



Clinical trial results:

AN INTERNATIONAL, OPEN, RANDOMIZED, CONTROLLED STUDY TO EVALUATE THE EFFICACY OF COMBINING PROPHYLACTIC CUROSURF WITH EARLY NASAL CPAP VERSUS EARLY NASAL CPAP ALONE IN VERY PRETERM INFANTS AT RISK OF RESPIRATORY DISTRESS SYNDROME

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2006-004105-25 |
| Trial protocol | CZ IT FR PT |
| Global end of trial date | 14 May 2008 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 (current) |
| This version publication date | 16 March 2018 |
| First version publication date | 16 March 2018 |

Trial information

Trial identification

| | |
|-----------------------|-------------------|
| Sponsor protocol code | DM/PR/5000/002/04 |
|-----------------------|-------------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00501982 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|------------------------------------------------------------------------------------------------------------------------------------|
| Sponsor organisation name | Chiesi Farmaceutici S.p.A. |
| Sponsor organisation address | Via Palermo 26/A, Parma, Italy, 43126 |
| Public contact | Clinical Trial Transparency, Chiesi Farmaceutici S.p.A., Chiesi Farmaceutici S.p.A., +39 0521 2791, ClinicalTrials_info@chiesi.com |
| Scientific contact | Clinical Trial Transparency, Chiesi Farmaceutici S.p.A., Chiesi Farmaceutici S.p.A., +39 0521 2791, ClinicalTrials_info@chiesi.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? | Yes |

Notes:

Results analysis stage

| | |
|------------------------------------------------------|------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 28 November 2008 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 14 May 2008 |
| Global end of trial reached? | Yes |
| Global end of trial date | 14 May 2008 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective is a comparative evaluation of the two methods of post-delivery stabilization and subsequent early respiratory care (nCPAP alone versus prophylactic surfactant [Curosurf®]+nCPAP) for reducing the need for mechanical ventilation (MV) and related secondary complications, such as BPD (Bronchopulmonary dysplasia), in premature babies at high risk of RDS (Respiratory Distress Syndrome):

1. Early stabilization on nCPAP (nasal continuous positive airway pressure).
2. Intubation, prophylactic surfactant (Curosurf) administration shortly after delivery, and rapid extubation to nCPAP.

Protection of trial subjects:

The study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice (GCP) guidelines and local law requirements. Other than routine care, no specific measures for protection of trial subjects were implemented.

Background therapy: -

Evidence for comparator: -

| | |
|-----------------------------------------------------------|---------------|
| Actual start date of recruitment | 13 March 2007 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|---------------------|
| Country: Number of subjects enrolled | Portugal: 5 |
| Country: Number of subjects enrolled | Spain: 9 |
| Country: Number of subjects enrolled | Czech Republic: 125 |
| Country: Number of subjects enrolled | France: 13 |
| Country: Number of subjects enrolled | Italy: 56 |
| Worldwide total number of subjects | 208 |
| EEA total number of subjects | 208 |

Notes:

Subjects enrolled per age group

| | |
|-------------------------------------------|-----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 208 |

| | |
|------------------------------------------|---|
| 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:

Premature infants breathing spontaneously and meeting inclusion criteria were randomised (n=208) immediately after birth to either nCPAP alone (n=103) or prophylactic Curosurf® + nCPAP (n=105). Neonates will be randomly assigned to one of the two treatment groups within one of the two strata with a 1: 1 ratio.

Pre-assignment

Screening details:

Screening of the infants will be initiated when a woman is expected to deliver a viable baby with a GA of $\geq 25+0$ weeks to $< 28+6$ weeks.

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Overall Trial (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

Blinding implementation details:

This was an open label unblinded study.

Arms

| | |
|------------------------------|-----------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Curosurf®+nCPAP Group |

Arm description:

Prophylactic Curosurf® at 200 mg/kg and further 100 mg/kg rescue doses in the event of clinical needs during their staying in Neonatal Intensive Care Unit (NICU) in addition to nasal Continuous Positive Airway Pressure (nCPAP).

| | |
|----------------------------------------|--------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Curosurf |
| Investigational medicinal product code | |
| Other name | Poractant alfa |
| Pharmaceutical forms | Suspension for oral suspension |
| Routes of administration | Intratracheal use |

Dosage and administration details:

Prophylactic dose of 200 mg/kg or rescue dose of 100 mg/kg administered via intratracheal route, taken from single dose 1.5ml vials containing phospholipid fraction from Porcine lung 120mg together with sodium chloride and water as excipients.

| | |
|------------------|-------------|
| Arm title | nCPAP Group |
|------------------|-------------|

Arm description:

Nasal Continuous Positive Airway Pressure (nCPAP).

(Infants in the nCPAP group were permitted to receive an initial rescue dose of 200 mg/kg in the event of nCPAP failure and further 100 mg/kg rescue doses in the event of clinical needs during their staying in NICU).

| | |
|----------------------------------------|--------------------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Curosurf |
| Investigational medicinal product code | |
| Other name | Poractant alfa |
| Pharmaceutical forms | Suspension for oral suspension |
| Routes of administration | Intratracheal use |

Dosage and administration details:

Prophylactic dose of 200 mg/kg or rescue dose of 100 mg/kg administered via intratracheal route, taken from single dose 1.5ml vials containing phospholipid fraction from Porcine lung 120mg together with sodium chloride and water

as excipients.

| Number of subjects in period 1 | Curosurf®+nCPAP Group | nCPAP Group |
|-------------------------------------------|-----------------------|-------------|
| Started | 105 | 103 |
| Completed | 91 | 87 |
| Not completed | 14 | 16 |
| Discretion of the investigator or sponsor | 1 | - |
| Adverse event, non-fatal | - | 2 |
| Death | 9 | 11 |
| No matching reasons found | 3 | 1 |
| Protocol deviation | 1 | 2 |

Baseline characteristics

Reporting groups

| | |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| Reporting group title | Curosurf®+nCPAP Group |
| Reporting group description: Prophylactic Curosurf® at 200 mg/kg and further 100 mg/kg rescue doses in the event of clinical needs during their staying in Neonatal Intensive Care Unit (NICU) in addition to nasal Continuous Positive Airway Pressure (nCPAP). | |
| Reporting group title | nCPAP Group |
| Reporting group description: Nasal Continuous Positive Airway Pressure (nCPAP). (Infants in the nCPAP group were permitted to receive an initial rescue dose of 200 mg/kg in the event of nCPAP failure and further 100 mg/kg rescue doses in the event of clinical needs during their staying in NICU). | |

| Reporting group values | Curosurf®+nCPAP Group | nCPAP Group | Total |
|-------------------------------------------------------|-----------------------|-------------|-------|
| Number of subjects | 105 | 103 | 208 |
| Age categorical Units: Subjects | | | |
| Preterm newborn infants (gestational age < 37 wks) | 105 | 103 | 208 |
| Gender categorical Units: Subjects | | | |
| Female | 48 | 49 | 97 |
| Male | 57 | 54 | 111 |

Subject analysis sets

| | |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------|
| Subject analysis set title | Curosurf®+nCPAP Group - ITT population |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: The Intention-to-Treat (ITT) population comprised all randomised infants who had at least one evaluation of any efficacy available. | |
| Subject analysis set title | nCPAP Group - ITT population |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: The Intention-to-Treat (ITT) population comprised all randomised infants who had at least one evaluation of any efficacy available | |

| Reporting group values | Curosurf®+nCPAP Group - ITT population | nCPAP Group - ITT population | |
|-------------------------------------------------------|----------------------------------------|------------------------------|--|
| Number of subjects | 105 | 103 | |
| Age categorical Units: Subjects | | | |
| Preterm newborn infants (gestational age < 37 wks) | 105 | 103 | |
| Gender categorical Units: Subjects | | | |
| Female | 48 | 49 | |
| Male | 57 | 54 | |

End points

End points reporting groups

| | |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------|
| Reporting group title | Curosurf®+nCPAP Group |
| Reporting group description: Prophylactic Curosurf® at 200 mg/kg and further 100 mg/kg rescue doses in the event of clinical needs during their staying in Neonatal Intensive Care Unit (NICU) in addition to nasal Continuous Positive Airway Pressure (nCPAP). | |
| Reporting group title | nCPAP Group |
| Reporting group description: Nasal Continuous Positive Airway Pressure (nCPAP). (Infants in the nCPAP group were permitted to receive an initial rescue dose of 200 mg/kg in the event of nCPAP failure and further 100 mg/kg rescue doses in the event of clinical needs during their staying in NICU). | |
| Subject analysis set title | Curosurf®+nCPAP Group - ITT population |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: The Intention-to-Treat (ITT) population comprised all randomised infants who had at least one evaluation of any efficacy available. | |
| Subject analysis set title | nCPAP Group - ITT population |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: The Intention-to-Treat (ITT) population comprised all randomised infants who had at least one evaluation of any efficacy available | |

Primary: Incidence of the Need for Mechanical Ventilation in the First 5 Days of Life

| | |
|-------------------------------------------------------------------------|------------------------------------------------------------------------------|
| End point title | Incidence of the Need for Mechanical Ventilation in the First 5 Days of Life |
| End point description: | |
| End point type | Primary |
| End point timeframe: From birth until Day 5 of life (post-treatment) | |

| End point values | Curosurf®+nCPAP Group - ITT population | nCPAP Group - ITT population | | |
|-----------------------------|----------------------------------------|------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 105 | 103 | | |
| Units: Subjects | | | | |
| Yes | 33 | 34 | | |
| No | 72 | 69 | | |

Statistical analyses

| | |
|----------------------------|-----------------------------------------------------------------------|
| Statistical analysis title | Curosurf®+nCPAP vs nCPAP |
| Comparison groups | Curosurf®+nCPAP Group - ITT population v nCPAP Group - ITT population |

| | |
|-----------------------------------------|----------------------------|
| Number of subjects included in analysis | 208 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[1] |
| P-value | = 0.7991 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 0.95 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.64 |
| upper limit | 1.41 |

Notes:

[1] - The primary efficacy analysis compared nCPAP alone to prophylactic Curosurf®+nCPAP for the proportion of subjects who had MV in the first 5 days of life. The Cochran-Mantel-Haenszel (CMH) test which adjusts for the stratification factors of GA was used. P-values, odds ratios (OR) and 95% confidence intervals (CI) were reported.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From birth throughout the study phase (the first 5 days of life) and the follow-up till the hospital discharge.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

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|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|-----|
| Dictionary version | 9.1 |
|--------------------|-----|

Reporting groups

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|-----------------------|--------------------------------------|
| Reporting group title | Curosurf + nCPAP - Safety population |
|-----------------------|--------------------------------------|

Reporting group description:

The safety population comprised all randomised infants.

| | |
|-----------------------|---------------------------|
| Reporting group title | nCPAP - Safety population |
|-----------------------|---------------------------|

Reporting group description:

The safety population comprised all randomised infants.

| Serious adverse events | Curosurf + nCPAP - Safety population | nCPAP - Safety population | |
|---------------------------------------------------|--------------------------------------|---------------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 15 / 105 (14.29%) | 23 / 103 (22.33%) | |
| number of deaths (all causes) | 9 | 11 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Injury, poisoning and procedural complications | | | |
| Skin laceration | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 1 / 103 (0.97%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Congenital, familial and genetic disorders | | | |
| Coarctation of the aorta | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 103 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Congenital anomaly | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 1 / 103 (0.97%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Vascular disorders | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|--|
| Hypotension | | | |
| subjects affected / exposed | 2 / 105 (1.90%) | 0 / 103 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | |
| Shock | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 1 / 103 (0.97%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Vena cava thrombosis | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 103 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Cardiac disorders | | | |
| Bradycardia | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 103 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Cardiac failure | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 1 / 103 (0.97%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Cardiopulmonary failure | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 1 / 103 (0.97%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Pneumopericardium | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 103 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Nervous system disorders | | | |
| Cerebral haemorrhage | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 1 / 103 (0.97%) | |
| 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 | 0 / 105 (0.00%) | 1 / 103 (0.97%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hydrocephalus | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 1 / 103 (0.97%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intraventricular haemorrhage | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 2 / 103 (1.94%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Periventricular leukomalacia | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 1 / 103 (0.97%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 103 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 103 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Abdominal distension | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 1 / 103 (0.97%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Inguinal hernia | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 103 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|--|
| Intestinal ischaemia | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 1 / 103 (0.97%) | |
| 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 | 1 / 105 (0.95%) | 0 / 103 (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 / 105 (0.00%) | 1 / 103 (0.97%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Necrotising colitis | | | |
| subjects affected / exposed | 3 / 105 (2.86%) | 6 / 103 (5.83%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | |
| Peritonitis | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 103 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumoperitoneum | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 103 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Apnoea | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 1 / 103 (0.97%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypercapnia | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 1 / 103 (0.97%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|--|
| Hypoxia | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 1 / 103 (0.97%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Laryngeal stenosis | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 1 / 103 (0.97%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumothorax | | | |
| subjects affected / exposed | 2 / 105 (1.90%) | 0 / 103 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 103 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Pulmonary haemorrhage | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 1 / 103 (0.97%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Respiratory failure | | | |
| subjects affected / exposed | 3 / 105 (2.86%) | 0 / 103 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 3 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Oliguria | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 103 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Renal failure | | | |
| subjects affected / exposed | 2 / 105 (1.90%) | 0 / 103 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | |
| Infections and infestations | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|--|
| Cytomegalovirus viraemia | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 103 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Neonatal infection | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 103 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Pneumonia cytomegaloviral | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 103 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Sepsis | | | |
| subjects affected / exposed | 4 / 105 (3.81%) | 3 / 103 (2.91%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 2 | |
| Septic shock | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 3 / 103 (2.91%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 3 | |
| Metabolism and nutrition disorders | | | |
| Lactic acidosis | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 1 / 103 (0.97%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Metabolic acidosis | | | |
| subjects affected / exposed | 2 / 105 (1.90%) | 0 / 103 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | |

Frequency threshold for reporting non-serious adverse events: 1 %

| Non-serious adverse events | Curosurf + nCPAP - Safety population | nCPAP - Safety population | |
|----------------------------------------------------------|-----------------------------------------|------------------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 55 / 105 (52.38%) | 45 / 103 (43.69%) | |
| Vascular disorders | | | |
| Hypoperfusion | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 1 / 103 (0.97%) | |
| occurrences (all) | 0 | 1 | |
| Hypotension | | | |
| subjects affected / exposed | 13 / 105 (12.38%) | 11 / 103 (10.68%) | |
| occurrences (all) | 13 | 12 | |
| Poor peripheral circulation | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 1 / 103 (0.97%) | |
| occurrences (all) | 1 | 1 | |
| Pregnancy, puerperium and perinatal conditions | | | |
| Jaundice neonatal | | | |
| subjects affected / exposed | 3 / 105 (2.86%) | 6 / 103 (5.83%) | |
| occurrences (all) | 3 | 6 | |
| General disorders and administration site conditions | | | |
| Catheter site haemorrhage | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 1 / 103 (0.97%) | |
| occurrences (all) | 0 | 1 | |
| Oedema | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 1 / 103 (0.97%) | |
| occurrences (all) | 0 | 1 | |
| Pain | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 1 / 103 (0.97%) | |
| occurrences (all) | 0 | 1 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Apnoea | | | |
| subjects affected / exposed | 14 / 105 (13.33%) | 22 / 103 (21.36%) | |
| occurrences (all) | 14 | 23 | |
| Asphyxia | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 103 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Atelectasis | | | |

