Clinical trial results:
A FIRST IN HUMAN CLINICAL STUDY ON THE SAFETY AND TOLERABILITY OF TWO ESCALATING SINGLE DOSES OF CHF 5633 (SYNTHETIC SURFACTANT) IN PRETERM NEONATES WITH RESPIRATORY DISTRESS SYNDROME

Summary

EudraCT number	2011-001331-22
Trial protocol	DE GB CZ
Global end of trial date	23 January 2015
Results information	
Result version number	v2 (current)
This version publication date	10 April 2019
First version publication date	27 July 2016
Version creation reason	• New data added to full data set To report the results of the stand-alone clinical assessment performed to check the neurological status of the preterm born children at 24 months (±3 months) corrected age (CA), previously treated with CHF5633 within 48 hours of life for Respiratory Distress Syndrome (RDS) in the above clinical study.
Summary attachment (see zip file)	CSR ADDENDUM FIH CHF5633 - RESULTS FOLLOW-UP 24MONTHS (CSR ADDENDUM FIH CHF5633 - RESULTS FOLLOW-UP 24MONTHS.pdf)

Trial information

Trial identification	
Sponsor protocol code	CCD-1011-PR-0059
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01651637
WHO universal trial number (UTN)	-

Notes:

Sponsors	
Sponsor organisation name	Chiesi Farmaceutici S.p.A.
Sponsor organisation address	Via Palermo, 26/A, Parma, Italy, 43122
Public contact	Clinical Trial Transparency, Chiesi Farmaceutici S.p.A., ClinicalTrials_info@chiesi.com
Scientific contact	Clinical Trial Transparency, Chiesi Farmaceutici S.p.A., ClinicalTrials_info@chiesi.com

Notes:

Paediatric regulatory details	
Is trial part of an agreed paediatric investigation plan (PIP)	No

Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	23 January 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 January 2015
Global end of trial reached?	Yes
Global end of trial date	23 January 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the safety and tolerability of intratracheal administration of two different single doses of CHF 5633 in preterm neonates with respiratory distress syndrome (RDS) in terms of adverse events (AEs), adverse drug reactions (ADRs), haematology and blood chemistry values, and incidence of major neonatal morbidities and mortality.

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	03 October 2012
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	United Kingdom: 21
Country: Number of subjects enrolled	Czech Republic: 11
Country: Number of subjects enrolled	Germany: 8
Worldwide total number of subjects	40
EEA total number of subjects	40

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	40

wk	
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

In both study cohorts, neonates were recruited/enrolled in a stepwise fashion, based on a safety evaluation following the administration of CHF 5633. If no major safety concerns were raised for each member of the first 4-neonate group and for the group overall, recruitment proceeded to the next 4-neonate group until 20 neonates were enrolled.

Pre-assignment

Screening details:

Seventy-five neonates were screened for the FIH study; 35 failed the screening, based on inclusion/exclusion criteria (n=33), investigator decision (n=1) or consent withdrawal (n=1)

Period 1

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

Blinding implementation details:

Not applicable; this was an open-label study.

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort A

Arm description:

Neonates in cohort A received a single dose of CHF 5633 (100 mg/kg birth weight) administered intratracheally within 48 hours from birth.

Arm type	Experimental
Investigational medicinal product name	CHF 5633
Investigational medicinal product code	
Other name	SP B analogue (CHF 5736.03) + SP-C analogue (CHF 4902.03) + dipalmitoylphosphatidylcholine + 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphoglycerol sodium salt
Pharmaceutical forms	Endotracheopulmonary instillation, suspension
Routes of administration	Intratracheal use

Dosage and administration details:

CHF 5633 (100 mg/kg birth weight) as a single intratracheal dose within 48 hours from birth.

Arm title	Cohort B

Arm description:

After completion of treatment in Cohort A neonates in cohort B received a single dose of CHF 5633 (200 mg/kg birth weight) administered intratracheally within 48 hours from birth.

Arm type	Experimental
Investigational medicinal product name	CHF 5633
Investigational medicinal product code	
Other name	SP B analogue (CHF 5736.03) + SP-C analogue (CHF 4902.03) + dipalmitoylphosphatidylcholine + 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphoglycerol sodium salt
Pharmaceutical forms	Endotracheopulmonary instillation, suspension
Routes of administration	Intratracheal use

Dosage and administration details:

CHF 5633 (200 mg/kg birth weight) as a single intratracheal dose within 48 hours from birth.

Number of subjects in period 1	Cohort A	Cohort B
Started	20	20
Completed	20	19
Not completed	0	1
Adverse event, serious fatal	-	1

Baseline characteristics

Reporting groups

Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	40	40	
Age categorical Units: Subjects			
Newborns (0-27 days)	40	40	
Age continuous			
Age is gestational age.			
Units: weeks arithmetic mean standard deviation	 29.6 ± 1.93	 -	
Gender categorical Units: Subjects			
Female	19	19	
Male	21	21	

Subject analysis sets

Subject analysis set title	Cohort A - Safety/Efficacy analysis
Subject analysis set type	Safety analysis

Subject analysis set description:

All neonates who received any dose level of IMPCHF5633.
This population was used for analysis of safety and efficacy analyses assessments

Subject analysis set title	Cohort B - Safety/Efficacy analysis
Subject analysis set type	Safety analysis

Subject analysis set description:

All neonates who received any dose level of IMPCHF5633.
This population was used for analysis of safety and efficacy analyses assessments

Subject analysis set title	Cohort A - Systemic absorption analysis
Subject analysis set type	Sub-group analysis

Subject analysis set description:

All neonates in the safety population with valid systemic absorption measurements.
This population was used for analysis of SP-B and SP-C analogues.

Subject analysis set title	Cohort B - Systemic absorption analysis
Subject analysis set type	Sub-group analysis

Subject analysis set description:

All neonates in the safety population with valid systemic absorption measurements.
This population was used for analysis of SP-B and SP-C analogues.

Reporting group values	Cohort A - Safety/Efficacy analysis	Cohort B - Safety/Efficacy analysis	Cohort A - Systemic absorption analysis
Number of subjects	20	20	20

Age categorical Units: Subjects			
Newborns (0-27 days)	20	20	20
Age continuous			
Age is gestational age.			
Units: weeks arithmetic mean standard deviation	 29.6 ± 2.04	 29.6 ± 1.88	 29.6 ± 2.04
Gender categorical Units: Subjects			
Female	9	10	9
Male	11	10	11

Reporting group values	Cohort B - Systemic absorption analysis		
Number of subjects	20		
Age categorical Units: Subjects			
Newborns (0-27 days)	20		
Age continuous			
Age is gestational age.			
Units: weeks arithmetic mean standard deviation	 29.6 ± 1.88		
Gender categorical Units: Subjects			
Female	10		
Male	10		

End points

End points reporting groups

Reporting group title	Cohort A

Reporting group description:

Neonates in cohort A received a single dose of CHF 5633 (100 mg/kg birth weight) administered intratracheally within 48 hours from birth.

Reporting group title	Cohort B

Reporting group description:

After completion of treatment in Cohort A neonates in cohort B received a single dose of CHF 5633 (200 mg/kg birth weight) administered intratracheally within 48 hours from birth.

Subject analysis set title	Cohort A - Safety/Efficacy analysis
Subject analysis set type	Safety analysis

Subject analysis set description:

All neonates who received any dose level of IMPCHF5633.
This population was used for analysis of safety and efficacy analyses assessments

Subject analysis set title	Cohort B - Safety/Efficacy analysis
Subject analysis set type	Safety analysis

Subject analysis set description:

All neonates who received any dose level of IMPCHF5633.
This population was used for analysis of safety and efficacy analyses assessments

Subject analysis set title	Cohort A - Systemic absorption analysis
Subject analysis set type	Sub-group analysis

Subject analysis set description:

All neonates in the safety population with valid systemic absorption measurements.
This population was used for analysis of SP-B and SP-C analogues.

Subject analysis set title	Cohort B - Systemic absorption analysis
Subject analysis set type	Sub-group analysis

Subject analysis set description:

All neonates in the safety population with valid systemic absorption measurements.
This population was used for analysis of SP-B and SP-C analogues.

Primary: Systolic blood pressure

End point title	Systolic blood pressure[1]

End point description:

Only changes from baseline at 24 hrs for the two cohorts separately are reported here.

End point type	Primary

End point timeframe:

Observed and change from baseline values of vital signs by cohort and overall were assessed following CHF 5633 administration at:
- 30 minutes
- 1, 3, 6, 12, 24 hours
- 2, 3, 5, 7 days
- in the follow-up period

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: No statistical analys was performed.

End point values	Cohort A - Safety/Efficacy analysis	Cohort B - Safety/Efficacy analysis		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	18	20		
Units: mmHg				
arithmetic mean (standard deviation)	3.8 (± 9.05)	4.7 (± 7.15)		

Statistical analyses

No statistical analyses for this end point

Primary: Diastolic blood pressure

End point title	Diastolic blood pressure[2]

End point description:

Only changes from baseline at 24 hrs for the two cohorts separately are reported here.

End point type	Primary

End point timeframe:

Observed and change from baseline values of vital signs by cohort and overall were assessed following CHF 5633 administration at:
- 30 minutes
- 1, 3, 6, 12, 24 hours
- 2, 3, 5, 7 days
- in the follow-up period

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 statistical analys was performed.

End point values	Cohort A - Safety/Efficacy analysis	Cohort B - Safety/Efficacy analysis		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	18	20		
Units: mmHg				
arithmetic mean (standard deviation)	3.6 (± 8.54)	5.8 (± 7.92)		

Statistical analyses

No statistical analyses for this end point

Primary: Heart rate

End point title	Heart rate[3]

End point description:

Only changes from baseline at 24 hrs for the two cohorts separately are reported here.

End point type	Primary

End point timeframe:

Observed and change from baseline values of vital signs by cohort and overall were assessed following CHF 5633 administration at:
- 30 minutes

- 1, 3, 6, 12, 24 hours
- 2, 3, 5, 7 days
- in the follow-up period

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 statistical analys was performed.

End point values	Cohort A - Safety/Efficacy analysis	Cohort B - Safety/Efficacy analysis		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	20		
Units: bpm				
arithmetic mean (standard deviation)	-0.4 (± 22.36)	-0.7 (± 11.17)		

Statistical analyses

No statistical analyses for this end point

Secondary: SpO2

End point title	SpO2

End point description:

Only changes from baseline at 24 hrs for the two cohorts separately are reported here

End point type	Secondary

End point timeframe:

Observed and change from baseline values by cohort and overall were assessed following CHF 5633 administration at:
- 30 minutes
- 1, 3, 6, 12, 24 hours
- 2, 3, 5, 7 days
- in the follow-up period

End point values	Cohort A - Safety/Efficacy analysis	Cohort B - Safety/Efficacy analysis		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	20		
Units: percent				
arithmetic mean (standard deviation)	2.3 (± 3.93)	2.6 (± 2.91)		

Statistical analyses

No statistical analyses for this end point

Secondary: FiO2

End point title	FiO2

End point description:

Only changes from baseline at 24 hrs for the two cohorts separately are reported here.

End point type	Secondary

End point timeframe:

Observed and change from baseline values by cohort and overall were assessed following CHF 5633 administration at:
- 30 minutes
- 1, 3, 6, 12, 24 hours
- 2, 3, 5, 7 days
- in the follow-up period

End point values	Cohort A - Safety/Efficacy analysis	Cohort B - Safety/Efficacy analysis		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	16	19		
Units: percent				
arithmetic mean (standard deviation)	-23.4 (± 19.09)	-29.4 (± 13.68)		

Statistical analyses

No statistical analyses for this end point

Secondary: FiO2 AUC0-6

End point title	FiO2 AUC0-6

End point description:

Only data for the two cohorts separately are reported here.

End point type	Secondary

End point timeframe:

FiO2 AUC0-6 was assessed for the two cohorts and for the overall population based on the measurements performed at 30 min and 1, 3 and 6 hours following CHF 5633 administration.

End point values	Cohort A - Safety/Efficacy analysis	Cohort B - Safety/Efficacy analysis		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	19	20		
Units: digit				
arithmetic mean (standard deviation)	160.3 (± 29.94)	159 (± 39.38)		

Statistical analyses

No statistical analyses for this end point

Secondary: FiO2 AUC0-12

End point title	FiO2 AUC0-12

End point description:

Only data for the two cohorts separately are reported here.

End point type	Secondary

End point timeframe:

FiO2 AUC0-12 was assessed for the two cohorts and for the overall population based on the measurements performed at 30 min and 1, 3, 6 and 12 hours following CHF 5633 administration.

End point values	Cohort A - Safety/Efficacy analysis	Cohort B - Safety/Efficacy analysis		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	19	20		
Units: digit				
arithmetic mean (standard deviation)	306.8 (± 55.34)	159 (± 39.38)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean airway pressure (MAP)

End point title	Mean airway pressure (MAP)

End point description:

Only changes from baseline at 24 hrs for the two cohorts separately are reported here.

End point type	Secondary

End point timeframe:

Observed and change from baseline values by cohort and overall were assessed following CHF 5633 administration at:
- 30 minutes
- 1, 3, 6, 12, 24 hours
- 2, 3, 5, 7 days
- in the follow-up period

End point values	Cohort A - Safety/Efficacy analysis	Cohort B - Safety/Efficacy analysis		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	5	2		
Units: cmH2O				
arithmetic mean (standard deviation)	-1 (± 1.17)	-3.1 (± 4.03)		

Statistical analyses

No statistical analyses for this end point

Secondary: Peak inspiratory pressure (PIP)

End point title	Peak inspiratory pressure (PIP)

End point description:

Only changes from baseline at 24 hrs for cohort A are reported here. Values for Cohort B were not estimable.

End point type	Secondary

End point timeframe:

Observed and change from baseline values by cohort and overall were assessed following CHF 5633 administration at:
- 30 minutes
- 1, 3, 6, 12, 24 hours
- 2, 3, 5, 7 days
- in the follow-up period

End point values	Cohort A - Safety/Efficacy analysis			
Subject group type	Subject analysis set			
Number of subjects analysed	2			
Units: cmH2O				
arithmetic mean (standard deviation)	-6 (± 0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Positive end-expiratory pressure (PEEP)

End point title	Positive end-expiratory pressure (PEEP)

End point description:

Only changes from baseline at 24 hrs for the two cohorts separately are reported here.

End point type	Secondary

End point timeframe:

Observed and change from baseline values by cohort and overall were assessed following CHF 5633 administration at:
- 30 minutes
- 1, 3, 6, 12, 24 hours
- 2, 3, 5, 7 days
- in the follow-up period

End point values	Cohort A - Safety/Efficacy analysis	Cohort B - Safety/Efficacy analysis		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	16		
Units: cmH2O				
arithmetic mean (standard deviation)	-0.3 (± 1.37)	0.3 (± 1.32)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of invasive ventilation

End point title	Duration of invasive ventilation

End point description:

End point type	Secondary

End point timeframe:

Assessments concerning ventilation following CHF 5633 administration were performed at:
- 30 minutes
- 1, 3, 6, 12, 24 hours
- 2, 3, 5, 7 days
- in the follow-up period

End point values	Cohort A - Safety/Efficacy analysis	Cohort B - Safety/Efficacy analysis		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	16	14		
Units: days				
arithmetic mean (standard deviation)	1.5 (± 2.56)	1.3 (± 3.04)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of non-invasive ventilation

End point title	Duration of non-invasive ventilation

End point description:

End point type	Secondary

End point timeframe:

Assessments concerning ventilation following CHF 5633 administration were performed at:
- 30 minutes
- 1, 3, 6, 12, 24 hours
- 2, 3, 5, 7 days
- in the follow-up period

End point values	Cohort A - Safety/Efficacy analysis	Cohort B - Safety/Efficacy analysis		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	18	20		
Units: days				
arithmetic mean (standard deviation)	17.6 (± 14.2)	10.7 (± 10.79)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of nasal continuous positive airway pressure (nCPAP)

End point title	Duration of nasal continuous positive airway pressure (nCPAP)

End point description:

End point type	Secondary

End point timeframe:

Assessments concerning nCPAP following CHF 5633 administration were performed at:
- 30 minutes
- 1, 3, 6, 12, 24 hours
- 2, 3, 5, 7 days
- in the follow-up period

End point values	Cohort A - Safety/Efficacy analysis	Cohort B - Safety/Efficacy analysis		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	18	20		
Units: days				
arithmetic mean (standard deviation)	17.5 (± 14.13)	10.7 (± 10.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of non-responders receiving rescue treatment

End point title	Number of non-responders receiving rescue treatment

End point description:

End point type	Secondary

End point timeframe:

Number of non-responders was assessed based on the administration of rescue treatment (poractant alfa) at 1, 3, 6, 12 and 24 hours as needed

End point values	Cohort A - Safety/Efficacy analysis	Cohort B - Safety/Efficacy analysis		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	20		
Units: integer	1	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were monitored on a continual basis for the first 7 days following treatment. Adverse events that were ongoing at Day 7, together with any new AEs were evaluated at Days 10 and 28, at discharge home, and the Week 36 PMA.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	12.0

Reporting groups

Reporting group title	Cohort A - Safety population
Reporting group description: -	
Reporting group title	Cohort B - Safety population

Reporting group description: -

Serious adverse events	Cohort A - Safety population	Cohort B - Safety population	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 20 (0.00%)	2 / 20 (10.00%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0	0	
Gastrointestinal disorders			
Necrotising enterocolitis neonatal			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Infections and infestations			
Bronchiolitis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Cohort A - Safety population	Cohort B - Safety population	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	19 / 20 (95.00%)	19 / 20 (95.00%)	

Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Pregnancy, puerperium and perinatal conditions			
Jaundice neonatal			
subjects affected / exposed	6 / 20 (30.00%)	2 / 20 (10.00%)	
occurrences (all)	7	3	
General disorders and administration site conditions			
Oedema			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Bronchopulmonary dysplasia			
subjects affected / exposed	2 / 20 (10.00%)	2 / 20 (10.00%)	
occurrences (all)	2	2	
Infantile apnoeic attack			
subjects affected / exposed	2 / 20 (10.00%)	5 / 20 (25.00%)	
occurrences (all)	2	5	
Neonatal respiratory distress syndrome			
subjects affected / exposed	2 / 20 (10.00%)	0 / 20 (0.00%)	
occurrences (all)	2	0	
Pneumothorax			
subjects affected / exposed	1 / 20 (5.00%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Pulmonary hypertension			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Pulmonary interstitial emphysema syndrome			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Pulmonary oedema			
subjects affected / exposed	3 / 20 (15.00%)	1 / 20 (5.00%)	
occurrences (all)	3	1	
Investigations			

Blood bilirubin increased			
subjects affected / exposed	1 / 20 (5.00%)	1 / 20 (5.00%)	
occurrences (all)	2	2	
Blood phosphorus decreased			
subjects affected / exposed	2 / 20 (10.00%)	0 / 20 (0.00%)	
occurrences (all)	2	0	
Cardiac murmur			
subjects affected / exposed	2 / 20 (10.00%)	0 / 20 (0.00%)	
occurrences (all)	2	0	
Chest X-ray abnormal			
subjects affected / exposed	2 / 20 (10.00%)	0 / 20 (0.00%)	
occurrences (all)	2	0	
Staphylococcal identification test positive			
subjects affected / exposed	2 / 20 (10.00%)	0 / 20 (0.00%)	
occurrences (all)	2	0	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Endotracheal intubation complication			
subjects affected / exposed	1 / 20 (5.00%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Congenital, familial and genetic disorders			
Atrial septal defect			
subjects affected / exposed	0 / 20 (0.00%)	2 / 20 (10.00%)	
occurrences (all)	0	2	
Patent ductus arteriosus			
subjects affected / exposed	4 / 20 (20.00%)	2 / 20 (10.00%)	
occurrences (all)	4	2	
Cardiac disorders			
Tachycardia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	2	0	
Nervous system disorders			

Cerebral haemorrage			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Intraventricular haemorrhage neonatal			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Periventricular leukomalacia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Anemia neonatal			
subjects affected / exposed	2 / 20 (10.00%)	2 / 20 (10.00%)	
occurrences (all)	3	2	
Leukocytosis			
subjects affected / exposed	2 / 20 (10.00%)	0 / 20 (0.00%)	
occurrences (all)	2	0	
Neutrophilia			
subjects affected / exposed	2 / 20 (10.00%)	0 / 20 (0.00%)	
occurrences (all)	2	0	
Eye disorders			
Conjunctivitis			
subjects affected / exposed	0 / 20 (0.00%)	2 / 20 (10.00%)	
occurrences (all)	0	2	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	4 / 20 (20.00%)	2 / 20 (10.00%)	
occurrences (all)	4	2	
Flatulence			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Necrotising colitis			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	

Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	3 / 20 (15.00%)	10 / 20 (50.00%)	
occurrences (all)	3	10	
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Osteopenia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Bacterial infection			
subjects affected / exposed	1 / 20 (5.00%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Bacterial sepsis			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	2	0	
Enterococcal sepsis			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Eye infection bacterial			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	2	
Eye infection staphylococcal			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Oral candidiasis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Sepsis			

subjects affected / exposed	1 / 20 (5.00%)	2 / 20 (10.00%)	
occurrences (all)	1	2	
Staphylococcal infection			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	2 / 20 (10.00%)	0 / 20 (0.00%)	
occurrences (all)	2	0	
Hypernatraemia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Hypoglycaemia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	3	0	
Hypokalaemia			
subjects affected / exposed	3 / 20 (15.00%)	0 / 20 (0.00%)	
occurrences (all)	3	0	
Hyponatraemia			
subjects affected / exposed	8 / 20 (40.00%)	3 / 20 (15.00%)	
occurrences (all)	9	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 April 2012	• Added central laboratory in charge of immunogenicity • Added role of clinical pharmacologist • Provided details and purpose of 24-month assessments • Clarified "original value" for blood chemistry results • Updated planned study start and end • Clarified the characteristics and role of the independent member of the Safety Monitoring Board • Clarified the stopping rules of the study and the processes for managing risk and escalating the dose • Added dedicated section for immunogenicity assessment • Added the Contract Research Organization safety contact • Clarified the serious adverse event reporting procedure • Added Safety Monitoring Board charter as protocol appendix
01 July 2013	• Increased number of sites from 6 to 12 to speed up enrolment • Extended period for IMP administration from within 24 hours to within 48 hours from birth to allow Investigators more time to speak with parents and explain procedures better. • Extended in agreement with the Central Laboratory the window to take the blood sample for immunogenicity assessments in serum from 4 to 12 weeks to 3 to 12 weeks to allow a more flexible interval to the Investigators. • Included the possibility that neonates might have been transferred to a continuing care site and added instructions for continued safety monitoring when this occurred • Allowed the use of a less invasive surfactant administration technique with rapid extubation (InSurE) • Redefined the end of the trial as the date of discharge home to take the continuing care sites into account • Extended the recruitment period

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.

No limitations or caveats are applicable to this summary of the results.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/28465315