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.

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	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Pregnancy, puerperium and perinatal conditions			
Jaundice neonatal			
subjects affected / exposed	0 / 9 (0.00%)	4 / 9 (44.44%)	4 / 9 (44.44%)
occurrences (all)	0	5	4
General disorders and administration site conditions			
Catheter site discharge			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Oedema peripheral			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Bronchopulmonary dysplasia			
subjects affected / exposed	1 / 9 (11.11%)	1 / 9 (11.11%)	1 / 9 (11.11%)
occurrences (all)	1	1	1
Infantile apnoea			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	2 / 9 (22.22%)
occurrences (all)	0	2	2
Neonatal hypoxia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	1 / 9 (11.11%)
occurrences (all)	0	3	1
Neonatal respiratory failure			
subjects affected / exposed	4 / 9 (44.44%)	6 / 9 (66.67%)	5 / 9 (55.56%)
occurrences (all)	4	8	5
Pulmonary congestion			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Rhinorrhoea			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	2 / 9 (22.22%)
occurrences (all)	0	0	2
Neonatal tachypnoea			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	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	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Congenital, familial and genetic disorders			
Atrial septal defect			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	1	0	1
Congenital infection			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Congenital pneumonia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Patent ductus arteriosus			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	2 / 9 (22.22%)
occurrences (all)	0	1	4
Cardiac disorders			
Bradycardia neonatal			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Neonatal tachycardia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Nervous system disorders			
Cerebral cyst			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Intraventricular haemorrhage neonatal			
subjects affected / exposed	2 / 9 (22.22%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	2	0	1
Blood and lymphatic system disorders			
Anaemia neonatal			
subjects affected / exposed	2 / 9 (22.22%)	3 / 9 (33.33%)	0 / 9 (0.00%)
occurrences (all)	2	4	0
Coagulopathy			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	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	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Hypotonia neonatal			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Osteopenia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Conjunctivitis			
subjects affected / exposed	1 / 9 (11.11%)	2 / 9 (22.22%)	1 / 9 (11.11%)
occurrences (all)	1	3	2
Conjunctivitis bacterial			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Neonatal infection			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Neonatal pneumonia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Ophthalmia neonatorum			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Pneumonia viral			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Rhinitis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	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	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	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	0 / 9 (0.00%)	3 / 42 (7.14%)	4 / 41 (9.76%)
occurrences (all)	0	4	4
Pregnancy, puerperium and perinatal conditions			
Jaundice neonatal			
subjects affected / exposed	4 / 9 (44.44%)	17 / 42 (40.48%)	17 / 41 (41.46%)
occurrences (all)	4	19	26
General disorders and administration site conditions			
Catheter site discharge			
subjects affected / exposed	0 / 9 (0.00%)	0 / 42 (0.00%)	0 / 41 (0.00%)
occurrences (all)	0	0	0
Oedema peripheral			
subjects affected / exposed	2 / 9 (22.22%)	0 / 42 (0.00%)	0 / 41 (0.00%)
occurrences (all)	2	0	0
Respiratory, thoracic and mediastinal disorders			
Bronchopulmonary dysplasia			
subjects affected / exposed	0 / 9 (0.00%)	7 / 42 (16.67%)	6 / 41 (14.63%)
occurrences (all)	0	7	6
Infantile apnoea			
subjects affected / exposed	2 / 9 (22.22%)	11 / 42 (26.19%)	6 / 41 (14.63%)
occurrences (all)	3	15	11
Neonatal hypoxia			
subjects affected / exposed	2 / 9 (22.22%)	7 / 42 (16.67%)	4 / 41 (9.76%)
occurrences (all)	3	9	4
Neonatal respiratory failure			
subjects affected / exposed	7 / 9 (77.78%)	0 / 42 (0.00%)	0 / 41 (0.00%)
occurrences (all)	7	0	0
Pulmonary congestion			

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

subjects affected / exposed	0 / 9 (0.00%)	1 / 42 (2.38%)	1 / 41 (2.44%)
occurrences (all)	0	1	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	1 / 9 (11.11%)	0 / 42 (0.00%)	0 / 41 (0.00%)
occurrences (all)	1	0	0
Umbilical hernia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 42 (2.38%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Hepatobiliary disorders			
Hyperbilirubinaemia neonatal			
subjects affected / exposed	1 / 9 (11.11%)	6 / 42 (14.29%)	2 / 41 (4.88%)
occurrences (all)	1	6	2
Renal and urinary disorders			
Oliguria			
subjects affected / exposed	1 / 9 (11.11%)	1 / 42 (2.38%)	1 / 41 (2.44%)
occurrences (all)	1	1	1
Musculoskeletal and connective tissue disorders			
Hypotonia neonatal			
subjects affected / exposed	0 / 9 (0.00%)	0 / 42 (0.00%)	0 / 41 (0.00%)
occurrences (all)	0	0	0
Osteopenia			
subjects affected / exposed	0 / 9 (0.00%)	3 / 42 (7.14%)	0 / 41 (0.00%)
occurrences (all)	0	3	0
Infections and infestations			
Cellulitis			
subjects affected / exposed	1 / 9 (11.11%)	0 / 42 (0.00%)	0 / 41 (0.00%)
occurrences (all)	1	0	0
Conjunctivitis			
subjects affected / exposed	1 / 9 (11.11%)	0 / 42 (0.00%)	0 / 41 (0.00%)
occurrences (all)	1	0	0
Conjunctivitis bacterial			
subjects affected / exposed	0 / 9 (0.00%)	2 / 42 (4.76%)	1 / 41 (2.44%)
occurrences (all)	0	2	1
Neonatal infection			
subjects affected / exposed	0 / 9 (0.00%)	6 / 42 (14.29%)	3 / 41 (7.32%)
occurrences (all)	0	6	4
Neonatal pneumonia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 42 (2.38%)	0 / 41 (0.00%)
occurrences (all)	0	1	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	8 / 43 (18.60%)		
occurrences (all)	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 occurrences (all)	0 / 43 (0.00%) 0		
Gastric haemorrhage subjects affected / exposed occurrences (all)	1 / 43 (2.33%) 1		
Gastrooesophageal reflux disease subjects affected / exposed occurrences (all)	1 / 43 (2.33%) 1		
Infantile vomiting subjects affected / exposed occurrences (all)	6 / 43 (13.95%) 6		
Meconium ileus subjects affected / exposed occurrences (all)	0 / 43 (0.00%) 0		
Necrotising enterocolitis neonatal subjects affected / exposed occurrences (all)	1 / 43 (2.33%) 1		
Umbilical hernia subjects affected / exposed occurrences (all)	0 / 43 (0.00%) 0		
Hepatobiliary disorders Hyperbilirubinaemia neonatal subjects affected / exposed occurrences (all)	6 / 43 (13.95%) 6		
Renal and urinary disorders Oliguria subjects affected / exposed occurrences (all)	1 / 43 (2.33%) 1		
Musculoskeletal and connective tissue disorders Hypotonia neonatal subjects affected / exposed occurrences (all)	0 / 43 (0.00%) 0		
Osteopenia subjects affected / exposed occurrences (all)	1 / 43 (2.33%) 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: 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: 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: 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: