CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20845

STATISTICAL REVIEW(S)

Statistical Review and Evaluation

NOV 4 1999

NDA: 20,845
Applicant: INO Therapeutics, Inc.
Drug Name: Inhaled Nitric Oxide (Nitric Oxide)
Indication: Persistent pulmonary hypertension of newborn (PPHN)
Document Reviewed: Vol. 9.1, 9.6, 9.7, 9.10, 9.11, 9.20, 9.21

The sponsor's resubmission of original NDA of Nitric Oxide (May 26, 1999) includes the results from a new randomized clinical trial, known as CINRGI. The original NDA was reviewed by FDA earlier but was withdrawn by the sponsor on September 16, 1997. This statistical review focuses on the sponsor's new study (CINRGI) in the resubmission.

1. Outline of CINRGI study

Design of study

Study CINRGI was a multicenter, placebo-controlled, double-blinded study and involved 212 full-term and near-full term neonates with echocardiographic or clinical evidence of pulmonary hypertension. The **objective** of the study was to assess the safety and efficacy of inhaled NO added to the conventional therapy for PPHN as compared to conventional therapy alone.

According to the sponsor, the patients in this study were receiving diluted treatment gas with endotracheal tube NO concentrations of 0 ppm (for placebo patients) or 5-20 ppm (NO patients) according to the randomization. The randomization was stratified by patient disease status (CDH, MAS, Pneumonia, PPHN, RDS, and other). Inhaled NO was started at 20ppm. For all patients the ventilator settings were held constant over the first 30 minutes of treatment. Weaning of the treatment gas was done by decreasing the percent of treatment gas. Neonates who had a PaO2 (arterial partial pressure of oxygen) larger or equal to 60 mmHg and a pH 7.35-7.55 after being in the study for 4 hours had the treatment gas concentration reduced to 5 ppm for the remainder of the treatment period. Treatment gas was continued at 5 ppm until the FiO2 was <0.7, the patient had received 96 hours of treatment, or the patient was 7 days old, whichever came first. The submitted data indicate that the gas treatment for the first patient started on 3/3/96 and for the last one on 12/18/98.

Endpoints / hypotheses / analyses / sample size

The **primary efficacy endpoint** was defined as the "need for ECMO" (NFE) in the original protocol (December, 1995). In the protocol, the criterion for treatment with ECMO was defined (See Appendix 1). The sponsor later (Amendment 1) clarified the meaning of "need for ECMO" as actual "use of ECMO" (UOE) rather than "met ECMO criteria" (MEC). For this reason, no detailed information on MEC was collected according to the sponsor (Appendix 2).

Table 1.1 Mean methemoglobin by treatment group

time	placebo (95% CI)	NO (95% CI)
Baseline	0.78 (0.66, 0.90)	0.79 (0.67, 0.91)
Hour 4	0.78 (0.63, 0.91)	1.34 (1.17, 1.51)
Hour 24	0.58 (0.44, 0.72)	0.92 (0.77, 1.07)

Follow-up duration / Patient withdrawal

No maximum follow-up duration was clearly specified for the primary variable, the use of ECMO. The conditions of exiting the trial were specified in the protocol (Appendix 4).

Sponsor's result

A total of 248 neonates were entered into the study. Of these, 36 were enrolled into the pilot study phase of the trial that was randomized but not blinded. A total of 212 patients were randomized in the blinded trial. Among them, 26 patients (with disease status as CDH or other) had an enrollment diagnosis of lung hypoplasia and were analyzed separately from the other patients. The efficacy population for this trial consisted of remaining 186 patients.

The two treatment groups seemed to be comparable with respect to demographic factors: age, gender, weight, Apgar score, and race. The two groups seemed to be comparable with respect to most baseline prognostic characteristics except for a few, including baseline airleak, arterial pressure, PaO2 (arterial partial pressure of oxygen), SaO2 (percent of oxygen saturation of the arterial blood), and OI (oxygen index). The imbalance with respect to these factors were generally in favor of NO group. For instance, a numerically higher mean value of OI (43.9) was observed in the placebo group as compared to that (35.0) in the NO group. The sponsor's explanation for the imbalances is that for some patients, the baseline oxygenation measurements were taken after the treatment started.

Table 1.2 Demographic and some baseline characteristics

characteristics	Placebo, n=89	NO, n=97	p-value
Mean age in hours	29.9	30.0	0.95
males	52 (58.4%)	44 (45.4%)	0.08
Gestational weeks (PE)*	38.8	39.2	0.20
white	44 (49.4)	40 (41.1)	0.30
Mean admission weight (kg)	3.3	3.4	0.24
Airleak syndrome (yes)	22 (24.7%)	11 (11.3%)	0.021
Arterial pressure (mmHg)	55.8	51.6	0.019
PaO_2 (mmHg)	54.3	77.6	0.007
SaO_2 (%)	84.1	89.6	0.018
OI (cm H_2O/mm H_g)	43.9	35.0	0.011

* by physical examination

The sponsor's analysis (Cohran-Mantel-Haenszel adjusting for underlying disease) based on the intent-to-treat patient population indicated a statistically significant group difference in use of ECMO (31/98 for NO and 50/88 for placebo, p=0.001). The

difference was still statistically significant when adjusted for baseline difference controlling by PaO2 or by OI categories (p=0.007 from both adjusted analyses). The difference in use of ECMO between the two treatment groups was not statistically significant in the 26 patients with lung hypoplasia (p=1.000).

Table 1.3 Number of use of ECMO by treatment

Population	PaO2 or OI	Placebo (%)	NO (%)	p-value
All 186 patients, ITT	Whole range	51/89 (57.3)	30/97 (30.9)	0.001
All 186 suj., adjusted for baseline PaO2 (mmHg) categories	unknown	4/7 (57.1)	4/8 (50.0)	0.007
	≤ 30	11/11 (100)	5/6 (83.3)	
	30 to ≤ 50	20/40 (50)	13/32 (40.6)	
	50 to ≤ 70	12/19 (63.2)	4/25 (16.0)	
	70 to ≤ 100	2/6 (33.3)	3/13 (23.1)	
	>100	1/5 (20.0)	2/14 (14.3)	
All 186 suj., adjusted for baseline OI (cm H_2O/mmHg) categories	unknown	9/13 (69.3)	4/15 (26.7)	0.007
	≤ 30	7/20 (35.0)	9/43 (20.9)	
	30 to ≤ 40	9/20 (45.0)	4/15 (26.7)	
	40 to ≤ 50	7/11 (63.6)	6/11 (54.5)	
	>50	12/24 (50.0)	8/14 (57.1)	
Patients with lung hypoplasia	Whole range	13/15 (86.7)	9/11 (81.8)	1.00

The sponsor compared the outcomes in oxygenation status between the two treatment groups and claimed a statistically significant difference between the groups with respect to several indicators of oxygenation (Tables 34-37, the sponsor's study report). However, the sponsor's analyses used, instead of an ITT patient population, only the information from the completers. These analyses might introduce a selection bias and thus not preferred.

The sponsor's analyses based on the 6-month or 12-month follow-up data showed no statistically significant difference in hospitalization. Six month death rates in the two groups were not statistically significantly different (5/89 for placebo and 4/97 for NO, p=0.738).

2. Reviewer's results and comments

This reviewer compared the numbers of use of ECMO between the two treatment groups using all 212 randomized or using only the 186 patients without lung hypoplasia (LH) at the time of enrollment (Table 2.1). There was a statistically significant difference in rate of use of ECMO between the two treatment groups. According to the sponsor, it was assumed in the protocol that all ECMO therapy would be captured by recording ECMO use during the initial hospitalization. The submitted data indicated that durations of patient hospitalization (calculated by this reviewer as the difference between the time of discharge to home and the time of the initiation of treatment gas) range from 6 days to several months. Majority of use of ECMO occurred within 6 days after an initiation of treatment gas except one case (7 days after the initiation of the treatment gas) and several cases with missing time of discharge to home (10 subjects in placebo and 3 subjects in the NO group). The patient follow-up seemed to be complete and comparable between the groups (Table 2.2).

Table 2.1 Comparison of incidence in use of ECMO

population	placebo	NO	p-value/not stratified*	p-value /stratified**
	# of ECMO / n (%)	# of ECMO / n (%)		
exclude LH	50/88 (56.8)	31/98 (31.6)	0.001	0.001
include LH	62/102 (60.8)	41/110 (37.3)	0.001	0.001

*χ^2-test, ** Cohran-Mantel-Haenszel controlling by strata (underlying disease)

Table 2.2 time to discharge (day)

ECMO / treat / n	Quantiles				
	0%	25%	50%	75%	100%
No / pla. / 34	6	12	14	26	114
No / NO / 64	7	13.5	17	22.5	64
Yes / pla. / 44	10	17	21	30.5	54
Yes / NO / 27	11	19	26	32	46

The question now is whether or not the observed group difference in use of ECMO can be attributed to the effect of nitric oxide treatment. To answer it, this reviewer focused on the following issues.

(i) Unbinding of treatment code

As explained before, there are sufficient grounds to suspect that the CINRGI study was largely unblinded. This is especially worrisome knowing that the primary endpoint, UOE (use of ECMO) can be subjective and initiation of ECMO depends on an investigator's judgement and discretion. It is possible for biases of the investigators to be introduced to the trial. For this study, extra cautions must be taken in examining and interpreting the trial results.

(ii) Potential bias due to delaying initiation of ECMO

To evaluate the effect of the NO treatment on use of ECMO, it is important to examine whether or not there was a delay of initiation of ECMO in the NO group as compared to placebo. The delay could be a result of more aggressive initiation of ECMO for placebo patients and/or more reluctant initiation of ECMO for the NO treated patients. If there was a delay in the NO group, the observed lower rate of use of ECMO in the NO group could be a direct consequence of the delay since with the delay of initiation of ECMO, a patient might pass the episode of need for ECMO and never needed ECMO again. In this case, one can not relate the effect of the nitric oxide treatment to the lowered rate of ECMO use in the NO group without knowing the causes of the delay. If there were causes unrelated to the effect of the NO treatment, the observed treatment effect would be confounded partially or completely with biases attributed to the delay from these causes.

A significant delay in initiation of ECMO in the NO group as compared to placebo was suggested by the data (Table 2.3a). The median duration from initiation of treatment gas to initiation of ECMO was 3.6 hours for placebo and 10.4 hours for the NO group. There

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.