Clinical trial results:
The Effects of Nitric Oxide for Inhalation on the Development of Chronic Lung Disease in Pre-term Infants

Summary

EudraCT number	2004-002312-29
Trial protocol	FI SE GB DE BE ES IT
Global end of trial date	17 July 2015

Results information

Result version number	v1 (current)
This version publication date	03 February 2021
First version publication date	03 February 2021

Trial information

Trial identification

Sponsor protocol code	INOT27

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00551642
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Mallinckrodt
Sponsor organisation address	1425 State Route 206, Bedminster, NJ, United States, 07921
Public contact	Medical Information Call Center, Mallinckrodt, Medinfo@mnk.com
Scientific contact	Medical Information Call Center, Mallinckrodt, Medinfo@mnk.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	29 September 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	17 July 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the safety and efficacy of inhaled nitric oxide to reduce the risk of chronic lung disease in pre-term 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.

Protection of trial subjects:

Trial performed in hospital setting; Follow up assessments made by study doctor to monitor progress of child.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 May 2005
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	7 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 155
Country: Number of subjects enrolled	Sweden: 44
Country: Number of subjects enrolled	United Kingdom: 63
Country: Number of subjects enrolled	Belgium: 74
Country: Number of subjects enrolled	Finland: 8
Country: Number of subjects enrolled	Germany: 231
Country: Number of subjects enrolled	Italy: 78
Country: Number of subjects enrolled	France: 107
Country: Number of subjects enrolled	Netherlands: 40
Worldwide total number of subjects	800
EEA total number of subjects	800

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	800
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Thirty-five Medical Centers participated and enrolled a total of 800 participants (Intent to treat population).

Pre-assignment

Screening details:

800 participants were enrolled at 35 medical centers around the world for the Treatment period, and 305 had data at the 7-year Follow-up period

Period 1

Period 1 title	Treatment Period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

Double-blind trial also had blinded Carer and Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Inhaled Nitric Oxide (INO)

Arm description:

INO administered by nasal continuous positive airway pressure, nasal cannula or face mask at 5 parts per million (ppm) for between 7 and 21 days during the Treatment period, but no intervention during the 7-year Follow-up

Arm type	Experimental
Investigational medicinal product name	Nitric oxide
Investigational medicinal product code	
Other name	INO max®
Pharmaceutical forms	Inhalation vapour
Routes of administration	Inhalation use

Dosage and administration details:

Nitric Oxide vapour (gas) for inhalation (400 ppm)

Arm title	Placebo

Arm description:

Placebo gas administered by nasal continuous positive airway pressure, nasal cannula or face mask, for a maximum of 21 days during the Treatment period, but no intervention during the 7-year Follow-up

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	Placebo gas for inhalation
Pharmaceutical forms	Inhalation vapour
Routes of administration	Inhalation use

Dosage and administration details:

Placebo gas for inhalation for a maximum of 21 days

Number of subjects in period 1	Inhaled Nitric Oxide (INO)	Placebo
Started	399	401
Safety Population	395	397
Completed	338	338
Not completed	61	63
Adverse event, serious fatal	33	31
Delivery device failure	1	3
Inclusion/exclusion criteria	4	4
Consent withdrawn by subject	2	1
Physician decision	-	1
Adverse event, non-fatal	15	12
Protocol deviation	6	11

Period 2

Period 2 title	7-year Follow-Up
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

The long-term follow-up analyses included all subjects who received study drug (Safety population), were alive at Week 36 of gestational age (GA), and had 7-year follow-up data (completed a CRF for 7-year follow-up).

Arms

Are arms mutually exclusive?	Yes
Arm title	Inhaled Nitric Oxide (INO)

Arm description:

INO administered by nasal continuous positive airway pressure, nasal cannula or face mask at 5 parts per million (ppm) for 7 to 21 days

Arm type	Experimental
Investigational medicinal product name	Nitric oxide
Investigational medicinal product code	
Other name	INO max®
Pharmaceutical forms	Inhalation vapour
Routes of administration	Inhalation use

Dosage and administration details:

Nitric Oxide vapour (gas) for inhalation (400 ppm)

Arm title	Placebo

Arm description:

Placebo gas administered by nasal continuous positive airway pressure, nasal cannula or face mask, for a maximum of 21 days during the Treatment period, but no intervention during the 7-year Follow-up

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	Placebo gas for inhalation
Pharmaceutical forms	Inhalation vapour
Routes of administration	Inhalation use

Dosage and administration details:

Placebo gas for inhalation for a maximum of 21 days

Number of subjects in period 2[1]	Inhaled Nitric Oxide (INO)	Placebo
Started	152	153
Completed	152	153

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Many patients did not participate in the 7-yearFollow-up

Baseline characteristics

Reporting groups	
Reporting group title	Inhaled Nitric Oxide (INO)
Reporting group description:	
INO administered by nasal continuous positive airway pressure, nasal cannula or face mask at 5 parts per million (ppm) for between 7 and 21 days during the Treatment period, but no intervention during the 7-year Follow-up	
Reporting group title	Placebo
Reporting group description:	
Placebo gas administered by nasal continuous positive airway pressure, nasal cannula or face mask, for a maximum of 21 days during the Treatment period, but no intervention during the 7-year Follow-up	

Reporting group values	Inhaled Nitric Oxide (INO)	Placebo	Total
Number of subjects	399	401	800
Age categorical Units: Subjects			
Preterm newborn infants (gestational age < 37 wks)	399	401	800
Gender categorical Units: Subjects			
Female	192	181	373
Male	207	220	427

End points

End points reporting groups

Reporting group title	Inhaled Nitric Oxide (INO)
Reporting group description: INO administered by nasal continuous positive airway pressure, nasal cannula or face mask at 5 parts per million (ppm) for between 7 and 21 days during the Treatment period, but no intervention during the 7-year Follow-up	
Reporting group title	Placebo
Reporting group description: Placebo gas administered by nasal continuous positive airway pressure, nasal cannula or face mask, for a maximum of 21 days during the Treatment period, but no intervention during the 7-year Follow-up	
Reporting group title	Inhaled Nitric Oxide (INO)
Reporting group description: INO administered by nasal continuous positive airway pressure, nasal cannula or face mask at 5 parts per million (ppm) for 7 to 21 days	
Reporting group title	Placebo
Reporting group description: Placebo gas administered by nasal continuous positive airway pressure, nasal cannula or face mask, for a maximum of 21 days during the Treatment period, but no intervention during the 7-year Follow-up	

Primary: Survival Without Bronchopulmonary Dysplasia (BPD) in Preterm Infants With Respiratory Distress

End point title	Survival Without Bronchopulmonary Dysplasia (BPD) in Preterm Infants With Respiratory Distress
End point description: The primary outcome was determined by assessment of survival and incidence of BPD, which was defined by the need for supplemental oxygen at 36 weeks gestational age (GA); an infant who was alive without BPD at 36 weeks GA was counted as success; an infant who died or had BPD at 36 weeks GA was counted as a failure.	
End point type	Primary
End point timeframe: 36 weeks gestational age	

End point values	Inhaled Nitric Oxide (INO)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	395[1]	400[2]		
Units: patients	258	262		

Notes:

[1] - Patients with efficacy data

[2] - Patients with efficacy data

Statistical analyses

Statistical analysis title	Arm Comparison
Statistical analysis description: Comparison	
Comparison groups	Inhaled Nitric Oxide (INO) v Placebo

Number of subjects included in analysis	795
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.734
Method	Wald Chi-square

Other pre-specified: Mortality at 7-year Follow-up

End point title	Mortality at 7-year Follow-up

End point description:

Number of participants who died between 2 years and the 7-year Follow-up

End point type	Other pre-specified

End point timeframe:

at 7 year follow-up

End point values	Inhaled Nitric Oxide (INO)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	152[3]	153[4]		
Units: patients	0	0		

Notes:

[3] - Patients who completed 7-year follow-up

[4] - Patients who completed 7-year follow-up

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Strengths and Difficulties Questionnaire Results for Subjects With 7-Year Follow-Up Data

End point title	Strengths and Difficulties Questionnaire Results for Subjects With 7-Year Follow-Up Data

End point description:

The Strengths and Difficulties Questionnaire contained 25 questions that were used to create 5 scales (ranging from 10=most normal to 0=most abnormal) for emotional symptoms, conduct problems, hyperactivity, peer problems, and (10=most abnormal, 0=most normal) for prosocial.

End point type	Other pre-specified

End point timeframe:

at 7-year follow-up

End point values	Inhaled Nitric Oxide (INO)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	147[5]	147[6]		
Units: score on a scale				
arithmetic mean (standard deviation)				
Emotional (0=most normal, 10=most abnormal)	1.9 (± 1.79)	2.1 (± 1.96)		
Conduct (0=most normal, 10=most abnormal)	1.4 (± 1.55)	1.4 (± 1.58)		
Hyperactivity (0=most normal, 10=most abnormal)	3.8 (± 2.64)	3.4 (± 2.66)		
Peer problems (0=most normal, 10=most abnormal)	1.2 (± 1.41)	1.5 (± 1.74)		
Prosocial (10=most abnormal, 0=most normal)	8.6 (± 1.73)	8.4 (± 1.81)		

Notes:

[5] - Patients with questionnaire data at 7-Year Follow-up

[6] - Patients with questionnaire data at 7-Year Follow-up

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events (including clinically significant changes in vital signs, oxygen saturation, and laboratory values) were collected in the safety population throughout screening and treatment for a maximum of 21 days (not during follow-up).

Adverse event reporting additional description:

All serious adverse events are listed. Non-serious treatment-emergent adverse events (TEAEs) are listed if 5% or more participants in any arm experienced any form of that preferred term. For example, the term "Sepsis" includes Bacterial Sepsis, Candida Sepsis, Catheter Sepsis, Enterobacter Sepsis, Enterococcal Sepsis, Escherichia Sepsis, etc.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	10.0

Reporting groups

Reporting group title	Inhaled Nitric Oxide (INO)

Reporting group description:

Safety population receiving INO administered by nasal continuous positive airway pressure, nasal cannula or face mask at 5 parts per million (ppm) for 7 to 21 days during the Treatment period, but no intervention during the 7-year Follow-up

Reporting group title	Placebo

Reporting group description:

Placebo gas administered by nasal continuous positive airway pressure (nasal cannula or face mask) for a maximum of 21 days during the Treatment period, but no intervention during the 7-year Follow-up

Serious adverse events	Inhaled Nitric Oxide (INO)	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	170 / 395 (43.04%)	177 / 397 (44.58%)	
number of deaths (all causes)	56	48	
number of deaths resulting from adverse events	43	39	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Hepatic haemangioma rupture			
subjects affected / exposed	0 / 395 (0.00%)	1 / 397 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 395 (0.00%)	1 / 397 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage			

subjects affected / exposed	0 / 395 (0.00%)	1 / 397 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	4 / 395 (1.01%)	1 / 397 (0.25%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 1	
Infarction			
subjects affected / exposed	1 / 395 (0.25%)	2 / 397 (0.50%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vena cava thrombosis			
subjects affected / exposed	0 / 395 (0.00%)	1 / 397 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Chest tube insertion			
subjects affected / exposed	0 / 395 (0.00%)	1 / 397 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Catheter related complication			
subjects affected / exposed	1 / 395 (0.25%)	0 / 397 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multi-organ failure			
subjects affected / exposed	1 / 395 (0.25%)	0 / 397 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Aspiration			

subjects affected / exposed	0 / 395 (0.00%)	1 / 397 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chylothorax			
subjects affected / exposed	0 / 395 (0.00%)	1 / 397 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Emphysema			
subjects affected / exposed	1 / 395 (0.25%)	0 / 397 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Foreign body aspiration			
subjects affected / exposed	0 / 395 (0.00%)	1 / 397 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	2 / 395 (0.51%)	3 / 397 (0.76%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 1	
Laryngeal oedema			
subjects affected / exposed	1 / 395 (0.25%)	0 / 397 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neonatal respiratory failure			
subjects affected / exposed	3 / 395 (0.76%)	3 / 397 (0.76%)	
occurrences causally related to treatment / all	1 / 3	0 / 3	
deaths causally related to treatment / all	1 / 3	0 / 2	
Pneumomediastinum			
subjects affected / exposed	1 / 395 (0.25%)	0 / 397 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			

subjects affected / exposed	12 / 395 (3.04%)	13 / 397 (3.27%)	
occurrences causally related to treatment / all	0 / 12	0 / 15	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary haemorrhage			
subjects affected / exposed	12 / 395 (3.04%)	14 / 397 (3.53%)	
occurrences causally related to treatment / all	3 / 12	7 / 14	
deaths causally related to treatment / all	2 / 3	3 / 4	
Pulmonary hypertension			
subjects affected / exposed	3 / 395 (0.76%)	3 / 397 (0.76%)	
occurrences causally related to treatment / all	1 / 3	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary interstitial emphysema syndrome			
subjects affected / exposed	1 / 395 (0.25%)	1 / 397 (0.25%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory acidosis			
subjects affected / exposed	0 / 395 (0.00%)	1 / 397 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory arrest			
subjects affected / exposed	1 / 395 (0.25%)	0 / 397 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	0 / 395 (0.00%)	1 / 397 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Investigations			
Bacterial test positive			
subjects affected / exposed	1 / 395 (0.25%)	0 / 397 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood cortisol decreased			

subjects affected / exposed	0 / 395 (0.00%)	1 / 397 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood growth hormone decreased			
subjects affected / exposed	0 / 395 (0.00%)	1 / 397 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain scan abnormal			
subjects affected / exposed	1 / 395 (0.25%)	0 / 397 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Injury, poisoning and procedural complications			
Feeding tube complication			
subjects affected / exposed	0 / 395 (0.00%)	1 / 397 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	0 / 395 (0.00%)	1 / 397 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound dehiscence			
subjects affected / exposed	1 / 395 (0.25%)	0 / 397 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Coarctation of the aorta			
subjects affected / exposed	0 / 395 (0.00%)	1 / 397 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Patent ductus arteriosus			
subjects affected / exposed	62 / 395 (15.70%)	54 / 397 (13.60%)	
occurrences causally related to treatment / all	13 / 62	11 / 54	
deaths causally related to treatment / all	0 / 0	0 / 0	

Persistent foetal circulation			
subjects affected / exposed	2 / 395 (0.51%)	0 / 397 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vitello-intestinal duct remnant			
subjects affected / exposed	1 / 395 (0.25%)	0 / 397 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	0 / 395 (0.00%)	1 / 397 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Bradycardia			
subjects affected / exposed	1 / 395 (0.25%)	0 / 397 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	2 / 395 (0.51%)	1 / 397 (0.25%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac tamponade			
subjects affected / exposed	0 / 395 (0.00%)	1 / 397 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest neonatal			
subjects affected / exposed	0 / 395 (0.00%)	1 / 397 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Cardiomyopathy			
subjects affected / exposed	1 / 395 (0.25%)	0 / 397 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiopulmonary failure			

subjects affected / exposed	0 / 395 (0.00%)	1 / 397 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Intracardiac thrombus			
subjects affected / exposed	1 / 395 (0.25%)	0 / 397 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	0 / 395 (0.00%)	1 / 397 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Central nervous system lesion			
subjects affected / exposed	1 / 395 (0.25%)	0 / 397 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral ischaemia			
subjects affected / exposed	0 / 395 (0.00%)	1 / 397 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral ventricle dilatation			
subjects affected / exposed	0 / 395 (0.00%)	1 / 397 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	50 / 395 (12.66%)	42 / 397 (10.58%)	
occurrences causally related to treatment / all	17 / 52	14 / 42	
deaths causally related to treatment / all	6 / 16	4 / 11	
Hydrocephalus			
subjects affected / exposed	4 / 395 (1.01%)	4 / 397 (1.01%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periventricular leukomalacia			

subjects affected / exposed	7 / 395 (1.77%)	2 / 397 (0.50%)	
occurrences causally related to treatment / all	0 / 7	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Blood and lymphatic system disorders			
Coagulopathy			
subjects affected / exposed	1 / 395 (0.25%)	1 / 397 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disseminated intravascular coagulation			
subjects affected / exposed	1 / 395 (0.25%)	0 / 397 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 395 (0.25%)	0 / 397 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Retinopathy of prematurity			
subjects affected / exposed	0 / 395 (0.00%)	1 / 397 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastric haemorrhage			
subjects affected / exposed	1 / 395 (0.25%)	1 / 397 (0.25%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric perforation			
subjects affected / exposed	1 / 395 (0.25%)	0 / 397 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 395 (0.00%)	1 / 397 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastrointestinal perforation			
subjects affected / exposed	2 / 395 (0.51%)	1 / 397 (0.25%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Ileus			
subjects affected / exposed	0 / 395 (0.00%)	1 / 397 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	0 / 395 (0.00%)	1 / 397 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation			
subjects affected / exposed	17 / 395 (4.30%)	14 / 397 (3.53%)	
occurrences causally related to treatment / all	2 / 17	0 / 14	
deaths causally related to treatment / all	0 / 2	0 / 2	
Intussusception			
subjects affected / exposed	1 / 395 (0.25%)	0 / 397 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meconium ileus			
subjects affected / exposed	0 / 395 (0.00%)	2 / 397 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meconium plug syndrome			
subjects affected / exposed	1 / 395 (0.25%)	0 / 397 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Necrotising enterocolitis neonatal			
subjects affected / exposed	16 / 395 (4.05%)	9 / 397 (2.27%)	
occurrences causally related to treatment / all	1 / 16	0 / 9	
deaths causally related to treatment / all	0 / 2	0 / 1	
Oesophageal perforation			

subjects affected / exposed	0 / 395 (0.00%)	1 / 397 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	0 / 395 (0.00%)	1 / 397 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumoperitoneum			
subjects affected / exposed	1 / 395 (0.25%)	1 / 397 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Volvulus			
subjects affected / exposed	1 / 395 (0.25%)	1 / 397 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Gallbladder perforation			
subjects affected / exposed	1 / 395 (0.25%)	0 / 397 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice			
subjects affected / exposed	0 / 395 (0.00%)	1 / 397 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	0 / 395 (0.00%)	4 / 397 (1.01%)	
occurrences causally related to treatment / all	0 / 0	1 / 4	
deaths causally related to treatment / all	0 / 0	1 / 3	
Endocrine disorders			
Hypopituitarism			
subjects affected / exposed	0 / 395 (0.00%)	1 / 397 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infections and infestations			
Candidiasis			
subjects affected / exposed	0 / 395 (0.00%)	1 / 397 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter related infection			
subjects affected / exposed	1 / 395 (0.25%)	0 / 397 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis			
subjects affected / exposed	1 / 395 (0.25%)	0 / 397 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 395 (0.00%)	1 / 397 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound infection			
subjects affected / exposed	0 / 395 (0.00%)	1 / 397 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomonas infection			
subjects affected / exposed	0 / 395 (0.00%)	1 / 397 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	34 / 395 (8.61%)	35 / 397 (8.82%)	
occurrences causally related to treatment / all	0 / 35	1 / 39	
deaths causally related to treatment / all	0 / 7	1 / 9	
Staphylococcal bacteraemia			
subjects affected / exposed	1 / 395 (0.25%)	0 / 397 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			

Acidosis			
subjects affected / exposed	1 / 395 (0.25%)	0 / 397 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hyperkalaemia			
subjects affected / exposed	1 / 395 (0.25%)	1 / 397 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 395 (0.25%)	0 / 397 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Inhaled Nitric Oxide (INO)	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	358 / 395 (90.63%)	334 / 397 (84.13%)	
Congenital, familial and genetic disorders			
Patent ductus arteriosus			
subjects affected / exposed	183 / 395 (46.33%)	158 / 397 (39.80%)	
occurrences (all)	187	163	
Vascular disorders			
Hypotension			
subjects affected / exposed	55 / 395 (13.92%)	50 / 397 (12.59%)	
occurrences (all)	57	54	
Nervous system disorders			
Haemorrhage intracranial			
subjects affected / exposed	73 / 395 (18.48%)	55 / 397 (13.85%)	
occurrences (all)	81	58	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	189 / 395 (47.85%)	168 / 397 (42.32%)	
occurrences (all)	253	226	
Thrombocytopenia			

subjects affected / exposed	29 / 395 (7.34%)	28 / 397 (7.05%)	
occurrences (all)	29	31	
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	122 / 395 (30.89%)	120 / 397 (30.23%)	
occurrences (all)	138	130	
Jaundice			
subjects affected / exposed	98 / 395 (24.81%)	89 / 397 (22.42%)	
occurrences (all)	107	97	
Respiratory, thoracic and mediastinal disorders			
Apnoea			
subjects affected / exposed	73 / 395 (18.48%)	78 / 397 (19.65%)	
occurrences (all)	78	79	
Infections and infestations			
Sepsis			
subjects affected / exposed	68 / 395 (17.22%)	60 / 397 (15.11%)	
occurrences (all)	75	66	
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	90 / 395 (22.78%)	68 / 397 (17.13%)	
occurrences (all)	100	75	
Hyponatraemia			
subjects affected / exposed	21 / 395 (5.32%)	19 / 397 (4.79%)	
occurrences (all)	22	21	
Metabolic acidosis			
subjects affected / exposed	49 / 395 (12.41%)	52 / 397 (13.10%)	
occurrences (all)	53	62	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 August 2004	Amendment changes that impacted the 7-year data (being reported in this full data set (after the summary results previously prepared and attached) were included in Amendment 1 and Amendment 7. Amendment 1: Deleted "Health related quality of life (child and caregiver) at one year, two years, and seven years corrected age.”
04 January 2012	Amendment 7: 1) Deletion of pulmonary function test assessment at the 7-year long term follow-up. 2) Two endpoints were revised (where applicable) throughout the protocol: - Incidence of death after 36 weeks of GA to 7 years actual postnatal age, stratified by gestational age at birth - Long-term neuro-developmental outcome assessed by a validated, age appropriate developmental assessment at 2 years corrected age and 7 years actual postnatal age

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported