



Clinical trial results:

A Multicenter, Randomized, Open-Label, Controlled Trial to Assess the Safety and Tolerability of Lucinactant for Inhalation in Preterm Neonates 26 to 28 Weeks PMA.

Summary

EudraCT number	2015-005624-26
Trial protocol	PL
Global end of trial date	09 July 2017

Results information

Result version number	v1
This version publication date	27 October 2022
First version publication date	27 October 2022
Summary attachment (see zip file)	03-CL-1401 CSR Version 1.0 FINAL (03-CL-1401 CSR Version 1.0 FINAL.pdf)

Trial information

Trial identification

Sponsor protocol code	03-CL-1401
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02528318
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Windtree Therapeutics, Inc.
Sponsor organisation address	2600 Kelly Road, Warrington, United States, 18976
Public contact	Steven G. Simonson, MD, MS, Windtree Therapeutics, Inc., +1 (215) 488-9300, psimmons@windtreetx.com
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Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	01 November 2017
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	09 July 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to evaluate the safety and tolerability of lucinactant for inhalation, administered as an aerosolized dose in 4 escalating doses to preterm, neonates 26 to 28 completed weeks PMA with receiving nCPAP for RDS compared with neonates receiving nCPAP alone.

Protection of trial subjects:

A Safety Review Committee was established to review safety data for this study. SRC was formed to evaluate the degree of risk involved in study subject participation within each dosing group to determine if study continuation in accordance with the current protocol held the potential to institute any undue harm, or threat to the safety and welfare of study subjects.

After all active subject within Dosing Group 1 completed Study Day 7, a safety assessment (AEs incl. ADEs, SAEs and additional safety endpoints) was performed. Dosing was allowed to continue to the next higher dosing group (ie. Dosing Group II) immediately following completion of enrollment within the current dosing group. The SRC provided recommendations following their review of the safety data. This process of continuing to the next higher dosing group and reviewing safety and tolerability was to be continued for the 100 and 150mg TPL/kg group. Subject were followed for safety evaluations until the subject were 36 weeks PMA or were discharged. A final visit occurred at 36 weeks PMA or at time of discharge or withdrawal for all subjects.

Background therapy:

Standard of care (nCPAP alone)

Evidence for comparator: -

Actual start date of recruitment	01 October 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 5
Country: Number of subjects enrolled	Canada: 16
Country: Number of subjects enrolled	Chile: 1
Country: Number of subjects enrolled	United States: 26
Worldwide total number of subjects	48
EEA total number of subjects	5

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	48
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: -

Pre-assignment

Screening details:

- 1.Signed ICF from legally representative
- 2.Gestational age 26 to 28 weeks PMA
3. Implementation of controlled nCPAP within 90min after birth
- 4.Spontaneous breathing
- 5.Chest radiograph consistent with RDS
- 6.Within first 20hours after birth, required nCPAP of 5-6cm H₂O and FiO₂ of 0,25-0,50 that was clinically indicated for min. 30mins

Period 1

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

Blinding implementation details:

This study was an open-label study to determine the safety and tolerability of lucinactant for inhalation. No blinding or masking procedures were implemented.

Arms

Are arms mutually exclusive?	Yes
Arm title	50mg/kg

Arm description:

Lucinactant for inhalation 50 mg total phospholipids (TPL)/kg with nCPAP (drug-device combination product)

1 repeat dose allowed if repeat dosing criteria are met.

Arm type	Experimental
Investigational medicinal product name	Lucinactant for inhalation
Investigational medicinal product code	
Other name	AEROSURF®
Pharmaceutical forms	Nebuliser suspension
Routes of administration	Inhalation use

Dosage and administration details:

50 mg TPL/kg administered over 30 minutes in conjunction with nCPAP.

1 Repeat dose of 50 mg TPL/kg administered was allowed if repeat dosing criteria were met

Arm title	75mg/kg
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Arm description:

Lucinactant inhalation 75 mg TPL/kg with nCPAP (drug-device combination product)

1 repeat dose allowed if repeat dosing criteria are met

Arm type	Experimental
Investigational medicinal product name	Lucinactant for inhalation
Investigational medicinal product code	
Other name	AEROSURF®
Pharmaceutical forms	Nebuliser suspension
Routes of administration	Inhalation use

Dosage and administration details:

75 mg TPL/kg administered over 45 minutes in conjunction with nCPAP

1 repeat dose of 75 mg TPL/kg was allowed if repeat dosing criteria are met

Arm title	100 mg/kg
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Arm description:

Lucinactant for inhalation 100mg TPL/kg with nCPAP (drug-device combination product)
1 repeat dosing will be allowed if repeat criteria are met.

Arm type	Experimental
Investigational medicinal product name	Lucinactant for inhalation
Investigational medicinal product code	
Other name	AEROSURF®
Pharmaceutical forms	Nebuliser suspension
Routes of administration	Inhalation use

Dosage and administration details:

100 mg TPL/kg administered over 60 minutes in conjunction with nCPAP
1 repeat dose ok 100 mg TPL/kg was allowed if repeat dosing criteria are met

Arm title	nCPAP only
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Arm description:

nCPAP therapy alone

Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 1	50mg/kg	75mg/kg	100 mg/kg
Started	8	8	8
Completed	8	8	8

Number of subjects in period 1	nCPAP only
Started	24
Completed	24

Baseline characteristics

Reporting groups

Reporting group title	50mg/kg
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Reporting group description:

Lucinactant for inhalation 50 mg total phospholipids (TPL)/kg with nCPAP (drug-device combination product)

1 repeat dose allowed if repeat dosing criteria are met.

Reporting group title	75mg/kg
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Reporting group description:

Lucinactant inhalation 75 mg TPL/kg with nCPAP (drug-device combination product)

1 repeat dose allowed if repeat dosing criteria are met

Reporting group title	100 mg/kg
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Reporting group description:

Lucinactant for inhalation 100mg TPL/kg with nCPAP (drug-device combination product)

1 repeat dosing will be allowed if repeat criteria are met.

Reporting group title	nCPAP only
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Reporting group description:

nCPAP therapy alone

Reporting group values	50mg/kg	75mg/kg	100 mg/kg
Number of subjects	8	8	8
Age categorical			
Units: Subjects			
<=18 years	8	8	8
Between 18 and 65 years	0	0	0
>=65 years	0	0	0
Gender categorical			
Units: Subjects			
Female	3	5	5
Male	5	3	3
Ethnicity			
Units: Subjects			
Hispanic or Latino	3	1	2
Not Hispanic or Latino	5	7	6
Unknown or not reported	0	0	0
Race			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	2	0	1
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	1	1	2
White	3	5	4
More than one race	0	0	0
Unknown or Not Reported	2	2	1
Region of Enrollment			
Units: Subjects			
Canada	1	3	4
United States	7	3	4

Poland	0	2	0
Chile	0	0	0

Gestational age			
Gestational age, based on obstetrician's best estimate			
Units: Weeks			
arithmetic mean	27.6	27.2	27.2
standard deviation	± 0.61	± 1.06	± 0.84
Birth Weight			
Units: gram(s)			
arithmetic mean	1052	855	839
standard deviation	± 174.7	± 84.6	± 224.9
Apgar Score at One Minute			
The Apgar Score measures a baby's health by assessing five characteristics (Appearance, Pulse, Grimace, Activity, and Respiration) . Each of the five characteristics are scored from 0 to 2, and the five scores are summed for the Apgar Score. Thus, the Apgar Score ranges from 0 (worst) to 10 (best), and scores over 7 indicate a baby in good health. Apgar Scores are performed at 1 minute and 5 minutes after birth.			
Units: Scores on a scale			
arithmetic mean	5.4	5.5	6.4
full range (min-max)	2 to 9	2 to 8	3 to 8
Apgar Score at Five Minutes			
The Apgar Score measures a baby's health by assessing five characteristics (Appearance, Pulse, Grimace, Activity, and Respiration) . Each of the five characteristics are scored from 0 to 2, and the five scores are summed for the Apgar Score. Thus, the Apgar Score ranges from 0 (worst) to 10 (best), and scores over 7 indicate a baby in good health. Apgar Scores are performed at 1 minute and 5 minutes after birth.			
Units: Scores on a scale			
arithmetic mean	7.8	6.4	8.1
full range (min-max)	7 to 9	1 to 9	6 to 9

Reporting group values	nCPAP only	Total	
Number of subjects	24	48	
Age categorical			
Units: Subjects			
≤18 years	24	48	
Between 18 and 65 years	0	0	
>=65 years	0	0	
Gender categorical			
Units: Subjects			
Female	8	21	
Male	16	27	
Ethnicity			
Units: Subjects			
Hispanic or Latino	7	13	
Not Hispanic or Latino	17	35	
Unknown or not reported	0	0	
Race			
Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	1	4	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	1	5	

White	20	32	
More than one race	0	0	
Unknown or Not Reported	2	7	
Region of Enrollment			
Units: Subjects			
Canada	8	16	
United States	12	26	
Poland	3	5	
Chile	1	1	
Gestational age			
Gestational age, based on obstetrician's best estimate			
Units: Weeks			
arithmetic mean	27.5		
standard deviation	± 0.76	-	
Birth Weight			
Units: gram(s)			
arithmetic mean	1005		
standard deviation	± 238.8	-	
Apgar Score at One Minute			
The Apgar Score measures a baby's health by assessing five characteristics (Appearance, Pulse, Grimace, Activity, and Respiration) . Each of the five characteristics are scored from 0 to 2, and the five scores are summed for the Apgar Score. Thus, the Apgar Score ranges from 0 (worst) to 10 (best), and scores over 7 indicate a baby in good health. Apgar Scores are performed at 1 minute and 5 minutes after birth.			
Units: Scores on a scale			
arithmetic mean	5.8		
full range (min-max)	1 to 9	-	
Apgar Score at Five Minutes			
The Apgar Score measures a baby's health by assessing five characteristics (Appearance, Pulse, Grimace, Activity, and Respiration) . Each of the five characteristics are scored from 0 to 2, and the five scores are summed for the Apgar Score. Thus, the Apgar Score ranges from 0 (worst) to 10 (best), and scores over 7 indicate a baby in good health. Apgar Scores are performed at 1 minute and 5 minutes after birth.			
Units: Scores on a scale			
arithmetic mean	7.9		
full range (min-max)	5 to 9	-	

End points

End points reporting groups

Reporting group title	50mg/kg
Reporting group description: Lucinactant for inhalation 50 mg total phospholipids (TPL)/kg with nCPAP (drug-device combination product) 1 repeat dose allowed if repeat dosing criteria are met.	
Reporting group title	75mg/kg
Reporting group description: Lucinactant inhalation 75 mg TPL/kg with nCPAP (drug-device combination product) 1 repeat dose allowed if repeat dosing criteria are met	
Reporting group title	100 mg/kg
Reporting group description: Lucinactant for inhalation 100mg TPL/kg with nCPAP (drug-device combination product) 1 repeat dosing will be allowed if repeat criteria are met.	
Reporting group title	nCPAP only
Reporting group description: nCPAP therapy alone	

Primary: Number of Participants With Peri-Dosing Adverse Events - Initial Dose

End point title	Number of Participants With Peri-Dosing Adverse Events - Initial Dose ^[1]
End point description: Number of Participants with adverse events that were experienced during the initial study treatment Peri-dosing events are events that occur during study treatment. Since this was an open-label study, no peri-dosing events were recorded for nCPAP alone. Any adverse events that occurred during the corresponding time for nCPAP alone were recorded as adverse events but not peri-dosing events.	
End point type	Primary
End point timeframe: Randomization to 24 Hours Post Randomization	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Because no a priori statistical analyses were conducted in this study, no statistical analysis have been specified

End point values	50mg/kg	75mg/kg	100 mg/kg	nCPAP only
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	8	8	24 ^[2]
Units: Participants				
number (not applicable)				
Bradycardia	0	2	1	0
Desaturation	1	2	3	0
Gagging/regurgitation	0	0	0	0
Apnea	1	1	1	0
Pallor	0	0	0	0

Notes:

[2] - There was no dosing in this group (no intervention, standard of care)

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Air Leak

End point title	Number of Participants With Air Leak ^[3]
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End point description:

Number of participants with air leak (includes pneumothorax, pulmonary interstitial emphysema (PIE), pneumomediastinum, pneumopericardium, subcutaneous emphysema)

This dose-escalation study was terminated after completion of the 100 mg/kg group for administrative purposes. No participants were enrolled in the 150 mg/kg group or received 150 mg/kg.

End point type	Primary
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End point timeframe:

7 days

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Because no a priori statistical analyses were conducted in this study, no statistical analysis have been specified

End point values	50mg/kg	75mg/kg	100 mg/kg	nCPAP only
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	8	8	24
Units: Participants				
number (not applicable)	3	0	2	4

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Worsening of Respiratory Status Criteria

End point title	Number of Participants With Worsening of Respiratory Status Criteria
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End point description:

Number of participants with worsening in one of 12 respiratory status criteria through 72 hours post randomization (need for additional surfactant therapy, desaturation < 80%, heart rate < 100 bpm, sustained fraction of inspired oxygen (FiO₂) > 0.50, arterial carbon dioxide (PCO₂) > 65 mmHg, sustained apnea, persistent arterial pH < 7.2, intubation for any reason, nCPAP > 7 cmH₂O, initiation of intermittent positive pressure ventilation, death, principal investigator determination of worsening status).

Intent-to-treat population.

This dose-escalation study was terminated after completion of the 100 mg/kg group for administrative purposes. No participants were enrolled in the 150 mg/kg group or received 150 mg/kg.

End point type	Secondary
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End point timeframe:

Randomization to 72 Hours Post Randomization

End point values	50mg/kg	75mg/kg	100 mg/kg	nCPAP only
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	8	8	24
Units: Participants				
number (not applicable)	6	7	6	18

Statistical analyses

No statistical analyses for this end point

Secondary: Bronchopulmonary Dysplasia

End point title	Bronchopulmonary Dysplasia
End point description:	
Number of participants with bronchopulmonary dysplasia (BPD) and number of participants alive and without BPD at 36 weeks post-menstrual age (PMA)	
This dose-escalation study was terminated after completion of the 100 mg/kg group for administrative purposes. No participants were enrolled in the 150 mg/kg group or received 150 mg/kg.	
End point type	Secondary
End point timeframe:	
Randomization to 36 weeks PMA	

End point values	50mg/kg	75mg/kg	100 mg/kg	nCPAP only
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	8	8	24
Units: Participants				
number (not applicable)				
BPD	0	0	0	6
Alive and without BPD	7	7	8	18

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Nasal Continuous Positive Airway Pressure (nCPAP) Failure

End point title	Number of Participants With Nasal Continuous Positive Airway Pressure (nCPAP) Failure
End point description:	
Participants who required intubation for mechanical ventilation or surfactant administration were defined as having failed nCPAP.	
This dose-escalation study was terminated after completion of the 100 mg/kg group for administrative purposes. No participants were enrolled in the 150 mg/kg group or received 150 mg/kg.	
End point type	Secondary
End point timeframe:	
Randomization to 72 Hours Post Randomization	

End point values	50mg/kg	75mg/kg	100 mg/kg	nCPAP only
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	8	8	24
Units: Participants				
number (not applicable)	5	7	5	16

Statistical analyses

No statistical analyses for this end point

Secondary: Death

End point title	Death
End point description:	Number of participants who died during the study. This dose-escalation study was terminated after completion of the 100 mg/kg group for administrative purposes. No participants were enrolled in the 150 mg/kg group or received 150 mg/kg.
End point type	Secondary
End point timeframe:	Randomization to 36 weeks PMA

End point values	50mg/kg	75mg/kg	100 mg/kg	nCPAP only
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	8	8	24
Units: Participants				
number (not applicable)	1	1	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: FiO2

End point title	FiO2
End point description:	Observed and change from baseline measurements for fraction of inspired oxygen (FiO2). Values represent the amount (fraction) of oxygen in the air the participant inspires; the values themselves do not have units. The normal amount of oxygen in air ("room air") is 21%, or 0.21. This dose-escalation study was terminated after completion of the 100 mg/kg group for administrative purposes. No participants were enrolled in the 150 mg/kg group or received 150 mg/kg.
Safety population	
End point type	Secondary

End point timeframe:

Randomization to 72 hours post randomization

End point values	50mg/kg	75mg/kg	100 mg/kg	nCPAP only
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	8	8	24
Units: Fraction of oxygen in inspired air				
arithmetic mean (standard deviation)				
Baseline (Randomization)	0.31 (± 0.058)	0.33 (± 0.071)	0.37 (± 0.072)	0.32 (± 0.061)
60 minutes post randomization - observed	0.31 (± 0.064)	0.35 (± 0.063)	0.37 (± 0.090)	0.34 (± 0.159)
60 minutes post randomization - change from baseline	0.01 (± 0.010)	0.02 (± 0.024)	0.01 (± 0.044)	0.01 (± 0.162)
3 hours post randomization - observed	0.37 (± 0.191)	0.37 (± 0.120)	0.37 (± 0.107)	0.29 (± 0.082)
3 hours post randomization - change from baseline	0.06 (± 0.154)	0.00 (± 0.066)	0.00 (± 0.047)	-0.03 (± 0.082)
12 hours post randomization - observed	0.30 (± 0.114)	0.30 (± 0.117)	0.30 (± 0.068)	0.33 (± 0.181)
12 hours post randomization - change from baseline	-0.02 (± 0.137)	-0.07 (± 0.074)	-0.08 (± 0.090)	0.00 (± 0.172)
24 hours post randomization - observed	0.28 (± 0.093)	0.25 (± 0.044)	0.28 (± 0.077)	0.29 (± 0.143)
24 hours post randomization - change from baseline	-0.03 (± 0.072)	-0.09 (± 0.046)	-0.08 (± 0.105)	-0.04 (± 0.140)
48 hours post randomization - observed	0.28 (± 0.058)	0.24 (± 0.038)	0.23 (± 0.071)	0.31 (± 0.188)
48 hours post randomization - change from baseline	-0.03 (± 0.083)	-0.09 (± 0.075)	-0.09 (± 0.091)	-0.02 (± 0.191)
72 hours post randomization - observed	0.3 (± 0.105)	0.23 (± 0.023)	0.25 (± 0.050)	0.27 (± 0.119)
72 hours post randomisation - change from baseline	-0.02 (± 0.133)	-0.10 (± 0.071)	-0.12 (± 0.066)	-0.05 (± 0.133)

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Complications of Prematurity

End point title	Number of Participants With Complications of Prematurity
End point description:	Number of participants with pre-specified common complications of prematurity. The study was terminated after completion of the 100 mg/kg group for administrative purposes. No participants were enrolled in the 150mg/kg group or received a 150mg/kg dose. Safety population.
End point type	Secondary
End point timeframe:	Randomization to 36 weeks PMA

End point values	50mg/kg	75mg/kg	100 mg/kg	nCPAP only
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	8	8	24
Units: Participants				
number (not applicable)				
Subject with any complication	8	7	7	22
Acquired sepsis	2	2	2	5
Apnea	8	5	6	19
Cystic Periventricular Leukomalacia	0	0	0	1
Patent Ductus Arteriosus	3	3	4	10
Pulmonary Hemorrhage	1	0	1	1
Intraventricular Hemorrhage	0	1	3	4
Necrotizing Enterocolitis	1	1	1	1
Retinopathy of Prematurity	2	1	1	9

Statistical analyses

No statistical analyses for this end point

Other pre-specified: nCPAP Failure Without Treatment Interruptions

End point title	nCPAP Failure Without Treatment Interruptions
End point description:	Number of subjects requiring mechanical ventilation or surfactant administration (nCPAP failure) but did not have a treatment interruption The study was terminated after completion of the 100 mg/kg group for administrative purposes. No participants were enrolled in the 150 mg/kg group.
End point type	Other pre-specified
End point timeframe:	Randomization to 72 Hours Post Randomization

End point values	50mg/kg	75mg/kg	100 mg/kg	nCPAP only
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	3	6	24
Units: Participants				
number (not applicable)	4	3	3	16

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From randomization to 36 weeks PMA

Adverse event reporting additional description:

This dose-escalation study was terminated after completion of the 100 mg/kg group for administrative purposes. No participants were enrolled in the 150 mg/kg group or received 150 mg/kg.

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	18.1
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Reporting groups

Reporting group title	50 mg/kg
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Reporting group description:

Lucinactant for inhalation 50 mg TPL/kg with nCPAP

1 repeat dose allowed if repeat dosing criteria are met.

Lucinactant for inhalation: Lucinactant for inhalation refers to the active investigational agent, lucinactant, in combination with the investigational delivery device (drug-device combination product)

Reporting group title	75 mg/kg
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Reporting group description:

Lucinactant for inhalation 75 mg TPL/kg with nCPAP

1 repeat dose allowed if repeat dosing criteria are met.

Lucinactant for inhalation: Lucinactant for inhalation refers to the active investigational agent, lucinactant, in combination with the investigational delivery device (drug-device combination product)

Reporting group title	100 mg/kg
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Reporting group description:

Lucinactant for inhalation 100 mg TPL/kg with nCPAP

1 repeat dose allowed if repeat dosing criteria are met.

Lucinactant for inhalation: Lucinactant for inhalation refers to the active investigational agent, lucinactant, in combination with the investigational delivery device (drug-device combination product)

Reporting group title	nCPAP alone
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Reporting group description:

nCPAP therapy alone

Serious adverse events	50 mg/kg	75 mg/kg	100 mg/kg
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 8 (50.00%)	3 / 8 (37.50%)	2 / 8 (25.00%)
number of deaths (all causes)	1	1	0
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Hepatic haemorrhage			

subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (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
Laryngeal injury	Additional description: Laryngeal trauma due to intubation		
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (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
Traumatic liver injury	Additional description: Liver laceration		
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (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
Vascular disorders			
Shock	Additional description: refractory shock		
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (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			
Cardiac arrest			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (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
Cardio-respiratory arrest			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (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
Pregnancy, puerperium and perinatal conditions			
Intraventricular haemorrhage neonatal			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	2 / 8 (25.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Necrotising enterocolitis neonatal			

subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Neonatal respiratory distress syndrome			
subjects affected / exposed	0 / 8 (0.00%)	2 / 8 (25.00%)	0 / 8 (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
Neonatal respiratory failure			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 8 (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
Blood and lymphatic system disorders			
Anaemia neonatal			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (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			
Gastric perforation			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (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
Intestinal perforation			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumoperitoneum			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Respiratory, thoracic and mediastinal disorders			
Apnoea neonatal			

subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (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 respiratory failure			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (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
Pneumothorax			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 8 (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	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	nCPAP alone		
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 24 (25.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Hepatic haemorrhage			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Laryngeal injury	Additional description: Laryngeal trauma due to intubation		

subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Traumatic liver injury			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Shock			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardio-respiratory arrest			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pregnancy, puerperium and perinatal conditions			
Intraventricular haemorrhage neonatal			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Necrotising enterocolitis neonatal			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neonatal respiratory distress syndrome			

subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neonatal respiratory failure			
subjects affected / exposed	0 / 24 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia neonatal			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Gastric perforation			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intestinal perforation			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumoperitoneum			
subjects affected / exposed	0 / 24 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Apnoea neonatal			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neonatal respiratory failure			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Pneumothorax subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	2 / 24 (8.33%) 0 / 2 0 / 0		
Infections and infestations Pneumonia subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 24 (4.17%) 0 / 1 0 / 0		
Sepsis neonatal subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 24 (0.00%) 0 / 0 0 / 0		

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

Non-serious adverse events	50 mg/kg	75 mg/kg	100 mg/kg
Total subjects affected by non-serious adverse events subjects affected / exposed	8 / 8 (100.00%)	8 / 8 (100.00%)	8 / 8 (100.00%)
Vascular disorders Haemangioma subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	1 / 8 (12.50%) 1	0 / 8 (0.00%) 0
Hypertension subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0
Hypotension subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1	2 / 8 (25.00%) 2	0 / 8 (0.00%) 0
Pregnancy, puerperium and perinatal conditions Agitation neonatal subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0	1 / 8 (12.50%) 1
Bradycardia neonatal			

subjects affected / exposed	0 / 8 (0.00%)	5 / 8 (62.50%)	3 / 8 (37.50%)
occurrences (all)	0	7	5
Fixed bowel loop			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Intraventricular haemorrhage neonatal			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	1 / 8 (12.50%)
occurrences (all)	0	1	1
Jaundice neonatal			
subjects affected / exposed	5 / 8 (62.50%)	3 / 8 (37.50%)	1 / 8 (12.50%)
occurrences (all)	5	3	1
Necrotising enterocolitis neonatal			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	1 / 8 (12.50%)
occurrences (all)	0	1	1
Neonatal respiratory distress syndrome			
subjects affected / exposed	1 / 8 (12.50%)	2 / 8 (25.00%)	2 / 8 (25.00%)
occurrences (all)	1	2	3
Periventricular haemorrhage neonatal			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Retinopathy of prematurity			
subjects affected / exposed	2 / 8 (25.00%)	1 / 8 (12.50%)	1 / 8 (12.50%)
occurrences (all)	2	1	1
Small for dates baby			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Endotracheal intubation complication			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Face oedema			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Hypothermia			

subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Oedema			
subjects affected / exposed	3 / 8 (37.50%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	3	0	0
Pain			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Pyrexia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Apnoea neonatal			
subjects affected / exposed	7 / 8 (87.50%)	4 / 8 (50.00%)	6 / 8 (75.00%)
occurrences (all)	7	5	9
Bronchopulmonary dysplasia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Chronic respiratory failure			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Hypercapnia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Nasal discomfort			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Nasal inflammation			
subjects affected / exposed	2 / 8 (25.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	3	0	0
Nasal mucosal ulcer			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Neonatal respiratory failure			

subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0
Neonatal tachypnoea subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1	0 / 8 (0.00%) 0	1 / 8 (12.50%) 1
Pneumothorax subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0
Pulmonary haemorrhage subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0	1 / 8 (12.50%) 1
Pulmonary hypertension subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0
Pulmonary interstitial emphysema syndrome subjects affected / exposed occurrences (all)	3 / 8 (37.50%) 3	0 / 8 (0.00%) 0	1 / 8 (12.50%) 1
Pulmonary oedema neonatal subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	1 / 8 (12.50%) 1	0 / 8 (0.00%) 0
Respiratory acidosis subjects affected / exposed occurrences (all)	2 / 8 (25.00%) 2	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0
Respiratory alkalosis subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0
Respiratory tract haemorrhage subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0	1 / 8 (12.50%) 1
Investigations			
Anticonvulsant drug level above therapeutic subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0
Blood urea increased			

subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0
Cardiac murmur subjects affected / exposed occurrences (all)	2 / 8 (25.00%) 2	1 / 8 (12.50%) 1	0 / 8 (0.00%) 0
Coagulation time prolonged subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0	1 / 8 (12.50%) 1
Neutrophil count increased subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0
Oxygen saturation decreased subjects affected / exposed occurrences (all)	2 / 8 (25.00%) 3	4 / 8 (50.00%) 6	6 / 8 (75.00%) 11
PO2 increased subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0
Reticulocyte count increased subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0
Injury, poisoning and procedural complications			
Blister alternative assessment type: Systematic subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0
Ear abrasion subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	1 / 8 (12.50%) 1	0 / 8 (0.00%) 0
Infusion site extravasation subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0
Laceration subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0
Skin abrasion			

subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0
Tracheal injury subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	1 / 8 (12.50%) 1	0 / 8 (0.00%) 0
Congenital, familial and genetic disorders			
Atrial septal defect subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	1 / 8 (12.50%) 1	1 / 8 (12.50%) 1
Cardiac septal defect subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0
Hydrocele subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0
Patent ductus arteriosus subjects affected / exposed occurrences (all)	3 / 8 (37.50%) 3	3 / 8 (37.50%) 3	4 / 8 (50.00%) 4
Cardiac disorders			
Arrhythmia subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0
Tachycardia subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	1 / 8 (12.50%) 1	1 / 8 (12.50%) 1
Nervous system disorders			
Hypotonia subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0
Lethargy subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0
Periventricular leukomalacia subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0
Seizure			

subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0
Blood and lymphatic system disorders			
Anaemia neonatal subjects affected / exposed occurrences (all)	6 / 8 (75.00%) 6	4 / 8 (50.00%) 6	2 / 8 (25.00%) 2
Bandaemia subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0
Coagulopathy subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0
Leukocystosis subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0
Leukopenia subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0
Neutropenia subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0
Thrombocytopenia subjects affected / exposed occurrences (all)	2 / 8 (25.00%) 2	2 / 8 (25.00%) 2	0 / 8 (0.00%) 0
Thrombocytosis subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0
Gastrointestinal disorders			
Abdominal distension subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0
Abdominal pain subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0
Constipation			

subjects affected / exposed	5 / 8 (62.50%)	0 / 8 (0.00%)	1 / 8 (12.50%)
occurrences (all)	13	0	1
Gastric haemorrhage			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Gastric hypomotility			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal hypomotility			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Haematemesis			
subjects affected / exposed	2 / 8 (25.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	2	0	0
Inguinal hernia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Salivary hypersecretion			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Umbilical hernia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	1 / 8 (12.50%)
occurrences (all)	0	1	1
Vomiting			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Hepatobiliary disorders			
Cholestasis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Gallbladder disorder			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0

<p>Skin and subcutaneous tissue disorders</p> <p>Dermatitis diaper</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>4 / 8 (50.00%)</p> <p>5</p>	<p>2 / 8 (25.00%)</p> <p>2</p>	<p>1 / 8 (12.50%)</p> <p>1</p>
<p>Rash</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>0 / 8 (0.00%)</p> <p>0</p>	<p>0 / 8 (0.00%)</p> <p>0</p>	<p>0 / 8 (0.00%)</p> <p>0</p>
<p>Renal and urinary disorders</p> <p>Azotaemia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Haematuria</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Oliguria</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Renal failure</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>0 / 8 (0.00%)</p> <p>0</p>	<p>0 / 8 (0.00%)</p> <p>0</p> <p>0 / 8 (0.00%)</p> <p>0</p> <p>1 / 8 (12.50%)</p> <p>1</p> <p>0 / 8 (0.00%)</p> <p>0</p>	<p>0 / 8 (0.00%)</p> <p>0</p> <p>0 / 8 (0.00%)</p> <p>0</p> <p>0 / 8 (0.00%)</p> <p>0</p>
<p>Endocrine disorders</p> <p>Adrenal insufficiency</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>0 / 8 (0.00%)</p> <p>0</p>	<p>0 / 8 (0.00%)</p> <p>0</p>	<p>0 / 8 (0.00%)</p> <p>0</p>
<p>Infections and infestations</p> <p>Bacteraemia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Bacterial disease carrier</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Conjunctivitis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Enterococcal sepsis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>0 / 8 (0.00%)</p> <p>0</p>	<p>1 / 8 (12.50%)</p> <p>1</p> <p>0 / 8 (0.00%)</p> <p>0</p> <p>0 / 8 (0.00%)</p> <p>0</p>	<p>0 / 8 (0.00%)</p> <p>0</p> <p>2 / 8 (25.00%)</p> <p>2</p> <p>0 / 8 (0.00%)</p> <p>0</p> <p>0 / 8 (0.00%)</p> <p>0</p>

Fungal skin infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Nosocomial infection			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Pneumonia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Pneumonia klebsiella			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Pneumonia staphylococcal			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Sepsis neonatal			
subjects affected / exposed	1 / 8 (12.50%)	1 / 8 (12.50%)	1 / 8 (12.50%)
occurrences (all)	1	1	1
Septic shock			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Urinary tract infection			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Urinary tract infection enterococcal			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Urosepsis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Electrolyte imbalance			

subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Feeding intolerance			
subjects affected / exposed	3 / 8 (37.50%)	1 / 8 (12.50%)	1 / 8 (12.50%)
occurrences (all)	3	1	1
Fluid retention			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Hypercalcaemia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Hyperchloraemia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Hyperglycaemia			
subjects affected / exposed	1 / 8 (12.50%)	2 / 8 (25.00%)	0 / 8 (0.00%)
occurrences (all)	1	2	0
Hyperkalaemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Hypermagnesaemia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Hypernatraemia			
subjects affected / exposed	1 / 8 (12.50%)	2 / 8 (25.00%)	0 / 8 (0.00%)
occurrences (all)	1	2	0
Hypertriglyceridaemia			
subjects affected / exposed	1 / 8 (12.50%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	1	1	0
Hypoalbuminaemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Hypocalcaemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Hypochloraemia			

subjects affected / exposed	2 / 8 (25.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	2	1	0
Hypokalaemia			
subjects affected / exposed	0 / 8 (0.00%)	2 / 8 (25.00%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Hypomagnesaemia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Hyponatraemia			
subjects affected / exposed	3 / 8 (37.50%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	3	0	0
Hypophosphataemia			
subjects affected / exposed	2 / 8 (25.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	2	0	0
Hypovolaemia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Metabolic acidosis			
subjects affected / exposed	3 / 8 (37.50%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	3	0	0
Metabolic alkalosis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Osteopenia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Vitamin D deficiency			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Hypoglycaemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	nCPAP alone		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 24 (100.00%)		

Vascular disorders			
Haemangioma			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Hypertension			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Hypotension			
subjects affected / exposed	4 / 24 (16.67%)		
occurrences (all)	7		
Pregnancy, puerperium and perinatal conditions			
Agitation neonatal			
subjects affected / exposed	0 / 24 (0.00%)		
occurrences (all)	0		
Bradycardia neonatal			
subjects affected / exposed	9 / 24 (37.50%)		
occurrences (all)	9		
Fixed bowel loop			
subjects affected / exposed	0 / 24 (0.00%)		
occurrences (all)	0		
Intraventricular haemorrhage neonatal			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Jaundice neonatal			
subjects affected / exposed	11 / 24 (45.83%)		
occurrences (all)	12		
Necrotising enterocolitis neonatal			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Neonatal respiratory distress syndrome			
subjects affected / exposed	9 / 24 (37.50%)		
occurrences (all)	12		
Periventricular haemorrhage neonatal			

<p>subjects affected / exposed occurrences (all)</p> <p>Retinopathy of prematurity subjects affected / exposed occurrences (all)</p> <p>Small for dates baby subjects affected / exposed occurrences (all)</p>	<p>1 / 24 (4.17%) 1</p> <p>9 / 24 (37.50%) 9</p> <p>1 / 24 (4.17%) 1</p>		
<p>General disorders and administration site conditions</p> <p>Endotracheal intubation complication subjects affected / exposed occurrences (all)</p> <p>Face oedema subjects affected / exposed occurrences (all)</p> <p>Hypothermia subjects affected / exposed occurrences (all)</p> <p>Oedema subjects affected / exposed occurrences (all)</p> <p>Pain alternative assessment type: Systematic subjects affected / exposed occurrences (all)</p> <p>Pyrexia subjects affected / exposed occurrences (all)</p>	<p>1 / 24 (4.17%) 1</p> <p>0 / 24 (0.00%) 0</p> <p>2 / 24 (8.33%) 2</p> <p>1 / 24 (4.17%) 1</p> <p>0 / 24 (0.00%) 0</p> <p>1 / 24 (4.17%) 1</p>		
<p>Respiratory, thoracic and mediastinal disorders</p> <p>Apnoea neonatal subjects affected / exposed occurrences (all)</p> <p>Bronchopulmonary dysplasia subjects affected / exposed occurrences (all)</p>	<p>19 / 24 (79.17%) 21</p> <p>7 / 24 (29.17%) 8</p>		

Chronic respiratory failure subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0		
Hypercapnia subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 4		
Nasal discomfort subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1		
Nasal inflammation subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 2		
Nasal mucosal ulcer subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0		
Neonatal respiratory failure subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1		
Neonatal tachypnoea subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 3		
Pneumothorax subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1		
Pulmonary haemorrhage subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1		
Pulmonary hypertension subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1		
Pulmonary interstitial emphysema syndrome subjects affected / exposed occurrences (all)	3 / 24 (12.50%) 3		
Pulmonary oedema neonatal			

subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 2		
Respiratory acidosis subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 2		
Respiratory alkalosis subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 2		
Respiratory tract haemorrhage subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0		
Investigations			
Anticonvulsant drug level above therapeutic subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1		
Blood urea increased subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1		
Cardiac murmur subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1		
Coagulation time prolonged subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0		
Neutrophil count increased subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1		
Oxygen saturation decreased subjects affected / exposed occurrences (all)	9 / 24 (37.50%) 11		
PO2 increased subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1		
Reticulocyte count increased			

subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1		
Injury, poisoning and procedural complications			
Blister			
alternative assessment type: Systematic			
subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0		
Ear abrasion			
subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0		
Infusion site extravasation			
subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1		
Laceration			
subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0		
Skin abrasion			
subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1		
Tracheal injury			
subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0		
Congenital, familial and genetic disorders			
Atrial septal defect			
subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0		
Cardiac septal defect			
subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1		
Hydrocele			
subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1		
Patent ductus arteriosus			
subjects affected / exposed occurrences (all)	10 / 24 (41.67%) 10		

<p>Cardiac disorders</p> <p>Arrhythmia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Tachycardia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 24 (4.17%)</p> <p>1</p> <p>0 / 24 (0.00%)</p> <p>0</p>		
<p>Nervous system disorders</p> <p>Hypotonia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Lethargy</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Periventricular leukomalacia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Seizure</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>0 / 24 (0.00%)</p> <p>0</p> <p>0 / 24 (0.00%)</p> <p>0</p> <p>1 / 24 (4.17%)</p> <p>1</p> <p>1 / 24 (4.17%)</p> <p>2</p>		
<p>Blood and lymphatic system disorders</p> <p>Anaemia neonatal</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Bandaemia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Coagulopathy</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Leukocystosis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Leukopenia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Neutropenia</p>	<p>12 / 24 (50.00%)</p> <p>16</p> <p>1 / 24 (4.17%)</p> <p>1</p> <p>1 / 24 (4.17%)</p> <p>1</p> <p>1 / 24 (4.17%)</p> <p>1</p> <p>2 / 24 (8.33%)</p> <p>2</p>		

subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1		
Thrombocytopenia subjects affected / exposed occurrences (all)	4 / 24 (16.67%) 4		
Thrombocytosis subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1		
Gastrointestinal disorders			
Abdominal distension subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1		
Abdominal pain subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1		
Constipation subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 2		
Gastric haemorrhage subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0		
Gastric hypomotility subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0		
Gastrointestinal hypomotility subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0		
Gastrooesophageal reflux disease subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0		
Haematemesis subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0		
Inguinal hernia subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 2		

Salivary hypersecretion subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0		
Umbilical hernia subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0		
Vomiting subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1		
Hepatobiliary disorders Cholestasis subjects affected / exposed occurrences (all)	3 / 24 (12.50%) 3		
Gallbladder disorder subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1		
Skin and subcutaneous tissue disorders Dermatitis diaper subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1		
Rash subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 2		
Renal and urinary disorders Azotaemia subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1		
Haematuria subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1		
Oliguria subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 2		
Renal failure subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 3		
Endocrine disorders			

Adrenal insufficiency subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1		
Infections and infestations			
Bacteraemia subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1		
Bacterial disease carrier subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0		
Conjunctivitis subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1		
Enterococcal sepsis subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1		
Fungal skin infection subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1		
Nosocomial infection subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0		
Pneumonia subjects affected / exposed occurrences (all)	3 / 24 (12.50%) 3		
Pneumonia klebsiella subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1		
Pneumonia staphylococcal subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1		
Sepsis neonatal subjects affected / exposed occurrences (all)	4 / 24 (16.67%) 4		
Septic shock			

subjects affected / exposed	0 / 24 (0.00%)		
occurrences (all)	0		
Urinary tract infection			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	2		
Urinary tract infection enterococcal			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Urosepsis			
subjects affected / exposed	0 / 24 (0.00%)		
occurrences (all)	0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 24 (0.00%)		
occurrences (all)	0		
Electrolyte imbalance			
subjects affected / exposed	0 / 24 (0.00%)		
occurrences (all)	0		
Feeding intolerance			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Fluid retention			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Hypercalcaemia			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Hyperchloraemia			
subjects affected / exposed	3 / 24 (12.50%)		
occurrences (all)	3		
Hyperglycaemia			
subjects affected / exposed	3 / 24 (12.50%)		
occurrences (all)	5		
Hyperkalaemia			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		

Hypermagnesaemia			
subjects affected / exposed	0 / 24 (0.00%)		
occurrences (all)	0		
Hypernatraemia			
subjects affected / exposed	4 / 24 (16.67%)		
occurrences (all)	5		
Hypertriglyceridaemia			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	3		
Hypoalbuminaemia			
subjects affected / exposed	3 / 24 (12.50%)		
occurrences (all)	3		
Hypocalcaemia			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Hypochloraemia			
subjects affected / exposed	3 / 24 (12.50%)		
occurrences (all)	4		
Hypokalaemia			
subjects affected / exposed	3 / 24 (12.50%)		
occurrences (all)	4		
Hypomagnesaemia			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Hyponatraemia			
subjects affected / exposed	7 / 24 (29.17%)		
occurrences (all)	7		
Hypophosphataemia			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Hypovolaemia			
subjects affected / exposed	0 / 24 (0.00%)		
occurrences (all)	0		
Metabolic acidosis			
subjects affected / exposed	5 / 24 (20.83%)		
occurrences (all)	5		

Metabolic alkalosis			
subjects affected / exposed	0 / 24 (0.00%)		
occurrences (all)	0		
Osteopenia			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Vitamin D deficiency			
subjects affected / exposed	0 / 24 (0.00%)		
occurrences (all)	0		
Hypoglycaemia			
subjects affected / exposed	3 / 24 (12.50%)		
occurrences (all)	3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 September 2015	<p>Rationale for protocol amendment</p> <ul style="list-style-type: none">- additional requirement of meeting criteria at treatment initiation added- additional clarification on repeat dose- typo corrections- clarification of "completion of study"- SRC approval not required to advance to next dosing level- repeat dosing criteria changed- concomitant medications - additional clarifications added- supplement to the instruction for ADP returns- clarification of when SRC meeting would be held following a death- clarification of peri-dosing events

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
09 July 2017	<p>The sponsor of study 03-CL-1401, Windtree Therapeutics, Inc. has made a decision to terminate the dose-escalation study early after the completion of enrollment into Dose Group 3 3. It was anticipated 64 subjects would be enrolled into the study in four dose groups; however, only 48 subjects were enrolled (Dose Groups 1,2,3; n=16 per group).</p> <p>The decision to terminate the study early was taken to incorporate learning from this study into a redesigned trial to continue studying neonates in the 26-28 week gestational age. To this end, sponsor planned to study the 26-28 week GA patients in the amendment (Amendment 2) to the 03-CL-1202 study.</p> <p>A preliminary review of the data through Dose Group 3 has shown no safety signal of concern and the overall safety and tolerability profile was generally similar to the control group treated with nCPAP alone. A maximum tolerated dose was not established, the overall objective of the study was met. Early termination of 03-CL-1401 study has no effect on the overall risk-benefit assessment of lucinactant for inhalation. Last subject randomized into the study was on 16 May 2017 and was followed through study completion, which is 36 weeks PMA (9 July 2017)</p>	-

Notes:

Limitations and caveats

None reported