20 May 2010
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

INOmax

International non-proprietary name: NITRIC OXIDE

Procedure No. EMEA/H/C/000337/A46/0018

CHMP assessment report for paediatric use studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted

Disclaimer: The assessment report was drafted before the launch of the European Medicines Agency's new corporate identity in December 2009. This report therefore has a different appearance to documents currently produced by the Agency

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7523 7455
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	INOmax
INN (or common name) of the active substance(s):	Nitric Oxide
MAH:	INO Therapeutics AB
Currently approved Indication(s)	treatment of newborns ≥ 34 weeks gestation with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension, in order to improve oxygenation and to reduce the need for extracorporeal membrane oxygenation.
Pharmaco-therapeutic group (ATC Code):	Other respiratory system products R07 AX
Pharmaceutical form(s) and strength(s):	400 ppm mol/mol inhalation gas

I. INTRODUCTION

On 11 January 2010 the MAH submitted a completed paediatric study for INOmax, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use.

A short critical expert overview has also been provided.

The MAH stated that the submitted paediatric study does not influence the benefit risk for Inomax and that there is no consequential regulatory action.

II. SCIENTIFIC DISCUSSION

II.1 Information on the pharmaceutical formulation used in the study

Nitric oxide (NO) is the active component of endothelium-derived relaxing factor. Exogenous inhaled NO acts selectively on the pulmonary circulation. In smooth muscle cells, NO activates soluble guanylate cyclase to form cyclic GMP, which in turn promotes a calcium dependent relaxation. It has little systemic effect because of its short half-life caused by inactivation by binding to haemoglobin, rapid oxidation and the interaction with free radicals.

INOmax 400 ppm contains the active drug substance, nitric oxide, formulated as a series of dilutions in nitrogen. It is delivered to the patient via mechanical ventilation after dilution with an air/oxygen mixture using approved (CE-marked) ventilators and delivery devices.

The current indication is for the treatment, in conjunction with ventilatory support and other appropriate agents, of newborns ≥ 34 weeks gestation with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension, in order to improve oxygenation and to reduce the need for extracorporeal membrane oxygenation. The maximum recommended dose is 20 ppm decreasing to 5 ppm within 4-24 hours provided arterial oxygenation is adequate at lower dose. The 20 ppm dose should not be exceeded. In the pivotal clinical trials, the starting dose was generally 20 ppm.

II.2 Clinical aspects

1. Introduction

The MAH submitted a final report for:

- INOT27 “The effects of nitric oxide for inhalation on the development of chronic lung disease in preterm infants”.

2. Clinical study

INOT27 "The effects of nitric oxide for inhalation on the development of chronic lung disease in preterm infants".

- **Description**

This was a prospective, multicentre, double-blind, placebo-controlled, randomised trial of nitric oxide therapy in preterm infants with respiratory distress.

- **Methods**

- Objective(s)

To assess the safety and efficacy of inhaled nitric oxide (iNO) to reduce the risk of chronic lung disease (CLD) in preterm infants with respiratory distress, and to assess the long-term effects of the therapy on the development of these children over 7 years of clinical follow-up.

- Study population /Sample size

The main criteria for inclusion into the study were as follows: Inborn preterm infants 24+0 days weeks to 28+6 days weeks gestational age (GA) (defined by first-trimester ultrasound or, if not available, based on the last menstrual period) who required the use of surfactant within 24 hours of birth (either prophylactically or for signs of developing respiratory distress), or who required the use of continuous positive airway pressure (CPAP) (fraction of inspired oxygen concentration [FiO2] of 0.30 or greater on a mean airway pressure of 4cm or greater H2O) within 24 hours of birth in order to maintain an oxygen saturation by pulse oximeter(SpO2) of 85% or greater.

A total of 800 subjects (400 in each group) were planned.

- Treatments

Subjects received nitric oxide 5 ppm or placebo (100% Grade 5 Nitrogen [N2] gas) for a minimum of 7 days, and a maximum of 21 days in a blinded fashion. Subjects who required less than 7 days of assisted ventilation completed the minimum duration of therapy via face mask or nasal cannula. Subjects otherwise remained on study treatment as long as respiratory support was required, or until 21 days of therapy were completed.

- Outcomes/endpoints

Primary: Success, defined as infant alive without bronchopulmonary dysplasia (BPD) at 36 weeks' Gestational age.

Secondary:

- Number of days of assisted ventilation;
- length of hospitalisation;
- survival without severe intraventricular hemorrhage (IVH), and periventricular leukomalacia (PVL);
- total number of days in hospital from 36 weeks' GA to 1 year and 2 years corrected age;
- average number of days in hospital for respiratory illness from 36 weeks' GA to 1 year and 2 years corrected age.

Safety:

- Incidence of methemoglobinemia and elevated nitrogen dioxide concentrations;
- incidence and types of reported adverse events (AEs);
- incidence of medically treated and/or surgically ligated ductus arteriosus;
- incidence of retinopathy of prematurity (ROP);
- incidence of death after 36 weeks' GA to 1 year and 2 years corrected age, stratified by GA at birth;
- incidence of death after 36 weeks' GA to 7 years corrected age, stratified by GA at birth;

- long-term neurodevelopmental outcome assessed by a validated, age-appropriate developmental assessment at 2 and 7 years corrected age;
- pulmonary function testing at 7 years corrected age.

➢ **Statistical Methods**

All efficacy analyses were performed on the Intend-to-Treat (ITT) Population that included all randomized subjects. Safety analyses were performed on the Safety Population including all treated subjects. The primary efficacy variable was analysed by logistic regression. The secondary efficacy variables were evaluated using either an analysis of variance (ANOVA) model or logistic regression. Additional statistical methods included the Kaplan-Meier method and log-rank test.
Safety data were summarized by either descriptive statistics or frequency table.

➢ **Results**

- Recruitment/ Number analysed

Two populations were used in the analyses of this study: the ITT Population and the Safety Population.

Table 4: Number of Subjects Randomly Assigned to Each Treatment Group

Population	iNO N (%)	Placebo N (%)	Total N (%)
All Subjects Enrolled			800
Intent-to-Treat Population[a]	399 (49.9)	401 (50.1)	800 (100.0)
Safety Population[b]	395 (49.4)	397 (49.6)	792 (99.0)

[a] All randomly assigned subjects
[b] All subjects who received at least one dose and reported safety data
Source: Section 14.1., Table 14.1.1.1

Table 5: Summary of Subject Enrollment

	iNO (N = 399)	Placebo (N = 401)	Total (N = 800)
All Subjects Randomized	399	401	800
Subjects Randomly Assigned but Did Not Have Primary Efficacy Data Available	4	1	5
Subjects Randomly Assigned Who Had Primary Efficacy Data Available	395	400	795
Subjects Randomly Assigned But Never Took Drug or Did Not Have Safety Data Available	4	4	8
Safety Subjects Who Took Drug	395	397	792

Source: Section 14.1, Table 14.1.1.1 and Listing 16.2.3

- Baseline data

In general, the demographic and baseline characteristics for subjects and mothers were similar between the iNO and placebo treatment groups for the 800 subjects in the ITT Population. The treatment groups were comparable in GA, race, age of mother, Apgar scores at 5 and 10 minutes, length, head circumference, oxygenation index, and intubation/CPAP. The use of prenatal corticosteroids was quite high in subjects in both

treatment groups; 89.5% of mothers of subjects of the iNO group and 90.3% of mothers of subjects in the placebo group. There were slightly more females (48.1% vs. 45.1%) and a slightly lower mean birth weight (851.5 grams vs. 864.1 grams) in subjects in the iNO group compared with subjects in the placebo group, respectively. Chorioamnionitis was more common in the mothers of subjects in the iNO treatment group compared with mothers of subjects in the placebo group (27.6% vs. 23.4%, respectively).

- Efficacy results

Primary Efficacy Analysis

In this study, treatment with iNO 5 ppm and less for 21 days was comparable with placebo (p = 0.7340) for survival without BPD in preterm infants with respiratory distress. There were 258 (65.3%) successes in the iNO group and 262 (65.5%) in the placebo group. The odds ratio of iNO compared with placebo was 1.05

Table 9: Primary Outcome Summary and Analysis (Intent-to-Treat Population)

Outcome	iNO (N = 395) n (%)	Placebo (N = 400) n (%)	Total (N = 795) n (%)	Odds Ratio[a]	p value[b]
Success: Alive Without BPD	258 (65.3)	262 (65.5)	520 (65.4)	1.05	0.7340
Failure: Death or BPD	137 (34.7)	138 (34.5)	275 (34.6)		

Subjects with no efficacy information were not included in the analysis.
[a] iNO vs. placebo
[b] Based on Wald Chi-square
Source: Section 14.2, Table 14.2.1.1

For subjects with at least 21 days of treatment, a higher success rate was observed in the iNO group compared with placebo; there were 98 (70.0%) successes in the iNO group and 90 (60.8%) in the placebo group (p = 0.0839) (Section 14.2, Table 14.2.1.10).

TABLE 14.2.1.10
PRIMARY OUTCOME SUMMARY AND ANALYSIS BY INTUBATION AT 21 FULL DAYS

PROTOCOL INOT-27
INTENT-TO-TREAT POPULATION, ONLY PATIENTS WHO HAD 21 DAYS OR MORE OF THERAPY

OUTCOME	PLACEBO N=148 n(%)	INO N=140 n(%)	TOTAL N=288 n(%)
FAILURE : DEATH OR CLD	58 (39.2)	42 (30.0)	100 (34.7)
SUCCESS : ALIVE WITHOUT CLD	90 (60.8)	98 (70.0)	188 (65.3)

MODEL VARIABLE	COEFFICIENT	STANDARD ERROR	WALD CHI-SQUARE	P-VALUE	ODDS RATIO	95% CI
INTERCEPT	-2.2269	2.7696	0.6465	0.4214	.	
TREATMENT (INO vs. Placebo)	0.2175	0.1258	2.9883	0.0839	1.54	(0.94, 2.53)
GESTATIONAL AGE	0.1101	0.1062	1.0743	0.3000	1.12	(0.91, 1.37)

No treatment difference was observed for the primary outcome by BPD severity.

Table 10: Primary Outcome by BPD Severity (Intent-to-Treat Population)

Patient Status	iNO (N = 395) n (%)	Placebo (N = 400) n (%)	p value
Alive and no BPD Because: 1) Subject Breathing Room Air, or 2) Subject Not on O2 or CPAP and Did Not Qualify for an ORT	244 (61.8)	239 (59.8)	0.0778
Alive and no BPD Because Subject Received an ORT and Did Not Have BPD	14 (3.5)	23 (5.8)	
Alive and Had BPD Because BPD Confirmed by an ORT	44 (11.1)	47 (11.8)	
Alive and Had BPD Because: 1) Subject Still on Mechanical Ventilation or 2) Subject Still Receiving O2 or CPAP	37 (9.4)	49 (12.3)	
Died	56 (14.2)	42 (10.5)	

p value is based on Klotz test
Source: Section 14.2, Table 14.2.1.4

The primary efficacy variable was also analysed in the ITT population by various strata of demographic characteristics using Wald Chi-square. In all stratifications (GA, race, birth weight, and type of ventilation) with the exceptions of race non-black, GA greater than or equal to 26 weeks and CPAP, subjects in the iNO group had a higher percentage of successes when compared with subjects in the placebo group. No differences were significant.

Gestational age was a significant covariate ($p < 0.0001$) in terms of survival without BPD. Subjects born at 26 weeks GA or older had a higher success rate (72.7%) than younger subjects (51.6%). However, there were no treatment differences observed in either age strata.

Secondary Efficacy Analyses

For secondary efficacy variables, length of assisted ventilation, survival without significant brain injury, and length of hospitalisation no treatment differences were observed.

Table 15: Descriptive Statistics of Secondary Outcomes (Intent-to-Treat Population)

Outcome	Category	iNO (N = 399)	Placebo (N = 401)
Length of Assisted Ventilation (Days)	Mean (SD)	44.40 (26.102)	45.18 (28.681)
	Median	44.00	41.50
	Range	(2.00, 190.00)	(2.00, 265.00)
Length of Hospitalization (Days)	Mean (SD)	94.18 (36.515)	92.96 (34.718)
	Median	88.00	86.00
	Range	(36.00, 375.00)	(35.00, 366.00)
Alive without Brain Injury	n (%)	181 (69.3)	188 (75.5)
Dead or Significant Brain Injury	n (%)	80 (30.7)	61 (24.5)

Source: Section 14.2, Tables 14.2.2.1, 14.2.2.3, and 14.2.2.5

Assessor's comments
The results for the primary efficacy endpoint (survival without BPD following treatment with nitric oxide 5 ppm and less for 21 days)showed no difference between the two groups; 65.3% for the nitric oxide group versus 65.5% for the placebo group. Although there was a small benefit in babies treated for at least 21 days with nitric oxide, the results were not statistically significant.

Not surprisingly, gestational age and birth weight were significant covariates with heavier and older infants more likely to survive without BPD. However, this was not affected by treatment.

There were no significant differences between the two groups for secondary outcomes length of assisted ventilation, length of hospitalisation or brain injury.

The results of this study failed to demonstrate efficacy of nitric oxide at the dose used in this study in premature babies with respiratory distress syndrome.

- Safety results

The 2 treatment groups were well matched at baseline and the extent of exposure was comparable between the treatment groups.

Adverse events were very common in both groups, and there were more AEs in the iNO-treated group than in the placebo group (96.2% vs. 91.9%). This difference was most noticeable in the cohort of subjects 26 weeks or older GA, with an AE incidence of 95.3% of subjects in the iNO group compared with 88.6% of subjects in the placebo group.

Study drug was temporarily stopped due to an AE for 4.1% of subjects in the iNO group and 3.0% of subjects in the placebo group. Study drug was permanently stopped due to an AE for 6.1% of subjects in the iNO group and 5.5% of subjects in the placebo group.

The incidence of severe AEs was similar in the 2 treatment groups; severe AEs experienced by 3% or more subjects in either treatment group included patent ductus arteriosus, intestinal perforation, sepsis, haemorrhage intracranial, and pulmonary haemorrhage.

Adverse events with a higher incidence rate in the iNO group compared with the placebo group (greater than 5%) included patent ductus arteriosus, haemorrhage intracranial, anaemia, and hyperglycaemia. The incidences of all other AEs were similar between the treatment groups. The 3 most frequently reported AEs in both treatment groups were patent ductus arteriosus, anaemia, and hyperbilirubinaemia. There were no incidences of methaemoglobinaemia reported during the treatment period. Two subjects, 1 in each treatment group, experienced elevated NO2 levels. Serious adverse events reported by greater than or equal to 3% of subjects in either treatment group were patent ductus arteriosus, intestinal perforation, sepsis, haemorrhage intracranial, pneumothorax and pulmonary haemorrhage. The incidences of these and all other SAEs were similar between the treatment groups.

Perinatal care was very good, and the overall death rate was relatively low in both groups. Reviewing outcomes through Week 36, there was a trend toward more deaths in the iNO group. The death rate during the treatment period was slightly higher in the iNO treated group than the placebo treated group: 8.9% of iNO subjects compared with 7.6% of placebo subjects. During the period after cessation of therapy and before 36 weeks, there were also more deaths in the iNO-treated group 4.6% vs. 2.8%; it is not clear why cessation of therapy would lead to an increased death rate. The overall death rate in the Safety Population at 36 weeks was not significantly different between the treatment groups; 13.4% and 10.6% of subjects in the iNO and placebo groups, respectively, for all treated subjects.

Assessor's comments
The incidence of adverse events was similar between the two groups. However, the death rate was slightly higher in the nitric oxide group during the treatment period, in the period after cessation of therapy before

36 weeks and overall. Given the lack of efficacy and the trend toward more deaths after nitric oxide treatment in premature infants, the use of nitric oxide in premature infants with respiratory distress syndrome cannot be recommended.

3. Discussion on clinical aspects

The MAH has submitted results of this study of therapy with nitric oxide in premature infants with respiratory distress syndrome. The primary efficacy endpoint was survival without BPD following treatment with nitric oxide 5 ppm and less for 21 days.

Patients were randomised to treatment with nitric oxide or placebo. 399 patients were included in the ITT population for the iNO group and 401 in the placebo group.

In general, the demographic and baseline characteristics for subjects and mothers were similar between the iNO and placebo treatment groups for the 800 subjects in the ITT Population. There were slightly more females and a slightly lower mean birth weight in subjects in the iNO group compared with subjects in the placebo group, respectively. Chorioamnionitis was more common in the mothers of subjects in the iNO treatment group compared with mothers of subjects in the placebo group.

The results for the primary efficacy endpoint (survival without BPD following treatment with nitric oxide 5 ppm and less for 21 days) showed no difference between the two groups; 65.3% for the nitric oxide group versus 65.5% for the placebo group. Although there was a small benefit in babies treated for at least 21 days with nitric oxide, the results were not statistically significant.

The safety results showed a similar pattern of adverse events between the two groups. However, the death rate was slightly higher in the nitric oxide group during the treatment period, in the period after cessation of therapy before 36 weeks and overall.

Given the lack of efficacy and the trend toward more deaths following nitric oxide therapy in this age group, the use of nitric oxide in premature infants with respiratory distress syndrome cannot be recommended. Furthermore, the MAH should submit a variation to include a summary of this study discussing both the lack of efficacy and the trend towards more deaths to section 5.1 of the SPC.

III. Rapporteur's Overall Conclusion AND RECOMMENDATION

➢ **Overall conclusion**

Given the lack of efficacy and the trend toward more deaths following nitric oxide therapy in this age group, the use of nitric oxide in premature infants with respiratory distress syndrome cannot be recommended. Furthermore, the MAH should submit a variation to include a summary of this study discussing both the lack of efficacy and the trend toward more deaths to section 5.1 of the SPC.

The following wording should also be included in section 4.2: "*The safety and efficacy of INOmax in premature infants less than 34 weeks gestation has not yet been established*."

➢ **Recommendation**

☒ **Fulfilled –**

Type II variation to be requested from the MAH to include a summary of this study discussing both the lack of efficacy and the trend toward more deaths to section 5.1 of the SPC, with a cross reference to section 4.2.

IV. ADDITIONAL CLARIFICATIONS REQUESTED

Not applicable