8.2.1.2 Cardiovascular System Adverse Events Possibly, Probably, or Definitely Related to I-NO (cont)

2) Heart rate (cont)

2) Subject 01-06006: a 4.1 kg black female was born after 42 weeks of gestation by difficult vaginal delivery including shoulder dystocia and a nuchal cord that had to be cut and clamped 4 minutes before delivery. The mother had gestational diabetes. The patient's Apgars were 1 and 6 and she required resuscitation in the delivery room. She developed PPHN and was started on study gas (I-NO 80 ppm). Due to methemoglobinemia (>7%) she was weaned to 32 ppm, and her PaO_2 remained between 60 and 100 (baseline 60) for 5 days. I-NO was discontinued after 6 days, and she was given HFOV. She developed a series of pneumothoraces, became bradycardic and progressively hypoxemic, and died 17 days after therapy started.

3) Subject 12-A01 became hypertensive and bradycardic after acute withdrawal from I-NO (20 ppm). Reinstitution of the I-NO caused a partial reversal of the bradycardia, and the infant was ultimately weaned off I-NO and was discharged.

In the published literature, an acute decrease in heart rate has also been reported following I-NO administration(5).

Conclusion

No effect of I-NO on heart rate was seen in the overall population exposed to I-NO. Following abrupt withdrawal of I-NO, some infants may be at risk for changes in heart rate, particularly bradycardia. For the purposes of this safety review, bradycardia should be considered to be possibly related to I-NO administration.

8.2.1.3 Cardiovascular System Adverse Events Considered Unlikely to be Related to I-NO

Two subjects were identified from the INO-01/-02 trial with specific adverse events related to the cardiovascular system.

1) Aortic Valve Vegetation

Patient 01-05006, developed PPHN with pneumonia and received I-NO 5 ppm for 13 hours. The infant later required ECMO and developed an aortic valve vegetation. After therapy, he was recorded to have 'improved' with regards to vegetation. On one year follow-up, no cardiovascular abnormalities were noted, had had no hospitalizations since discharge.

Conclusion

No evidence exists to link the development of the vegetation to the use of I-NO.

2) Aortic Thrombosis

Patient 01-07008, developed PPHN after meconium aspiration and sepsis, received control gas. She later developed an aortic thrombosis which was recorded as moderate in severity and improved with treatment.

Conclusion

No evidence exists to link the development of aortic thrombosis to the administration of I-NO.

8.2.2 Gastrointestinal System

The following potential adverse events related to the gastrointestinal system were identified from the NDA, from secondary sources, or are adverse events normally explored as part of a safety review:

1) Hepatotoxicity, reflected in abnormal liver function tests (LFTs).

2) Gastrointestinal bleeding.

8.2.2.1 Adequacy of Development Program in Assessing Gastrointestinal Risk for I-NO

The NDA database collected data on all adverse events in the INO-01/ INO-02 and -03 trials only, as detailed in section 8.1.7. This includes gastrointestinal adverse events, as shown in the table below. For overall gastrointestinal adverse events, then, the database included 41 control subjects and 128 subjects exposed to I-NO.

Table 8.2.2.1.1 (from table 8.1.5.4.2) Gastrointestinal adverse events from INO-01/ -02 and INO-03 trials[a].

Body System/ adverse experience	Control Group n=41	I-NO 5 ppm n=45	I-NO 20 ppm n=44	I-NO 80 ppm n=39	Combined I-NO n=128
Gastrointestinal system			1 (2%)	1 (3%)	2 (2%)
Gastrointestinal hemorrhage				1 (3%)	1 (<1%)
Gastrointestinal anomaly			1 (2%)		1 (<1%)

a. Data from NDA, volume 2.17, page 089808 to 092408, volume 2.29 page 353108 to 353308, and from individual case report forms.

Gastrointestinal bleeding was a specific adverse events looked for in the NINOS trial, where it was defined as 'frank blood per rectum or NG tube'. In this trial, data on GI bleeding before and after randomization was collected. For GI bleeding, then, data from an additional 121 controls and 114 I-NO subjects was collected (169 controls and 242 I-NO subjects total).

The collection of lab data, available from the INO-01/ -02 and /-03 trials, has been discussed previously in section 8.1.6.1 and 8.1.6.2. Two values, one at baseline and one within 12 hours of discontinuation of I-NO, are available. Follow-up for markedly abnormal labs, and labs which were identified as adverse events by the investigators was requested from the sponsor. Whenever available, this has been included in this review. For overall gastrointestinal adverse laboratory events, then, the database includes 41 control subjects and 128 subjects exposed to I-NO.

The interpretation of I-NO effects on LFTs is complicated four things.

1) the high incidence of abnormal LFTs at baseline. The table below shows the number of subjects with abnormal labs at baseline, including high percentages of both alkaline phosphatase and LDH abnormalities at baseline.

Table 8.2.2.1.2 (from table 8.1.6.2.1) Number of subjects with normal baseline LFTs from INO-01/ -02[a,c].

Laboratory	Placebo	I-NO 5 ppm	I-NO 20 ppm	I-NO 80 ppm
Alkaline Phosphatase	16/34 (47%)	12/32 (38%)	19/29 (66%)	19/29 (66%)
LDH	2/28 (7%)	5/31 (16%)	1/25 (4%)	2/29 (7%)
SGOT[b]	8/33 (24%)	7/32 (22%)	5/29 (17%)	6/28 (21%)
Total Bilirubin	19/34 (56%)	22/39 (56%)	16/32 (52%)	19/32 (59%)

a. Data from NDA volume 2.18, Table T-21.

b. SGOT (serum glutamate pyruvate transaminase) = AST (aspartate transaminase); SGPT (serum glutamic-oxaloacetic transaminase) or ALT (alanine transaminase); GGT (gamma-glutamyl transferase).

c. No data was collected during the INO-01/ -02 and /-03 trials on GGT or SGPT levels.

2) the absence of data on changes in SGPT (serum glutamic-oxaloacetic transaminase) and GGT(gamma-glutamyl transferase).

No data was collected during the INO-01/ -02 and /-03 trials on GGT or SGPT levels. This limits the ability of this database to detect hepatocellular injury largely to detected changes in SGOT (in the context of altered alkaline phosphatase, LDH, and total bilirubin, which were collected).

3) the lack of available follow-up for abnormal labs.

As discussed above, two sets of labs were collected, and no follow-up labs are available for abnormalities identified on the second set.

4) the changing normal ranges for individual labs shortly after birth.

The normal values for some labs (total bilirubin in particular) change from day to day in the early neonatal period. Labs were deemed normal or abnormal depending on the limits associated with each individual lab sample and subject.

8.2.2.2 Gastrointestinal System Adverse Events Possibly, Probably, or Definitely Related to I-NO

1) Hepatotoxicity, evidenced by elevated LFTs

No subjects were identified by the investigators as having an adverse events related to hepatic injury (Table 8.1.5.4.2). The following subjects had an elevation in serum bilirubin identified as an adverse event. Control and I-NO subjects had a similar incidence of bilirubinemia as an adverse event. No other LFT abnormalities were identified as adverse events in the INO-01/ -02 trial.

Table 8.2.2.2.1 Hyperbilirubinemia identified as an adverse events from INO-01/ -02 and INO-03 trials[a].

Metabolic & Nutritional	Control Group n=41	I-NO 5 ppm n=45	I-NO 20 ppm n=44	I-NO 80 ppm n=39	Combined I-NO n=128
Bilirubinemia	2 (5%)	4 (9%)	3 (6%)	1 (3%)	8 (6%)

a. Data from NDA, volume 2.17, page 089808 to 092408, volume 2.29 page 353108 to 353308, and from individual case report forms.

Available subject identified with increased bilirubin as an adverse event in the INO-01/ -02 and /-03 trials.

Controls

1) Subject 01-15001 received control gas for 56 hours and was discharged without ECMO, chronic lung disease or seizures.

2) Subject 02-15003 received control gas for 3 hours and was discharged without ECMO, chronic lung disease or seizures.

3) Subject 02-15004 received control gas for 8 hours. The infant had dysmorphic features and his karyotype was XXXXY. Given the poor prognosis, support was withdrawn and he ultimately died.

I-NO 5 ppm

1) Subject 01-06009 received I-NO 5 ppm for 3 hours, and recovered without ECMO. Other long-term data is missing.

2) Subject 01-14003 received I-NO 5 ppm for 24 hours, and was discharged without ECMO, chronic lung disease or seizures.

3) Subject 02-11004 received I-NO 5 ppm for 115 hours, and was discharged without ECMO, chronic lung disease or seizures.

4) Subject 02-11008 received I-NO 5 ppm for 58 hours, and was discharged without ECMO, but with reactive airways disease.

I-NO 20 ppm

1) Subject 02-07007 received I-NO 20 ppm for 2 hours, was declared a therapeutic failure, and recovered after ECMO.

2) Subject 02-15002 received I-NO 20 ppm for 6 hours, recovered and was discharged without ECMO, chronic lung disease or seizures.

3) Third subject in the 20 ppm group was not identified from the electronic datasets.

I-NO 80 ppm

1) Subject 01-01002 received I-NO 80 ppm for 8 hours, recovered, and was discharged without ECMO, but with a seizure disorder.

Drop-outs due to abnormal LFTs

There was one individual who dropped out of the INO-01/ -02 study with an elevation in LDH listed as a contributing factor.

Table 8.2.2.2.2 (from table 8.1.3.2.1.1) Subject from the INO-01/ -02 and INO-3 trials who dropped out, in part, due to an elevated LDH. No follow-up of the elevated LDH is available.

Study Group	Subject #	Adverse Event	Outcome
I-NO 5 ppm	01-01004	Acute pulmonary decompensation Elevated LDH	ECMO, HFOV, Discharged without chronic lung disease

8.2.2.2 Gastrointestinal System Adverse Events Possibly, Probably, or Definitely Related to I-NO (cont)

1) Hepatotoxicity, evidenced by elevated LFTs (cont)

Overall, the mean LFTs tended to fall from baseline to post-INO[b]. In all groups except I-NO 20 ppm, alkaline phosphatase fell significantly. Mean values for LDH and SGOT also fell, but the differences were not significant.

Table 8.2.2.2.3 Mean LFT values from INO-01/ -02[a,b,c].

Lab Test[c]	Placebo		I-NO 5 ppm		I-NO 20 ppm		I-NO 80 ppm	
	Baseline	Post-I-NO	Baseline	Post-I-NO	Baseline	Post-I-NO	Baseline	Post-I-NO
Alkaline Phosphatase	302.8±313 (n=40)	164±206 (n=34)	465±581 (n=38)	175±285 (n=34)	353±552 (n=36)	155±217 (n=30)	366±514 (n-34)	141±92 (n=33)
LDH	1617 ±1519 n=38	1069 ±1275 n=32	1479 ±1096 n=36	1134 ±937 n=33	3060 ±6615 n=32	1218 ±1783 n=29	1976 ±2160 n=34	1338 ±1271 n=31
SGOT	109 ±101 n=39	69 ±72 n=34	121 ±89 n=38	64 ±53 n=34	312 ±760 n=35	81 ±86 n=30	258 ±584 n=34	78 ±61 n=31
Total Bilirubin	4.8 ±3.1 n=41	5.0 ±4.8 n=35	4.2 ±2.7 n=40	5.3 ±4.9 n=40	5.0 ±3.6 n=36	6.8 ±6.3 n=31	4.6 ±3.2 n=35	5.1 ±3.4 n=34

a. Source: NDA volume 2.50, pages 341010-341510 and volume 2.25.

b. Per protocol, follow-up labs were to be taken no more than 12 hours after end of exposure to treatment gas.

c. Data shown as mean±standard deviation (# of subjects with data). Shaded boxes indicate that baseline and post-study gas labs differ significantly using 2-sided unpaired t test.

In the database from INO-01/ INO-02 and -03, newly-abnormal SGOT occurred in 1 control subject (2%) and in 3 I-NO subjects (2%). SGOT values which became more abnormal, including those who started with abnormal baselines, occurred in 5% of control subjects and 11% of I-NO subjects. The table below shows the number of subjects in each I-NO group. The numbers are too small to infer a relationship between I-NO dose and SGOT abnormalities.

Table 8.2.2.2.4 (from Table 8.1.6.2.2.1) Abnormal LFTs from INO-01/ -02 and INO-03[c].

	Control n =38	I-NO 5 ppm n = 45	I-NO 20 ppm n =41	I-NO 80 ppm n = 37	I-NO combined n = 123
Elevated Total Bilirubin					
New abnormalities[a]	1 (3%)	4 (9%)	1 (2%)	1 (3%)	6 (5%)
Values >12	3 (8%)	4 (9%)	5 (12%)	3 (8%)	12 (10%)
Elevated SGOT					
New abnormalities[a]	1 (3%)	1 (2%)	0 (0%)	2 (5%)	3 (2%)
New or worsening abnormalities[b]	2 (5%)	6 (13%)	2 (5%)	6 16%)	14 (11%)
Elevated Alkaline Phosphatase					
New abnormalities[a]	0 (0%)	1 (2%)	0 (0%)	0 (0%)	1 (<1%)
New or worsening abnormalities[b]	0 (0%)	2 (4%)	0 (0%)	0 (0%)	2 (2%)

a. These subjects had a normal value at baseline and an abnormal value within 12 hours of discontinuation of I-NO.

b. These subjects include all of those in the 'new abnormalities' category, as well as any subject who had an abnormal value at baseline which was more abnormal on the follow-up lab.

c. Data was obtained from NDA volume 2.31, Data Listing 13.1; volume 2.25, Appendix 16.2.2.12; and volume 2.18, Table T-30, and electronic datasets.

8.2.2.2 Gastrointestinal System Adverse Events Possibly, Probably, or Definitely Related to I-NO (cont)

1) Hepatotoxicity, evidenced by elevated LFTs (cont)

Another source of data on the effects of I-NO on LFTs is the individual subject lab data. The subjects who experienced a markedly abnormal SGOT from the individual labs was identified (from Table 8.1.6.2.2.1a.1). While no control subject was identified, 4 I-NO subjects (3%) were identified. No follow-up labs are available for the subjects listed.

Table 8.2.2.2.5 Individuals with markedly abnormal SGOT post-I-NO from INO-01/ -02 and /-03[a,b].

Patient #	Lab Test	Baseline value	Post-I-NO value	Notes
Placebo	None			
I-NO 5 ppm				
02-11008	SGOT	78	145	Discharged without ECMO with CLD[c]
I-NO 20 ppm				
01-03025	SGOT	109	358	Died (see below)
01-03008	SGOT	181	264	Discharged without ECMO with seizures
I-NO 80 ppm				
01-02003	SGOT	69	120	Discharged without ECMO data missing

a. Data from NDA, volume 2.25, individual patient listings, and from electronic datasets.

b. Lab tests were identified as markedly abnormal were >2X upper limits of normal on post-I-NO value. Normal values were taken from individual lab ranges associated with each specimen.

c. CLD chronic lung disease.

A similar trend is seen towards increased numbers of markedly abnormal LDH and total bilirubin values in the I-NO group, relative to the control group. No markedly abnormal alkaline phosphatase values were identified.

Table 8.2.2.2.6 (from table 8.1.6.2.2.1a.1) Individuals with markedly abnormal LDH and total bilirubin post-I-NO chemistry labs from INO-01/ -02 and /-03 trials[a,b].

Patient #	Lab Test	Baseline value	Post-I-NO value	Notes
Placebo				
01-03013	LDH	550	720	high
01-04001	LDH	515	527	high
02-14004	Bilirubin	9.3	14.3	high
01-14002	Bilirubin	9	17.2	high
01-07007	Bilirubin	10.5	15	high
I-NO 5 ppm				
01-03002	LDH	517	939	high
01-06002	LDH	1955	3981	high
02-14001	LDH	530	1235	high
02-15001	LDH	510	1022	high
01-01004	Bilirubin	5.5	13.7	high
I-NO 20 ppm				
01-17006	LDH	2939	3946	high
01-07003	Bilirubin	5.9	14.2	high
01-07005	Bilirubin	12.9	13.9	high
01-09003	Bilirubin	18.9	30.1	high
01-14001	Bilirubin	9.5	14.1	high
03-52001	Bilirubin	11	15.3	high
I-NO 80 ppm				
01-03003	LDH	475	692	high
01-06003	LDH	1936	2995	high
01-11004	LDH	3429	6270	high
02-04004	LDH	508	1098	high
01-02003	LDH	763	1623	high
02-11007	LDH	1534	2517	high
03-59003	LDH	NA	1634	high
01-05003	Bilirubin	10.9	13.4	high
01-03005	Bilirubin	9.8	13.5	high
02-13001	Bilirubin	9.4	13.1	high

a. Data from NDA, volume 2.25, individual patient listings, and electronic datasets.

b. Lab tests were identified as markedly abnormal were >2X upper limits of normal on post-I-NO value.

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