

**Clinical trial results:**

A RANDOMIZED, OPEN, MULTINATIONAL, MULTICENTRE, 2-PART STUDY IN SPONTANEOUSLY BREATHING PRETERM NEONATES WITH MILD TO MODERATE RESPIRATORY DISTRESS SYNDROME TO INVESTIGATE THE SAFETY, TOLERABILITY AND EFFICACY OF INHALED NEBULISED PORACTANT ALFA (PORCINE SURFACTANT, CUROSURF®) IN COMPARISON WITH nCPAP ALONE.

Summary

| | |
|--------------------------|----------------------|
| EudraCT number | 2016-004547-36 |
| Trial protocol | HU CZ GB AT FR PL IT |
| Global end of trial date | 05 May 2020 |

Results information

| | |
|-----------------------------------|--|
| Result version number | v1 (current) |
| This version publication date | 02 April 2021 |
| First version publication date | 02 April 2021 |
| Summary attachment (see zip file) | CURONEB CSR ADDENDUM Synopsis (CURONEB CSR ADDENDUM Synopsis_for publication 3_Redacted.pdf) |

Trial information**Trial identification**

| | |
|-----------------------|-----------------|
| Sponsor protocol code | CCD-01534CA1-01 |
|-----------------------|-----------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03235986 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Chiesi Farmaceutici S.p.A. |
| Sponsor organisation address | Via Palermo 26/A, Parma, Italy, 43122 |
| Public contact | Clinical Trial Transparency, CHIESI FARMACEUTICI S.p.A., clinicaltrials_info@chiesi.com |
| Scientific contact | Clinical Trial Transparency, CHIESI FARMACEUTICI S.p.A., 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 | 11 February 2021 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 05 May 2020 |
| Global end of trial reached? | Yes |
| Global end of trial date | 05 May 2020 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

Part I objective:

To assess the safety and tolerability of three single ascending doses of nebulised Curosurf®.

Part II objective:

To compare the efficacy of nebulised Curosurf®, administered at low dose (dose 1*) or high dose (dose 2), during nasal continuous positive airway pressure (nCPAP), versus (v) nCPAP alone in terms of incidence of respiratory failure in the first 72 hours of life in spontaneously breathing preterm neonates with mild to moderate respiratory distress syndrome (RDS).

*Note: actual doses used were: 200 mg/kg as low dose and 400 mg/kg as high dose.

Protection of trial subjects:

The study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice guidelines and all other requirements of local laws.

In both parts of the study, from screening (Day -1) to Day 7:

- Neonatal concomitant medication and adverse events (AEs) were recorded during all periods; peri-dosing AEs and adverse drug reactions (ADRs) were assessed;
- Peripheral oxygen saturation (SpO₂) and fraction of inspired oxygen (FiO₂) were measured and respiratory support evaluated during all periods;
- Vital signs were measured during all periods;
- Blood gas analysis was performed up to Day 7;
- Supplemental oxygen use and respiratory failure were monitored during all periods except Day -1.

- SpO₂ and FiO₂ were measured, respiratory support evaluated, respiratory failure monitored and neonatal concomitant medication and AEs recorded at 28 days post-natal age (PNA), at discharge home and at either 36 weeks post-menstrual age (PMA) or between 28 and 56 days PNA (depending on gestational age);
- Presence of bronchopulmonary dysplasia (BPD) was assessed at either discharge home, 36 weeks PMA or between 28 and 56 days PNA, as appropriate;
- Assessment of development and health status was performed at 24 months (±3 months) corrected age (Part I only). Data from this assessment are the subject of an addendum, the synopsis of which is appended.

An independent safety monitoring board (ISMB) was convened to evaluate safety and preliminary efficacy during the study. In Part I, neonates were enrolled in 3 cohorts, planned to receive escalating doses of Curosurf®. After a stop to evaluate the first 7-day safety data of each cohort, the ISMB's positive decision triggered the continuation of the dose escalation scheme to the next dose. Similarly, in Part II, the ISMB reviewed the safety profile of Curosurf® after enrolment of every 40 neonates.

Background therapy:

Not applicable.

Evidence for comparator:

In both parts of the study, neonates received single doses of nebulised Curosurf® (200, 400 and 600

mg/kg in Part I and 200 and 400 mg/kg in Part II) in addition to nCPAP. Guidelines for treatment of RDS available at the time of study preparation recommended early initiation of non-invasive respiratory support (e.g. nCPAP) with early rescue surfactant in case of worsening of respiratory parameters (FiO2 > 0.40 for neonates of > 26 weeks gestational age). On this basis, the control group in this study was composed of preterm neonates receiving nCPAP alone, i.e. standard of care.

| | |
|---|----------------|
| Actual start date of recruitment | 28 August 2017 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety |
| Long term follow-up duration | 24 Months |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | United Kingdom: 30 |
| Country: Number of subjects enrolled | Czech Republic: 32 |
| Country: Number of subjects enrolled | Hungary: 42 |
| Country: Number of subjects enrolled | Austria: 5 |
| Country: Number of subjects enrolled | Italy: 47 |
| Country: Number of subjects enrolled | Poland: 10 |
| Worldwide total number of subjects | 166 |
| EEA total number of subjects | 166 |

Notes:

Subjects enrolled per age group

| | |
|---|-----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 166 |
| 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:

In Part I, 85 neonates were screened according to inclusion/exclusion criteria, and 37 neonates were randomised.

In Part II, 307 neonates were screened according to inclusion/exclusion criteria, and 129 neonates were randomised.

Pre-assignment

Screening details:

In Part I, 48 neonates failed screening (Day -1) due to: inclusion/exclusion criteria (44 neonates), consent withdrawal (1 neonate) and other reasons (3 neonates).

In Part II, 178 neonates failed screening (Day -1) due to: inclusion/exclusion criteria (166 neonates), consent withdrawal (1 neonate) and other reasons (11 neonates).

Period 1

| | |
|------------------------------|---------------------------------------|
| Period 1 title | Study Parts I and II (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|--|
| Are arms mutually exclusive? | Yes |
| Arm title | Part I - 200 mg/kg nebulised Curosurf® |

Arm description:

Neonates were randomised to receive a single dose of nebulised Curosurf® at 200 mg/kg.

| | |
|--|---|
| Arm type | Experimental |
| Investigational medicinal product name | 200 mg/kg nebulised Curosurf® |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Endotracheopulmonary instillation, suspension |
| Routes of administration | Inhalation use |

Dosage and administration details:

A single dose of Curosurf® at 200 mg/kg was administered within 60 minutes and 12 hours after birth whilst nCPAP was ongoing. The total duration of nebulisation was variable according to body weight but was not allowed to last more than 30 minutes for the 200 mg/kg dose.

| | |
|------------------|--|
| Arm title | Part I - 400 mg/kg nebulised Curosurf® |
|------------------|--|

Arm description:

Neonates were randomised to receive a single dose of nebulised Curosurf® at 400 mg/kg.

| | |
|--|---|
| Arm type | Experimental |
| Investigational medicinal product name | 400 mg/kg nebulised Curosurf® |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Endotracheopulmonary instillation, suspension |
| Routes of administration | Inhalation use |

Dosage and administration details:

A single dose of Curosurf® at 400 mg/kg was administered within 60 minutes and 12 hours after birth whilst nCPAP was ongoing. The total duration of nebulisation was variable according to body weight but was not allowed to last more than 60 minutes for the 400 mg/kg dose.

| | |
|------------------|--|
| Arm title | Part I - 600 mg/kg nebulised Curosurf® |
|------------------|--|

| | |
|--|---|
| Arm description: | |
| Neonates were randomised to receive a single dose of nebulised Curosurf® at 600 mg/kg. | |
| Arm type | Experimental |
| Investigational medicinal product name | 600 mg/kg nebulised Curosurf® |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Endotracheopulmonary instillation, suspension |
| Routes of administration | Inhalation use |

Dosage and administration details:

A single dose of Curosurf® at 600 mg/kg was administered within 60 minutes and 12 hours after birth whilst nCPAP was ongoing. The total duration of nebulisation was variable according to body weight but was not allowed to last more than 90 minutes for the 600 mg/kg dose.

| | |
|------------------|----------------|
| Arm title | Part I - nCPAP |
|------------------|----------------|

| | |
|---|---|
| Arm description: | |
| Neonates were randomised to receive nCPAP only. | |
| Arm type | Control |
| No investigational medicinal product assigned in this arm | |
| Arm title | Part II - 200 mg/kg nebulised Curosurf® |

| | |
|--|---|
| Arm description: | |
| Neonates were randomised to receive a single dose of nebulised Curosurf® at 200 mg/kg. | |
| Arm type | Experimental |
| Investigational medicinal product name | 200 mg/kg nebulised Curosurf® |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Endotracheopulmonary instillation, suspension |
| Routes of administration | Inhalation use |

Dosage and administration details:

A single dose of Curosurf® at 200 mg/kg was administered within 60 minutes and 12 hours after birth whilst nCPAP was ongoing. The total duration of nebulisation was variable according to body weight but was not allowed to last more than 30 minutes for the 200 mg/kg dose. An additional dose of nebulised Curosurf® at 200 mg/kg was allowed, with re-dosing to occur between 3 and 12 hours after the start of the first dose.

| | |
|------------------|---|
| Arm title | Part II - 400 mg/kg nebulised Curosurf® |
|------------------|---|

| | |
|--|---|
| Arm description: | |
| Neonates were randomised to receive a single dose of nebulised Curosurf® at 400 mg/kg. | |
| Arm type | Experimental |
| Investigational medicinal product name | 400 mg/kg nebulised Curosurf® |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Endotracheopulmonary instillation, suspension |
| Routes of administration | Inhalation use |

Dosage and administration details:

A single dose of Curosurf® at 400 mg/kg was administered within 60 minutes and 12 hours after birth whilst nCPAP was ongoing. The total duration of nebulisation was variable according to body weight but was not allowed to last more than 60 minutes for the 400 mg/kg dose. An additional dose of nebulised Curosurf® at 200 mg/kg was allowed, with re-dosing to occur between 3 and 12 hours after the start of the first dose.

| | |
|------------------|-----------------|
| Arm title | Part II - nCPAP |
|------------------|-----------------|

| | |
|---|---------|
| Arm description: | |
| Neonates were randomised to receive nCPAP only. | |
| Arm type | Control |
| No investigational medicinal product assigned in this arm | |

| Number of subjects in period 1 | Part I - 200 mg/kg nebulised Curosurf® | Part I - 400 mg/kg nebulised Curosurf® | Part I - 600 mg/kg nebulised Curosurf® |
|---------------------------------------|---|---|---|
| Started | 10 | 9 | 9 |
| Completed | 10 | 9 | 9 |
| Not completed | 0 | 0 | 0 |
| Adverse event, serious fatal | - | - | - |
| Untreated | - | - | - |

| Number of subjects in period 1 | Part I - nCPAP | Part II - 200 mg/kg nebulised Curosurf® | Part II - 400 mg/kg nebulised Curosurf® |
|---------------------------------------|----------------|--|--|
| Started | 9 | 43 | 43 |
| Completed | 9 | 42 | 40 |
| Not completed | 0 | 1 | 3 |
| Adverse event, serious fatal | - | - | 1 |
| Untreated | - | 1 | 2 |

| Number of subjects in period 1 | Part II - nCPAP |
|---------------------------------------|-----------------|
| Started | 43 |
| Completed | 43 |
| Not completed | 0 |
| Adverse event, serious fatal | - |
| Untreated | - |

Baseline characteristics

Reporting groups

| | |
|--|---|
| Reporting group title | Part I - 200 mg/kg nebulised Curosurf® |
| Reporting group description: | |
| Neonates were randomised to receive a single dose of nebulised Curosurf® at 200 mg/kg. | |
| Reporting group title | Part I - 400 mg/kg nebulised Curosurf® |
| Reporting group description: | |
| Neonates were randomised to receive a single dose of nebulised Curosurf® at 400 mg/kg. | |
| Reporting group title | Part I - 600 mg/kg nebulised Curosurf® |
| Reporting group description: | |
| Neonates were randomised to receive a single dose of nebulised Curosurf® at 600 mg/kg. | |
| Reporting group title | Part I - nCPAP |
| Reporting group description: | |
| Neonates were randomised to receive nCPAP only. | |
| Reporting group title | Part II - 200 mg/kg nebulised Curosurf® |
| Reporting group description: | |
| Neonates were randomised to receive a single dose of nebulised Curosurf® at 200 mg/kg. | |
| Reporting group title | Part II - 400 mg/kg nebulised Curosurf® |
| Reporting group description: | |
| Neonates were randomised to receive a single dose of nebulised Curosurf® at 400 mg/kg. | |
| Reporting group title | Part II - nCPAP |
| Reporting group description: | |
| Neonates were randomised to receive nCPAP only. | |

| Reporting group values | Part I - 200 mg/kg nebulised Curosurf® | Part I - 400 mg/kg nebulised Curosurf® | Part I - 600 mg/kg nebulised Curosurf® |
|--|--|--|--|
| Number of subjects | 10 | 9 | 9 |
| Age categorical | | | |
| Units: Subjects | | | |
| Preterm newborn infants (gestational age < 37 wks) | 10 | 9 | 9 |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 5 | 2 | 3 |
| Male | 5 | 7 | 6 |

| Reporting group values | Part I - nCPAP | Part II - 200 mg/kg nebulised Curosurf® | Part II - 400 mg/kg nebulised Curosurf® |
|--|----------------|---|---|
| Number of subjects | 9 | 43 | 43 |
| Age categorical | | | |
| Units: Subjects | | | |
| Preterm newborn infants (gestational age < 37 wks) | 9 | 43 | 43 |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 3 | 20 | 14 |
| Male | 6 | 23 | 29 |

| Reporting group values | Part II - nCPAP | Total | |
|------------------------|-----------------|-------|--|
| Number of subjects | 43 | 166 | |

| | | | |
|---|----|-----|--|
| Age categorical Units: Subjects | | | |
| Preterm newborn infants (gestational age < 37 wks) | 43 | 166 | |
| Gender categorical Units: Subjects | | | |
| Female | 23 | 70 | |
| Male | 20 | 96 | |

Subject analysis sets

| | |
|--|---|
| Subject analysis set title | Part I - 200 mg/kg nebulised Curosurf® - ITT |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: The Intention-to-treat population (ITT) was defined as all randomised neonates with a gestational age from 28+0 to 32+6 weeks, who received nCPAP and then started nebulisation with Curosurf® (active treatment group only) and with at least one available evaluation of efficacy after baseline. | |
| Subject analysis set title | Part I - 400 mg/kg nebulised Curosurf® - ITT |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: The ITT was defined as all randomised neonates with a gestational age from 28+0 to 32+6 weeks, who received nCPAP and then started nebulisation with Curosurf® (active treatment group only) and with at least one available evaluation of efficacy after baseline. | |
| Subject analysis set title | Part I - 600 mg/kg nebulised Curosurf® - ITT |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: The ITT was defined as all randomised neonates with a gestational age from 28+0 to 32+6 weeks, who received nCPAP and then started nebulisation with Curosurf® (active treatment group only) and with at least one available evaluation of efficacy after baseline. | |
| Subject analysis set title | Part I - nCPAP - ITT |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: The ITT was defined as all randomised neonates with a gestational age from 28+0 to 32+6 weeks, who received nCPAP and then started nebulisation with Curosurf® (active treatment group only) and with at least one available evaluation of efficacy after baseline. | |
| Subject analysis set title | Part II - 200 mg/kg nebulised Curosurf® - ITT |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: The ITT was defined as all randomised neonates with a gestational age from 28+0 to 32+6 weeks, who received nCPAP and then started nebulisation with Curosurf® (active treatment group only) and with at least one available evaluation of efficacy after baseline. | |
| Subject analysis set title | Part II - 400 mg/kg nebulised Curosurf® - ITT |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: The ITT was defined as all randomised neonates with a gestational age from 28+0 to 32+6 weeks, who received nCPAP and then started nebulisation with Curosurf® (active treatment group only) and with at least one available evaluation of efficacy after baseline. | |
| Subject analysis set title | Part II - nCPAP - ITT |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: The ITT was defined as all randomised neonates with a gestational age from 28+0 to 32+6 weeks, who received nCPAP and then started nebulisation with Curosurf® (active treatment group only) and with at least one available evaluation of efficacy after baseline. | |
| Subject analysis set title | Part I - 200 mg/kg nebulised Curosurf® - SAF |
| Subject analysis set type | Safety analysis |

Subject analysis set description:

The Safety population (SAF) was defined as all randomised neonates, with a gestational age from 28+0 to 32+6 weeks, who either received nCPAP alone (nCPAP group) or who received nCPAP and then started nebulisation with Curosurf® (active treatment group).

| | |
|----------------------------|--|
| Subject analysis set title | Part I - 400 mg/kg nebulised Curosurf® - SAF |
| Subject analysis set type | Safety analysis |

Subject analysis set description:

The SAF was defined as all randomised neonates, with a gestational age from 28+0 to 32+6 weeks, who either received nCPAP alone (nCPAP group) or who received nCPAP and then started nebulisation with Curosurf® (active treatment group).

| | |
|----------------------------|--|
| Subject analysis set title | Part I - 600 mg/kg nebulised Curosurf® - SAF |
| Subject analysis set type | Safety analysis |

Subject analysis set description:

The SAF was defined as all randomised neonates, with a gestational age from 28+0 to 32+6 weeks, who either received nCPAP alone (nCPAP group) or who received nCPAP and then started nebulisation with Curosurf® (active treatment group).

| | |
|----------------------------|----------------------|
| Subject analysis set title | Part I - nCPAP - SAF |
| Subject analysis set type | Safety analysis |

Subject analysis set description:

The SAF was defined as all randomised neonates, with a gestational age from 28+0 to 32+6 weeks, who either received nCPAP alone (nCPAP group) or who received nCPAP and then started nebulisation with Curosurf® (active treatment group).

| | |
|----------------------------|---|
| Subject analysis set title | Part II - 200 mg/kg nebulised Curosurf® - SAF |
| Subject analysis set type | Safety analysis |

Subject analysis set description:

The SAF was defined as all randomised neonates, with a gestational age from 28+0 to 32+6 weeks, who either received nCPAP alone (nCPAP group) or who received nCPAP and then started nebulisation with Curosurf® (active treatment group).

| | |
|----------------------------|---|
| Subject analysis set title | Part II - 400 mg/kg nebulised Curosurf® - SAF |
| Subject analysis set type | Safety analysis |

Subject analysis set description:

The SAF was defined as all randomised neonates, with a gestational age from 28+0 to 32+6 weeks, who either received nCPAP alone (nCPAP group) or who received nCPAP and then started nebulisation with Curosurf® (active treatment group).

| | |
|----------------------------|-----------------------|
| Subject analysis set title | Part II - nCPAP - SAF |
| Subject analysis set type | Safety analysis |

Subject analysis set description:

The SAF was defined as all randomised neonates, with a gestational age from 28+0 to 32+6 weeks, who either received nCPAP alone (nCPAP group) or who received nCPAP and then started nebulisation with Curosurf® (active treatment group).

| Reporting group values | Part I - 200 mg/kg nebulised Curosurf® - ITT | Part I - 400 mg/kg nebulised Curosurf® - ITT | Part I - 600 mg/kg nebulised Curosurf® - ITT |
|--|--|--|--|
| Number of subjects | 9 | 9 | 9 |
| Age categorical Units: Subjects | | | |
| Preterm newborn infants (gestational age < 37 wks) | 9 | 9 | 9 |
| Gender categorical Units: Subjects | | | |
| Female | 4 | 2 | 3 |

| | | | |
|------|---|---|---|
| Male | 5 | 7 | 6 |
|------|---|---|---|

| Reporting group values | Part I - nCPAP - ITT | Part II - 200 mg/kg nebulised Curosurf® - ITT | Part II - 400 mg/kg nebulised Curosurf® - ITT |
|--|----------------------|---|---|
| Number of subjects | 9 | 42 | 41 |
| Age categorical Units: Subjects | | | |
| Preterm newborn infants (gestational age < 37 wks) | 9 | 42 | 41 |
| Gender categorical Units: Subjects | | | |
| Female | 3 | 20 | 13 |
| Male | 6 | 22 | 28 |

| Reporting group values | Part II - nCPAP - ITT | Part I - 200 mg/kg nebulised Curosurf® - SAF | Part I - 400 mg/kg nebulised Curosurf® - SAF |
|--|-----------------------|--|--|
| Number of subjects | 43 | 9 | 9 |
| Age categorical Units: Subjects | | | |
| Preterm newborn infants (gestational age < 37 wks) | 43 | | |
| Gender categorical Units: Subjects | | | |
| Female | 23 | | |
| Male | 20 | | |

| Reporting group values | Part I - 600 mg/kg nebulised Curosurf® - SAF | Part I - nCPAP - SAF | Part II - 200 mg/kg nebulised Curosurf® - SAF |
|--|--|----------------------|---|
| Number of subjects | 9 | 9 | 42 |
| Age categorical Units: Subjects | | | |
| Preterm newborn infants (gestational age < 37 wks) | | | |
| Gender categorical Units: Subjects | | | |
| Female | | | |
| Male | | | |

| Reporting group values | Part II - 400 mg/kg nebulised Curosurf® - SAF | Part II - nCPAP - SAF | |
|--|---|-----------------------|--|
| Number of subjects | 41 | 43 | |
| Age categorical Units: Subjects | | | |
| Preterm newborn infants (gestational age < 37 wks) | | | |
| Gender categorical Units: Subjects | | | |
| Female | | | |
| Male | | | |

End points

End points reporting groups

| | |
|--|---|
| Reporting group title | Part I - 200 mg/kg nebulised Curosurf® |
| Reporting group description: Neonates were randomised to receive a single dose of nebulised Curosurf® at 200 mg/kg. | |
| Reporting group title | Part I - 400 mg/kg nebulised Curosurf® |
| Reporting group description: Neonates were randomised to receive a single dose of nebulised Curosurf® at 400 mg/kg. | |
| Reporting group title | Part I - 600 mg/kg nebulised Curosurf® |
| Reporting group description: Neonates were randomised to receive a single dose of nebulised Curosurf® at 600 mg/kg. | |
| Reporting group title | Part I - nCPAP |
| Reporting group description: Neonates were randomised to receive nCPAP only. | |
| Reporting group title | Part II - 200 mg/kg nebulised Curosurf® |
| Reporting group description: Neonates were randomised to receive a single dose of nebulised Curosurf® at 200 mg/kg. | |
| Reporting group title | Part II - 400 mg/kg nebulised Curosurf® |
| Reporting group description: Neonates were randomised to receive a single dose of nebulised Curosurf® at 400 mg/kg. | |
| Reporting group title | Part II - nCPAP |
| Reporting group description: Neonates were randomised to receive nCPAP only. | |
| Subject analysis set title | Part I - 200 mg/kg nebulised Curosurf® - ITT |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: The Intention-to-treat population (ITT) was defined as all randomised neonates with a gestational age from 28+0 to 32+6 weeks, who received nCPAP and then started nebulisation with Curosurf® (active treatment group only) and with at least one available evaluation of efficacy after baseline. | |
| Subject analysis set title | Part I - 400 mg/kg nebulised Curosurf® - ITT |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: The ITT was defined as all randomised neonates with a gestational age from 28+0 to 32+6 weeks, who received nCPAP and then started nebulisation with Curosurf® (active treatment group only) and with at least one available evaluation of efficacy after baseline. | |
| Subject analysis set title | Part I - 600 mg/kg nebulised Curosurf® - ITT |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: The ITT was defined as all randomised neonates with a gestational age from 28+0 to 32+6 weeks, who received nCPAP and then started nebulisation with Curosurf® (active treatment group only) and with at least one available evaluation of efficacy after baseline. | |
| Subject analysis set title | Part I - nCPAP - ITT |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: The ITT was defined as all randomised neonates with a gestational age from 28+0 to 32+6 weeks, who received nCPAP and then started nebulisation with Curosurf® (active treatment group only) and with at least one available evaluation of efficacy after baseline. | |
| Subject analysis set title | Part II - 200 mg/kg nebulised Curosurf® - ITT |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: The ITT was defined as all randomised neonates with a gestational age from 28+0 to 32+6 weeks, who received nCPAP and then started nebulisation with Curosurf® (active treatment group only) and with at least one available evaluation of efficacy after baseline. | |

least one available evaluation of efficacy after baseline.

| | |
|----------------------------|---|
| Subject analysis set title | Part II - 400 mg/kg nebulised Curosurf® - ITT |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

The ITT was defined as all randomised neonates with a gestational age from 28+0 to 32+6 weeks, who received nCPAP and then started nebulisation with Curosurf® (active treatment group only) and with at least one available evaluation of efficacy after baseline.

| | |
|----------------------------|-----------------------|
| Subject analysis set title | Part II - nCPAP - ITT |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

The ITT was defined as all randomised neonates with a gestational age from 28+0 to 32+6 weeks, who received nCPAP and then started nebulisation with Curosurf® (active treatment group only) and with at least one available evaluation of efficacy after baseline.

| | |
|----------------------------|--|
| Subject analysis set title | Part I - 200 mg/kg nebulised Curosurf® - SAF |
| Subject analysis set type | Safety analysis |

Subject analysis set description:

The Safety population (SAF) was defined as all randomised neonates, with a gestational age from 28+0 to 32+6 weeks, who either received nCPAP alone (nCPAP group) or who received nCPAP and then started nebulisation with Curosurf® (active treatment group).

| | |
|----------------------------|--|
| Subject analysis set title | Part I - 400 mg/kg nebulised Curosurf® - SAF |
| Subject analysis set type | Safety analysis |

Subject analysis set description:

The SAF was defined as all randomised neonates, with a gestational age from 28+0 to 32+6 weeks, who either received nCPAP alone (nCPAP group) or who received nCPAP and then started nebulisation with Curosurf® (active treatment group).

| | |
|----------------------------|--|
| Subject analysis set title | Part I - 600 mg/kg nebulised Curosurf® - SAF |
| Subject analysis set type | Safety analysis |

Subject analysis set description:

The SAF was defined as all randomised neonates, with a gestational age from 28+0 to 32+6 weeks, who either received nCPAP alone (nCPAP group) or who received nCPAP and then started nebulisation with Curosurf® (active treatment group).

| | |
|----------------------------|----------------------|
| Subject analysis set title | Part I - nCPAP - SAF |
| Subject analysis set type | Safety analysis |

Subject analysis set description:

The SAF was defined as all randomised neonates, with a gestational age from 28+0 to 32+6 weeks, who either received nCPAP alone (nCPAP group) or who received nCPAP and then started nebulisation with Curosurf® (active treatment group).

| | |
|----------------------------|---|
| Subject analysis set title | Part II - 200 mg/kg nebulised Curosurf® - SAF |
| Subject analysis set type | Safety analysis |

Subject analysis set description:

The SAF was defined as all randomised neonates, with a gestational age from 28+0 to 32+6 weeks, who either received nCPAP alone (nCPAP group) or who received nCPAP and then started nebulisation with Curosurf® (active treatment group).

| | |
|----------------------------|---|
| Subject analysis set title | Part II - 400 mg/kg nebulised Curosurf® - SAF |
| Subject analysis set type | Safety analysis |

Subject analysis set description:

The SAF was defined as all randomised neonates, with a gestational age from 28+0 to 32+6 weeks, who either received nCPAP alone (nCPAP group) or who received nCPAP and then started nebulisation with Curosurf® (active treatment group).

| | |
|----------------------------|-----------------------|
| Subject analysis set title | Part II - nCPAP - SAF |
| Subject analysis set type | Safety analysis |

Subject analysis set description:

The SAF was defined as all randomised neonates, with a gestational age from 28+0 to 32+6 weeks, who either received nCPAP alone (nCPAP group) or who received nCPAP and then started nebulisation with Curosurf® (active treatment group).

Primary: Percentage of neonates with respiratory failure in the first 72 hours of life - Part II

| | |
|-----------------|---|
| End point title | Percentage of neonates with respiratory failure in the first 72 hours of life - Part II |
|-----------------|---|

End point description:

Note: this was the primary endpoint for Part II of the study, an error in the EudraCT system means that it is presented before endpoints relating to Part I of the study.

Respiratory failure was defined as a neonate needing endotracheal surfactant administration and/or mechanical ventilation due to one or more of the following reasons:

- FiO₂ > 0.40 to maintain SpO₂ between 88 and 95% for at least 30 minutes, unless rapid clinical deterioration occurred;
- Significant apnoea (more than four episodes of apnoea per hour or more than two episodes of apnoea per hour which required positive pressure ventilation);
- Persistent respiratory acidosis despite the initiation of non-invasive respiratory support (partial pressure of carbon dioxide [pCO₂] > 65 mmHg/8.5 kPa and pH < 7.20 on blood gas).

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

The first 72 hours of life.

| End point values | Part II - 200 mg/kg nebulised Curosurf® - ITT | Part II - 400 mg/kg nebulised Curosurf® - ITT | Part II - nCPAP - ITT | |
|-------------------------------|---|---|-----------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 42 | 41 | 43 | |
| Units: Percentage of neonates | | | | |
| number (not applicable) | 57.1 | 48.8 | 58.1 | |

Statistical analyses

| | |
|----------------------------|--|
| Statistical analysis title | 400 mg/kg nebulised Curosurf v nCPAP - Part II |
|----------------------------|--|

Statistical analysis description:

The percentage of neonates with respiratory failure in the first 72 hours of life was compared between 400 mg/kg nebulised Curosurf® and the nCPAP group using a chi-square test. The relative risk with its 95% confidence intervals was also calculated.

| | |
|---|---|
| Comparison groups | Part II - 400 mg/kg nebulised Curosurf® - ITT v Part II - nCPAP - ITT |
| Number of subjects included in analysis | 84 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[1] |
| P-value | = 0.39 |
| Method | Chi-squared |
| Parameter estimate | Relative risk |
| Point estimate | 0.84 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.56 |
| upper limit | 1.26 |

Notes:

[1] - The comparisons of nebulised Curosurf® dose v nCPAP alone were performed hierarchically starting from the highest dose.

| | |
|-----------------------------------|--|
| Statistical analysis title | 200 mg/kg nebulised Curosurf v nCPAP - Part II |
|-----------------------------------|--|

Statistical analysis description:

The percentage of neonates with respiratory failure in the first 72 hours of life was compared between 200 mg/kg nebulised Curosurf® and the nCPAP group using a chi-square test. The relative risk with its 95% confidence intervals was also calculated.

| | |
|---|---|
| Comparison groups | Part II - nCPAP - ITT v Part II - 200 mg/kg nebulised Curosurf® - ITT |
| Number of subjects included in analysis | 85 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[2] |
| P-value | = 0.926 |
| Method | Chi-squared |
| Parameter estimate | Relative risk |
| Point estimate | 0.98 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.68 |
| upper limit | 1.42 |

Notes:

[2] - The comparisons of nebulised Curosurf® dose v nCPAP alone were performed hierarchically starting from the highest dose.

Other pre-specified: Percentage of neonates with respiratory failure in the first 72 hours of life - Part I

| | |
|-----------------|--|
| End point title | Percentage of neonates with respiratory failure in the first 72 hours of life - Part I |
|-----------------|--|

End point description:

Respiratory failure was defined as a neonate needing endotracheal surfactant administration and/or mechanical ventilation due to one or more of the following reasons:

- FiO₂ > 0.40 to maintain SpO₂ between 88 and 95% for at least 30 minutes, unless rapid clinical deterioration occurred;
- Significant apnoea (more than four episodes of apnoea per hour or more than two episodes of apnoea per hour which required positive pressure ventilation);
- Persistent respiratory acidosis despite the initiation of non-invasive respiratory support pCO₂ > 65 mmHg/8.5 kPa and pH < 7.20 on blood gas).

| | |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

The first 72 hours of life.

| End point values | Part I - 200 mg/kg nebulised Curosurf® - ITT | Part I - 400 mg/kg nebulised Curosurf® - ITT | Part I - 600 mg/kg nebulised Curosurf® - ITT | Part I - nCPAP - ITT |
|-------------------------------|--|--|--|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 9 | 9 | 9 | 9 |
| Units: Percentage of neonates | | | | |
| number (not applicable) | 44.4 | 66.7 | 55.6 | 66.7 |

Statistical analyses

| Statistical analysis title | 600 mg/kg nebulised Curosurf v nCPAP - Part I |
|--|---|
| Statistical analysis description: | |
| The percentage of neonates with respiratory failure in the first 72 hours of life was compared between 600 mg/kg nebulised Curosurf® and the nCPAP group using a Fisher's exact test. The relative risk with its 95% confidence intervals was also calculated. | |
| Comparison groups | Part I - nCPAP - ITT v Part I - 600 mg/kg nebulised Curosurf® - ITT |
| Number of subjects included in analysis | 18 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[3] |
| P-value | > 0.999 |
| Method | Fisher exact |
| Parameter estimate | Relative risk |
| Point estimate | 0.83 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.4 |
| upper limit | 1.76 |

Notes:

[3] - This analysis was exploratory.

| Statistical analysis title | 400 mg/kg nebulised Curosurf v nCPAP - Part I |
|--|---|
| Statistical analysis description: | |
| The percentage of neonates with respiratory failure in the first 72 hours of life was compared between 400 mg/kg nebulised Curosurf® and the nCPAP group using a Fisher's exact test. The relative risk with its 95% confidence intervals was also calculated. | |
| Comparison groups | Part I - nCPAP - ITT v Part I - 400 mg/kg nebulised Curosurf® - ITT |
| Number of subjects included in analysis | 18 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[4] |
| P-value | > 0.999 |
| Method | Fisher exact |
| Parameter estimate | Relative risk |
| Point estimate | 1 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.52 |
| upper limit | 1.92 |

Notes:

[4] - This analysis was exploratory.

| | |
|-----------------------------------|---|
| Statistical analysis title | 200 mg/kg nebulised Curosurf v nCPAP - Part I |
|-----------------------------------|---|

Statistical analysis description:

The percentage of neonates with respiratory failure in the first 72 hours of life was compared between 200 mg/kg nebulised Curosurf® and the nCPAP group using a Fisher's exact test. The relative risk with its 95% confidence intervals was also calculated.

| | |
|---|---|
| Comparison groups | Part I - nCPAP - ITT v Part I - 200 mg/kg nebulised Curosurf® - ITT |
| Number of subjects included in analysis | 18 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[5] |
| P-value | = 0.637 |
| Method | Fisher exact |
| Parameter estimate | Relative risk |
| Point estimate | 0.67 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.28 |
| upper limit | 1.58 |

Notes:

[5] - This analysis was exploratory.

Other pre-specified: Number of neonates with AEs - Part I

| | |
|-----------------|--------------------------------------|
| End point title | Number of neonates with AEs - Part I |
|-----------------|--------------------------------------|

End point description:

An AE was defined as any untoward medical occurrence in a patient or clinical trial neonate administered a medicinal product and which did not necessarily have a causal relationship with this treatment. An AE could therefore be any unfavourable and unintended sign (including abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Only treatment-emergent AEs were considered in this analysis.

| | |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

All AEs which started between treatment start (for active treatment) or after randomisation (for control) and discharge or 36 weeks PMA (whichever was sooner).

| End point values | Part I - 200 mg/kg nebulised Curosurf® - SAF | Part I - 400 mg/kg nebulised Curosurf® - SAF | Part I - 600 mg/kg nebulised Curosurf® - SAF | Part I - nCPAP - SAF |
|-----------------------------|--|--|--|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 9 | 9 | 9 | 9 |
| Units: Neonates | 9 | 9 | 9 | 9 |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage of neonates with AEs - Part I

| | |
|---|--|
| End point title | Percentage of neonates with AEs - Part I |
| End point description: As per the endpoint 'Number of neonates with AEs - Part I'. | |
| End point type | Other pre-specified |
| End point timeframe: As per the endpoint 'Number of neonates with AEs - Part I'. | |

| End point values | Part I - 200 mg/kg nebulised Curosurf® - SAF | Part I - 400 mg/kg nebulised Curosurf® - SAF | Part I - 600 mg/kg nebulised Curosurf® - SAF | Part I - nCPAP - SAF |
|-------------------------------|--|--|--|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 9 | 9 | 9 | 9 |
| Units: Percentage of neonates | | | | |
| number (not applicable) | 100.0 | 100.0 | 100.0 | 100.0 |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of AEs - Part I

| | |
|---|------------------------|
| End point title | Number of AEs - Part I |
| End point description: As per the endpoint 'Number of neonates with AEs - Part I'. | |
| End point type | Other pre-specified |
| End point timeframe: As per the endpoint 'Number of neonates with AEs - Part I'. | |

| End point values | Part I - 200 mg/kg nebulised Curosurf® - SAF | Part I - 400 mg/kg nebulised Curosurf® - SAF | Part I - 600 mg/kg nebulised Curosurf® - SAF | Part I - nCPAP - SAF |
|-----------------------------|--|--|--|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 9 | 9 | 9 | 9 |
| Units: Events | 34 | 51 | 52 | 59 |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of neonates with ADRs - Part I

| | |
|-----------------|---------------------------------------|
| End point title | Number of neonates with ADRs - Part I |
|-----------------|---------------------------------------|

End point description:

An ADR was defined as an untoward and unintended responses to an investigational product related to any dose administered. All AEs judged by either the reporting Investigator or the Sponsor as having a reasonable causal relationship to an investigational product qualified as ADRs. The expression "reasonable causal relationship" meant to convey in general that there were facts (evidence) or arguments meant to suggest a causal relationship. The definition covered also medication errors and uses outside what was foreseen in the protocol, including misuse and abuse of the product. Only treatment-emergent ADRs were considered in this analysis.

| | |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

All ADRs which started between treatment start (for active treatment) or after randomisation (for control) and discharge or 36 weeks PMA (whichever was sooner).

| End point values | Part I - 200 mg/kg nebulised Curosurf® - SAF | Part I - 400 mg/kg nebulised Curosurf® - SAF | Part I - 600 mg/kg nebulised Curosurf® - SAF | Part I - nCPAP - SAF |
|-----------------------------|--|--|--|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 9 | 9 | 9 | 9 |
| Units: Neonates | 0 | 0 | 0 | 0 |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage of neonates with ADRs - Part I

| | |
|-----------------|---|
| End point title | Percentage of neonates with ADRs - Part I |
|-----------------|---|

End point description:

As per the endpoint 'Number of neonates with ADRs - Part I'.

| | |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

As per the endpoint 'Number of neonates with ADRs - Part I'.

| End point values | Part I - 200 mg/kg nebulised Curosurf® - SAF | Part I - 400 mg/kg nebulised Curosurf® - SAF | Part I - 600 mg/kg nebulised Curosurf® - SAF | Part I - nCPAP - SAF |
|-------------------------------|--|--|--|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 9 | 9 | 9 | 9 |
| Units: Percentage of neonates | | | | |
| number (not applicable) | 0.0 | 0.0 | 0.0 | 0.0 |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of ADRs - Part I

| | |
|--|-------------------------|
| End point title | Number of ADRs - Part I |
| End point description: As per the endpoint 'Number of neonates with ADRs - Part I'. | |
| End point type | Other pre-specified |
| End point timeframe: As per the endpoint 'Number of neonates with ADRs - Part I'. | |

| End point values | Part I - 200 mg/kg nebulised Curosurf® - SAF | Part I - 400 mg/kg nebulised Curosurf® - SAF | Part I - 600 mg/kg nebulised Curosurf® - SAF | Part I - nCPAP - SAF |
|-----------------------------|--|--|--|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 9 | 9 | 9 | 9 |
| Units: Events | 0 | 0 | 0 | 0 |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of neonates with AEs - Part II

| | |
|---|---------------------------------------|
| End point title | Number of neonates with AEs - Part II |
| End point description: As per the endpoint 'Number of neonates with AEs - Part I'. | |
| End point type | Other pre-specified |
| End point timeframe: As per the endpoint 'Number of neonates with AEs - Part I'. | |

| End point values | Part II - 200 mg/kg nebulised Curosurf® - SAF | Part II - 400 mg/kg nebulised Curosurf® - SAF | Part II - nCPAP - SAF | |
|-----------------------------|---|---|-----------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 42 | 41 | 43 | |
| Units: Neonates | 38 | 33 | 40 | |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage of neonates with AEs - Part II

| | |
|------------------------|---|
| End point title | Percentage of neonates with AEs - Part II |
| End point description: | As per the endpoint 'Number of neonates with AEs - Part I'. |
| End point type | Other pre-specified |
| End point timeframe: | As per the endpoint 'Number of neonates with AEs - Part I'. |

| End point values | Part II - 200 mg/kg nebulised Curosurf® - SAF | Part II - 400 mg/kg nebulised Curosurf® - SAF | Part II - nCPAP - SAF | |
|-------------------------------|---|---|-----------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 42 | 41 | 43 | |
| Units: Percentage of neonates | | | | |
| number (not applicable) | 90.5 | 80.5 | 93.0 | |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of AEs - Part II

| | |
|------------------------|---|
| End point title | Number of AEs - Part II |
| End point description: | As per the endpoint 'Number of neonates with AEs - Part I'. |
| End point type | Other pre-specified |
| End point timeframe: | As per the endpoint 'Number of neonates with AEs - Part I'. |

| End point values | Part II - 200 mg/kg nebulised Curosurf® - SAF | Part II - 400 mg/kg nebulised Curosurf® - SAF | Part II - nCPAP - SAF | |
|-----------------------------|---|---|-----------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 42 | 41 | 43 | |
| Units: Events | 173 | 162 | 152 | |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of neonates with ADRs - Part II

| | |
|--|--|
| End point title | Number of neonates with ADRs - Part II |
| End point description: As per the endpoint 'Number of neonates with ADRs - Part I'. | |
| End point type | Other pre-specified |
| End point timeframe: As per the endpoint 'Number of neonates with ADRs - Part I'. | |

| End point values | Part II - 200 mg/kg nebulised Curosurf® - SAF | Part II - 400 mg/kg nebulised Curosurf® - SAF | Part II - nCPAP - SAF | |
|-----------------------------|---|---|-----------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 42 | 41 | 43 | |
| Units: Neonates | 0 | 0 | 0 | |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage of neonates with ADRs - Part II

| | |
|--|--|
| End point title | Percentage of neonates with ADRs - Part II |
| End point description: As per the endpoint 'Number of neonates with ADRs - Part I'. | |
| End point type | Other pre-specified |
| End point timeframe: As per the endpoint 'Number of neonates with ADRs - Part I'. | |

| End point values | Part II - 200 mg/kg nebulised Curosurf® - SAF | Part II - 400 mg/kg nebulised Curosurf® - SAF | Part II - nCPAP - SAF | |
|-------------------------------|---|---|-----------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 42 | 41 | 43 | |
| Units: Percentage of neonates | | | | |
| number (not applicable) | 0.0 | 0.0 | 0.0 | |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of ADRs - Part II

| | |
|--|--------------------------|
| End point title | Number of ADRs - Part II |
| End point description: As per the endpoint 'Number of neonates with ADRs - Part I'. | |
| End point type | Other pre-specified |
| End point timeframe: As per the endpoint 'Number of neonates with ADRs - Part I'. | |

| End point values | Part II - 200 mg/kg nebulised Curosurf® - SAF | Part II - 400 mg/kg nebulised Curosurf® - SAF | Part II - nCPAP - SAF | |
|-----------------------------|---|---|-----------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 42 | 41 | 43 | |
| Units: Events | 0 | 0 | 0 | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were reported from the signature of the patient information sheet/informed consent form (PIS/ICF; or from birth if the PIS/ICF was signed before birth) until the neonate's study participation ended.

Adverse event reporting additional description:

Treatment-emergent AEs were defined as AEs that started after treatment start (for active treatment) or randomisation (for control). Only treatment-emergent AEs are presented in this analysis.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 20.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|--|
| Reporting group title | Part I - 200 mg/kg nebulised Curosurf® - SAF |
|-----------------------|--|

Reporting group description:

The SAF was defined as all randomised neonates, with a gestational age from 28+0 to 32+6 weeks, who either received nCPAP alone (nCPAP group) or who received nCPAP and then started nebulisation with Curosurf® (active treatment group).

| | |
|-----------------------|--|
| Reporting group title | Part I - 400 mg/kg nebulised Curosurf® - SAF |
|-----------------------|--|

Reporting group description:

The SAF was defined as all randomised neonates, with a gestational age from 28+0 to 32+6 weeks, who either received nCPAP alone (nCPAP group) or who received nCPAP and then started nebulisation with Curosurf® (active treatment group).

| | |
|-----------------------|--|
| Reporting group title | Part I - 600 mg/kg nebulised Curosurf® - SAF |
|-----------------------|--|

Reporting group description:

The SAF was defined as all randomised neonates, with a gestational age from 28+0 to 32+6 weeks, who either received nCPAP alone (nCPAP group) or who received nCPAP and then started nebulisation with Curosurf® (active treatment group).

| | |
|-----------------------|----------------------|
| Reporting group title | Part I - nCPAP - SAF |
|-----------------------|----------------------|

Reporting group description:

The SAF was defined as all randomised neonates, with a gestational age from 28+0 to 32+6 weeks, who either received nCPAP alone (nCPAP group) or who received nCPAP and then started nebulisation with Curosurf® (active treatment group).

| | |
|-----------------------|---|
| Reporting group title | Part II - 200 mg/kg nebulised Curosurf® - SAF |
|-----------------------|---|

Reporting group description:

The SAF was defined as all randomised neonates, with a gestational age from 28+0 to 32+6 weeks, who either received nCPAP alone (nCPAP group) or who received nCPAP and then started nebulisation with Curosurf® (active treatment group).

| | |
|-----------------------|---|
| Reporting group title | Part II - 400 mg/kg nebulised Curosurf® - SAF |
|-----------------------|---|

Reporting group description:

The SAF was defined as all randomised neonates, with a gestational age from 28+0 to 32+6 weeks, who either received nCPAP alone (nCPAP group) or who received nCPAP and then started nebulisation with Curosurf® (active treatment group).

| | |
|-----------------------|-----------------------|
| Reporting group title | Part II - nCPAP - SAF |
|-----------------------|-----------------------|

Reporting group description:

The SAF was defined as all randomised neonates, with a gestational age from 28+0 to 32+6 weeks, who either received nCPAP alone (nCPAP group) or who received nCPAP and then started nebulisation with Curosurf® (active treatment group).

| Serious adverse events | Part I - 200 mg/kg nebulised Curosurf® - SAF | Part I - 400 mg/kg nebulised Curosurf® - SAF | Part I - 600 mg/kg nebulised Curosurf® - SAF |
|---|--|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 9 (0.00%) | 0 / 9 (0.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Vascular disorders | | | |
| Neonatal hypotension | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 9 (0.00%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Cardiopulmonary failure | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 9 (0.00%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Intraventricular haemorrhage neonatal | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 9 (0.00%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebral haemorrhage neonatal | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 9 (0.00%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Necrotising enterocolitis neonatal | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 9 (0.00%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neonatal gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 9 (0.00%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Meconium ileus | | | |

| | | | |
|--|----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 9 (0.00%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pneumothorax | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 9 (0.00%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary haemorrhage | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 9 (0.00%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Neonatal infection | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 9 (0.00%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sepsis neonatal | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 9 (0.00%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Septic shock | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 9 (0.00%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 9 (0.00%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Serious adverse events | | | |
| Part I - nCPAP - SAF | | | |
| Part II - 200 mg/kg nebulised Curosurf® - SAF | | | |
| Part II - 400 mg/kg nebulised Curosurf® - SAF | | | |
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 2 / 9 (22.22%) | 8 / 42 (19.05%) | 3 / 41 (7.32%) |

| | | | |
|---|----------------|----------------|----------------|
| number of deaths (all causes) | 0 | 0 | 1 |
| number of deaths resulting from adverse events | 0 | 0 | 1 |
| Vascular disorders | | | |
| Neonatal hypotension | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 42 (0.00%) | 1 / 41 (2.44%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Cardiopulmonary failure | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 42 (0.00%) | 1 / 41 (2.44%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Nervous system disorders | | | |
| Intraventricular haemorrhage neonatal | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 1 / 42 (2.38%) | 0 / 41 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebral haemorrhage neonatal | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 42 (0.00%) | 0 / 41 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Necrotising enterocolitis neonatal | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 0 / 42 (0.00%) | 1 / 41 (2.44%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neonatal gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 2 / 42 (4.76%) | 0 / 41 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Meconium ileus | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 1 / 42 (2.38%) | 0 / 41 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---------------|----------------|----------------|
| Respiratory, thoracic and mediastinal disorders | | | |
| Pneumothorax | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 3 / 42 (7.14%) | 0 / 41 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary haemorrhage | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 42 (0.00%) | 0 / 41 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Neonatal infection | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 1 / 42 (2.38%) | 0 / 41 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sepsis neonatal | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 1 / 42 (2.38%) | 0 / 41 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Septic shock | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 42 (0.00%) | 0 / 41 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 42 (0.00%) | 1 / 41 (2.44%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------------|--|--|
| Serious adverse events | Part II - nCPAP - SAF | | |
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 5 / 43 (11.63%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |
| Vascular disorders | | | |
| Neonatal hypotension | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Cardiopulmonary failure | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Intraventricular haemorrhage neonatal | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cerebral haemorrhage neonatal | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Necrotising enterocolitis neonatal | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Neonatal gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Meconium ileus | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pneumothorax | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pulmonary haemorrhage | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Neonatal infection | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sepsis neonatal | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Septic shock | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metabolism and nutrition disorders | | | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| Non-serious adverse events | Part I - 200 mg/kg nebulised Curosurf® - SAF | Part I - 400 mg/kg nebulised Curosurf® - SAF | Part I - 600 mg/kg nebulised Curosurf® - SAF |
|---|--|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 9 / 9 (100.00%) | 9 / 9 (100.00%) | 9 / 9 (100.00%) |
| Vascular disorders | | | |
| Neonatal hypotension | | | |

| | | | |
|---|--|--|---|
| subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 0 / 9 (0.00%) 0 | 0 / 9 (0.00%) 0 |
| Pregnancy, puerperium and perinatal conditions Jaundice neonatal subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 4 / 9 (44.44%) 5 | 4 / 9 (44.44%) 4 |
| General disorders and administration site conditions Catheter site discharge subjects affected / exposed occurrences (all) Oedema peripheral subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 0 / 9 (0.00%) 0 | 1 / 9 (11.11%) 1 0 / 9 (0.00%) 0 | 0 / 9 (0.00%) 0 0 / 9 (0.00%) 0 |
| Respiratory, thoracic and mediastinal disorders Bronchopulmonary dysplasia subjects affected / exposed occurrences (all) Infantile apnoea subjects affected / exposed occurrences (all) Neonatal hypoxia subjects affected / exposed occurrences (all) Neonatal respiratory failure subjects affected / exposed occurrences (all) Pulmonary congestion subjects affected / exposed occurrences (all) Rhinorrhoea subjects affected / exposed occurrences (all) Neonatal tachypnoea subjects affected / exposed occurrences (all) | 1 / 9 (11.11%) 1 0 / 9 (0.00%) 0 0 / 9 (0.00%) 0 4 / 9 (44.44%) 4 0 / 9 (0.00%) 0 0 / 9 (0.00%) 0 0 / 9 (0.00%) 0 | 1 / 9 (11.11%) 1 1 / 9 (11.11%) 2 1 / 9 (11.11%) 3 6 / 9 (66.67%) 8 0 / 9 (0.00%) 0 0 / 9 (0.00%) 0 0 / 9 (0.00%) 0 | 1 / 9 (11.11%) 1 2 / 9 (22.22%) 2 1 / 9 (11.11%) 1 5 / 9 (55.56%) 5 0 / 9 (0.00%) 0 2 / 9 (22.22%) 2 0 / 9 (0.00%) 0 |

| | | | |
|--------------------------------------|----------------|----------------|----------------|
| Psychiatric disorders | | | |
| Selective eating disorder | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 0 / 9 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Investigations | | | |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 0 / 9 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 1 / 9 (11.11%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Blood iron decreased | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 0 / 9 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Blood phosphorus decreased | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 1 / 9 (11.11%) | 2 / 9 (22.22%) |
| occurrences (all) | 2 | 1 | 2 |
| Blood potassium decreased | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 0 / 9 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| C-reactive protein increased | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 2 / 9 (22.22%) | 1 / 9 (11.11%) |
| occurrences (all) | 0 | 2 | 1 |
| Cardiac murmur | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 9 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Haematocrit decreased | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 9 (0.00%) | 1 / 9 (11.11%) |
| occurrences (all) | 0 | 0 | 2 |
| Haemoglobin decreased | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 1 / 9 (11.11%) | 2 / 9 (22.22%) |
| occurrences (all) | 0 | 1 | 2 |
| PCO2 increased | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 9 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Platelet count decreased | | | |

| | | | |
|---|---------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 1 / 9 (11.11%) 1 | 0 / 9 (0.00%) 0 |
| Congenital, familial and genetic disorders | | | |
| Atrial septal defect subjects affected / exposed occurrences (all) | 1 / 9 (11.11%) 1 | 0 / 9 (0.00%) 0 | 1 / 9 (11.11%) 1 |
| Congenital infection subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 0 / 9 (0.00%) 0 | 0 / 9 (0.00%) 0 |
| Congenital pneumonia subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 0 / 9 (0.00%) 0 | 1 / 9 (11.11%) 1 |
| Patent ductus arteriosus subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 1 / 9 (11.11%) 1 | 2 / 9 (22.22%) 4 |
| Cardiac disorders | | | |
| Bradycardia neonatal subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 0 / 9 (0.00%) 0 | 1 / 9 (11.11%) 1 |
| Neonatal tachycardia subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 0 / 9 (0.00%) 0 | 1 / 9 (11.11%) 1 |
| Nervous system disorders | | | |
| Cerebral cyst subjects affected / exposed occurrences (all) | 1 / 9 (11.11%) 1 | 0 / 9 (0.00%) 0 | 0 / 9 (0.00%) 0 |
| Intraventricular haemorrhage neonatal subjects affected / exposed occurrences (all) | 2 / 9 (22.22%) 2 | 0 / 9 (0.00%) 0 | 1 / 9 (11.11%) 1 |
| Blood and lymphatic system disorders | | | |
| Anaemia neonatal subjects affected / exposed occurrences (all) | 2 / 9 (22.22%) 2 | 3 / 9 (33.33%) 4 | 0 / 9 (0.00%) 0 |
| Coagulopathy subjects affected / exposed occurrences (all) | 1 / 9 (11.11%) 1 | 0 / 9 (0.00%) 0 | 0 / 9 (0.00%) 0 |

| | | | |
|------------------------------------|----------------|----------------|----------------|
| Eye disorders | | | |
| Cataract | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 1 / 9 (11.11%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Retinopathy of prematurity | | | |
| subjects affected / exposed | 2 / 9 (22.22%) | 0 / 9 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Gastrointestinal disorders | | | |
| Abdominal distension | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 9 (0.00%) | 2 / 9 (22.22%) |
| occurrences (all) | 0 | 0 | 3 |
| Constipation | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 2 / 9 (22.22%) | 2 / 9 (22.22%) |
| occurrences (all) | 0 | 3 | 3 |
| Gastric haemorrhage | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 9 (0.00%) | 1 / 9 (11.11%) |
| occurrences (all) | 0 | 0 | 1 |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 9 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Infantile vomiting | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 9 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Meconium ileus | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 0 / 9 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Necrotising enterocolitis neonatal | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 9 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Umbilical hernia | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 1 / 9 (11.11%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hepatobiliary disorders | | | |
| Hyperbilirubinaemia neonatal | | | |
| subjects affected / exposed | 5 / 9 (55.56%) | 1 / 9 (11.11%) | 3 / 9 (33.33%) |
| occurrences (all) | 5 | 1 | 3 |
| Renal and urinary disorders | | | |

| | | | |
|--|---------------------|---------------------|---------------------|
| Oliguria subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 0 / 9 (0.00%) 0 | 0 / 9 (0.00%) 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Hypotonia neonatal subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 1 / 9 (11.11%) 1 | 0 / 9 (0.00%) 0 |
| Osteopenia subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 1 / 9 (11.11%) 1 | 0 / 9 (0.00%) 0 |
| Infections and infestations | | | |
| Cellulitis subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 0 / 9 (0.00%) 0 | 0 / 9 (0.00%) 0 |
| Conjunctivitis subjects affected / exposed occurrences (all) | 1 / 9 (11.11%) 1 | 2 / 9 (22.22%) 3 | 1 / 9 (11.11%) 2 |
| Conjunctivitis bacterial subjects affected / exposed occurrences (all) | 1 / 9 (11.11%) 1 | 0 / 9 (0.00%) 0 | 0 / 9 (0.00%) 0 |
| Neonatal infection subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 0 / 9 (0.00%) 0 | 0 / 9 (0.00%) 0 |
| Neonatal pneumonia subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 1 / 9 (11.11%) 1 | 0 / 9 (0.00%) 0 |
| Ophthalmia neonatorum subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 0 / 9 (0.00%) 0 | 0 / 9 (0.00%) 0 |
| Pneumonia viral subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 1 / 9 (11.11%) 1 | 0 / 9 (0.00%) 0 |
| Rhinitis subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 1 / 9 (11.11%) 1 | 0 / 9 (0.00%) 0 |
| Sepsis neonatal | | | |

| | | | |
|------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 4 / 9 (44.44%) | 0 / 9 (0.00%) | 2 / 9 (22.22%) |
| occurrences (all) | 5 | 0 | 2 |
| Skin infection | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 9 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Staphylococcal sepsis | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 9 (0.00%) | 1 / 9 (11.11%) |
| occurrences (all) | 0 | 0 | 1 |
| Staphylococcal skin infection | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 9 (0.00%) | 1 / 9 (11.11%) |
| occurrences (all) | 0 | 0 | 1 |
| Metabolism and nutrition disorders | | | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 9 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hyperkalaemia | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 1 / 9 (11.11%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hypernatraemia | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 0 / 9 (0.00%) | 1 / 9 (11.11%) |
| occurrences (all) | 1 | 0 | 1 |
| Hypoglycaemia neonatal | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 9 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypokalaemia | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 9 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hyponatraemia | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 1 / 9 (11.11%) | 1 / 9 (11.11%) |
| occurrences (all) | 0 | 1 | 2 |
| Metabolic acidosis | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 2 / 9 (22.22%) | 1 / 9 (11.11%) |
| occurrences (all) | 0 | 2 | 1 |
| Neonatal hypocalcaemia | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 1 / 9 (11.11%) | 1 / 9 (11.11%) |
| occurrences (all) | 0 | 1 | 1 |

| | | | |
|--|--------------------|--------------------|--------------------|
| Neonatal hyponatraemia subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 0 / 9 (0.00%) 0 | 0 / 9 (0.00%) 0 |
|--|--------------------|--------------------|--------------------|

| Non-serious adverse events | Part I - nCPAP - SAF | Part II - 200 mg/kg nebulised Curosurf® - SAF | Part II - 400 mg/kg nebulised Curosurf® - SAF |
|---|---|---|---|
| Total subjects affected by non-serious adverse events subjects affected / exposed | 9 / 9 (100.00%) | 38 / 42 (90.48%) | 33 / 41 (80.49%) |
| Vascular disorders Neonatal hypotension subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 3 / 42 (7.14%) 4 | 4 / 41 (9.76%) 4 |
| Pregnancy, puerperium and perinatal conditions Jaundice neonatal subjects affected / exposed occurrences (all) | 4 / 9 (44.44%) 4 | 17 / 42 (40.48%) 19 | 17 / 41 (41.46%) 26 |
| General disorders and administration site conditions Catheter site discharge subjects affected / exposed occurrences (all) Oedema peripheral subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 2 / 9 (22.22%) 2 | 0 / 42 (0.00%) 0 0 / 42 (0.00%) 0 | 0 / 41 (0.00%) 0 0 / 41 (0.00%) 0 |
| Respiratory, thoracic and mediastinal disorders Bronchopulmonary dysplasia subjects affected / exposed occurrences (all) Infantile apnoea subjects affected / exposed occurrences (all) Neonatal hypoxia subjects affected / exposed occurrences (all) Neonatal respiratory failure subjects affected / exposed occurrences (all) Pulmonary congestion | 0 / 9 (0.00%) 0 2 / 9 (22.22%) 3 2 / 9 (22.22%) 3 7 / 9 (77.78%) 7 | 7 / 42 (16.67%) 7 11 / 42 (26.19%) 15 7 / 42 (16.67%) 9 0 / 42 (0.00%) 0 | 6 / 41 (14.63%) 6 6 / 41 (14.63%) 11 4 / 41 (9.76%) 4 0 / 41 (0.00%) 0 |

| | | | |
|--------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 9 (11.11%) | 0 / 42 (0.00%) | 0 / 41 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Rhinorrhoea | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 42 (0.00%) | 0 / 41 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Neonatal tachypnoea | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 1 / 42 (2.38%) | 3 / 41 (7.32%) |
| occurrences (all) | 0 | 1 | 3 |
| Psychiatric disorders | | | |
| Selective eating disorder | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 42 (0.00%) | 0 / 41 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Investigations | | | |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 42 (0.00%) | 1 / 41 (2.44%) |
| occurrences (all) | 0 | 0 | 1 |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 42 (0.00%) | 2 / 41 (4.88%) |
| occurrences (all) | 0 | 0 | 2 |
| Blood iron decreased | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 0 / 42 (0.00%) | 0 / 41 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Blood phosphorus decreased | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 0 / 42 (0.00%) | 0 / 41 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Blood potassium decreased | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 42 (0.00%) | 0 / 41 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| C-reactive protein increased | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 42 (0.00%) | 1 / 41 (2.44%) |
| occurrences (all) | 0 | 0 | 2 |
| Cardiac murmur | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 1 / 42 (2.38%) | 3 / 41 (7.32%) |
| occurrences (all) | 0 | 1 | 3 |
| Haematocrit decreased | | | |

| | | | |
|--|---------------------|----------------------|----------------------|
| subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 0 / 42 (0.00%) 0 | 0 / 41 (0.00%) 0 |
| Haemoglobin decreased subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 0 / 42 (0.00%) 0 | 0 / 41 (0.00%) 0 |
| PCO2 increased subjects affected / exposed occurrences (all) | 1 / 9 (11.11%) 1 | 0 / 42 (0.00%) 0 | 0 / 41 (0.00%) 0 |
| Platelet count decreased subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 0 / 42 (0.00%) 0 | 0 / 41 (0.00%) 0 |
| Congenital, familial and genetic disorders | | | |
| Atrial septal defect subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 0 / 42 (0.00%) 0 | 1 / 41 (2.44%) 1 |
| Congenital infection subjects affected / exposed occurrences (all) | 1 / 9 (11.11%) 1 | 0 / 42 (0.00%) 0 | 0 / 41 (0.00%) 0 |
| Congenital pneumonia subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 0 / 42 (0.00%) 0 | 0 / 41 (0.00%) 0 |
| Patent ductus arteriosus subjects affected / exposed occurrences (all) | 2 / 9 (22.22%) 2 | 5 / 42 (11.90%) 5 | 6 / 41 (14.63%) 6 |
| Cardiac disorders | | | |
| Bradycardia neonatal subjects affected / exposed occurrences (all) | 1 / 9 (11.11%) 1 | 2 / 42 (4.76%) 2 | 0 / 41 (0.00%) 0 |
| Neonatal tachycardia subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 0 / 42 (0.00%) 0 | 1 / 41 (2.44%) 1 |
| Nervous system disorders | | | |
| Cerebral cyst subjects affected / exposed occurrences (all) | 1 / 9 (11.11%) 1 | 0 / 42 (0.00%) 0 | 0 / 41 (0.00%) 0 |
| Intraventricular haemorrhage neonatal | | | |

| | | | |
|--|--------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 1 / 42 (2.38%) 1 | 1 / 41 (2.44%) 1 |
| Blood and lymphatic system disorders | | | |
| Anaemia neonatal | | | |
| subjects affected / exposed | 3 / 9 (33.33%) | 9 / 42 (21.43%) | 5 / 41 (12.20%) |
| occurrences (all) | 4 | 17 | 8 |
| Coagulopathy | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 42 (0.00%) | 0 / 41 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Eye disorders | | | |
| Cataract | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 42 (0.00%) | 0 / 41 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Retinopathy of prematurity | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 1 / 42 (2.38%) | 0 / 41 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Gastrointestinal disorders | | | |
| Abdominal distension | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 42 (0.00%) | 1 / 41 (2.44%) |
| occurrences (all) | 0 | 0 | 1 |
| Constipation | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 0 / 42 (0.00%) | 0 / 41 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Gastric haemorrhage | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 42 (0.00%) | 0 / 41 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 2 / 9 (22.22%) | 1 / 42 (2.38%) | 0 / 41 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Infantile vomiting | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 1 / 42 (2.38%) | 3 / 41 (7.32%) |
| occurrences (all) | 1 | 1 | 3 |
| Meconium ileus | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 1 / 42 (2.38%) | 0 / 41 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Necrotising enterocolitis neonatal | | | |

| | | | |
|---|---------------------|----------------------|---------------------|
| subjects affected / exposed occurrences (all) | 1 / 9 (11.11%) 1 | 0 / 42 (0.00%) 0 | 0 / 41 (0.00%) 0 |
| Umbilical hernia subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 1 / 42 (2.38%) 1 | 0 / 41 (0.00%) 0 |
| Hepatobiliary disorders Hyperbilirubinaemia neonatal subjects affected / exposed occurrences (all) | 1 / 9 (11.11%) 1 | 6 / 42 (14.29%) 6 | 2 / 41 (4.88%) 2 |
| Renal and urinary disorders Oliguria subjects affected / exposed occurrences (all) | 1 / 9 (11.11%) 1 | 1 / 42 (2.38%) 1 | 1 / 41 (2.44%) 1 |
| Musculoskeletal and connective tissue disorders Hypotonia neonatal subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 0 / 42 (0.00%) 0 | 0 / 41 (0.00%) 0 |
| Osteopenia subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 3 / 42 (7.14%) 3 | 0 / 41 (0.00%) 0 |
| Infections and infestations Cellulitis subjects affected / exposed occurrences (all) | 1 / 9 (11.11%) 1 | 0 / 42 (0.00%) 0 | 0 / 41 (0.00%) 0 |
| Conjunctivitis subjects affected / exposed occurrences (all) | 1 / 9 (11.11%) 1 | 0 / 42 (0.00%) 0 | 0 / 41 (0.00%) 0 |
| Conjunctivitis bacterial subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 2 / 42 (4.76%) 2 | 1 / 41 (2.44%) 1 |
| Neonatal infection subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 6 / 42 (14.29%) 6 | 3 / 41 (7.32%) 4 |
| Neonatal pneumonia subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 1 / 42 (2.38%) 1 | 0 / 41 (0.00%) 0 |

| | | | |
|------------------------------------|----------------|-----------------|----------------|
| Ophthalmia neonatorum | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 3 / 42 (7.14%) | 1 / 41 (2.44%) |
| occurrences (all) | 0 | 4 | 1 |
| Pneumonia viral | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 42 (0.00%) | 0 / 41 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rhinitis | | | |
| subjects affected / exposed | 2 / 9 (22.22%) | 0 / 42 (0.00%) | 0 / 41 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Sepsis neonatal | | | |
| subjects affected / exposed | 2 / 9 (22.22%) | 6 / 42 (14.29%) | 3 / 41 (7.32%) |
| occurrences (all) | 4 | 7 | 3 |
| Skin infection | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 0 / 42 (0.00%) | 0 / 41 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Staphylococcal sepsis | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 1 / 42 (2.38%) | 1 / 41 (2.44%) |
| occurrences (all) | 0 | 1 | 1 |
| Staphylococcal skin infection | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 42 (0.00%) | 0 / 41 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Metabolism and nutrition disorders | | | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 0 / 42 (0.00%) | 4 / 41 (9.76%) |
| occurrences (all) | 1 | 0 | 5 |
| Hyperkalaemia | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 1 / 42 (2.38%) | 1 / 41 (2.44%) |
| occurrences (all) | 0 | 1 | 1 |
| Hypernatraemia | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 42 (0.00%) | 2 / 41 (4.88%) |
| occurrences (all) | 0 | 0 | 2 |
| Hypoglycaemia neonatal | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 2 / 42 (4.76%) | 0 / 41 (0.00%) |
| occurrences (all) | 1 | 3 | 0 |
| Hypokalaemia | | | |

| | | | |
|-----------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 9 (11.11%) | 1 / 42 (2.38%) | 2 / 41 (4.88%) |
| occurrences (all) | 1 | 2 | 2 |
| Hyponatraemia | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 0 / 42 (0.00%) | 0 / 41 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Metabolic acidosis | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 3 / 42 (7.14%) | 4 / 41 (9.76%) |
| occurrences (all) | 0 | 4 | 5 |
| Neonatal hypocalcaemia | | | |
| subjects affected / exposed | 2 / 9 (22.22%) | 3 / 42 (7.14%) | 2 / 41 (4.88%) |
| occurrences (all) | 2 | 3 | 2 |
| Neonatal hyponatraemia | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 2 / 42 (4.76%) | 2 / 41 (4.88%) |
| occurrences (all) | 1 | 2 | 3 |

| | | | |
|---|-----------------------|--|--|
| Non-serious adverse events | Part II - nCPAP - SAF | | |
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 40 / 43 (93.02%) | | |
| Vascular disorders | | | |
| Neonatal hypotension | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences (all) | 0 | | |
| Pregnancy, puerperium and perinatal conditions | | | |
| Jaundice neonatal | | | |
| subjects affected / exposed | 27 / 43 (62.79%) | | |
| occurrences (all) | 34 | | |
| General disorders and administration site conditions | | | |
| Catheter site discharge | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences (all) | 0 | | |
| Oedema peripheral | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences (all) | 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |

| | | | |
|--|----------------------|--|--|
| Bronchopulmonary dysplasia subjects affected / exposed occurrences (all) | 4 / 43 (9.30%) 4 | | |
| Infantile apnoea subjects affected / exposed occurrences (all) | 4 / 43 (9.30%) 8 | | |
| Neonatal hypoxia subjects affected / exposed occurrences (all) | 5 / 43 (11.63%) 5 | | |
| Neonatal respiratory failure subjects affected / exposed occurrences (all) | 0 / 43 (0.00%) 0 | | |
| Pulmonary congestion subjects affected / exposed occurrences (all) | 0 / 43 (0.00%) 0 | | |
| Rhinorrhoea subjects affected / exposed occurrences (all) | 0 / 43 (0.00%) 0 | | |
| Neonatal tachypnoea subjects affected / exposed occurrences (all) | 2 / 43 (4.65%) 2 | | |
| Psychiatric disorders Selective eating disorder subjects affected / exposed occurrences (all) | 0 / 43 (0.00%) 0 | | |
| Investigations Blood alkaline phosphatase increased subjects affected / exposed occurrences (all) | 0 / 43 (0.00%) 0 | | |
| Blood bilirubin increased subjects affected / exposed occurrences (all) | 0 / 43 (0.00%) 0 | | |
| Blood iron decreased subjects affected / exposed occurrences (all) | 0 / 43 (0.00%) 0 | | |
| Blood phosphorus decreased | | | |

| | | | |
|--|----------------|--|--|
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |
| Blood potassium decreased | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |
| C-reactive protein increased | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |
| Cardiac murmur | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences (all) | 0 | | |
| Haematocrit decreased | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences (all) | 0 | | |
| Haemoglobin decreased | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |
| PCO2 increased | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences (all) | 0 | | |
| Platelet count decreased | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences (all) | 0 | | |
| Congenital, familial and genetic disorders | | | |
| Atrial septal defect | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences (all) | 0 | | |
| Congenital infection | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences (all) | 0 | | |
| Congenital pneumonia | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences (all) | 0 | | |
| Patent ductus arteriosus | | | |

| | | | |
|--|----------------------|--|--|
| subjects affected / exposed occurrences (all) | 8 / 43 (18.60%) 8 | | |
| Cardiac disorders | | | |
| Bradycardia neonatal | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences (all) | 0 | | |
| Neonatal tachycardia | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |
| Nervous system disorders | | | |
| Cerebral cyst | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences (all) | 0 | | |
| Intraventricular haemorrhage neonatal | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences (all) | 0 | | |
| Blood and lymphatic system disorders | | | |
| Anaemia neonatal | | | |
| subjects affected / exposed | 5 / 43 (11.63%) | | |
| occurrences (all) | 7 | | |
| Coagulopathy | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences (all) | 0 | | |
| Eye disorders | | | |
| Cataract | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences (all) | 0 | | |
| Retinopathy of prematurity | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |
| Gastrointestinal disorders | | | |
| Abdominal distension | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences (all) | 0 | | |
| Constipation | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences (all) | 0 | | |
| Gastric haemorrhage | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |
| Infantile vomiting | | | |
| subjects affected / exposed | 6 / 43 (13.95%) | | |
| occurrences (all) | 6 | | |
| Meconium ileus | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences (all) | 0 | | |
| Necrotising enterocolitis neonatal | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |
| Umbilical hernia | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hepatobiliary disorders | | | |
| Hyperbilirubinaemia neonatal | | | |
| subjects affected / exposed | 6 / 43 (13.95%) | | |
| occurrences (all) | 6 | | |
| Renal and urinary disorders | | | |
| Oliguria | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Hypotonia neonatal | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences (all) | 0 | | |
| Osteopenia | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |
| Infections and infestations | | | |

| | | | |
|-------------------------------|-----------------|--|--|
| Cellulitis | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |
| Conjunctivitis | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences (all) | 0 | | |
| Conjunctivitis bacterial | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences (all) | 0 | | |
| Neonatal infection | | | |
| subjects affected / exposed | 7 / 43 (16.28%) | | |
| occurrences (all) | 9 | | |
| Neonatal pneumonia | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences (all) | 0 | | |
| Ophthalmia neonatorum | | | |
| subjects affected / exposed | 6 / 43 (13.95%) | | |
| occurrences (all) | 6 | | |
| Pneumonia viral | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences (all) | 0 | | |
| Rhinitis | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences (all) | 0 | | |
| Sepsis neonatal | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |
| Skin infection | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences (all) | 0 | | |
| Staphylococcal sepsis | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences (all) | 0 | | |
| Staphylococcal skin infection | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences (all) | 0 | | |

| | | | |
|------------------------------------|----------------|--|--|
| Metabolism and nutrition disorders | | | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 2 | | |
| Hyperkalaemia | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hypernatraemia | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |
| Hypoglycaemia neonatal | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hypokalaemia | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hyponatraemia | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences (all) | 0 | | |
| Metabolic acidosis | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |
| Neonatal hypocalcaemia | | | |
| subjects affected / exposed | 4 / 43 (9.30%) | | |
| occurrences (all) | 4 | | |
| Neonatal hyponatraemia | | | |
| subjects affected / exposed | 2 / 43 (4.65%) | | |
| occurrences (all) | 2 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 10 November 2017 | A global and substantial amendment (protocol version 2.0, dated 01 August 2017) clarified the following: <ol style="list-style-type: none">1. Section 3.1.1: Change in stopping rules and addition of plan to disseminate safety data among study sites, as per UK-specific protocol version 1.1;2. Section 3.3: Change in the definition of end of trial;3. Section 6: Alignment of the protocol with the nebuliser instructions for use;4. Section 7: Timing to perform BPD assessment to be aligned with the BPD definition;5. Addition of mean blood pressure (MBP) recording. |
| 30 April 2018 | A global and substantial amendment (protocol version 3.0, dated 08 February 2018) clarified the following: <ol style="list-style-type: none">1. Section 5.1: Change in concomitant medications recording instructions;2. Sections 10.1 and 10.8: Change in recording of AEs;3. Section 7.1.2: Cerebral echography to be additionally performed within 6 hours from randomisation/start of nebulisation;4. Blood gas analysis: Better clarification of sampling time points;5. Neonates with 26+0 to 27+6 weeks gestational age were removed from the study population. All protocol sections were impacted. |
| 24 January 2019 | A global and substantial amendment (protocol version 4.0, dated 16 November 2018) clarified the following: <ol style="list-style-type: none">1. Sections 3, 6 and 7: inclusion of re-dosing when indicated;2. Sections 8 and 9: addition of efficacy and safety parameters related to re-dosing;3. Section 10: clarifications for AE recording;4. Section 12: statistical analysis updated in line with changes in Sections 8 and 9. Hierarchical testing defined. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date | Interruption | Restart date |
|---------------|---|---------------|
| 24 March 2020 | Recruitment was halted as of 24 March 2020 due to the COVID-19 emergency. | 23 April 2020 |
| 23 April 2020 | A notification of permanent recruitment stop was submitted on 23 April 2020 following the ISMB recommendation to stop the study. This recommendation was based on the evaluation of the safety profile of the first 120 randomised neonates in Part II of the study as there was a change in the benefit-risk balance driven by a negligible efficacy profile. The study was considered as terminated early because the planned sample size of 252 neonates was not reached. The last visit of the last enrolled patient was held on 05 May 2020. | - |

Notes:

Limitations and caveats

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

| |
|---|
| The early termination of Part II of the study led to a smaller sample size analysed than originally foreseen (120 neonates v the 252 neonates planned). |
|---|

Notes: