Clinical trial results:
A MULTINATIONAL, MULTICENTER, MASKED, RANDOMIZED, CONTROLLED
STUDY TO ASSESS THE SAFETY AND EFFICACY OF LUCINACTANT FOR
INHALATION IN PRETERM NEONATES 26 TO 32 WEEKS GESTATIONAL AGE
WITH RESPIRATORY DISTRESS SYNDROME.

Summary

EudraCT number	2015-003519-40
Trial protocol	PL IE NL HU
Global end of trial date	06 August 2019

Results information

Result version number	v1
This version publication date	11 January 2022
First version publication date	11 January 2022
Summary attachment (see zip file)	03-CL-1202 Synopsis v1.1_11JUN2020 (03-CL-1202 CSR Synopsis v1.1_11JUN2020.pdf)

Trial information

Trial identification

Sponsor protocol code	03-CL-1202

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02636868
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, Windtree Therapeutics, Inc., 215 488-9300, ssimonson@windtreetx.com
Scientific contact	Steven G. Simonson, MD, Windtree Therapeutics, Inc., 215 488-9300, ssimonson@windtreetx.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	11 June 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	06 August 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety and efficacy of lucinactant for inhalation in conjuction with nasal continuous positive airway pressure (nCPAP), in comparison to nCPAP alone, in preterm neonates with RDS, as assessed by the time to, and incidence of, respiratory failure and/or death due to RDS, incidence of bronchopulmonary dysplasia (BPD) at 36 weeks postmenstrual age (PMA), and change in physiologic parameters (fraction of inspired oxygen [FiO2] and partial pressure of carbon dioxide [PCO2]) over the first 72 hours of life.

Protection of trial subjects:

A DMC was established to evaluate the degree of risk involved in study subject participation within each treatment group and to determine if study continuation in accordance with the current protocol holds the potential to institute any undue harm or threat to the safety and welfare of study subjects. Safety and tolerability data from the time all active subjects completed assessments and procedures through 72 hours of life were assessed at pre-specified enrollment milestones. DMC responsibilities, authorities and procedures were documented in a DMC charter endorsed by members of the DMC.

Background therapy:

Standard of Care (nCPAP alone)

Evidence for comparator:

Preterm neonates who are treated for RDS initially with non-invasive ventilation (including nCPAP) are the appropriate controls for this study, since the addition of aerosolized surfactant would be the only difference in treatment in the active groups compared to the controls. Current guidelines allow use of non-invasive ventilation such as nCPAP as an initial modality for the treatment of RDS in preterm newborns, with the goal of avoiding endotracheal intubation.
Each of the 4 components of lucinactant plays a role in its biological activity. Aerosolized vehicles (eg, sterile water or saline) may have an adverse effect on pulmonary function. Thus, no inert placebo exists. Therefore, “sham” treatment, in which the ADS is brought to the subject’s bedside but not used to deliver study drug, is the optimal control. All study treatments (whether active or control) are given only if subjects are stable enough that they do not require intubation. Such subjects would typically be maintained on standard nCPAP or other forms of non-invasive ventilation and since control/sham treatment is equivalent to standard care, it is therefore ethical to administer for initial or repeat dosing.

Actual start date of recruitment	14 April 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Safety
Long term follow-up duration	12 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 5
Country: Number of subjects enrolled	Poland: 65
Country: Number of subjects enrolled	Hungary: 18
Country: Number of subjects enrolled	Ireland: 3
Country: Number of subjects enrolled	United States: 66
Country: Number of subjects enrolled	Canada: 9
Country: Number of subjects enrolled	Chile: 39
Country: Number of subjects enrolled	Colombia: 16
Worldwide total number of subjects	221
EEA total number of subjects	91

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	221
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:

Preterm neonates who successfully met eligibility criteria were randomly assigned to one of 3 treatment groups in a 1:1:1 ratio using centralized allocation electronically. Randomization information was provided to the study drug preparer (eg, pharmacist). The PI, study staff, and attending physicians were masked to treatment assignment.

Pre-assignment

Screening details:

1Signed ICF from legally authorized representative
2 26 0/7 to 32 6/7 compl. weeks gestation PMA
3Sucessful implement. of n/invasive support or ventilation within 90 min after birth
4Spontaneous breathing
5Chest radiograph consistent with RDS
6Within first 20h after birth, requires nCAP of 5-7cm H2O with FiO2>0,25 to 0,4 for minimum 30minutes

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

Details of the masking procedure are provided in the 03-CL-1202 Overall Blinding Plan, Blinding Procedure, Blinding Maintenance and Assurance Plan, and Statistical Analysis Plan documents. The blinding plan is outlined as follows:
a. Subject safety took precedence over maintenance of study masking.
b. Personnel who made or influenced clinical decisions were masked from treatment assignment.
c. Each site created a site-specific blinding plan, to be approved by Windtree prior to participation.

Arms

Are arms mutually exclusive?	Yes
Arm title	40 mg/kg

Arm description:

Lucinactant for inhalation 40 mg TPL/kg (administered over 25 minutes) in conjunction with nCPAP (n=80)
Up to 2 repeat doses of 40 mg TPL/kg were to be given if repeat dosing criteria were met

Arm type	Experimental
Investigational medicinal product name	Lucinactant for inhalation
Investigational medicinal product code	20377
Other name	Aerosurf
Pharmaceutical forms	Inhalation vapour, liquid
Routes of administration	Inhalation use

Dosage and administration details:

The study treatment, ‘lucinactant for inhalation,’ consists of the investigational drug lucinactant and the delivery system (ADS). The ADS has two components, the AEROSURF® Delivery Pack (ADP) and the AEROSURF® Control Unit (ACU).
Details for study drug preparation and ADS operation were provided in the AEROSURF Investigator’s Brochure and in the ADS Operator’s Manual. Briefly, lyophilized drug was reconstituted immediately before use by adding 10 mL of sterile water for injection to each of 7 vials of lyophilized lucinactant, after which the vials were gently inverted to mix the suspension. The vials were drawn up into a single 60 mL syringe and transferred into the provided ADP syringe, which is then loaded into the ACU. The ADS was brought to the subject’s bedside and connected to the subject’s nCPAP via the patient interface connector. The ADS aerosolized lucinactant through heat and pressure created within the capillary located within the heater assembly.

Arm title	80 mg/k

Arm description:

Lucinactant for inhalation 80 mg TPL/kg (administered over 50 minutes) in conjunction with nCPAP (n=80)
Up to 2 repeat doses of 80 mg TPL/kg were to be given if repeat dosing criteria were met

Arm type	Experimental
Investigational medicinal product name	Lucinactant for inhalation
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Arm title	Control

Arm description:

nCPAP alone

Arm type	Standard of Care

No investigational medicinal product assigned in this arm

Number of subjects in period 1	40 mg/kg	80 mg/k	Control
Started	73	76	72
Completed	73	75	70
Not completed	0	1	2
Adverse event, serious fatal	-	-	2
Adverse event, non-fatal	-	1	-

Baseline characteristics

Reporting groups	
Reporting group title	40 mg/kg
Reporting group description:	
Lucinactant for inhalation 40 mg TPL/kg (administered over 25 minutes) in conjunction with nCPAP (n=80) Up to 2 repeat doses of 40 mg TPL/kg were to be given if repeat dosing criteria were met	
Reporting group title	80 mg/k
Reporting group description:	
Lucinactant for inhalation 80 mg TPL/kg (administered over 50 minutes) in conjunction with nCPAP (n=80) Up to 2 repeat doses of 80 mg TPL/kg were to be given if repeat dosing criteria were met	
Reporting group title	Control
Reporting group description:	
nCPAP alone	

Reporting group values	40 mg/kg	80 mg/k	Control
Number of subjects	73	76	72
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	73	76	72
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: weeks			
arithmetic mean	30.8	30.7	30.7
standard deviation	± 1.24	± 1.17	± 1.17
Gender categorical Units: Subjects			
Female	31	39	37
Male	42	37	35
Ethnicity Units: Subjects			
Hispanic or Latino	19	24	18
Not Hispanic or Latino	54	52	54
Unknown or Not Reported	0	0	0
Race Units: Subjects			
White	62	64	58
Black/African American	4	6	6
Asian	1	0	1
Other or Unknown	6	6	7

Ruptured Membranes Units: Subjects			
Spontaneous	23	16	19
Artificial	50	60	53
Chorioamnionitis Units: Subjects			
yes	3	3	2
no	70	73	70
Mode of Delivery Units: Subjects			
Vaginal	17	12	16
C-section	56	64	56
Birth Status Units: Subjects			
Single Birth	44	53	50
Multiple Birth	29	23	22
Congenital Anomaly Units: Subjects			
Yes	1	0	0
No	72	76	72
Region of Enrollment Units: Subjects			
Canada	4	2	3
Colombia	4	7	5
Netherlands	2	1	2
Hungary	6	3	9
United States	20	25	21
Ireland	1	2	0
Poland	23	21	21
Chile	13	15	11
Steroid Use Units: Subjects			
Used Steroids	68	69	70
No Steroids	5	7	2
Birth Weight Units: grams			
arithmetic mean	1557.0	1505.8	1446.4
standard deviation	± 342.38	± 378.5	± 359.13
Appearance, Pulse, Grimace, Activity, and Respiration (Apgar) Score at One Minute Units: scores on a scale			
arithmetic mean	6.7	6.5	6.8
standard deviation	± 1.74	± 1.71	± 1.61
Apgar Score at Five Minutes Units: Scores on a scale			
arithmetic mean	8.1	8.0	8.1
standard deviation	± 0.90	± 1.02	± 1.00

Reporting group values	Total		
Number of subjects	221		

Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	221		
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 65-84 years	0		
85 years and over	0		
Age continuous Units: weeks			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	107		
Male	114		
Ethnicity Units: Subjects			
Hispanic or Latino	61		
Not Hispanic or Latino	160		
Unknown or Not Reported	0		
Race Units: Subjects			
White	184		
Black/African American	16		
Asian	2		
Other or Unknown	19		
Ruptured Membranes Units: Subjects			
Spontaneous	58		
Artificial	163		
Chorioamnionitis Units: Subjects			
yes	8		
no	213		
Mode of Delivery Units: Subjects			
Vaginal	45		
C-section	176		
Birth Status Units: Subjects			
Single Birth	147		
Multiple Birth	74		
Congenital Anomaly Units: Subjects			
Yes	1		
No	220		

Region of Enrollment Units: Subjects			
Canada	9		
Colombia	16		
Netherlands	5		
Hungary	18		
United States	66		
Ireland	3		
Poland	65		
Chile	39		
Steroid Use Units: Subjects			
Used Steroids	207		
No Steroids	14		
Birth Weight Units: grams arithmetic mean standard deviation	- -		
Appearance, Pulse, Grimace, Activity, and Respiration (Apgar) Score at One Minute Units: scores on a scale arithmetic mean standard deviation	- -		
Apgar Score at Five Minutes Units: Scores on a scale arithmetic mean standard deviation	- -		

End points

End points reporting groups

Reporting group title	40 mg/kg
Reporting group description:	
Lucinactant for inhalation 40 mg TPL/kg (administered over 25 minutes) in conjunction with nCPAP (n=80) Up to 2 repeat doses of 40 mg TPL/kg were to be given if repeat dosing criteria were met	
Reporting group title	80 mg/k
Reporting group description:	
Lucinactant for inhalation 80 mg TPL/kg (administered over 50 minutes) in conjunction with nCPAP (n=80) Up to 2 repeat doses of 80 mg TPL/kg were to be given if repeat dosing criteria were met	
Reporting group title	Control
Reporting group description:	
nCPAP alone	

Primary: Number of Participants With Respiratory Failure or Death Due to Respiratory Distress Syndrome (RDS)

End point title	Number of Participants With Respiratory Failure or Death Due to Respiratory Distress Syndrome (RDS)
End point description:	
Number of participants who had respiratory failure due to RDS or death due to RDS; known as nasal continuous positive airway pressure (nCPAP) failure	
End point type	Primary
End point timeframe:	
72 hours	

End point values	40 mg/kg	80 mg/k	Control	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	70	72	71	
Units: count of participants	31	32	31	

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description:	
Aerosolized Lucinactant (40 mg TPL/kg), Aerosolized Lucinactant (80 mg TPL/kg), nCPAP Only Null hypothesis is no difference across treatment groups	
Comparison groups	40 mg/kg v 80 mg/k v Control

Number of subjects included in analysis	213
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.363 [1]
Method	Regression, Logistic

Notes:

[1] - a priori threshold of statistical significance set at 0.05

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

Aerosolized Lucinactant (40 mg TPL/kg), nCPAP Only
Null hypothesis is no difference across treatment groups

Comparison groups	40 mg/kg v Control
Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.36 [2]
Method	Regression, Logistic

Notes:

[2] - a priori threshold of statistical significance set at 0.05

Statistical analysis title	Statistical analysis 3

Statistical analysis description:

Aerosolized Lucinactant (80 mg TPL/kg), nCPAP Only
Null hypothesis is no difference across treatment groups

Comparison groups	Control v 80 mg/k
Number of subjects included in analysis	143
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.461 [3]
Method	Regression, Logistic

Notes:

[3] - a priori threshold of statistical significance set at 0.05

Secondary: Incidence of Respiratory Failure or Death Due to RDS

End point title	Incidence of Respiratory Failure or Death Due to RDS

End point description:

Incidence of Respiratory Failure or Death Due to RDS by Intubation or Failure Criteria

End point type	Secondary

End point timeframe:

72 hours

End point values	40 mg/kg	80 mg/k	Control	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	64	44	71	
Units: count of participants	28	14	31	

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Aerosolized Lucinactant (40 mg TPL/kg), Aerosolized Lucinactant (80 mg TPL/kg), nCPAP Only
Null hypothesis is no difference across treatment groups

Comparison groups	80 mg/k v Control v 40 mg/kg
Number of subjects included in analysis	179
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.401 [4]
Method	Regression, Logistic

Notes:

[4] - a priori threshold of statistical significance set at 0.05

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

Aerosolized Lucinactant (40 mg TPL/kg), nCPAP Only
Null hypothesis is no difference across treatment groups

Comparison groups	40 mg/kg v Control
Number of subjects included in analysis	135
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.372 [5]
Method	Regression, Logistic

Notes:

[5] - a priori threshold of statistical significance set at 0.05

Statistical analysis title	Statistical analysis 3

Statistical analysis description:

Aerosolized Lucinactant (80 mg TPL/kg), nCPAP Only
Null hypothesis is no difference across treatment groups

Comparison groups	Control v 80 mg/k
Number of subjects included in analysis	115
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.648 [6]
Method	Regression, Logistic

Notes:

[6] - a priori threshold of statistical significance set at 0.05

Secondary: Time to nCPAP Failure

End point title	Time to nCPAP Failure

End point description: Time from birth to nCPAP Failure	
End point type	Secondary
End point timeframe: 72 hours	

End point values	40 mg/kg	80 mg/k	Control	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	70	72	71	
Units: hours				
least squares mean (standard error)	39.3 (± 2.06)	44.8 (± 2.69)	70.7 (± 2.44)	

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description: Aerosolized Lucinactant (40 mg TPL/kg), Aerosolized Lucinactant (80 mg TPL/kg), nCPAP Only Null hypothesis of no difference across treatments	
Comparison groups	40 mg/kg v 80 mg/k v Control
Number of subjects included in analysis	213
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.996 [7]
Method	Logrank

Notes:

[7] - a priori threshold of statistical significance set at 0.05

Statistical analysis title	Statistical analysis 2
Statistical analysis description: Aerosolized Lucinactant (40 mg TPL/kg), nCPAP Only Null hypothesis of no difference across treatments	
Comparison groups	40 mg/kg v Control
Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.951 [8]
Method	Logrank

Notes:

[8] - a priori threshold of statistical significance set at 0.05

Statistical analysis title	Statistical analysis 3
Statistical analysis description: Aerosolized Lucinactant (80 mg TPL/kg), nCPAP Only Null hypothesis of no difference across treatments	
Comparison groups	Control v 80 mg/k

Number of subjects included in analysis	143
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.995 [9]
Method	Logrank

Notes:

[9] - a priori threshold of statistical significance set at 0.05

Secondary: Incidence of Respiratory Failure or Death Due to RDS With Poisson Distribution Modeling

End point title	Incidence of Respiratory Failure or Death Due to RDS With Poisson Distribution Modeling

End point description:

The measure tests the differences between treatments on respiratory failure or death due to RDS using Poisson distribution modeling, which accounts for the time over which the event could have occurred.

End point type	Secondary

End point timeframe:

72 hours

End point values	40 mg/kg	80 mg/k	Control	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	70	72	71	
Units: count of participants	31	32	31	

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Aerosolized Lucinactant (40 mg TPL/kg), Aerosolized Lucinactant (80 mg TPL/kg), nCPAP Only
Null hypothesis of no difference between treatment groups

Comparison groups	80 mg/k v 40 mg/kg v Control
Number of subjects included in analysis	213
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.312 [10]
Method	Regression, Linear

Notes:

[10] - A priori threshold of statistical significance set at 0.10

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

Aerosolized Lucinactant (40 mg TPL/kg), nCPAP Only
Null hypothesis of no difference between treatment groups

Comparison groups	40 mg/kg v Control

Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.094 [11]
Method	Regression, Linear

Notes:

[11] - A priori threshold of statistical significance set at 0.10

Statistical analysis title	Statistical analysis 3

Statistical analysis description:

Aerosolized Lucinactant (80 mg TPL/kg), nCPAP Only
Null hypothesis of no difference between treatment groups

Comparison groups	Control v 80 mg/k
Number of subjects included in analysis	143
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.414 [12]
Method	Regression, Linear

Notes:

[12] - A priori threshold of statistical significance set at 0.10

Secondary: Incidence of Respiratory Failure or Death Due to RDS

End point title	Incidence of Respiratory Failure or Death Due to RDS

End point description:

Incidence of Respiratory Failure or Death due to RDS by Intubation or Failure Criteria

End point type	Secondary

End point timeframe:

28 days

End point values	40 mg/kg	80 mg/k	Control	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	70	72	71	
Units: count of participants	35	32	31	

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Aerosolized Lucinactant (40 mg TPL/kg), Aerosolized Lucinactant (80 mg TPL/kg), nCPAP Only
Null hypothesis of no difference between treatment groups

Comparison groups	40 mg/kg v 80 mg/k v Control

Number of subjects included in analysis	213
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.099 [13]
Method	Regression, Logistic

Notes:

[13] - A priori statistical significance of 0.05

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

Aerosolized Lucinactant (40 mg TPL/kg), nCPAP Only
Null hypothesis of no difference between treatment groups

Comparison groups	40 mg/kg v Control
Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.09 [14]
Method	Regression, Logistic

Notes:

[14] - A priori statistical significance of 0.05

Statistical analysis title	Statistical analysis 3

Statistical analysis description:

Aerosolized Lucinactant (80 mg TPL/kg), nCPAP Only
Null hypothesis of no difference between treatment groups

Comparison groups	Control v 80 mg/k
Number of subjects included in analysis	143
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.461 [15]
Method	Regression, Logistic

Notes:

[15] - A priori statistical significance of 0.05

Secondary: Number of Participants With Bronchopulmonary Dysplasia (BPD)

End point title	Number of Participants With Bronchopulmonary Dysplasia (BPD)

End point description:

Summarizes the number of participants with BPD or alive without BPD

End point type	Secondary

End point timeframe:

36 weeks post-menstrual age (PMA)

End point values	40 mg/kg	80 mg/k	Control	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	70	72	71	
Units: count of participants				
BPD	7	7	10	
Alive without BPD	62	64	59	

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Aerosolized Lucinactant (40 mg TPL/kg), Aerosolized Lucinactant (80 mg TPL/kg), nCPAP Only
Null hypothesis of no treatment between treatments

Comparison groups	40 mg/kg v 80 mg/k v Control
Number of subjects included in analysis	213
Analysis specification	Pre-specified
Analysis type	superiority[16]
P-value	= 0.534
Method	ANOVA

Notes:

[16] - A priori threshold for statistical significance set at 0.05

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

Aerosolized Lucinactant (80 mg TPL/kg), nCPAP Only
Null hypothesis of no treatment between treatments

Comparison groups	80 mg/k v Control
Number of subjects included in analysis	143
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.48 [17]
Method	ANOVA

Notes:

[17] - A priori threshold for statistical significance set at 0.05

Statistical analysis title	Statistical analysis 3

Statistical analysis description:

Aerosolized Lucinactant (80 mg TPL/kg), nCPAP Only
Null hypothesis of no treatment between treatments

Comparison groups	80 mg/k v Control
Number of subjects included in analysis	143
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.313 [18]
Method	ANOVA

Notes:

[18] - A priori threshold for statistical significance set at 0.05

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Information regarding occurence of AEs was assessed from the time of randomization until completion of Final Study Observation

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	40 mg/kg

Reporting group description:

Lucinactant for inhalation 40 mg TPL/kg (administered over 25 minutes) in conjunction with nCPAP (n=80)
Up to 2 repeat doses of 40 mg TPL/kg were to be given if repeat dosing criteria were met

Reporting group title	80 mg/k

Reporting group description:

Lucinactant for inhalation 80 mg TPL/kg (administered over 50 minutes) in conjunction with nCPAP (n=80)
Up to 2 repeat doses of 80 mg TPL/kg were to be given if repeat dosing criteria were met

Reporting group title	Control

Reporting group description:

nCPAP alone

Serious adverse events	40 mg/kg	80 mg/k	Control
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 70 (22.86%)	14 / 72 (19.44%)	20 / 71 (28.17%)
number of deaths (all causes)	0	1	2
number of deaths resulting from adverse events			
Congenital, familial and genetic disorders			
Coarctation of the aorta			
subjects affected / exposed	0 / 70 (0.00%)	0 / 72 (0.00%)	1 / 71 (1.41%)
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			
Patent ductus arteriosus			
subjects affected / exposed	1 / 70 (1.43%)	0 / 72 (0.00%)	0 / 71 (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
Nervous system disorders			
Hydrocephalus			

subjects affected / exposed	1 / 70 (1.43%)	0 / 72 (0.00%)	0 / 71 (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
Pregnancy, puerperium and perinatal conditions			
Intraventricular haemorrhage neonatal			
subjects affected / exposed	1 / 70 (1.43%)	1 / 72 (1.39%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Necrotising enterocolitis neonatal			
subjects affected / exposed	0 / 70 (0.00%)	1 / 72 (1.39%)	0 / 71 (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
Neonatal respiratory distress syndrome			
subjects affected / exposed	4 / 70 (5.71%)	2 / 72 (2.78%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	4 / 4	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	0 / 70 (0.00%)	1 / 72 (1.39%)	0 / 71 (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
Gastrointestinal disorders			
Large intestine perforation			
subjects affected / exposed	1 / 70 (1.43%)	0 / 72 (0.00%)	0 / 71 (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
Necrotising enterocolitis neonatal			
subjects affected / exposed	0 / 70 (0.00%)	2 / 72 (2.78%)	2 / 71 (2.82%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Apnoea			

subjects affected / exposed	0 / 70 (0.00%)	0 / 72 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
apnoea neonatal			
subjects affected / exposed	0 / 70 (0.00%)	0 / 72 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchopulmonary dysplasia			
subjects affected / exposed	1 / 70 (1.43%)	1 / 72 (1.39%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	1 / 1	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epistaxis			
subjects affected / exposed	0 / 70 (0.00%)	1 / 72 (1.39%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumomediastinum			
subjects affected / exposed	1 / 70 (1.43%)	0 / 72 (0.00%)	0 / 71 (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
Pulmonary haemorrhage			
subjects affected / exposed	0 / 70 (0.00%)	0 / 72 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary hypertension			
subjects affected / exposed	0 / 70 (0.00%)	1 / 72 (1.39%)	0 / 71 (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
Pulmonary interstitial emphysema syndrome			
subjects affected / exposed	1 / 70 (1.43%)	0 / 72 (0.00%)	3 / 71 (4.23%)
occurrences causally related to treatment / all	1 / 1	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			

subjects affected / exposed	3 / 70 (4.29%)	4 / 72 (5.56%)	7 / 71 (9.86%)
occurrences causally related to treatment / all	3 / 3	4 / 4	7 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary oedema neonatal			
subjects affected / exposed	0 / 70 (0.00%)	0 / 72 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bacteraemia			
subjects affected / exposed	2 / 70 (2.86%)	1 / 72 (1.39%)	2 / 71 (2.82%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocarditis staphylococcal			
subjects affected / exposed	0 / 70 (0.00%)	0 / 72 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningitis bacterial			
subjects affected / exposed	1 / 70 (1.43%)	0 / 72 (0.00%)	0 / 71 (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
Neurological infection			
subjects affected / exposed	0 / 70 (0.00%)	0 / 72 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
nocosomial infection			
subjects affected / exposed	1 / 70 (1.43%)	1 / 72 (1.39%)	0 / 71 (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
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	0 / 70 (0.00%)	1 / 72 (1.39%)	0 / 71 (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
Pseudomonal sepsis			

subjects affected / exposed	0 / 70 (0.00%)	1 / 72 (1.39%)	0 / 71 (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	2 / 70 (2.86%)	3 / 72 (4.17%)	5 / 71 (7.04%)
occurrences causally related to treatment / all	0 / 3	0 / 3	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic embolus			
subjects affected / exposed	0 / 70 (0.00%)	0 / 72 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	0 / 70 (0.00%)	0 / 72 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	40 mg/kg	80 mg/k	Control
Total subjects affected by non-serious adverse events			
subjects affected / exposed	65 / 70 (92.86%)	69 / 72 (95.83%)	66 / 71 (92.96%)
Congenital, familial and genetic disorders			
Atrial septal defect			
subjects affected / exposed	4 / 70 (5.71%)	4 / 72 (5.56%)	2 / 71 (2.82%)
occurrences (all)	5	4	2
Vascular disorders			
Hypotension			
subjects affected / exposed	2 / 70 (2.86%)	4 / 72 (5.56%)	3 / 71 (4.23%)
occurrences (all)	3	4	4
Pallor			
subjects affected / exposed	10 / 70 (14.29%)	4 / 72 (5.56%)	3 / 71 (4.23%)
occurrences (all)	11	5	3
Cardiac disorders			

Patent ductus arteriosus			
subjects affected / exposed	18 / 70 (25.71%)	24 / 72 (33.33%)	24 / 71 (33.80%)
occurrences (all)	18	24	26
Tachycardia			
subjects affected / exposed	6 / 70 (8.57%)	6 / 72 (8.33%)	2 / 71 (2.82%)
occurrences (all)	6	9	2
Pregnancy, puerperium and perinatal conditions			
Agitation neonatal			
subjects affected / exposed	7 / 70 (10.00%)	9 / 72 (12.50%)	3 / 71 (4.23%)
occurrences (all)	8	10	3
Bradycardia neonatal			
subjects affected / exposed	6 / 70 (8.57%)	8 / 72 (11.11%)	3 / 71 (4.23%)
occurrences (all)	7	8	3
Intraventricular haemorrhage neonatal			
subjects affected / exposed	7 / 70 (10.00%)	10 / 72 (13.89%)	12 / 71 (16.90%)
occurrences (all)	8	11	15
Jaundice neonatal			
subjects affected / exposed	41 / 70 (58.57%)	49 / 72 (68.06%)	41 / 71 (57.75%)
occurrences (all)	47	50	46
Neonatal respiratory distress syndrome			
subjects affected / exposed	10 / 70 (14.29%)	8 / 72 (11.11%)	13 / 71 (18.31%)
occurrences (all)	12	8	13
Retinopathy of prematurity			
subjects affected / exposed	3 / 70 (4.29%)	6 / 72 (8.33%)	3 / 71 (4.23%)
occurrences (all)	3	6	3
Weight decrease neonatal			
subjects affected / exposed	2 / 70 (2.86%)	4 / 72 (5.56%)	2 / 71 (2.82%)
occurrences (all)	2	4	2
Blood and lymphatic system disorders			
Anaemia neonatal			
subjects affected / exposed	22 / 70 (31.43%)	31 / 72 (43.06%)	31 / 71 (43.66%)
occurrences (all)	26	37	52
Coagulation disorder neonatal			
subjects affected / exposed	2 / 70 (2.86%)	5 / 72 (6.94%)	1 / 71 (1.41%)
occurrences (all)	2	5	1

Thrombocytopenia			
subjects affected / exposed	4 / 70 (5.71%)	6 / 72 (8.33%)	5 / 71 (7.04%)
occurrences (all)	5	6	5
General disorders and administration site conditions			
Oedema			
subjects affected / exposed	7 / 70 (10.00%)	5 / 72 (6.94%)	7 / 71 (9.86%)
occurrences (all)	7	7	7
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	6 / 70 (8.57%)	5 / 72 (6.94%)	6 / 71 (8.45%)
occurrences (all)	7	8	8
Constipation			
subjects affected / exposed	6 / 70 (8.57%)	9 / 72 (12.50%)	6 / 71 (8.45%)
occurrences (all)	7	9	7
Gastric haemorrhage			
subjects affected / exposed	3 / 70 (4.29%)	2 / 72 (2.78%)	6 / 71 (8.45%)
occurrences (all)	3	2	6
Necrotising enterocolitis neonatal			
subjects affected / exposed	3 / 70 (4.29%)	2 / 72 (2.78%)	6 / 71 (8.45%)
occurrences (all)	3	2	6
Regurgitation			
subjects affected / exposed	10 / 70 (14.29%)	12 / 72 (16.67%)	1 / 71 (1.41%)
occurrences (all)	10	13	1
Vomiting			
subjects affected / exposed	9 / 70 (12.86%)	9 / 72 (12.50%)	8 / 71 (11.27%)
occurrences (all)	9	10	9
Respiratory, thoracic and mediastinal disorders			
apnoea neonatal			
subjects affected / exposed	31 / 70 (44.29%)	26 / 72 (36.11%)	27 / 71 (38.03%)
occurrences (all)	39	29	31
Bronchopulmonary dysplasia			
subjects affected / exposed	6 / 70 (8.57%)	6 / 72 (8.33%)	9 / 71 (12.68%)
occurrences (all)	6	6	9
Hypercapnia			
subjects affected / exposed	3 / 70 (4.29%)	4 / 72 (5.56%)	1 / 71 (1.41%)
occurrences (all)	3	5	1

Nasal inflammation			
subjects affected / exposed	7 / 70 (10.00%)	10 / 72 (13.89%)	7 / 71 (9.86%)
occurrences (all)	7	10	7
Neonatal tachypnoea			
subjects affected / exposed	12 / 70 (17.14%)	10 / 72 (13.89%)	8 / 71 (11.27%)
occurrences (all)	14	11	9
Pneumothorax			
subjects affected / exposed	4 / 70 (5.71%)	3 / 72 (4.17%)	2 / 71 (2.82%)
occurrences (all)	4	3	2
Skin and subcutaneous tissue disorders			
Dermatitis diaper			
subjects affected / exposed	7 / 70 (10.00%)	6 / 72 (8.33%)	2 / 71 (2.82%)
occurrences (all)	7	7	2
Renal and urinary disorders			
Atelectasis neonatal			
subjects affected / exposed	0 / 70 (0.00%)	4 / 72 (5.56%)	4 / 71 (5.63%)
occurrences (all)	0	4	5
Metabolism and nutrition disorders			
Feeding intolerance			
subjects affected / exposed	11 / 70 (15.71%)	17 / 72 (23.61%)	10 / 71 (14.08%)
occurrences (all)	11	17	11
Hyperglycaemia			
subjects affected / exposed	2 / 70 (2.86%)	5 / 72 (6.94%)	3 / 71 (4.23%)
occurrences (all)	2	5	3
Hypermagnesaemia			
subjects affected / exposed	3 / 70 (4.29%)	4 / 72 (5.56%)	4 / 71 (5.63%)
occurrences (all)	3	4	4
Hypocalcaemia			
subjects affected / exposed	3 / 70 (4.29%)	7 / 72 (9.72%)	3 / 71 (4.23%)
occurrences (all)	4	7	3
Hypoglycaemia			
subjects affected / exposed	4 / 70 (5.71%)	1 / 72 (1.39%)	3 / 71 (4.23%)
occurrences (all)	6	1	5
Hyponatraemia			
subjects affected / exposed	5 / 70 (7.14%)	6 / 72 (8.33%)	5 / 71 (7.04%)
occurrences (all)	7	6	6
Metabolic acidosis			

subjects affected / exposed occurrences (all)	4 / 70 (5.71%) 4	5 / 72 (6.94%) 5	9 / 71 (12.68%) 11

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 March 2016	Previous version of the protocol has been revised based upon discussions regarding the design and description of study 03-CL-1202 and based on lessons learned from this study's predecessor, study 03-CL-1201. Key changes: - study treatment - criteria for repeat study treatment dosing changed to encourage repeat dosing and to reflect revision of respiratory support in inclusion criteria -endpoints - definition of primary endpoint revised to be consistent with clinical practice and for clarity -results of Non-Clinical and Clinical Studies - results of study 03-CL-1201 added, data from preliminary studies KL4-CPAP-01 and KL4-ASTH-01 clarified and augmented -inclusion/exclusion criteria - Use of respiratory support in inclusion criteria (3 and 6) revised to be consistent with clinical practice and for clarity; exclusion criterion 7 revised to be consistent with clinical practice; exclusion criterion 11 added due to inadvertent omission from original protocol -statistics - enrollment stratification changed to allow greater enrollment of subjects in higher gestation age stratum -Data safety Monitoring Committee - rules for Data Monitoring Committee reviev had been inadvertently carried over from Study 03-CL-1201 so were changed to reflect the larger study population of Study 03-CL-1202 -Changes for Clarity- extensive revisions made for clarity to introduction and descriptions of study design/rationale, study treatment dosing and administration, study procedures and guidelines, and study evaluations

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Clogging of a in-line filter led to a higher number of treatment interruptions than expected. This primarily affected one batch of supplies that were, by chance, predominantly used in European sites.

Notes: