6.0.1.13.2c Subject deaths (cont)

The individual patient deaths are listed in the table below. No death narratives for the individuals are available.

Table 6.0.1.13.2c.2 (from table 8.1.1.2) Deaths in the NINOS study[a,b].

Trial	Subject	Received ECMO?	Time of Death (days)	Description[b,c]
Control group				
	3-A05	Yes	12	Multi-organ failure, withdrawal of support
	3-A08	No	2	Severe hypoxia
	7-01	Yes	6	Severe intracranial hemorrhage
	10-A05	No	2	Refractory pulmonary hypertension
	12-A13	Yes	9	Severe intracranial hemorrhage, withdrawal of support
	14-A02	Yes	20	Suspected sepsis/infection
	15-A08	Yes	12	Alveolar-capillary dysplasia
	51-A11	Yes	16	Alveolar-capillary dysplasia
	52-A02	No	2	Suspected sepsis/infection
	52-A09	No	3	Left ventricular failure
	52-A14	No	3	RDS
	54-A03	No	1	Suspected sepsis/infection
	54-A14	No	5	Severe pulmonary hypertension
	55-A05	Yes	14	Polycystic kidneys
	56-A08	Yes	1	Proven sepsis/infection
	57-A01	No	2	Pulmonary hypoplasia
	58-A03	No	1	Proven sepsis/infection
	59-A03	No	5	Suspected sepsis/infection
	59-A08	Yes	3	Severe intracranial hemorrhage
	60-A02	No	43	Broncho-pulmonary dysplasia
I-NO group				
	3-A04	No	20	Respiratory failure
	5-A07	Yes	16	Severe CNS ischemia
	5-A14	No	4	Suspected sepsis/infection
	5-A20	Yes	1	RDS
	5-A25	Yes	60	'Thrombi', Withdrawal of support
	12-A11	Yes	15	Alveolar-capillary dysplasia
	15-A09	Yes	5	Proven sepsis/infection
	51-A08	Yes	18	Pulmonary lymphangiectasia
	52-A04	No	2	Meconium aspiration
	51-A06	Yes	5	
	55-A09	No	10	Withdrawal of support
	55-A21	Yes	136	Proven sepsis/infection
	56-A14	No	1	Suspected sepsis/infection
	57-A02	No	1	Proven sepsis/infection
	58-A01	No	1	Surgical death
	59-A02	No	8	RDS

a. Any death prior to 120 days is included in the NINOS data.
b. Study subjects are identified by center # and patient # (e.g., 05-A04).
c. Cause of death from electronic datasets of summary clinical data.

6.0.1.13.3 Long-term safety results of the NINOS trial

Data on the neurodevelopmental outcomes of the survivors is to be collected at 18 to 24 months corrected age. No interim results are available.

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6.0.1.14 NINOS Efficacy Summary

Trial Design

This was a multi-center, multi-national, double-blind, placebo-controlled trial to evaluate the efficacy of I-NO in the treatment of term and near-term infants with hypoxic respiratory failure.

Subjects with hypoxic respiratory failure (see inclusion and exclusion criteria) were randomized to receive either O_2 (no flow of I-NO) or I-NO, 20 ppm for up to 336 hours (14 days). A total of 121 control and 114 I-NO subjects were enrolled.

Subjects who responded fully to treatment gas (either control or I-NO) were continued on the 'low-flow' study gas. For the subjects who received control gas, 17/117 (14.5%) had a full response. In the 20 ppm I-NO group, 57/113 (50.4%) had a full response (p value vs. control <0.001).

Subjects who had no response, or responded partially, were entered into the 'high-flow gas' protocol. These subjects were administered either placebo gas (O_2) or to I-NO, 80 ppm), depending on their initial randomization, and their response measured after another 30 minutes. For the subjects who received control gas, none had a full response (0%) to high-flow control gas (O_2). In the 80 ppm I-NO group, 1/17 (6%) had a full response (no statistical comparison possible).

Non-responders to the high-flow gas were weaned off of the study gas. They were eligible for a repeat trial of the same study gas (either low- or high-flow) after 6 hours, so long as the infant was still otherwise eligible. This process could be repeated 3 times. If no positive response was observed after 3 repeat trials (a total of 4 trials), the subject was labeled a non-responder. Despite this detailed repeat trial protocol, only 3 subjects in the control group (3%) and 2 in the I-NO group (2%) underwent re-initiation of study gas.

Primary and Secondary Endpoints

Primary endpoint

The incidence of death before discharge or 120 days (whichever comes first), and/or the initiation of ECMO between placebo- and I-NO-treated subjects.

The primary endpoint included one part looking at an unquestioned clinical benefit (reduction in mortality) and a component with a less-clear clinical benefit (initiation of ECMO). The results (see below) were completely driven by the reduction in the percentage of infants who received ECMO.

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-DO_2 levels before and 30 minutes after initial administration of the study gas.
4. Neurodevelopmental outcomes assessed at 18-24 months corrected age.
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.

The secondary endpoints can be broken into three groups: 1) measures of acute effects of I-NO on oxygenation; 2) measures of clinical outcomes measured at time of discharge; and 3) long-term neurodevelopmental outcomes.

Number of subjects/ randomization

A total of 250 subjects were planned for enrollment. A total of 235 enrolled: 121 subjects in the control group and 114 in the I-NO group. While the trial was multi-center, three centers accounted for 37% of the enrolled infants (Wayne State University, Stanford University/Packard Children's Hospital, and Baylor Hospital/Texas Children's Hospital).

Two teams were used to accomplish the blinding in the trial. The first team consisted of the patient caregivers, who were blinded to the treatment gas being administered. The second team consisted of a least one unblinded investigator, who was responsible for all activities that revealed the treatment gas. These activities included maintenance of the bedside stock of treatment gas, daily calibration of the gas blender, and recording the methemoglobin, I-NO, and NO_2 levels.

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6.0.1.14 NINOS Efficacy Summary (cont)

Inclusion/ Exclusion Criteria

NINOS has several important differences from the INOSG and INO-01/ -02 trials with regard to the subjects included in the trial.

First, subjects did not have to have echocardiographic proof of pulmonary hypertension. Indeed, 19% of control and 26% of I-NO infants did not have the clinical diagnosis of PPHN (see table 6.0.1.12.1.3). Additionally, 37% of the control subjects and 41% of the I-NO subjects had left-to-right shunting of blood across the patent foramen ovale.

Second, infants who had previously received surfactant and/or high-frequency ventilation were not excluded from the trial (see table 6.0.1.12.1.6). Over 70% of the infants in both groups had received surfactant, and over 30% had received high-frequency ventilation.

Congenital diaphragmatic hernia (CDH) was not an exclusion criteria in the NINOS trial, although those subjects were not included in the subjects for the primary analysis. This contrasts with the INOSG trial and INO-01/ -02 trial, where CDH was an exclusion criteria. No data on the effects of I-NO in the CDH population were submitted with this NDA.

The impact of these differences in the NINOS trial was that even critically ill neonates, who were already receiving maximal standard therapy, were eligible for enrollment. In distinction, the INO-01/ -02 trial excluded infants who had recently received surfactant or high-frequency ventilation, and required that the infant have PPHN prior to enrollment. For this reason, they had to be stable enough that the investigator was not forced to start these interventions while the enrollment process went on (including the determination of PPHN by ECHO). Additionally, the investigators in the INO-01/ -02 trial may have selected only 'less-ill' infants for consideration for that trial, preferring to start other, established, therapies for the critically ill infants. These differences are reflected in the significantly higher OI in the NINOS trial, relative to the INO-01/ -02 trial (averaging 22-25 in the INO-01/ -02 trial versus 42-44 in the NINOS trial (see tables 6.0.3.12.1.3 and 6.0.1.12.1.4).

Dosage/ Administration

Of the infants enrolled in the trial, 117 infants received control gas and 113 received I-NO, 20 ppm. In the I-NO group, 57/113 of the infants responded initially to 20 ppm I-NO, while 55/113 infants did not have a full response to I-NO 20 ppm, and so were administered I-NO 80 ppm.

Individuals in both groups received treatment gas promptly after randomization, save for one individual in the placebo group who started treatment gas 43 hours after randomization: 26.3 minutes was the mean time to start of treatment gas in the control group and 29.3 minutes in the I-NO group. Over 50% of the infants in both groups started treatment gas in <15 minutes.

Five individuals did not receive study gas after enrollment in the trial. Another seven individuals received I-NO after being randomized to receive control gas. These individuals are listed in section 6.0.1.12.3a above, along with an analysis of the results according the actual gas received.

Finally, isolated individuals received non-standard amounts of I-NO. The table below lists the subjects in the NINOS trial by the concentration of I-NO actually received.

Table 6.0.1.14.1 (from table 8.0.3.1) Enumeration of subjects from NINOS according to study gas received[b].

Trial	Control	I-NO 5 ppm	I-NO 10 ppm	I-NO 20 ppm	I-NO 40 ppm	I-NO 80 ppm	I-NO 100 ppm	Combined I-NO
NINOS[a]	110	1	1	50	1	55	2	120

a. All subjects in the I-NO group in NINOS were first exposed to 20 ppm. A subset of the subjects who did not respond were then given I-NO, 80 ppm. Small numbers of subjects also received either more, or less, then the intended 20 or 80 ppm (protocol violations).

b. Does not include the 4 control and 1 I-NO infants who were randomized but did not receive study gas (see section 6.0.1.12.3a).

Duration/ Adjustment of Therapy

In the NINOS trial, the median duration of exposure to control gas was 21 hours, compared with 71 hours for the I-NO group. This reflects the higher fraction of control infants who were discontinued from study gas after failing to increase their PaO_2.

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6.0.1.14 NINOS Efficacy Summary (cont)

Statistical Considerations

There are several statistical issues which need to be addressed with regards to the NINOS trial. The first is the pivotal efficacy analysis, comparing the incidence of death and/or initiation of ECMO in the control and I-NO groups. Based on the sponsor's primary analysis, shown in Table 6.0.1.12.2d.2, there was a highly significant advantage for the group who received I-NO, such that the trial was stopped early and a clinical alert issued. This analysis, which was intent-to-treat, included several subjects who were randomized but never received study gas, as well as subjects who were randomized to control, but received I-NO. This latter group, listed in section 6.0.1.12.3a above, included a large number of subjects who later went on to die and/or receive ECMO. When an analysis is performed according to the gas actually received, the p value for the difference between the two groups is significantly diminished.

Second, the use of an arbitrary p value <0.05 as the threshold for significance needs to be re-thought. The trial had three interim analyses. Under such circumstances, the p value for significance at the end of the trial must be adjusted downwards to a p value of 0.044.

Third, there was evidence of a center effect, as detected by variability in the rate of the primary endpoint among the centers. Correction of this variability can be performed by analyzing the data using the Cochran-Mantel-Haenszel test, rather that the unadjusted chi-square analysis.

Finally, one can analyze the data for the primary endpoint from the NINOS trial using the Cochran-Mantel-Haenszel test, separating the subjects according to the study gas they actually received, and excluding the subjects who did not receive any study gas. The results of such an analysis are presented in the section below for the primary endpoint and for the incidence of ECMO.

Patient Demographics & Baseline Characteristics

The baseline data for the NINOS trial are summarized in tables 6.0.1.12.1.1 to 6.0.1.12.1.6. Overall, the two groups were well-balanced with regards to their demographics and baseline characteristics.

Disposition of Subjects

A larger percentage of the subjects screened for the NINOS trial were enrolled when compared with the INO-01/ -02 trial. From a personal conversation with the principle investigator of the NINOS trail, Dr. Ehrenkranz, a large fraction (>50%) of subjects who were evaluated were ultimately randomized. This contrasts with the INO-01/ -02 study, where only 12% of the screened infants were randomized.

Table 6.0.1.12.2c shows the treatments received in addition to study gas after randomization. The two groups were well-matched with regard to the other therapies they received in addition to study gas, including HFOV/HFJV, surfactant and alkalinization.

Protocol Violations & Deviations

The protocol violations and deviations are listed in Table 6.0.1.12.2b.1 above. The two most significant violations were the infants who were randomized but did not receive study gas, and the infants who received I-NO after being randomized to control gas. These infants are discussed above in section 6.0.1.12.3a. The fact that all of the infants who received the wrong study gas were randomized to receive placebo, and instead received I-NO, raises the possibility that the treatment was unblinded somehow for these infants. There is no other evidence of unblinding for these subjects, who all received ECMO and/or died. The 8 subjects came from 7 different centers, all of whom administered I-NO and control gas to other infants without reported protocol violation.

Concomitant Therapies used after Trial Initiation

As summarized in table 6.0.1.12.2c.1, the two treatment groups were well-balanced with regard to the concomitant therapies received.

Analysis of Primary and Secondary Efficacy Outcomes (see Table 6.0.1.12.2d.2)

1. Incidence of death and/or initiation of ECMO

The table below summarizes the results of the NINOS trial from the primary and secondary endpoints, based on either the Intent-to-Treat study population or on population according to the actual gas received. In the latter population, those infants who were randomized but did not receive study gas are eliminated from analysis.

Table 6.0.1.14.2 Incidence of primary endpoint (death and/or ECMO) in NINOS trial.

Primary Endpoint	% of control subjects	% of I-NO subjects	p value
ITT population	77/121 (63.6%)	52/114 (45.6%)	0.006[a]
'Gas received' population[b]	71/112 (63%)	56/118 (47.4%)	0.015[a]
'Gas received' population[b]	71/112 (63%)	56/118 (47.4%)	0.022[c]

a. p value calculated using unadjusted chi-square

b. Subjects who did not receive any study gas were excluded from the analysis, while the remaining subjects were classified according to the actual gas received.

c. p value calculated using Cochran-Mantel-Haenszel adjusted chi-square test.

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6.0.1.14 NINOS Efficacy Summary (cont)

Analysis of Primary and Secondary Efficacy Outcomes (see Table 6.0.1.12.2d.2) (cont)

2. Incidence of death.

No difference in the rate of death was detected between the two groups. This was true both for the ITT population as well as the population analyzed according to the gas actually received.

Table 6.0.1.14.3 Incidence of death in NINOS trial.

Death	% of control subjects	% of I-NO subjects	p value[a]
ITT population	20/121 (16.5%)	16/114 (14%)	0.596
'Gas received' population[b]	17/112 (15%)	17/119 (14.2%)	0.869

a. p value calculated using unadjusted chi-square

b. Subjects who did not receive any study gas were excluded from the analysis, while the remaining subjects were classified according to the actual gas received.

3. Initiation of ECMO

Significantly more subjects in the control group received ECMO using the ITT population. If the populations were corrected to reflect the actual gas received, however, the p value for the difference became less significant. Correcting for center effect, using the pre-specified Cochran-Mantel-Haenszel adjusted chi-square test, the reduction in ECMO is not significant. Given the three interim looks used in the trial, Dr. Nuri recommends using 0.044 as the cut-off for nominal significance.

Table 6.0.1.14.4 Incidence of ECMO in NINOS trial.

Initiation of ECMO	% of control subjects	% of I-NO subjects	p value
ITT population	66/121 (54.5)	44/114 (38.5%)	0.014[a]
'Gas received' population[b]	62/112 (55%)	48/118 (41%)	0.026[a]
'Gas received' population[b]	62/112 (55%)	48/118 (41%)	0.067[c]

a. p value calculated using unadjusted chi-square.

b. Subjects who did not receive any study gas were excluded from the analysis, while the remaining subjects were classified according to the actual gas received.

c. p value calculated using Cochran-Mantel-Haenszel adjusted chi-square test.

4. Meeting criteria for ECMO

Importantly, there was no significant difference in the number of subjects who met the criteria for ECMO between the two groups.

Table 6.0.1.14.5 Incidence of meeting criteria for ECMO in NINOS trial.

Met criteria for ECMO	% of control subjects	% of I-NO subjects	p value[a]
ITT population	83/121 (69%)	67/114 (59%)	0.12
'Gas received' population[b]	76/111 (68%)	72/119 (60.5%)	0.208

a. p value calculated using unadjusted chi-square

b. Subjects who did not receive any study gas were excluded from the analysis, while the remaining subjects were classified according to the actual gas received.

The reasons for subjects meeting the ECMO criteria but not receiving it are listed in table 6.0.1.12.2d.5. The most common reason was 'Improved', which occurred more frequently in the infants receiving I-NO. Unfortunately, no further details are available for the crucial time period between when an infant was evaluated and 'met' the criteria for ECMO, and when the decision was made either to go to ECMO or not. In discussions with Dr. Ehrenkranz, the NINOS principle investigator, there was no set time when the infants were evaluated for ECMO criteria. Thus, some infants were evaluated prior to initiating study gas, while other infants were evaluated after significant time on study gas had elapsed. The time the evaluation took place was also not recorded. The effect of this missing data is to make interpretation of this discrepancy between meeting criteria and receiving ECMO impossible to resolve.

5. Survivor endpoints.

There was no significant difference between the two groups in either the length of hospital stay or assisted ventilation (see Table 6.0.1.12.2d.2). The length of hospital stay was numerically longer in the I-NO group (36.4±45 in the I-NO group versus 29.5±23 in the control group).

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