



Clinical trial results:

A RANDOMIZED CONTROLLED STUDY TO EVALUATE THE EFFICACY OF A SUPPLEMENTAL DOSE OF CUROSURF IN PRE-TERM INFANTS ON MECHANICAL VENTILATION FOR RESPIRATORY DISTRESS SYNDROME (RDS) IN PREVENTING EXTUBATION FAILURE.

Summary

EudraCT number	2005-005371-15
Trial protocol	IT
Global end of trial date	24 December 2007

Results information

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

Trial information

Trial identification

Sponsor protocol code	DM/PR/5000/004/05
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Additional study identifiers

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

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	27 June 2008
Is this the analysis of the primary completion data?	Yes
Primary completion date	24 December 2007
Global end of trial reached?	Yes
Global end of trial date	24 December 2007
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy and safety of a supplemental pre-extubation dose of Curosurf® compared to the standard posology (one or two doses) in pre-term neonates, after extubation from mechanical ventilation (MV).

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 May 2006
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects**Subjects enrolled per country**

Country: Number of subjects enrolled	Italy: 42
Worldwide total number of subjects	42
EEA total number of subjects	42

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	42
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:

Number of Patients (planned and analyzed):

Planned: approximately 200 evaluable pre-term neonates (100/group).

Analyzed: 42 pre-term neonates, 23 in the supplemental Curosurf® group and 19 in the no supplemental Curosurf® group.

Pre-assignment

Screening details:

All infants of birth weight (BW) 500–1500 g were screened for eligibility based upon the study selection criteria.

Period 1

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

Blinding implementation details:

This was an open label study.

Arms

Are arms mutually exclusive?	Yes
Arm title	Supplemental Curosurf

Arm description:

After randomization, this patient group received a supplemental dose of Curosurf® (100 mg/kg) 1–6 hours before extubation.

Following extubation, patients were monitored for 48 hours to assess extubation success or failure.

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

Dosage and administration details:

Curosurf® for intratracheal or intrabronchial administration as prophylactic or rescue treatment for RDS according to manufacturer's instructions.

All patients received treatment with one dose of Curosurf® (100 or 200 mg/kg) and a second dose (100 mg/kg, if needed) according to standard practice.

Patients were then randomized in a 1:1 ratio to receive either a supplemental dose of Curosurf® (100 mg/kg) 1–6 hours before extubation (Group A) or to receive no supplemental treatment before extubation (Group B).

Following extubation, patients were monitored for 48 hours to assess extubation success or failure.

Arm title	No supplemental Curosurf
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Arm description:

After randomization this patient group did not receive a supplemental dose of Curosurf® (100 mg/kg) 1–6 hours before extubation.

Following extubation, patients were monitored for 48 hours to assess extubation success or failure.

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

Dosage and administration details:

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Patients were then randomized in a 1:1 ratio to receive either a supplemental dose of Curosurf® (100 mg/kg) 1–6 hours before extubation (Group A) or to receive no supplemental treatment before extubation (Group B).

Following extubation, patients were monitored for 48 hours to assess extubation success or failure.

Number of subjects in period 1	Supplemental Curosurf	No supplemental Curosurf
Started	23	19
Completed	20	18
Not completed	3	1
Adverse event, serious fatal	1	-
Adverse event, non-fatal	-	1
Lost to follow-up	2	-

Baseline characteristics

Reporting groups

Reporting group title	Supplemental Curosurf
Reporting group description: After randomization, this patient group received a supplemental dose of Curosurf® (100 mg/kg) 1–6 hours before extubation. Following extubation, patients were monitored for 48 hours to assess extubation success or failure.	
Reporting group title	No supplemental Curosurf
Reporting group description: After randomization this patient group did not receive a supplemental dose of Curosurf® (100 mg/kg) 1–6 hours before extubation. Following extubation, patients were monitored for 48 hours to assess extubation success or failure.	

Reporting group values	Supplemental Curosurf	No supplemental Curosurf	Total
Number of subjects	23	19	42
Age categorical Units: Subjects			
Preterm newborn infants (gestational age < 37 wks)	23	19	42
Age continuous Units: days arithmetic mean standard deviation	5.6 ± 1.83	5.4 ± 2.04	-
Gender categorical Units: Subjects			
Female	8	7	15
Male	15	12	27

Subject analysis sets

Subject analysis set title	Supplemental Curosurf - Full Analysis Population
Subject analysis set type	Full analysis
Subject analysis set description: The full analysis population comprised all patients randomized into the study, in which each patient's treatment was as allocated at randomization.	
Subject analysis set title	Supplemental Curosurf - Safety Population
Subject analysis set type	Safety analysis
Subject analysis set description: The safety population comprised all patients randomized into the study, in which each patient's treatment was as taken on the study.	
Subject analysis set title	No supplemental Curosurf - Full Analysis Population
Subject analysis set type	Full analysis
Subject analysis set description: The full analysis population comprised all patients randomized into the study, in which each patient's treatment was as allocated at randomization.	
Subject analysis set title	No supplemental Curosurf - Safety Population
Subject analysis set type	Safety analysis
Subject analysis set description: The safety population comprised all patients randomized into the study, in which each patient's treatment was as taken on the study.	

Reporting group values	Supplemental Curosurf - Full Analysis Population	Supplemental Curosurf - Safety Population	No supplemental Curosurf - Full Analysis Population
Number of subjects	23	23	19
Age categorical Units: Subjects			
Preterm newborn infants (gestational age < 37 wks)	23	23	19
Age continuous Units: days arithmetic mean standard deviation	5.6 ± 1.83	5.6 ± 1.83	5.4 ± 2.04
Gender categorical Units: Subjects			
Female	8	8	7
Male	15	15	12

Reporting group values	No supplemental Curosurf - Safety Population		
Number of subjects	19		
Age categorical Units: Subjects			
Preterm newborn infants (gestational age < 37 wks)	19		
Age continuous Units: days arithmetic mean standard deviation	5.4 ± 2.04		
Gender categorical Units: Subjects			
Female	7		
Male	12		

End points

End points reporting groups

Reporting group title	Supplemental Curosurf
Reporting group description: After randomization, this patient group received a supplemental dose of Curosurf® (100 mg/kg) 1–6 hours before extubation. Following extubation, patients were monitored for 48 hours to assess extubation success or failure.	
Reporting group title	No supplemental Curosurf
Reporting group description: After randomization this patient group did not receive a supplemental dose of Curosurf® (100 mg/kg) 1–6 hours before extubation. Following extubation, patients were monitored for 48 hours to assess extubation success or failure.	
Subject analysis set title	Supplemental Curosurf - Full Analysis Population
Subject analysis set type	Full analysis
Subject analysis set description: The full analysis population comprised all patients randomized into the study, in which each patient's treatment was as allocated at randomization.	
Subject analysis set title	Supplemental Curosurf - Safety Population
Subject analysis set type	Safety analysis
Subject analysis set description: The safety population comprised all patients randomized into the study, in which each patient's treatment was as taken on the study.	
Subject analysis set title	No supplemental Curosurf - Full Analysis Population
Subject analysis set type	Full analysis
Subject analysis set description: The full analysis population comprised all patients randomized into the study, in which each patient's treatment was as allocated at randomization.	
Subject analysis set title	No supplemental Curosurf - Safety Population
Subject analysis set type	Safety analysis
Subject analysis set description: The safety population comprised all patients randomized into the study, in which each patient's treatment was as taken on the study.	

Primary: Extubation failure overall at 48 h

End point title	Extubation failure overall at 48 h
End point description: Assessment begins at time of extubation, at least every hour between extubation and 48 hours post-extubation	
End point type	Primary
End point timeframe: 48 h post-extubation +/-15 min	

End point values	Supplemental Curosurf - Full Analysis Population	No supplemental Curosurf - Full Analysis Population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23	19		
Units: number of failures	5	4		

Statistical analyses

Statistical analysis title	Supplemental Curosurf vs no Supplemental Curosurf
Comparison groups	Supplemental Curosurf - Full Analysis Population v No supplemental Curosurf - Full Analysis Population
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[1]
Parameter estimate	Odds ratio (OR)
Point estimate	0.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.19
upper limit	5

Notes:

[1] - The proportion of pre-term patients who experienced extubation failures was compared between the two treatment groups by logistic regression, with treatment group, and BW group as covariates.

Primary: Indices of respiratory failure - Blood pH

End point title	Indices of respiratory failure - Blood pH ^[2]
End point description:	
Pre- versus post-extubation overall mean values for Supplemental Curosurf and No Supplemental Curosurf groups (Full Analysis Population) are reported.	
End point type	Primary

End point timeframe:

For the indices of respiratory failure, within-group differences between overall pre- and post-extubation mean values were compared using a paired t-test.

Notes:

[2] - 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: No between-group statistical analysis was performed.

End point values	Supplemental Curosurf - Full Analysis Population	No supplemental Curosurf - Full Analysis Population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	22	17		
Units: pH				
arithmetic mean (standard deviation)	7.2777 (± 0.05536)	7.2914 (± 0.06285)		

Statistical analyses

No statistical analyses for this end point

Primary: Indices of respiratory failure - PaO2

End point title	Indices of respiratory failure - PaO2 ^[3]
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End point description:

Pre- versus post-extubation overall mean values for Supplemental Curosurf and No Supplemental Curosurf groups (Full Analysis Population) are reported.

End point type	Primary
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End point timeframe:

For the indices of respiratory failure, within-group differences between overall pre- and post-extubation mean values were compared using a paired t-test.

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: No between-group statistical analysis was performed.

End point values	Supplemental Curosurf - Full Analysis Population	No supplemental Curosurf - Full Analysis Population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	19	14		
Units: mmHg				
arithmetic mean (standard deviation)	44.639 (± 14.0930)	49.560 (± 17.1049)		

Statistical analyses

No statistical analyses for this end point

Primary: Indices of respiratory failure - PaCO2

End point title	Indices of respiratory failure - PaCO2 ^[4]
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End point description:

Pre- versus post-extubation overall mean values for Supplemental Curosurf and No Supplemental Curosurf groups (Full Analysis Population) are reported.

End point type	Primary
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End point timeframe:

Pre- versus post-extubation overall mean values for Supplemental Curosurf and No Supplemental Curosurf groups (Full Analysis Population) are reported.

Notes:

[4] - 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: No between-group statistical analysis was performed.

End point values	Supplemental Curosurf - Full Analysis Population	No supplemental Curosurf - Full Analysis Population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	22	17		
Units: mmHg				
arithmetic mean (standard deviation)	47.911 ($\pm$ 8.5708)	46.702 ($\pm$ 11.1231)		

Statistical analyses

No statistical analyses for this end point

Primary: Indices of respiratory failure - Blood base excess

End point title	Indices of respiratory failure - Blood base excess ^[5]
End point description: Pre- versus post-extubation overall mean values for Supplemental Curosurf and No Supplemental Curosurf groups (Full Analysis Population) are reported.	
End point type	Primary
End point timeframe: For the indices of respiratory failure, within-group differences between overall pre- and post-extubation mean values were compared using a paired t-test.	

Notes:

[5] - 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: No between-group statistical analysis was performed.

End point values	Supplemental Curosurf - Full Analysis Population	No supplemental Curosurf - Full Analysis Population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	22	17		
Units: mEq				
arithmetic mean (standard deviation)	-4.463 ($\pm$ 2.6424)	-4.021 ($\pm$ 4.3291)		

Statistical analyses

No statistical analyses for this end point

Primary: Indices of respiratory failure - FiO2

End point title	Indices of respiratory failure - FiO2 ^[6]
End point description: Pre- versus post-extubation overall mean values for Supplemental Curosurf and No Supplemental Curosurf groups (Full Analysis Population) are reported.	

End point type	Primary			
End point timeframe:				
For the indices of respiratory failure, within-group differences between overall pre- and post-extubation mean values were compared using a paired t-test.				
Notes:				
[6] - 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: No between-group statistical analysis was performed.				
End point values	Supplemental Curosurf - Full Analysis Population	No supplemental Curosurf - Full Analysis Population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23	19		
Units: percentage				
arithmetic mean (standard deviation)	28.82 (± 7.585)	25.48 (± 5.657)		

Statistical analyses

No statistical analyses for this end point

Primary: Indices of respiratory failure - SaO2

End point title	Indices of respiratory failure - SaO2 ^[7]			
End point description:				
Pre- versus post-extubation overall mean values for Supplemental Curosurf and No Supplemental Curosurf groups (Full Analysis Population) are reported.				
End point type	Primary			
End point timeframe:				
For the indices of respiratory failure, within-group differences between overall pre- and post-extubation mean values were compared using a paired t-test.				
Notes:				
[7] - 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: No between-group statistical analysis was performed.				
End point values	Supplemental Curosurf - Full Analysis Population	No supplemental Curosurf - Full Analysis Population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23	19		
Units: percentage				
arithmetic mean (standard deviation)	94.59 (± 1.812)	95.74 (± 2.359)		

Statistical analyses

No statistical analyses for this end point

Primary: Indices of respiratory failure - Oxygenation index

End point title	Indices of respiratory failure - Oxygenation index ^[8]
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End point description:

Pre- versus post-extubation overall mean values for Supplemental Curosurf and No Supplemental Curosurf groups (Full Analysis Population) are reported.

End point type	Primary
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End point timeframe:

For the indices of respiratory failure, within-group differences between overall pre- and post-extubation mean values were compared using a paired t-test.

Notes:

[8] - 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: No between-group statistical analysis was performed.

End point values	Supplemental Curosurf - Full Analysis Population	No supplemental Curosurf - Full Analysis Population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	18	10		
Units: number				
arithmetic mean (standard deviation)	3.6062 (± 1.50953)	2.9788 (± 1.94566)		

Statistical analyses

No statistical analyses for this end point

Primary: Indices of respiratory failure - Ventilatory index

End point title	Indices of respiratory failure - Ventilatory index ^[9]
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End point description:

Pre- versus post-extubation overall mean values for Supplemental Curosurf and No Supplemental Curosurf groups (Full Analysis Population) are reported.

End point type	Primary
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End point timeframe:

For the indices of respiratory failure, within-group differences between overall pre- and post-extubation mean values were compared using a paired t-test.

Notes:

[9] - 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: No between-group statistical analysis was performed.

End point values	Supplemental Curosurf - Full Analysis Population	No supplemental Curosurf - Full Analysis Population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	7	3		
Units: number				
arithmetic mean (standard deviation)	19.273 ($\pm$ 16.8912)	19.939 ($\pm$ 23.8648)		

Statistical analyses

No statistical analyses for this end point

Primary: Indices of respiratory failure - Aa oxygen gradient

End point title	Indices of respiratory failure - Aa oxygen gradient ^[10]
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End point description:

Pre- versus post-extubation overall mean values for Supplemental Curosurf and No Supplemental Curosurf groups (Full Analysis Population) are reported.

End point type	Primary
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End point timeframe:

For the indices of respiratory failure, within-group differences between overall pre- and post-extubation mean values were compared using a paired t-test.

Notes:

[10] - 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: No between-group statistical analysis was performed.

End point values	Supplemental Curosurf - Full Analysis Population	No supplemental Curosurf - Full Analysis Population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	19	14		
Units: mmHg				
arithmetic mean (standard deviation)	99.81 ($\pm$ 66.905)	82.89 ($\pm$ 42.539)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AE were assessed:

- 1-6 hours pre-extubation;
- at 0 hour extubation;
- 48 hours post-extubation (+/-15 min);
- after 28 days +/- 1 day (follow-up);
- after 36 weeks +/- 3 days (follow-up).

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	8.1
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Reporting groups

Reporting group title	Supplemental Curosurf - Safety Population
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Reporting group description:

The safety population comprised all patients randomized into the study, in which each patient's treatment was as taken on the study.

Reporting group title	No supplemental Curosurf - Safety population
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Reporting group description:

The safety population comprised all patients randomized into the study, in which each patient's treatment was as taken on the study.

Serious adverse events	Supplemental Curosurf - Safety Population	No supplemental Curosurf - Safety population	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 23 (13.04%)	1 / 19 (5.26%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	0	0	
Congenital, familial and genetic disorders			
Pyloric stenosis			
subjects affected / exposed	1 / 23 (4.35%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Intestinal perforation			
subjects affected / exposed	0 / 23 (0.00%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			

Pneumothorax			
subjects affected / exposed	1 / 23 (4.35%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 23 (4.35%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Meningitis			
subjects affected / exposed	1 / 23 (4.35%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 23 (4.35%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 4.3 %

Non-serious adverse events	Supplemental Curosurf - Safety Population	No supplemental Curosurf - Safety population	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	23 / 23 (100.00%)	17 / 19 (89.47%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 23 (8.70%)	1 / 19 (5.26%)	
occurrences (all)	2	1	
Hypotension			
subjects affected / exposed	1 / 23 (4.35%)	1 / 19 (5.26%)	
occurrences (all)	1	1	
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	1 / 23 (4.35%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Oedema			

subjects affected / exposed occurrences (all)	4 / 23 (17.39%) 6	0 / 19 (0.00%) 0	
Respiratory, thoracic and mediastinal disorders			
Apnoea			
subjects affected / exposed	8 / 23 (34.78%)	5 / 19 (26.32%)	
occurrences (all)	11	7	
Bronchial dysplasia			
subjects affected / exposed	1 / 23 (4.35%)	1 / 19 (5.26%)	
occurrences (all)	1	1	
Bronchopulmonary dysplasia			
subjects affected / exposed	2 / 23 (8.70%)	2 / 19 (10.53%)	
occurrences (all)	2	2	
Bronchospasm			
subjects affected / exposed	3 / 23 (13.04%)	2 / 19 (10.53%)	
occurrences (all)	5	2	
Hypercapnia			
subjects affected / exposed	1 / 23 (4.35%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Neonatal respiratory distress syndrome			
subjects affected / exposed	1 / 23 (4.35%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Respiratory disorder			
subjects affected / exposed	0 / 23 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Investigations			
Bilirubin conjugated increased			
subjects affected / exposed	1 / 23 (4.35%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Cardiac murmur			
subjects affected / exposed	1 / 23 (4.35%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Culture positive			
subjects affected / exposed	1 / 23 (4.35%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Echocardiogram abnormal			

subjects affected / exposed occurrences (all)	1 / 23 (4.35%) 1	0 / 19 (0.00%) 0	
Oxygen consumption increased subjects affected / exposed occurrences (all)	1 / 23 (4.35%) 1	0 / 19 (0.00%) 0	
Oxygen saturation decreased subjects affected / exposed occurrences (all)	2 / 23 (8.70%) 3	3 / 19 (15.79%) 7	
Platelet count increased subjects affected / exposed occurrences (all)	1 / 23 (4.35%) 1	0 / 19 (0.00%) 0	
Protein C decreased subjects affected / exposed occurrences (all)	1 / 23 (4.35%) 1	0 / 19 (0.00%) 0	
Congenital, familial and genetic disorders Patent ductus arteriosus subjects affected / exposed occurrences (all)	4 / 23 (17.39%) 5	0 / 19 (0.00%) 0	
Cardiac disorders Bradycardia subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0	1 / 19 (5.26%) 5	
Ventricular hypertrophy subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0	1 / 19 (5.26%) 1	
Nervous system disorders Intraventricular haemorrhage subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0	1 / 19 (5.26%) 1	
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	6 / 23 (26.09%) 6	6 / 19 (31.58%) 10	
Neutropenia subjects affected / exposed occurrences (all)	1 / 23 (4.35%) 1	0 / 19 (0.00%) 0	

Neutrophilia subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0	1 / 19 (5.26%) 1	
Eye disorders			
Conjunctivitis subjects affected / exposed occurrences (all)	3 / 23 (13.04%) 3	3 / 19 (15.79%) 3	
Lenticular opacities subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0	1 / 19 (5.26%) 1	
Retinopathy of prematurity subjects affected / exposed occurrences (all)	8 / 23 (34.78%) 8	6 / 19 (31.58%) 6	
Gastrointestinal disorders			
Diarrhoea subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0	1 / 19 (5.26%) 1	
Enterocolitis subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0	1 / 19 (5.26%) 1	
Gastric disorder subjects affected / exposed occurrences (all)	2 / 23 (8.70%) 2	2 / 19 (10.53%) 2	
Gastrooesophageal reflux disease subjects affected / exposed occurrences (all)	1 / 23 (4.35%) 1	0 / 19 (0.00%) 0	
Vomiting subjects affected / exposed occurrences (all)	1 / 23 (4.35%) 1	0 / 19 (0.00%) 0	
Hepatobiliary disorders			
Cholestasis subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0	2 / 19 (10.53%) 2	
Hyperbilirubinaemia subjects affected / exposed occurrences (all)	1 / 23 (4.35%) 1	0 / 19 (0.00%) 0	
Skin and subcutaneous tissue disorders			

Dermatitis subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0	2 / 19 (10.53%) 2	
Renal and urinary disorders Oliguria subjects affected / exposed occurrences (all)	1 / 23 (4.35%) 1	0 / 19 (0.00%) 0	
Infections and infestations Enterobacter infection subjects affected / exposed occurrences (all) Enterococcal infection subjects affected / exposed occurrences (all) Infection subjects affected / exposed occurrences (all) Klebsiella infection subjects affected / exposed occurrences (all) Pseudomonas infection subjects affected / exposed occurrences (all) Sepsis subjects affected / exposed occurrences (all) Staphylococcal infection subjects affected / exposed occurrences (all) Staphylococcal sepsis subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0 1 / 23 (4.35%) 1 2 / 23 (8.70%) 2 1 / 23 (4.35%) 1 0 / 23 (0.00%) 0 5 / 23 (21.74%) 7 1 / 23 (4.35%) 1 1 / 23 (4.35%) 1	2 / 19 (10.53%) 2 0 / 19 (0.00%) 0 2 / 19 (10.53%) 4 0 / 19 (0.00%) 0 1 / 19 (5.26%) 1 4 / 19 (21.05%) 5 0 / 19 (0.00%) 0 0 / 19 (0.00%) 0	
Metabolism and nutrition disorders Acidosis subjects affected / exposed occurrences (all) Fluid retention	0 / 23 (0.00%) 0	3 / 19 (15.79%) 3	

subjects affected / exposed	0 / 23 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	1
Hyperglycaemia		
subjects affected / exposed	1 / 23 (4.35%)	1 / 19 (5.26%)
occurrences (all)	1	1
Hypoalbuminaemia		
subjects affected / exposed	1 / 23 (4.35%)	0 / 19 (0.00%)
occurrences (all)	1	0
Hypocalcaemia		
subjects affected / exposed	1 / 23 (4.35%)	0 / 19 (0.00%)
occurrences (all)	1	0
Hypochloraemia		
subjects affected / exposed	1 / 23 (4.35%)	0 / 19 (0.00%)
occurrences (all)	1	0
Hypokalaemia		
subjects affected / exposed	2 / 23 (8.70%)	1 / 19 (5.26%)
occurrences (all)	2	1
Hyponatraemia		
subjects affected / exposed	3 / 23 (13.04%)	2 / 19 (10.53%)
occurrences (all)	3	2
Hypovitaminosis		
subjects affected / exposed	1 / 23 (4.35%)	0 / 19 (0.00%)
occurrences (all)	1	0
Metabolic acidosis		
subjects affected / exposed	4 / 23 (17.39%)	5 / 19 (26.32%)
occurrences (all)	4	5

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 February 2006	The original protocol was dated 21 November 2005. There was one protocol amendment dated 14 February 2006. The amendment introduced the following changes to the study: · The planned start date of the study was delayed from January 2006 to March 2006. · The number of centers and investigators was increased from 16 to 19. · The secondary endpoint "Death before discharge" was changed to "Death before 36 weeks PCA" to ensure all patients would be followed until the same time point. · The procedure "physical examination" was removed from the protocol as study patients would not be undergoing "typical" physical examinations during the study. · To ensure more accurate terminology was used, the phrase "critical events" was replaced by "major clinical diagnoses" (MCDs) and these were defined. The event "asphyxia" was added to the list of MCDs. The sensitivity analysis was not performed. · To correct inconsistencies, the schedule of events was updated to reflect the frequency of procedures outlined in Section 7.5. · It was clarified that AEs would not be recorded as such if they occurred before randomization. · The protocol was updated to say that ventilator parameters would be monitored at the follow-up assessments. This was an error in the protocol; if ventilation was still required at follow-up, its parameters are of interest and must be recorded. · The procedures for reporting and recording AEs were updated to comply with the sponsor's Standard Operating Procedures. · Other administrative changes (see protocol amendment included in Section 13.1.1). All modifications were considered to be medically and ethically relevant and the patients' risk was not increased by the amendment.

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.

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

Notes: