6.3 Chronic Pulmonary Injury (cont)

Review of Systems/Illnesses During Follow-up in INO-01/ -02

The INO-01/ -02 trials also performed a review of systems at the follow-up visit. Note that while the use of home O_2 occurred only in the I-NO groups, there was no detectable differences in the occurrence of other pulmonary disease. Fewer patients in the I-NO group were reported to have had severe URIs.

Table 6.3.6 Pulmonary review of systems for the infants seen in follow-up from the INO-01/ -02 trial[a].

	Placebo N=36	I-NO 5 ppm N=36	I-NO 20 ppm N=29	I-NO 80 ppm N=31	Combined I-NO N=96
Home Oxygen	0 (0%)	8 (22.2%)	1 (3.4%)	5 (16.1%)	14 (14.6%)
Mean age when O_2 was D/C'd (months)[b]	–	4.0±3.0	1.0±0.0	3.3±1.3	3.5±2.5
Asthma	5 (13.9%)	7 (19.4%)	3 (10.3%)	2 (6.5%)	12 (12.5%)
Bronchiolitis	4 (11.1%)	7 (19.4%)	4 (13.8%)	2 (6.5%)	13 (13.5%)
Bronchitis	2 (5.6%)	4 (11.1%)	3 (10.3%)	2 (6.5%)	9 (9.4%)
Pneumonia	3 (8.3%)	3 (8.3%)	3 (10.3%)	2 (6.5%)	8 (8.3%)
Severe URI	11 (30.6%)	8 (22.2%)	6 (20.7%)	6 (19.4%)	20 (20.8%)

a. Data from NDA vol. 9.3, Tables 11.

b. For infants who received O_2 at time of initial discharge.

In conclusion, the data regarding the long-term pulmonary toxicity of I-NO is conflicted, and depends on the trial data used. In the INO-01/ -02 trial, more infants were taking pulmonary medications at time of follow-up, and used O_2 after discharge. In the CINRGI trial, the trends for chronic lung injury instead favor I-NO. NINOS appears to be neutral with respect to the occurrence of chronic pulmonary injury. Whether this scatter is a result of the imprecise tools being used to identify pulmonary disease (medicines used, use of O_2) or the result of differences in the trials (e.g., dose of I-NO, duration of administration, patient populations) simply cannot be determined with any certainty in these small datasets. In aggregate, the data do not allow us to conclude that there is either a salutary or adverse effect of I-NO on chronic pulmonary disease, but it also does not exclude the occurrence of either effect in susceptible (and undefined) populations. Additional information is necessary.

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6.4 Acute Neurological Injury

CINRGI

The CINRGI trial collected radiological information about the neurologic changes seen in a subset of the population. In that subset, a higher fraction of the I-NO group had abnormal CT scans reported. No difference in the rate of abnormal neurologic examinations was detected.

Table 6.4.1 Discharge neurologic status in the CINRGI trial[a].

	Placebo	I-NO
Abnormal Head U/S	12/52 (23.1%)	5/42 (11.9%)
Abnormal Head CT	8/34 (23.5)	12/25 (48.0%)
Abnormal Neurologic Exam	8/41 (19.5%)	7/48 (14.6%)
Abnormal CT, U/S or Neurologic Exam	19/89 (21.3%)	17/9 (17.5%)

a. Data from CINRGI study report, table 67. p Values per sponsor.

NINOS

No differences between treatment groups in the incidence of seizures or other markers of acute neurologic changes were noted in the NINOS trial.

Table 6.4.2 (from 6.0.1.13.1.2) Comparison of specific safety parameters during the NINOS trial[a].

Neurologic Adverse Events	Placebo Group (n=121)	I-NO Group (n=114)
Seizures requiring therapy	20/122 (17%)	13/114 (11%)
Brain Infarct	4/82 (5%)	7/77 (9%)
Interventricular hemorrhage (IVH)[a]	21/108 (19%)	16/111 (14%)
IVH Grade I	10/21 (62%)	9/16 (56%)
IVH Grade II	3/21 (14%)	0/16 (0%)
IVH Grade III-IV	8/21 (38%)	7/16 (44%)
Periventricular leukomalacia	3/82 (4%)	4/77 (5%)

INO-01/ -02

The table below summarizes the results of the specified safety parameters measured at the end of hospitalization or 28 days in the INO-01/ -02 trial. There were no significant differences between control and I-NO groups for any of the endpoints. Note that not all subjects have data for a given parameter.

Table 6.4.3 (from 6.0.3.13.1.1) Neurologic disease in INO-01/ -02.[a]

Changes in safety endpoints	Control	I-NO 5 ppm	I-NO 20 ppm	I-NO 80 ppm	Combined I-NO
Incidence of seizures	7/41 (17%)	5/40 (12%)	10/35 (28%)	7/37 (19%)	22/112 (20%)
Incidence of sensorineural hearing loss[a]	5/36 (14%)	3/38 (8%)	6/29 (21%)	7/31 (23%)	16/98 (16%)
Abnormality on cranial ultrasound[b]	4/28 (14%)	3/27 (11%)	3/23 (13%)	2/21 (10%)	7/71 (10%)
Intracranial hemorrhage or infarct detected by ultrasound[c]	1/28 (4%)	0/27 (0%)	1/23 (4%)	0/21 (0%)	1/71 (2%)
Abnormality on CT or MRI scan of head[d]	9/18 (50%)	2/15 (13%)	8/19 (42%)	4/11 (36%)	14/45 (31%)
Interventricular hemorrhage	2/18 (11%)	0/15 (0%)	0/23 (0%)	0/11 (0%)	0/45 (0%)
Periventricular hemorrhage	0/18 (0%)	0/15 (0%)	1/23 (5%)	1/11 (9%)	2/45 (4%)
Intracranial hemorrhage[e]	1/18 (6%)				2/45 (4%)
Periventricular leukomalacia	0/18 (0%)	0/15 (0%)	1/23 (5%)	1/11 (9%)	2/45 (4%)
Extensive cytotoxic edema	0/18 (0%)	0/15 (0%)	0/23 (0%)	1/11 (9%)(	1/45 (2%)
Subdural hematoma	0/18 (0%)	0/15 (0%)	1/23 (5%)	0/11 (0%)	1/45 (2%

a. The sponsor identified the changes in methemoglobin and NO_2 levels, along with overall adverse events, as the most important markers.

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. Category includes one subject with suspected white matter hemorrhage, one grade one germinal matrix hemorrhage, and one infarct, detected by ultrasound. Only subjects with normal baseline ultrasound were included.

d. Abnormalities detected at any time during the hospitalization. No baseline scans are available in most cases, making it difficult to date the onset of the abnormality.

e. Category includes parietal lobe, posterior fossa and frontal lobe hemorrhages.

The INOSG trial did not collect information about neurological injury.

In conclusion, the data do not suggest an effect of I-NO on the incidence of neurologic injury during the

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6.5 Chronic Neurological Injury

In this discussion, and in the discussion of chronic pulmonary injury, it is essential to remember that the degree of follow-up for each of the trials was <90% for almost all endpoint, and <50% for some endpoints of interest. This will be apparent by comparing the numbers in the denominators of the results with the number of patients enrolled in each of the trials. This obviously introduces potential biases (both positive and negative) in the interpretation of the results.

CINRGI

The CINRGI trial collected 6- and 12-month data from a fraction of the population. Recall that there were 89 infants in the control group and 97 in the I-NO group. The results are of limited interpretability.

Table 6.5.1 Six-month follow-up data from the CINRGI trial[a].

	Placebo	I-NO
Abnormal Neurologic Exam-6 Month	7/38 (18.4%)	9/32 (28.1%)
Abnormal Neurologic Exam- 12 Month	0/24 (0%)	3/20 (15.0%)

a. Data from CINRGI study report, table 38-39.

NINOS

NINOS enrolled 121 placebo patients and 114 I-NO patients. No significant differences were detected with regard to any chronic neurologic abnormalities in the NINOS trial. In data not shown here, assessments of mental development (Bayley's), psychomotor development and audiology were similar in both treatment groups. A lower incidence of seizures at follow-up was noted in the I-NO group.

Table 6.5.2 Neurologic diagnoses for the subjects with long-term F/U in the NINOS trial[a].

	Control N=88	I-NO N=85
Normal	69 (79.3%)	66 (77.6%)
Global hypotonia	3 (3.4%)	0 (0%)
Monoplegia	2 (2.3%)	2 (2.4%)
Diplegia	3 (3.4%)	2 (2.4%)
Hemiplegia-right side	1 (1.1%)	2 (2.4%)
Quadraplegia	5 (5.7%)	4 (4.7%)
Truncal hypotonia	4 (4.6%)	4 (4.7%)

a. Data from NDA vol. 11.1, Table 52.

Table 6.5.3 Cerebral palsy and seizures in the subjects with long-term F/U in the NINOS trial[a].

	Control N=88	I-NO N=85
Cerebral palsy present	9 (10.3%)	10 (11.9%)
Mild or Moderate Cerebral Palsy	4 (4.6%)	5 (6.0%)
Severe Cerebral Palsy	5 (5.7%)	5 (6.0%)
Seizures present	13 (14.9%)	4 (4.7%)

a. Data from NDA vol. 11.1, Table 53.

INO-01/-02

The INO-01/-02 trial collected data on the use of anticonvulsants at the end of 1 year follow-up for the 41 placebo and 104 I-NO patients. Few infants were using anticonvulsants at the time of follow-up--two individuals in the I-NO 20 ppm group.

Table 6.5.4 Post-discharge medications at the one-year follow-up visit in the INO-01/-02 trial[a].

	Placebo N=36	I-NO 5 ppm N=36	I-NO 20 ppm N=29	I-NO 80 ppm N=31	Combined I-NO N=96
Anticonvulsants	0 (0%)	0 (0%)	2 (6.9%)	0 (0%)	2 (2.1%)

a. Data from NDA vol. 9.3, Tables 9.

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6.5 Chronic Neurological Injury (cont)

Review of Systems/Illnesses During Follow-up in INO-01/ -02

A review of systems performed at the follow-up visit found relatively few problems. The respiratory ROS is summarized separately. The occurrence of abnormalities in the neurologic Review of Systems is summarized below. Reports of strabismus were more common in the I-NO groups.

Table 6.5.5 Review of systems for the infants seen in follow-up from the INO-01/ -02 trial[a].

	Placebo N=36	I-NO 5 ppm N=36	I-NO 20 ppm N=29	I-NO 80 ppm N=31	Combined I-NO N=96
Strabismus	1 (2.8%)	1 (2.8%)	6 (20.7%)	4 (12.9%)	11 (11.5%)
Hearing problems	3 (8.3%)	5 (13.9%)	3 (10.3%)	1 (3.2%)	9 (9.4%)
Speech problems	4 (11.1%)	5 (13.9%)	6 (20.7%)	4 (12.9%)	15 (15.6%)

a. Data from NDA vol. 9.3, Tables 10.

The sponsor also collected data on the occurrence of seizures in the follow-up population. The only infants with seizures were in the 20 ppm and 80 ppm I-NO groups. There were, however, no differences noted in the incidence of abnormal neurologic examinations at 1 year.

Table 6.5.6 Incidence of seizures and neurologic abnormalities at follow-up in the INO-01/ -02 trial[a].

	Placebo N=36	I-NO 5 ppm N=36	I-NO 20 ppm N=29	I-NO 80 ppm N=31	Combined I-NO N=96
Seizures Present	0 (0%)	0 (0%)	4 (13.8%)	3 (9.7%)	7 (7.3%)
Cerebral Palsy Present	2 (5.6%)	0 (0%)	4 (13.8%)	3 (9.7%)	7 (7.3%)
Neurologic Abnormalities on Physical Exam					
None	28 (77.8%)	31 (86.1%)	20 (69.0%)	23 (74.2%)	74 (77.1%)
Mild	3 (8.3%)	1 (2.8%)	2 (6.9%)	1 (3.2%)	4 (4.2%)
Moderate	4 (11.1%)	3 (8.3%)	5 (17.2%)	5 (16.1%)	13 (13.5%)
Missing	1 (2.8%)	1 (2.8%)	2 (6.9%)	2 (6.5%)	5 (5.2%)

a. Data from NDA vol. 9.3, Table 16.

Finally, in data not shown here (see INO-01/ -02 update elsewhere in this document), the incidence of abnormalities in mental development, psychomotor development and audiology were assessed at follow-up. No worrisome patterns were evident in the data obtained from those patients with available follow-up.

In conclusion, the data available do not reveal a clear pattern of long-term neurologic adverse outcomes following I-NO therapy. In data not shown here, assessments of mental development (Bayley's), psychomotor development and audiology were similar in both treatment groups from the INO-01/ -02 and NINOS trial follow-up data (sections 4.1 and 4.2 of this review).

The increased incidence of seizures reported in the INO-01/ -02 trial is countered by their decreased incidence in the I-NO group of NINOS. The increased frequency of strabismus was only assessed in the INO-01/ -02, and is difficult to interpret with the small numbers of patients. There is a striking increase in strabismus relative to placebo in both the 20 and 80 ppm groups, however, raising the possibility of an adverse effect. Further data are needed to address the issue of strabismus following I-NO use.

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6.6 Laboratory Abnormalities

a. Increased Methemoglobin and NO_2 concentrations

CINRGI

CINRGI had a maximum dose of 20 ppm I-NO for the first 4 hours, after which time the infants were reduced to 5 ppm as tolerated.

Elevated Methemoglobin levels

Two infants in the I-NO group had methemoglobinemia >4% during the treatment period (1.9% of the infants exposed to I-NO). No control infant had elevated methemoglobin. The I-NO group also had a higher mean methemoglobin level during the treatment period on average, when compared with the control group (p = 0.001 per sponsor).

Elevated NO_2 Levels

No infant in either treatment group developed NO_2 levels >5 ppm during the study. Likewise, there was no significant difference between the two treatment groups with regard to the changes in mean NO_2 levels during the treatment period (p=0.83).

NINOS

NINOS used an initial dose of 20 ppm I-NO. If the infant failed to respond with an increase in PaO_2, the I-NO could be increased to 80 ppm.

Elevated Methemoglobin levels

A total of 11 subjects (4 controls, 7 I-NO) had their study gas decreased because their methemoglobin levels were >5%. All continued on study gas at lower flow rate. No subject was discontinued because of NO_2 >7 ppm or methemoglobin >10%.

Table 6.6.1 (from 6.0.1.13.2b.1) Peak Methemoglobin levels from the NINOS trial.

Changes in safety endpoints	Control	Combined I-NO	p value
Peak methemoglobin level during first 12 hours of study gas	1.0±0.6	2.0±1.5	<0.001
Peak methemoglobin level at any time	1.2±0.8%	2.4±1.8%	<0.001
Peak methemoglobin level at any time 0.0 - 1.0% 1.1 - 2.0 2.1 – 30 3.1 - 5.0 5.1 to 10	 52/112 (46%) 49/112 (44%) 6/112 (5%) 4/112 (4%) 1/112 (1%)	 15/110 (14%) 49/110 (45%) 23/110 (21%) 12/110 (11%) 11/110 (10%)	<0.001
Peak methemoglobin level at any time, excluding 8 subjects who received wrong study gas	1.2±0.8%	2.4±1.8%	<0.001

Elevated NO_2 Levels

Only one individual had a NO_2 level >7.0 % during the trial (subject #A08 from center 55). The level was 9.1, and the subject underwent a successful wean of study gas.

Table 6.6.2 (from 6.0.1.13.2a.1) Peak NO_2 levels in ppm from the NINOS trial.

Changes in safety endpoints	Control	Combined I-NO	p value
Peak NO_2 level during first 12 hours of study gas	0.1±0.3	0.6±0.9	<0.001
Peak NO_2 level at any time	0.1±0.3	0.8±1.2	<0.001
Peak NO_2 level at any time 0.0 - 1.0 1.1 - 3.0 3.1 - 5.0 5.1 - 7.0 7.1 to 10	 98/101 (97%) 3/101 (3%) 0/101 (0%) 0/101 (0%) 0/101 (0%)	 85/110 (77%) 21/110 (19%) 2/110 (2%) 1/110 (1%) 1/110 (1%)	<0.001
Peak NO_2 level at any time, excluding 8 subjects who received wrong study gas	0.0±0.3	0.8±1.2	<0.001

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