



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-year Follow-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 occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 395 (0.00%) 0 / 0 0 / 0 | 1 / 397 (0.25%) 0 / 1 0 / 0 | |
| Catheter related infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 395 (0.25%) 0 / 1 0 / 0 | 0 / 397 (0.00%) 0 / 0 0 / 0 | |
| Endocarditis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 395 (0.25%) 0 / 1 0 / 1 | 0 / 397 (0.00%) 0 / 0 0 / 0 | |
| Pneumonia subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 395 (0.00%) 0 / 0 0 / 0 | 1 / 397 (0.25%) 0 / 1 0 / 0 | |
| Postoperative wound infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 395 (0.00%) 0 / 0 0 / 0 | 1 / 397 (0.25%) 0 / 1 0 / 0 | |
| Pseudomonas infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 395 (0.00%) 0 / 0 0 / 0 | 1 / 397 (0.25%) 0 / 1 0 / 0 | |
| Sepsis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 34 / 395 (8.61%) 0 / 35 0 / 7 | 35 / 397 (8.82%) 1 / 39 1 / 9 | |
| Staphylococcal bacteraemia subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 395 (0.25%) 0 / 1 0 / 0 | 0 / 397 (0.00%) 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 occurrences (all) | 29 / 395 (7.34%) 29 | 28 / 397 (7.05%) 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: <ul style="list-style-type: none">- 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