| | | | |
|------------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 103 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Bronchospasm | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 1 / 103 (0.97%) | |
| occurrences (all) | 0 | 1 | |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 1 / 103 (0.97%) | |
| occurrences (all) | 0 | 1 | |
| Infantile apnoeic attack | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 1 / 103 (0.97%) | |
| occurrences (all) | 1 | 1 | |
| Pulmonary haemorrhage | | | |
| subjects affected / exposed | 2 / 105 (1.90%) | 0 / 103 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Pulmonary hypertension | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 1 / 103 (0.97%) | |
| occurrences (all) | 0 | 1 | |
| Respiratory acidosis | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 103 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Tachypnoea | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 103 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Psychiatric disorders | | | |
| Agitation | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 1 / 103 (0.97%) | |
| occurrences (all) | 0 | 1 | |
| Investigations | | | |
| Blood culture positive | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 1 / 103 (0.97%) | |
| occurrences (all) | 0 | 1 | |
| C-reactive protein increased | | | |
| subjects affected / exposed | 2 / 105 (1.90%) | 1 / 103 (0.97%) | |
| occurrences (all) | 2 | 1 | |
| Cardiac murmur | | | |

| | | | |
|--------------------------------------------------------------------------------|----------------------|----------------------|--|
| subjects affected / exposed occurrences (all) | 0 / 105 (0.00%) 0 | 3 / 103 (2.91%) 5 | |
| Neutrophil count abnormal subjects affected / exposed occurrences (all) | 0 / 105 (0.00%) 0 | 2 / 103 (1.94%) 2 | |
| Respiratory rate increased subjects affected / exposed occurrences (all) | 0 / 105 (0.00%) 0 | 1 / 103 (0.97%) 1 | |
| Urine output decreased subjects affected / exposed occurrences (all) | 2 / 105 (1.90%) 2 | 0 / 103 (0.00%) 0 | |
| Injury, poisoning and procedural complications | | | |
| Operative haemorrhage subjects affected / exposed occurrences (all) | 1 / 105 (0.95%) 1 | 0 / 103 (0.00%) 0 | |
| Transfusion reaction subjects affected / exposed occurrences (all) | 1 / 105 (0.95%) 1 | 1 / 103 (0.97%) 1 | |
| Congenital, familial and genetic disorders | | | |
| Hypospadias subjects affected / exposed occurrences (all) | 2 / 105 (1.90%) 2 | 1 / 103 (0.97%) 1 | |
| Patent ductus arteriosus subjects affected / exposed occurrences (all) | 2 / 105 (1.90%) 2 | 1 / 103 (0.97%) 1 | |
| Talipes subjects affected / exposed occurrences (all) | 1 / 105 (0.95%) 1 | 0 / 103 (0.00%) 0 | |
| Cardiac disorders | | | |
| Bradycardia subjects affected / exposed occurrences (all) | 0 / 105 (0.00%) 0 | 2 / 103 (1.94%) 2 | |
| Tachycardia subjects affected / exposed occurrences (all) | 0 / 105 (0.00%) 0 | 1 / 103 (0.97%) 1 | |
| Ventricular hypokinesia | | | |

| | | | |
|--------------------------------------------------|----------------------|----------------------|--|
| subjects affected / exposed occurrences (all) | 1 / 105 (0.95%) 1 | 0 / 103 (0.00%) 0 | |
| Nervous system disorders | | | |
| Cerebral haematoma | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 103 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Intraventricular haemorrhage | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 2 / 103 (1.94%) | |
| occurrences (all) | 0 | 2 | |
| Blood and lymphatic system disorders | | | |
| Anaemia neonatal | | | |
| subjects affected / exposed | 5 / 105 (4.76%) | 6 / 103 (5.83%) | |
| occurrences (all) | 5 | 6 | |
| Anaemia | | | |
| subjects affected / exposed | 5 / 105 (4.76%) | 4 / 103 (3.88%) | |
| occurrences (all) | 6 | 5 | |
| Coagulopathy | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 103 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Leukaemoid reaction | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 103 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Leukocytosis | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 103 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Leukopenia | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 2 / 103 (1.94%) | |
| occurrences (all) | 1 | 2 | |
| Thrombocythaemia | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 1 / 103 (0.97%) | |
| occurrences (all) | 0 | 1 | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 1 / 103 (0.97%) | |
| occurrences (all) | 1 | 1 | |
| Eye disorders | | | |

| | | | |
|--------------------------------------------------------------------------------------|-------------------------|-------------------------|--|
| Conjunctivitis subjects affected / exposed occurrences (all) | 2 / 105 (1.90%) 2 | 3 / 103 (2.91%) 4 | |
| Retinopathy subjects affected / exposed occurrences (all) | 0 / 105 (0.00%) 0 | 1 / 103 (0.97%) 1 | |
| Gastrointestinal disorders | | | |
| Colitis ulcerative subjects affected / exposed occurrences (all) | 0 / 105 (0.00%) 0 | 1 / 103 (0.97%) 1 | |
| Gastrointestinal disorder subjects affected / exposed occurrences (all) | 1 / 105 (0.95%) 1 | 0 / 103 (0.00%) 0 | |
| Gastrooesophageal reflux disease subjects affected / exposed occurrences (all) | 0 / 105 (0.00%) 0 | 3 / 103 (2.91%) 3 | |
| Inguinal hernia subjects affected / exposed occurrences (all) | 4 / 105 (3.81%) 5 | 4 / 103 (3.88%) 5 | |
| Intestinal perforation subjects affected / exposed occurrences (all) | 1 / 105 (0.95%) 1 | 0 / 103 (0.00%) 0 | |
| Rectal haemorrhage subjects affected / exposed occurrences (all) | 0 / 105 (0.00%) 0 | 1 / 103 (0.97%) 1 | |
| Umbilical hernia subjects affected / exposed occurrences (all) | 0 / 105 (0.00%) 0 | 1 / 103 (0.97%) 1 | |
| Hepatobiliary disorders | | | |
| Cholestasis subjects affected / exposed occurrences (all) | 0 / 105 (0.00%) 0 | 1 / 103 (0.97%) 1 | |
| Hyperbilirubinaemia subjects affected / exposed occurrences (all) | 21 / 105 (20.00%) 21 | 12 / 103 (11.65%) 12 | |
| Jaundice | | | |

| | | | |
|---------------------------------------------------------------------------------|----------------------|----------------------|--|
| subjects affected / exposed occurrences (all) | 3 / 105 (2.86%) 3 | 5 / 103 (4.85%) 5 | |
| Skin and subcutaneous tissue disorders | | | |
| Erythema toxicum neonatorum subjects affected / exposed occurrences (all) | 1 / 105 (0.95%) 1 | 0 / 103 (0.00%) 0 | |
| Rash generalised subjects affected / exposed occurrences (all) | 0 / 105 (0.00%) 0 | 1 / 103 (0.97%) 1 | |
| Skin erosion subjects affected / exposed occurrences (all) | 1 / 105 (0.95%) 1 | 0 / 103 (0.00%) 0 | |
| Renal and urinary disorders | | | |
| Haematuria subjects affected / exposed occurrences (all) | 1 / 105 (0.95%) 1 | 0 / 103 (0.00%) 0 | |
| Oliguria subjects affected / exposed occurrences (all) | 1 / 105 (0.95%) 1 | 3 / 103 (2.91%) 3 | |
| Infections and infestations | | | |
| Bacterial sepsis subjects affected / exposed occurrences (all) | 1 / 105 (0.95%) 1 | 0 / 103 (0.00%) 0 | |
| Brain abscess subjects affected / exposed occurrences (all) | 1 / 105 (0.95%) 1 | 0 / 103 (0.00%) 0 | |
| Bronchopneumonia subjects affected / exposed occurrences (all) | 0 / 105 (0.00%) 0 | 1 / 103 (0.97%) 1 | |
| Candidiasis subjects affected / exposed occurrences (all) | 1 / 105 (0.95%) 1 | 1 / 103 (0.97%) 1 | |
| Conjunctivitis infective subjects affected / exposed occurrences (all) | 2 / 105 (1.90%) 2 | 0 / 103 (0.00%) 0 | |
| Infection | | | |

| | | | |
|---------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 105 (0.00%) | 1 / 103 (0.97%) | |
| occurrences (all) | 0 | 1 | |
| Omphalitis | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 1 / 103 (0.97%) | |
| occurrences (all) | 1 | 1 | |
| Pneumonia klebsiella | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 1 / 103 (0.97%) | |
| occurrences (all) | 1 | 1 | |
| Pseudomonas infection | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 2 / 103 (1.94%) | |
| occurrences (all) | 0 | 2 | |
| Respiratory tract infection bacterial | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 1 / 103 (0.97%) | |
| occurrences (all) | 0 | 1 | |
| Rhinitis | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 103 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Sepsis neonatal | | | |
| subjects affected / exposed | 3 / 105 (2.86%) | 2 / 103 (1.94%) | |
| occurrences (all) | 4 | 3 | |
| Sepsis | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 5 / 103 (4.85%) | |
| occurrences (all) | 0 | 6 | |
| Staphylococcal infection | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 103 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Staphylococcal sepsis | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 1 / 103 (0.97%) | |
| occurrences (all) | 0 | 1 | |
| Streptococcal bacteraemia | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 103 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Metabolism and nutrition disorders | | | |
| Diabetes mellitus | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 1 / 103 (0.97%) | |
| occurrences (all) | 0 | 1 | |

| | | |
|-----------------------------|-------------------|-------------------|
| Hypercalcaemia | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 1 / 103 (0.97%) |
| occurrences (all) | 0 | 1 |
| Hyperglycaemia | | |
| subjects affected / exposed | 3 / 105 (2.86%) | 3 / 103 (2.91%) |
| occurrences (all) | 3 | 3 |
| Hyperkalaemia | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 5 / 103 (4.85%) |
| occurrences (all) | 0 | 5 |
| Hypernatraemia | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 1 / 103 (0.97%) |
| occurrences (all) | 0 | 1 |
| Hypoglycaemia | | |
| subjects affected / exposed | 3 / 105 (2.86%) | 0 / 103 (0.00%) |
| occurrences (all) | 3 | 0 |
| Hypokalaemia | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 1 / 103 (0.97%) |
| occurrences (all) | 0 | 1 |
| Hyponatraemia | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 5 / 103 (4.85%) |
| occurrences (all) | 0 | 5 |
| Metabolic acidosis | | |
| subjects affected / exposed | 12 / 105 (11.43%) | 12 / 103 (11.65%) |
| occurrences (all) | 12 | 16 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 30 November 2006 | Amendment 1 was prepared after the Investigators' Meeting, held in Madrid on November 27th 2006. In fact, it reports the final list of countries involved and the investigators who definitely accepted to participate. UK's participation was cancelled and Brazil was added. Moreover this amendment includes some minor modifications, requested during the meeting, to have a more feasible protocol in each involved Neonatal Intensive Care Unit. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

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|-----------------------------------------------------------------------------|
| There are no limitations nor caveats applicable to this summary of results. |
|-----------------------------------------------------------------------------|

Notes:

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/20439601>

<http://www.ncbi.nlm.nih.gov/pubmed/18196932>