Clinical trial results:
AN INTERNATIONAL, OPEN, RANDOMIZED, CONTROLLED STUDY TO EVALUATE THE EFFICACY OF COMBINING PROPHYLACTIC CUROSURF WITH EARLY NASAL CPAP VERSUS EARLY NASAL CPAP ALONE IN VERY PRETERM INFANTS AT RISK OF RESPIRATORY DISTRESS SYNDROME

Summary

EudraCT number	2006-004105-25
Trial protocol	CZ IT FR PT
Global end of trial date	14 May 2008

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/5000/002/04

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00501982
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	28 November 2008
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 May 2008
Global end of trial reached?	Yes
Global end of trial date	14 May 2008
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is a comparative evaluation of the two methods of post-delivery stabilization and subsequent early respiratory care (nCPAP alone versus prophylactic surfactant [Curosurf®]+nCPAP) for reducing the need for mechanical ventilation (MV) and related secondary complications, such as BPD (Bronchopulmonary dysplasia), in premature babies at high risk of RDS (Respiratory Distress Syndrome):
1. Early stabilization on nCPAP (nasal continuous positive airway pressure).
2. Intubation, prophylactic surfactant (Curosurf) administration shortly after delivery, and rapid extubation to nCPAP.

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	13 March 2007
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	Portugal: 5
Country: Number of subjects enrolled	Spain: 9
Country: Number of subjects enrolled	Czech Republic: 125
Country: Number of subjects enrolled	France: 13
Country: Number of subjects enrolled	Italy: 56
Worldwide total number of subjects	208
EEA total number of subjects	208

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	208

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:

Premature infants breathing spontaneously and meeting inclusion criteria
were randomised (n=208) immediately after birth to either nCPAP alone (n=103) or prophylactic Curosurf® + nCPAP (n=105). Neonates will be randomly assigned to one of the two treatment groups within one of the two strata with a 1: 1 ratio.

Pre-assignment

Screening details:

Screening of the infants will be initiated when a woman is expected to deliver a viable baby with a GA of ≥ 25+0 weeks to < 28+6 weeks.

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 unblinded study.

Arms

Are arms mutually exclusive?	Yes
Arm title	Curosurf®+nCPAP Group

Arm description:

Prophylactic Curosurf® at 200 mg/kg and further 100 mg/kg rescue doses in the event of clinical needs during their staying in Neonatal Intensive Care Unit (NICU) in addition to nasal Continuous Positive Airway Pressure (nCPAP).

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:

Prophylactic dose of 200 mg/kg or rescue dose of 100 mg/kg administered via intratracheal route, taken from single dose 1.5ml
vials containing phopholipid fraction from Porcine lung 120mg together with sodium chloride and water as excipients.

Arm title	nCPAP Group

Arm description:

Nasal Continuous Positive Airway Pressure (nCPAP).
(Infants in the nCPAP group were permitted to receive an initial rescue dose of 200 mg/kg in the event of nCPAP failure and further 100 mg/kg rescue doses in the event of clinical needs during their staying in NICU).

Arm type	Active comparator
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:

Prophylactic dose of 200 mg/kg or rescue dose of 100 mg/kg administered via intratracheal route, taken from single dose 1.5ml
vials containing phopholipid fraction from Porcine lung 120mg together with sodium chloride and water

as excipients.

Number of subjects in period 1	Curosurf®+nCPAP Group	nCPAP Group
Started	105	103
Completed	91	87
Not completed	14	16
Discretion of the investigator or sponsor	1	-
Adverse event, non-fatal	-	2
Death	9	11
No matching reasons found	3	1
Protocol deviation	1	2

Baseline characteristics

Reporting groups

Reporting group title	Curosurf®+nCPAP Group

Reporting group description:

Prophylactic Curosurf® at 200 mg/kg and further 100 mg/kg rescue doses in the event of clinical needs during their staying in Neonatal Intensive Care Unit (NICU) in addition to nasal Continuous Positive Airway Pressure (nCPAP).

Reporting group title	nCPAP Group

Reporting group description:

Nasal Continuous Positive Airway Pressure (nCPAP).
(Infants in the nCPAP group were permitted to receive an initial rescue dose of 200 mg/kg in the event of nCPAP failure and further 100 mg/kg rescue doses in the event of clinical needs during their staying in NICU).

Reporting group values	Curosurf®+nCPAP Group	nCPAP Group	Total
Number of subjects	105	103	208
Age categorical Units: Subjects			
Preterm newborn infants (gestational age < 37 wks)	105	103	208
Gender categorical Units: Subjects			
Female	48	49	97
Male	57	54	111

Subject analysis sets

Subject analysis set title	Curosurf®+nCPAP Group - ITT population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The Intention-to-Treat (ITT) population comprised all randomised infants who had at least one evaluation of any efficacy available.

Subject analysis set title	nCPAP Group - ITT population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The Intention-to-Treat (ITT) population comprised all randomised infants who had at least one evaluation of any efficacy available

Reporting group values	Curosurf®+nCPAP Group - ITT population	nCPAP Group - ITT population	
Number of subjects	105	103	
Age categorical Units: Subjects			
Preterm newborn infants (gestational age < 37 wks)	105	103	
Gender categorical Units: Subjects			
Female	48	49	
Male	57	54	

End points

End points reporting groups

Reporting group title	Curosurf®+nCPAP Group

Reporting group description:

Prophylactic Curosurf® at 200 mg/kg and further 100 mg/kg rescue doses in the event of clinical needs during their staying in Neonatal Intensive Care Unit (NICU) in addition to nasal Continuous Positive Airway Pressure (nCPAP).

Reporting group title	nCPAP Group

Reporting group description:

Nasal Continuous Positive Airway Pressure (nCPAP).
(Infants in the nCPAP group were permitted to receive an initial rescue dose of 200 mg/kg in the event of nCPAP failure and further 100 mg/kg rescue doses in the event of clinical needs during their staying in NICU).

Subject analysis set title	Curosurf®+nCPAP Group - ITT population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The Intention-to-Treat (ITT) population comprised all randomised infants who had at least one evaluation of any efficacy available.

Subject analysis set title	nCPAP Group - ITT population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The Intention-to-Treat (ITT) population comprised all randomised infants who had at least one evaluation of any efficacy available

Primary: Incidence of the Need for Mechanical Ventilation in the First 5 Days of Life

End point title	Incidence of the Need for Mechanical Ventilation in the First 5 Days of Life

End point description:

End point type	Primary

End point timeframe:

From birth until Day 5 of life (post-treatment)

End point values	Curosurf®+nCPAP Group - ITT population	nCPAP Group - ITT population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	105	103		
Units: Subjects				
Yes	33	34		
No	72	69		

Statistical analyses

Statistical analysis title	Curosurf®+nCPAP vs nCPAP
Comparison groups	Curosurf®+nCPAP Group - ITT population v nCPAP Group - ITT population

Number of subjects included in analysis	208
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.7991
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk ratio (RR)
Point estimate	0.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.64
upper limit	1.41

Notes:

[1] - The primary efficacy analysis compared nCPAP alone to prophylactic Curosurf®+nCPAP for the proportion of subjects who had MV in the first 5 days of life. The Cochran-Mantel-Haenszel (CMH) test which adjusts for the stratification factors of GA was used. P-values, odds ratios (OR) and 95% confidence intervals (CI) were reported.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From birth throughout the study phase (the first 5 days of life) and the follow-up till the hospital discharge.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	9.1

Reporting groups

Reporting group title	Curosurf + nCPAP - Safety population

Reporting group description:

The safety population comprised all randomised infants.

Reporting group title	nCPAP - Safety population

Reporting group description:

The safety population comprised all randomised infants.

Serious adverse events	Curosurf + nCPAP - Safety population	nCPAP - Safety population	
Total subjects affected by serious adverse events			
subjects affected / exposed	15 / 105 (14.29%)	23 / 103 (22.33%)	
number of deaths (all causes)	9	11	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Skin laceration			
subjects affected / exposed	0 / 105 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Coarctation of the aorta			
subjects affected / exposed	1 / 105 (0.95%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital anomaly			
subjects affected / exposed	0 / 105 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Vascular disorders			

Hypotension			
subjects affected / exposed	2 / 105 (1.90%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Shock			
subjects affected / exposed	1 / 105 (0.95%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Vena cava thrombosis			
subjects affected / exposed	1 / 105 (0.95%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac disorders			
Bradycardia			
subjects affected / exposed	1 / 105 (0.95%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 105 (0.95%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Cardiopulmonary failure			
subjects affected / exposed	0 / 105 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumopericardium			
subjects affected / exposed	1 / 105 (0.95%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorders			
Cerebral haemorrhage			
subjects affected / exposed	0 / 105 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Haemorrhage intracranial			
subjects affected / exposed	0 / 105 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrocephalus			
subjects affected / exposed	0 / 105 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intraventricular haemorrhage			
subjects affected / exposed	1 / 105 (0.95%)	2 / 103 (1.94%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Periventricular leukomalacia			
subjects affected / exposed	0 / 105 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 105 (0.95%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 105 (0.95%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 105 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	1 / 105 (0.95%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Intestinal ischaemia			
subjects affected / exposed	0 / 105 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation			
subjects affected / exposed	1 / 105 (0.95%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meconium ileus			
subjects affected / exposed	0 / 105 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Necrotising colitis			
subjects affected / exposed	3 / 105 (2.86%)	6 / 103 (5.83%)	
occurrences causally related to treatment / all	0 / 3	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 2	
Peritonitis			
subjects affected / exposed	1 / 105 (0.95%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumoperitoneum			
subjects affected / exposed	1 / 105 (0.95%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Apnoea			
subjects affected / exposed	0 / 105 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercapnia			
subjects affected / exposed	0 / 105 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hypoxia			
subjects affected / exposed	1 / 105 (0.95%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Laryngeal stenosis			
subjects affected / exposed	0 / 105 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	2 / 105 (1.90%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 105 (0.95%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary haemorrhage			
subjects affected / exposed	0 / 105 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory failure			
subjects affected / exposed	3 / 105 (2.86%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 3	0 / 0	
Renal and urinary disorders			
Oliguria			
subjects affected / exposed	1 / 105 (0.95%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Renal failure			
subjects affected / exposed	2 / 105 (1.90%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Infections and infestations			

Cytomegalovirus viraemia			
subjects affected / exposed	1 / 105 (0.95%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Neonatal infection			
subjects affected / exposed	1 / 105 (0.95%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonia cytomegaloviral			
subjects affected / exposed	1 / 105 (0.95%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Sepsis			
subjects affected / exposed	4 / 105 (3.81%)	3 / 103 (2.91%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 2	0 / 2	
Septic shock			
subjects affected / exposed	0 / 105 (0.00%)	3 / 103 (2.91%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 3	
Metabolism and nutrition disorders			
Lactic acidosis			
subjects affected / exposed	0 / 105 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metabolic acidosis			
subjects affected / exposed	2 / 105 (1.90%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Curosurf + nCPAP - Safety population	nCPAP - Safety population	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	55 / 105 (52.38%)	45 / 103 (43.69%)	
Vascular disorders			
Hypoperfusion			
subjects affected / exposed	0 / 105 (0.00%)	1 / 103 (0.97%)	
occurrences (all)	0	1	
Hypotension			
subjects affected / exposed	13 / 105 (12.38%)	11 / 103 (10.68%)	
occurrences (all)	13	12	
Poor peripheral circulation			
subjects affected / exposed	1 / 105 (0.95%)	1 / 103 (0.97%)	
occurrences (all)	1	1	
Pregnancy, puerperium and perinatal conditions			
Jaundice neonatal			
subjects affected / exposed	3 / 105 (2.86%)	6 / 103 (5.83%)	
occurrences (all)	3	6	
General disorders and administration site conditions			
Catheter site haemorrhage			
subjects affected / exposed	0 / 105 (0.00%)	1 / 103 (0.97%)	
occurrences (all)	0	1	
Oedema			
subjects affected / exposed	0 / 105 (0.00%)	1 / 103 (0.97%)	
occurrences (all)	0	1	
Pain			
subjects affected / exposed	0 / 105 (0.00%)	1 / 103 (0.97%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Apnoea			
subjects affected / exposed	14 / 105 (13.33%)	22 / 103 (21.36%)	
occurrences (all)	14	23	
Asphyxia			
subjects affected / exposed	1 / 105 (0.95%)	0 / 103 (0.00%)	
occurrences (all)	1	0	
Atelectasis			

subjects affected / exposed	1 / 105 (0.95%)	0 / 103 (0.00%)	
occurrences (all)	1	0	
Bronchospasm			
subjects affected / exposed	0 / 105 (0.00%)	1 / 103 (0.97%)	
occurrences (all)	0	1	
Dyspnoea			
subjects affected / exposed	0 / 105 (0.00%)	1 / 103 (0.97%)	
occurrences (all)	0	1	
Infantile apnoeic attack			
subjects affected / exposed	1 / 105 (0.95%)	1 / 103 (0.97%)	
occurrences (all)	1	1	
Pulmonary haemorrhage			
subjects affected / exposed	2 / 105 (1.90%)	0 / 103 (0.00%)	
occurrences (all)	2	0	
Pulmonary hypertension			
subjects affected / exposed	0 / 105 (0.00%)	1 / 103 (0.97%)	
occurrences (all)	0	1	
Respiratory acidosis			
subjects affected / exposed	1 / 105 (0.95%)	0 / 103 (0.00%)	
occurrences (all)	1	0	
Tachypnoea			
subjects affected / exposed	1 / 105 (0.95%)	0 / 103 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 105 (0.00%)	1 / 103 (0.97%)	
occurrences (all)	0	1	
Investigations			
Blood culture positive			
subjects affected / exposed	0 / 105 (0.00%)	1 / 103 (0.97%)	
occurrences (all)	0	1	
C-reactive protein increased			
subjects affected / exposed	2 / 105 (1.90%)	1 / 103 (0.97%)	
occurrences (all)	2	1	
Cardiac murmur			

subjects affected / exposed	0 / 105 (0.00%)	3 / 103 (2.91%)	
occurrences (all)	0	5	
Neutrophil count abnormal			
subjects affected / exposed	0 / 105 (0.00%)	2 / 103 (1.94%)	
occurrences (all)	0	2	
Respiratory rate increased			
subjects affected / exposed	0 / 105 (0.00%)	1 / 103 (0.97%)	
occurrences (all)	0	1	
Urine output decreased			
subjects affected / exposed	2 / 105 (1.90%)	0 / 103 (0.00%)	
occurrences (all)	2	0	
Injury, poisoning and procedural complications			
Operative haemorrhage			
subjects affected / exposed	1 / 105 (0.95%)	0 / 103 (0.00%)	
occurrences (all)	1	0	
Transfusion reaction			
subjects affected / exposed	1 / 105 (0.95%)	1 / 103 (0.97%)	
occurrences (all)	1	1	
Congenital, familial and genetic disorders			
Hypospadias			
subjects affected / exposed	2 / 105 (1.90%)	1 / 103 (0.97%)	
occurrences (all)	2	1	
Patent ductus arteriosus			
subjects affected / exposed	2 / 105 (1.90%)	1 / 103 (0.97%)	
occurrences (all)	2	1	
Talipes			
subjects affected / exposed	1 / 105 (0.95%)	0 / 103 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Bradycardia			
subjects affected / exposed	0 / 105 (0.00%)	2 / 103 (1.94%)	
occurrences (all)	0	2	
Tachycardia			
subjects affected / exposed	0 / 105 (0.00%)	1 / 103 (0.97%)	
occurrences (all)	0	1	
Ventricular hypokinesia			

subjects affected / exposed	1 / 105 (0.95%)	0 / 103 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Cerebral haematoma			
subjects affected / exposed	1 / 105 (0.95%)	0 / 103 (0.00%)	
occurrences (all)	1	0	
Intraventricular haemorrhage			
subjects affected / exposed	0 / 105 (0.00%)	2 / 103 (1.94%)	
occurrences (all)	0	2	
Blood and lymphatic system disorders			
Anaemia neonatal			
subjects affected / exposed	5 / 105 (4.76%)	6 / 103 (5.83%)	
occurrences (all)	5	6	
Anaemia			
subjects affected / exposed	5 / 105 (4.76%)	4 / 103 (3.88%)	
occurrences (all)	6	5	
Coagulopathy			
subjects affected / exposed	1 / 105 (0.95%)	0 / 103 (0.00%)	
occurrences (all)	1	0	
Leukaemoid reaction			
subjects affected / exposed	1 / 105 (0.95%)	0 / 103 (0.00%)	
occurrences (all)	1	0	
Leukocytosis			
subjects affected / exposed	1 / 105 (0.95%)	0 / 103 (0.00%)	
occurrences (all)	1	0	
Leukopenia			
subjects affected / exposed	1 / 105 (0.95%)	2 / 103 (1.94%)	
occurrences (all)	1	2	
Thrombocythaemia			
subjects affected / exposed	0 / 105 (0.00%)	1 / 103 (0.97%)	
occurrences (all)	0	1	
Thrombocytopenia			
subjects affected / exposed	1 / 105 (0.95%)	1 / 103 (0.97%)	
occurrences (all)	1	1	
Eye disorders			

Conjunctivitis			
subjects affected / exposed	2 / 105 (1.90%)	3 / 103 (2.91%)	
occurrences (all)	2	4	
Retinopathy			
subjects affected / exposed	0 / 105 (0.00%)	1 / 103 (0.97%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Colitis ulcerative			
subjects affected / exposed	0 / 105 (0.00%)	1 / 103 (0.97%)	
occurrences (all)	0	1	
Gastrointestinal disorder			
subjects affected / exposed	1 / 105 (0.95%)	0 / 103 (0.00%)	
occurrences (all)	1	0	
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 105 (0.00%)	3 / 103 (2.91%)	
occurrences (all)	0	3	
Inguinal hernia			
subjects affected / exposed	4 / 105 (3.81%)	4 / 103 (3.88%)	
occurrences (all)	5	5	
Intestinal perforation			
subjects affected / exposed	1 / 105 (0.95%)	0 / 103 (0.00%)	
occurrences (all)	1	0	
Rectal haemorrhage			
subjects affected / exposed	0 / 105 (0.00%)	1 / 103 (0.97%)	
occurrences (all)	0	1	
Umbilical hernia			
subjects affected / exposed	0 / 105 (0.00%)	1 / 103 (0.97%)	
occurrences (all)	0	1	
Hepatobiliary disorders			
Cholestasis			
subjects affected / exposed	0 / 105 (0.00%)	1 / 103 (0.97%)	
occurrences (all)	0	1	
Hyperbilirubinaemia			
subjects affected / exposed	21 / 105 (20.00%)	12 / 103 (11.65%)	
occurrences (all)	21	12	
Jaundice			

subjects affected / exposed	3 / 105 (2.86%)	5 / 103 (4.85%)	
occurrences (all)	3	5	
Skin and subcutaneous tissue disorders			
Erythema toxicum neonatorum			
subjects affected / exposed	1 / 105 (0.95%)	0 / 103 (0.00%)	
occurrences (all)	1	0	
Rash generalised			
subjects affected / exposed	0 / 105 (0.00%)	1 / 103 (0.97%)	
occurrences (all)	0	1	
Skin erosion			
subjects affected / exposed	1 / 105 (0.95%)	0 / 103 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 105 (0.95%)	0 / 103 (0.00%)	
occurrences (all)	1	0	
Oliguria			
subjects affected / exposed	1 / 105 (0.95%)	3 / 103 (2.91%)	
occurrences (all)	1	3	
Infections and infestations			
Bacterial sepsis			
subjects affected / exposed	1 / 105 (0.95%)	0 / 103 (0.00%)	
occurrences (all)	1	0	
Brain abscess			
subjects affected / exposed	1 / 105 (0.95%)	0 / 103 (0.00%)	
occurrences (all)	1	0	
Bronchopneumonia			
subjects affected / exposed	0 / 105 (0.00%)	1 / 103 (0.97%)	
occurrences (all)	0	1	
Candidiasis			
subjects affected / exposed	1 / 105 (0.95%)	1 / 103 (0.97%)	
occurrences (all)	1	1	
Conjunctivitis infective			
subjects affected / exposed	2 / 105 (1.90%)	0 / 103 (0.00%)	
occurrences (all)	2	0	
Infection			

subjects affected / exposed	0 / 105 (0.00%)	1 / 103 (0.97%)	
occurrences (all)	0	1	
Omphalitis			
subjects affected / exposed	1 / 105 (0.95%)	1 / 103 (0.97%)	
occurrences (all)	1	1	
Pneumonia klebsiella			
subjects affected / exposed	0 / 105 (0.00%)	1 / 103 (0.97%)	
occurrences (all)	1	1	
Pseudomonas infection			
subjects affected / exposed	0 / 105 (0.00%)	2 / 103 (1.94%)	
occurrences (all)	0	2	
Respiratory tract infection bacterial			
subjects affected / exposed	0 / 105 (0.00%)	1 / 103 (0.97%)	
occurrences (all)	0	1	
Rhinitis			
subjects affected / exposed	1 / 105 (0.95%)	0 / 103 (0.00%)	
occurrences (all)	1	0	
Sepsis neonatal			
subjects affected / exposed	3 / 105 (2.86%)	2 / 103 (1.94%)	
occurrences (all)	4	3	
Sepsis			
subjects affected / exposed	0 / 105 (0.00%)	5 / 103 (4.85%)	
occurrences (all)	0	6	
Staphylococcal infection			
subjects affected / exposed	1 / 105 (0.95%)	0 / 103 (0.00%)	
occurrences (all)	1	0	
Staphylococcal sepsis			
subjects affected / exposed	0 / 105 (0.00%)	1 / 103 (0.97%)	
occurrences (all)	0	1	
Streptococcal bacteraemia			
subjects affected / exposed	1 / 105 (0.95%)	0 / 103 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	0 / 105 (0.00%)	1 / 103 (0.97%)	
occurrences (all)	0	1	

Hypercalcaemia			
subjects affected / exposed	0 / 105 (0.00%)	1 / 103 (0.97%)	
occurrences (all)	0	1	
Hyperglycaemia			
subjects affected / exposed	3 / 105 (2.86%)	3 / 103 (2.91%)	
occurrences (all)	3	3	
Hyperkalaemia			
subjects affected / exposed	0 / 105 (0.00%)	5 / 103 (4.85%)	
occurrences (all)	0	5	
Hypernatraemia			
subjects affected / exposed	0 / 105 (0.00%)	1 / 103 (0.97%)	
occurrences (all)	0	1	
Hypoglycaemia			
subjects affected / exposed	3 / 105 (2.86%)	0 / 103 (0.00%)	
occurrences (all)	3	0	
Hypokalaemia			
subjects affected / exposed	0 / 105 (0.00%)	1 / 103 (0.97%)	
occurrences (all)	0	1	
Hyponatraemia			
subjects affected / exposed	0 / 105 (0.00%)	5 / 103 (4.85%)	
occurrences (all)	0	5	
Metabolic acidosis			
subjects affected / exposed	12 / 105 (11.43%)	12 / 103 (11.65%)	
occurrences (all)	12	16	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 November 2006	Amendment 1 was prepared after the Investigators' Meeting, held in Madrid on November 27th 2006. In fact, it reports the final list of countries involved and the investigators who definitely accepted to particpate. UK's participation was cancelled and Brazil was added. Moreover this amendment includes some minor modifications, requested during the meeting, to have a more feasible protocol in each involved Neonatal Intensive Care Unit.

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:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/20439601

http://www.ncbi.nlm.nih.gov/pubmed/18196932