primary and secondary efficacy endpoints from the NINOS, INOSG, and INO-01/ -02 trials

Primary efficacy endpoints

I. NINOS primary endpoint

1. Death before discharge or 120 days (whichever comes first), and/or the initiation of ECMO.

II. INOSG primary endpoint

1. Number of acute oxygenation 'successes' following 20 minutes of treatment gas.

III. INO-01/ -02 primary endpoint

1. The occurrence of one or more of the PPHN major sequelae prior to discharge:
   a.. Death.
   b. Initiation of ECMO.
   c. Evidence of abnormal neurological sequelae.
   d. Bronchopulmonary dysplasia.

Secondary efficacy endpoints

I. NINOS Secondary Endpoints

1. Change in PaO_2 levels measured 30 minutes after initial administration of the study gas.
2. Change in mean OI levels measured 30 minutes after initial administration of the study gas.
3. Change in $Aa\text{-}DO_2$ levels before and 30 minutes after initial administration of the study gas.
4. Neurodevelopmental outcomes assessed at 18-24 months corrected age (data not yet submitted).
5. The average length of hospitalization among surviving infants.
6. The number of days of assisted ventilation.
7. The incidence of air leak.
8. The incidence of chronic lung disease.
9. The proportion of infants transferred for potential ECMO.

II. INOSG Secondary and post-hoc analyses

1. The number of subject deaths within 120 days and/or receipt of ECMO
2. Percentage of subjects receiving oxygen therapy at 28 days.
3. Percentage of subjects surviving.

IIIa. I-NO-01/ -02 secondary endpoints

1. Physiologic response to I-NO, measured by change in OI and time-weighted OI.
2. Number of days requiring supplemental oxygen.
3. Number of days requiring mechanical ventilation.
4. Number of days in hospital (defined as to end of medically indicated hospitalization, not related to social issues).

IIIb. I-NO-01/ -02 long-term follow-up endpoints (measured at 1 year follow-up examination)

1. Incidence of hearing abnormalities.
2. Incidence of developmental delay.

IIIc. I-NO-01/ -02 exploratory variables

1. Postductal PaO_2.
2. Preductal O_2 saturation.
3. Postductal O_2 saturation.
4. Mean Arterial Pressure.
5. Positive Inspiratory Pressure.
6. Positive End-Expiratory Pressure (PEEP).
7. Arterial-alveolar O_2 ratio.
8. Arterial-alveolar O_2 gradient.

7.0.1 Success of trials in meeting pre-specified primary endpoints

Two of the three trials submitted in support of efficacy met their pre-specified primary endpoint: the NINOS and INOSG trials. Of these, only the NINOS trial endpoint was previously held to be of sufficient clinical benefit to support approval of I-NO. The INOSG endpoint, acute improvement in oxygenation, was felt by the Cardiovascular and Renal Drugs Advisory Committee to be an inadequate endpoint to demonstrate clinical efficacy (see section 2.3).

The table below summarizes the rates of the pre-specified, primary endpoints from the three efficacy trials in NDA 20845[d].

Table 7.0.1.1 Primary endpoints from the NINOS, INOSG, and INO-01/ -02 trials.

Study Endpoint	Control	I-NO 5 ppm	I-NO 20 ppm	I-NO 80 ppm	I-NO Pooled	p value
NINOS: death before 120 days and/or initiation of ECMO	70/111 (63%)				57/119 (47.9%)	0.021[a]
INOSG: acute oxygenation success	2/28 (7%)			16/30 (53%)		0.0002[b]
INO-01/ -02: PPHN major sequelae[c]	23/41 (56%)	18/36 (50%)	21/35 (60%)	13/33 (39%)	52/104 (50%)	0.34[c]

a. p value calculated from the subjects who actually received study gas, grouped according to the study gas actually received, using unadjusted chi-square.

b. p value calculated using unadjusted chi-square.

c. PPHN major sequelae: death; initiation of ECMO; bronchopulmonary dysplasia; neurologic abnormalities. p value calculated using unadjusted chi-square.

d. Data from individual study reports, sections 6.0.1, 6.0.2, and 6.0.3.

7.0.2 Analysis of the NINOS primary endpoint in the INOSG and INO-01/ -02 trials

Another way of analyzing the data is to ask whether the significant effect of I-NO as regards the NINOS primary endpoint was seen in any of the other trials. The table below summarizes that information.

Table 7.0.2.1 Post-hoc analysis of the NINOS primary endpoint (death before 120 days and/or initiation of ECMO) from the NINOS, INOSG and INO-01/ -02 databases[b].

Study	Control	I-NO 5 ppm	I-NO 20 ppm	I-NO 80 ppm	I-NO Pooled	p value
NINOS[c]	77/121 (63.6%)				52/114 (45.6%)	0.006[a]
NINOS[d]	71/112 (63%)				56/118 (47.4%)	0.022[c]
INOSG	21/28 (75%)			13/30 (43%)		0.0182[a]
INO-01/ -02	16/41 (39%)	11/40 (28%)	14/36 (39%)	8/37 (22%)	33/113 (29%)	0.25[c]

a. p value calculated using unadjusted chi-square.

b. Data from individual study reports, sections 6.0.1, 6.0.2 an 6.0.3.

c. Analysis based on intent to treat (ITT) population.

d. Analysis based on 'gas received' population. p value calculated using Cochran-Mantel-Haenszel adjusted chi-square test.

a. p value calculated using one-way ANOVA.

As can be seen from the table above, while there was a significant difference in the NINOS and INOSG trials in this endpoint, no significant difference in the INO-01/ -02 trial was seen. There was a reduction in the % of subjects who met the primary endpoint in two of the three I-NO groups in the INO-01/ -02 trial, however. The table below expresses the reductions in the rate of the primary endpoint in the three trials, using the ITT population in the NINOS.

Table 7.0.2.2 Percent of subjects who met the NINOS primary endpoint (death before 120 days and/or initiation of ECMO) in the NINOS, INOSG, and INO-01/ -02 trials[a].

Study	Control	I-NO 5 ppm	I-NO 20 ppm	I-NO 80 ppm	I-NO Pooled
NINOS	63.6%				45.6% (-28%)
INOSG	75%			43% (-43%)	
INO-01/ -02	39%	28% (-28%)	39% (0%)	22% (-44%)	29% (-26%)

a. Percent reduction calculated as control minus I-NO/control X100.

The initiation of ECMO can also be compared across the three trials, in a search for demonstration of efficacy. The first table below shows the absolute rates, while the following table shows the % reductions from the control rate for each of the trials. Note the lower rate of use of ECMO in the INO-01/ -02 trial in the control group (34%), when compared with either NINOS (55%) or INOSG (71%).

7.0.2 Analysis of the NINOS primary endpoint in the INOSG and INO-01/ -02 trials (cont)

Table 7.0.2.3 Rate of the initiation of ECMO in the NINOS, INOSG, and INO-01/ -02 trials[b].

Study	Control	I-NO 5 ppm	I-NO 20 ppm	I-NO 80 ppm	I-NO Pooled	p value[a]
NINOS[a]	66/121 (54.5)				44/114 (38.5%)	0.014
NINOS[c]	62/112 (55%)		0.067[c]		48/118 (41%)	0.067[c]
INOSG	20/28 (71%)			12/30 (40%)		0.0198
INO-01/ -02	14/41 (34%)	10/41 (24%)	9/36 (25%)	6/37 (16%)	25/114 (22%)	0.34

a. Based on ITT population, p value calculated using unadjusted chi-square.
b. Data from individual study reports, sections 6.0.1, 6.0.2 and 6.0.3.
c. Based on 'gas received' population. p value calculated using Cochran-Mantel-Haenszel adjusted chi-square test.

Table 7.0.2.4 Percent reduction in the rate of the initiation of ECMO in the NINOS, INOSG, and INO-01/ -02 trials[a].

Study	Control	I-NO 5 ppm	I-NO 20 ppm	I-NO 80 ppm	I-NO Pooled
NINOS	55%				41% (-25%)
INOSG	71%			40% (-44%)	
INO-01/ -02	34%	24% (-29%)	25% (26%)	16% (-53%)	22% (-35%)

a. Percent reduction calculated as control minus I-NO/control X100.

The other component of the NINOS primary endpoint, the mortality rate, is discussed in section 8.1.1. There was, however, no detected difference between the control and I-NO groups overall with regards to the mortality rate. The two overall rates calculated below yield a relative risk of 1.098 with 95% confidence interval from 0.78 to 1.54 using the method of Katz and Fisher's Exact Chi-square test.

Table 7.0.2.5 (from table 8.1.1.1) Incidence of death in the NINOS, INOSG, INO-01/ -02 and INO-03 studies[b].

Study	Control group	I-NO group	p value
NINOS (0-120 days)[d]	20/121 (16.5%)	16/114 (14%)	0.596
NINOS (0-120 days)[c]	17/112 (15.1%)	17/118 (14.4%)	0.87
INOSG (0-445 days)	3/28 (10.7%)	2/30 (6.7%)	0.70
INO-01/ -02 (0-28 day)	1/41 (2.4%)	9/113 (8%)	0.29
INO-01/ -02 (0-1 yr)	2/41 (4.9%)	10/113 (8.8%)	0.42
INO-03 (0-28 days)	No control group	0/14 (0%)	N/A
Total[a,e]	24/190 (12.6%)	27/271 (9.9%)	0.43
Total[a,f]	22/181 (12.1%)	29/275 (10.5%)	0.28

a. The comparability of the incidence rates between the trials is limited by the varying length of follow-up for each trial.
b. Data from individual study reports and electronic datasets.
c. Grouped from the NINOS subjects who actually received study gas, according to the gas actually received, using unadjusted chi-square.
d. Based on NINOS ITT population, p value calculated using unadjusted chi-square.
e. This overall incidence figure includes the ITT NINOS population, the INOSG trial, the INO-01/ -02 0-28 day population, and the INO-03 trial population.
f. This overall incidence figure includes all known deaths out to one year, using the 'gas received' population in the NINOS trial.

It is reasonable to conclude from this data that I-NO administration was associated with a significant reduction in the number of infants who were started on ECMO in the NINOS trial. The other two trials supported this effect of I-NO. In these trials, the percent reduction in the rate of both the primary endpoint and in the initiation of ECMO were reduced by amounts which were similar to those seen in the NINOS trial. The INOSG data suffers from problems with blinding and incomplete data. The INO-01/ -02 trial data did not show a significant effect of I-NO on the use of ECMO, due in part to the small numbers of subjects in each group. The subjects in the INO-01/ -02 trial were also less critically ill at time of entry, and the control infants received ECMO at a lower rate than in the INOSG or NINOS trials (see Table 6.0.3.12.1.3). This lower 'event rate' meant that a larger number of subjects would be needed to detect a significant difference between the two groups.

There was no effect of I-NO on the mortality rate detected, and this component contributed little to the overall significance for the NINOS primary endpoint.

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