Clinical trial results:
TRaitement CIblé et PrécOce du Canal Artériel du Prématuré par Ibuprofène

Summary

EudraCT number	2011-003063-30
Trial protocol	FR
Global end of trial date	21 June 2019

Results information

Result version number	v1 (current)
This version publication date	27 August 2022
First version publication date	27 August 2022

Trial information

Trial identification

Sponsor protocol code	BRD10/6-O

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01630278
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	CHU NANTES
Sponsor organisation address	5 allée de l'ile Gloriette, NANTES, France, 44093
Public contact	Direction de la Recherche, CHU NANTES, 0033 2 53 48 28 84, elodie.faurelpaul@chu-nantes.fr
Scientific contact	Direction de la Recherche, CHU NANTES, 0244768144 2 53 48 28 84, elodie.faurelpaul@chu-nantes.fr

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	29 May 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 June 2019
Global end of trial reached?	Yes
Global end of trial date	21 June 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To examine the effects of early echocardiography-targeted ibuprofen treatment of large patentductus arteriosus(PDA) on survival without cerebral palsy at 24 months of corrected age

Protection of trial subjects:

Very close follow-up of the patients with biological analysis and clinical exams.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 January 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 337
Worldwide total number of subjects	337
EEA total number of subjects	337

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	337
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Infants were eligible if they delivered between 24 and 27 weeks of gestation.

Pre-assignment period milestones

Number of subjects started	337
Number of subjects completed	337

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	IBUPROFEN

Arm description:

A cardiac ultrasound was performed on eligible infants by certified neonatologists 20 at 6-12 hours after birth to establish structural normality, measure the PDA diameter and assess the direction of ductal shunt.
Ibuprofen was administred (intraveinous) within 12 hours after birth if large patent ductus arteriosus

Arm type	Experimental
Investigational medicinal product name	IBUPROFEN
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

IBUPROFEN was administered as a short infusion of 20 minutes. The injection volume is brought to 2 ml using either a 9 mg/ml (0.9%) sodium chloride injection or a 50 mg/ml (5%) glucose injection.

Arm title	PLACEBO

Arm description: -

Arm type	Placebo
Investigational medicinal product name	Sodium chloride
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Placebo was an equivalent volume (2 mL) of 9 mg/mL (0.9%) sodium chloride injection administered intravenously as a short 20-minute infusion

Arm title	SMALL DUCTUS ARTERIOSUS

Arm description:

No intervention for this group of patient

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

Number of subjects in period 1	IBUPROFEN	PLACEBO	SMALL DUCTUS ARTERIOSUS
Started	114	114	109
Completed	108	102	101
Not completed	6	12	8
refusal	3	6	2
Lost to follow-up	3	6	6

Baseline characteristics

Reporting groups	
Reporting group title	IBUPROFEN
Reporting group description:	
A cardiac ultrasound was performed on eligible infants by certified neonatologists 20 at 6-12 hours after birth to establish structural normality, measure the PDA diameter and assess the direction of ductal shunt. Ibuprofen was administred (intraveinous) within 12 hours after birth if large patent ductus arteriosus	
Reporting group title	PLACEBO
Reporting group description: -	
Reporting group title	SMALL DUCTUS ARTERIOSUS
Reporting group description:	
No intervention for this group of patient	

Reporting group values	IBUPROFEN	PLACEBO	SMALL DUCTUS ARTERIOSUS
Number of subjects	114	114	109
Age categorical Units: Subjects			
Preterm newborn infants (gestational age < 28 wks)	114	114	109
Gender categorical Units: Subjects			
Female	61	54	54
Male	53	60	55

Reporting group values	Total		
Number of subjects	337		
Age categorical Units: Subjects			
Preterm newborn infants (gestational age < 28 wks)	337		
Gender categorical Units: Subjects			
Female	169		
Male	168		

End points

End points reporting groups

Reporting group title	IBUPROFEN
Reporting group description:	
A cardiac ultrasound was performed on eligible infants by certified neonatologists 20 at 6-12 hours after birth to establish structural normality, measure the PDA diameter and assess the direction of ductal shunt. Ibuprofen was administred (intraveinous) within 12 hours after birth if large patent ductus arteriosus	
Reporting group title	PLACEBO
Reporting group description: -	
Reporting group title	SMALL DUCTUS ARTERIOSUS
Reporting group description:	
No intervention for this group of patient	
Subject analysis set title	ITTm
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
Our primary analysis used a modified intention-to-treat approach including all infants who were randomized and received the first study dose.	

Primary: 2-year cerebral palsy-free survival rate

End point title	2-year cerebral palsy-free survival rate[1]
End point description:	
End point type	Primary
End point timeframe:	
at 2 years	

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Patients in group 3 were not randomized and were not analyzed as patients in groups 1 and 2.

End point values	IBUPROFEN	PLACEBO	ITTm	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	108	102	210	
Units: subjects	77	73	150	

Statistical analyses

Statistical analysis title	primary end point
Comparison groups	PLACEBO v IBUPROFEN
Number of subjects included in analysis	210
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.83
Method	Mixed models analysis

Adverse events

Adverse events information	
Timeframe for reporting adverse events: until end of hospitalization	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups	
Reporting group title	all patients

Reporting group description: -

Serious adverse events	all patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	113 / 337 (33.53%)		
number of deaths (all causes)	104		
number of deaths resulting from adverse events			
Vascular disorders			
Shock			
subjects affected / exposed	3 / 337 (0.89%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	1 / 3		
Neonatal hypotension			
subjects affected / exposed	1 / 337 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haemodynamic instability			
subjects affected / exposed	2 / 337 (0.59%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Patent ductus arteriosus repair			
subjects affected / exposed	2 / 337 (0.59%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pregnancy, puerperium and perinatal			

conditions			
Jaundice neonatal			
subjects affected / exposed	1 / 337 (0.30%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	1 / 337 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infusion site extravasation			
subjects affected / exposed	3 / 337 (0.89%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 1		
Multiple organ dysfunction syndrome			
subjects affected / exposed	6 / 337 (1.78%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 6		
Immune system disorders			
Bacillus infection			
subjects affected / exposed	1 / 337 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Reproductive system and breast disorders			
Ovarian cyst			
subjects affected / exposed	1 / 337 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 337 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Apparent life threatening event			

subjects affected / exposed	2 / 337 (0.59%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Bronchopulmonary dysplasia				
subjects affected / exposed	1 / 337 (0.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Hypoxia				
subjects affected / exposed	3 / 337 (0.89%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	1 / 3			
Pulmonary arterial hypertension				
subjects affected / exposed	4 / 337 (1.19%)			
occurrences causally related to treatment / all	1 / 4			
deaths causally related to treatment / all	0 / 1			
Pulmonary haemorrhage				
subjects affected / exposed	10 / 337 (2.97%)			
occurrences causally related to treatment / all	1 / 10			
deaths causally related to treatment / all	0 / 3			
Apnoea				
subjects affected / exposed	2 / 337 (0.59%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Bronchospasm				
subjects affected / exposed	1 / 337 (0.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Neonatal hypoxia				
subjects affected / exposed	1 / 337 (0.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory acidosis				

subjects affected / exposed	1 / 337 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Investigations			
Oxygen saturation decreased			
subjects affected / exposed	1 / 337 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Injury, poisoning and procedural complications			
Endotracheal intubation complication			
subjects affected / exposed	1 / 337 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Cardiac disorders			
Atrial thrombosis			
subjects affected / exposed	1 / 337 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bradycardia			
subjects affected / exposed	2 / 337 (0.59%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cardiac failure			
subjects affected / exposed	1 / 337 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac tamponade			
subjects affected / exposed	1 / 337 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardio-respiratory arrest neonatal			
subjects affected / exposed	4 / 337 (1.19%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 3		

Pericardial effusion				
subjects affected / exposed	1 / 337 (0.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumopericardium				
subjects affected / exposed	1 / 337 (0.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Nervous system disorders				
Central nervous system haemorrhage				
subjects affected / exposed	1 / 337 (0.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Cerebral haemorrhage				
subjects affected / exposed	3 / 337 (0.89%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	1 / 3			
Intraventricular haemorrhage neonatal				
subjects affected / exposed	23 / 337 (6.82%)			
occurrences causally related to treatment / all	5 / 23			
deaths causally related to treatment / all	2 / 18			
Periventricular leukomalacia				
subjects affected / exposed	1 / 337 (0.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Cerebral infarction				
subjects affected / exposed	2 / 337 (0.59%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 2			
Intracranial pressure increased				
subjects affected / exposed	1 / 337 (0.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			

Anuria			
subjects affected / exposed	3 / 337 (0.89%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	1 / 2		
Hydrocephalus			
subjects affected / exposed	1 / 337 (0.30%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	6 / 337 (1.78%)		
occurrences causally related to treatment / all	1 / 6		
deaths causally related to treatment / all	1 / 1		
Gastrointestinal disorders			
Enterocolitis			
subjects affected / exposed	4 / 337 (1.19%)		
occurrences causally related to treatment / all	2 / 4		
deaths causally related to treatment / all	0 / 1		
Gastrointestinal perforation			
subjects affected / exposed	13 / 337 (3.86%)		
occurrences causally related to treatment / all	10 / 13		
deaths causally related to treatment / all	1 / 2		
Necrotising enterocolitis neonatal			
subjects affected / exposed	7 / 337 (2.08%)		
occurrences causally related to treatment / all	5 / 7		
deaths causally related to treatment / all	1 / 1		
Pneumoperitoneum			
subjects affected / exposed	5 / 337 (1.48%)		
occurrences causally related to treatment / all	2 / 5		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorder			
subjects affected / exposed	1 / 337 (0.30%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 337 (0.30%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Intussusception			
subjects affected / exposed	1 / 337 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Hepatic cyst			
subjects affected / exposed	1 / 337 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Hepatorenal syndrome			
subjects affected / exposed	1 / 337 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Hyperbilirubinaemia			
subjects affected / exposed	3 / 337 (0.89%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Jaundice neonatal			
subjects affected / exposed	1 / 337 (0.30%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Portal hypertension			
subjects affected / exposed	1 / 337 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Renal and urinary disorders			
Oliguria			
subjects affected / exposed	2 / 337 (0.59%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 1		

Renal failure neonatal				
subjects affected / exposed	9 / 337 (2.67%)			
occurrences causally related to treatment / all	8 / 10			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Bacillus infection				
subjects affected / exposed	1 / 337 (0.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Escherichia sepsis				
subjects affected / exposed	1 / 337 (0.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Fungal infection				
subjects affected / exposed	1 / 337 (0.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Group B streptococcus neonatal sepsis				
subjects affected / exposed	1 / 337 (0.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Infection				
subjects affected / exposed	1 / 337 (0.30%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
Meningitis bacterial				
subjects affected / exposed	1 / 337 (0.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Peritonitis				
subjects affected / exposed	1 / 337 (0.30%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			

Respiratory syncytial virus bronchiolitis				
subjects affected / exposed	1 / 337 (0.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	2 / 337 (0.59%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Septic shock				
subjects affected / exposed	8 / 337 (2.37%)			
occurrences causally related to treatment / all	0 / 8			
deaths causally related to treatment / all	0 / 7			
Superinfection				
subjects affected / exposed	1 / 337 (0.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Systemic candida				
subjects affected / exposed	1 / 337 (0.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Acidosis				
subjects affected / exposed	1 / 337 (0.30%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Dehydration				
subjects affected / exposed	1 / 337 (0.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hyponatraemia				
subjects affected / exposed	1 / 337 (0.30%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			

Metabolic acidosis			
subjects affected / exposed	4 / 337 (1.19%)		
occurrences causally related to treatment / all	1 / 4		
deaths causally related to treatment / all	0 / 1		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	all patients		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	82 / 337 (24.33%)		
Surgical and medical procedures			
Abdominal cavity drainage			
subjects affected / exposed	1 / 337 (0.30%)		
occurrences (all)	1		
Colostomy closure			
subjects affected / exposed	1 / 337 (0.30%)		
occurrences (all)	1		
Enterostomy			
subjects affected / exposed	4 / 337 (1.19%)		
occurrences (all)	5		
Enterostomy closure			
subjects affected / exposed	3 / 337 (0.89%)		
occurrences (all)	3		
Gastrointestinal surgery			
subjects affected / exposed	1 / 337 (0.30%)		
occurrences (all)	1		
Ileostomy			
subjects affected / exposed	1 / 337 (0.30%)		
occurrences (all)	1		
Ileostomy closure			
subjects affected / exposed	1 / 337 (0.30%)		
occurrences (all)	1		
Inguinal hernia repair			
subjects affected / exposed	4 / 337 (1.19%)		
occurrences (all)	4		
Intestinal operation			

subjects affected / exposed	1 / 337 (0.30%)		
occurrences (all)	1		
Intestinal resection			
subjects affected / exposed	1 / 337 (0.30%)		
occurrences (all)	1		
Patent ductus arteriosus repair			
subjects affected / exposed	4 / 337 (1.19%)		
occurrences (all)	4		
Skin graft			
subjects affected / exposed	1 / 337 (0.30%)		
occurrences (all)	1		
Small intestinal resection			
subjects affected / exposed	1 / 337 (0.30%)		
occurrences (all)	1		
Therapy cessation			
subjects affected / exposed	1 / 337 (0.30%)		
occurrences (all)	1		
Pregnancy, puerperium and perinatal conditions			
Jaundice neonatal			
subjects affected / exposed	3 / 337 (0.89%)		
occurrences (all)	3		
Respiratory, thoracic and mediastinal disorders			
Bronchial dysplasia			
subjects affected / exposed	1 / 337 (0.30%)		
occurrences (all)	1		
Bronchopulmonary dysplasia			
subjects affected / exposed	1 / 337 (0.30%)		
occurrences (all)	1		
Neonatal respiratory distress syndrome			
subjects affected / exposed	1 / 337 (0.30%)		
occurrences (all)	1		
Pulmonary arterial hypertension			
subjects affected / exposed	1 / 337 (0.30%)		
occurrences (all)	1		
Pulmonary haemorrhage			

subjects affected / exposed	2 / 337 (0.59%)		
occurrences (all)	2		
Pulmonary hypertension			
subjects affected / exposed	1 / 337 (0.30%)		
occurrences (all)	1		
Congenital, familial and genetic disorders			
Patent ductus arteriosus			
subjects affected / exposed	1 / 337 (0.30%)		
occurrences (all)	1		
Beckwith-Wiedemann syndrome			
subjects affected / exposed	1 / 337 (0.30%)		
occurrences (all)	1		
Cardiac disorders			
Atrial thrombosis			
subjects affected / exposed	1 / 337 (0.30%)		
occurrences (all)	1		
Nervous system disorders			
Intraventricular haemorrhage neonatal			
subjects affected / exposed	1 / 337 (0.30%)		
occurrences (all)	1		
Periventricular leukomalacia			
subjects affected / exposed	1 / 337 (0.30%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	5 / 337 (1.48%)		
occurrences (all)	6		
Thrombocytopenia			
subjects affected / exposed	1 / 337 (0.30%)		
occurrences (all)	1		
Eye disorders			
Retinopathy			
subjects affected / exposed	2 / 337 (0.59%)		
occurrences (all)	2		
Gastrointestinal disorders			

Abdominal distension subjects affected / exposed occurrences (all)	8 / 337 (2.37%) 8		
Gastrointestinal perforation subjects affected / exposed occurrences (all)	1 / 337 (0.30%) 1		
Gastrooesophageal reflux disease subjects affected / exposed occurrences (all)	1 / 337 (0.30%) 1		
Ileal perforation subjects affected / exposed occurrences (all)	1 / 337 (0.30%) 1		
Inguinal hernia subjects affected / exposed occurrences (all)	1 / 337 (0.30%) 1		
Rectal haemorrhage subjects affected / exposed occurrences (all)	1 / 337 (0.30%) 1		
Vomiting subjects affected / exposed occurrences (all)	4 / 337 (1.19%) 4		
Hepatobiliary disorders Hyperbilirubinaemia subjects affected / exposed occurrences (all)	1 / 337 (0.30%) 1		
Jaundice subjects affected / exposed occurrences (all)	1 / 337 (0.30%) 1		
Skin and subcutaneous tissue disorders Skin necrosis subjects affected / exposed occurrences (all)	1 / 337 (0.30%) 1		
Renal and urinary disorders Anuria subjects affected / exposed occurrences (all)	1 / 337 (0.30%) 1		
Kidney injury molecule-1			

subjects affected / exposed	1 / 337 (0.30%)		
occurrences (all)	1		
Renal failure neonatal			
subjects affected / exposed	6 / 337 (1.78%)		
occurrences (all)	6		
Infections and infestations			
Bacillus infection			
subjects affected / exposed	1 / 337 (0.30%)		
occurrences (all)	1		
Candida infection			
subjects affected / exposed	1 / 337 (0.30%)		
occurrences (all)	1		
Conjunctivitis			
subjects affected / exposed	1 / 337 (0.30%)		
occurrences (all)	1		
Cytomegalovirus infection			
subjects affected / exposed	1 / 337 (0.30%)		
occurrences (all)	1		
Enterococcal infection			
subjects affected / exposed	1 / 337 (0.30%)		
occurrences (all)	1		
Gardnerella infection			
subjects affected / exposed	1 / 337 (0.30%)		
occurrences (all)	1		
Gastrointestinal bacterial infection			
subjects affected / exposed	1 / 337 (0.30%)		
occurrences (all)	1		
Infection			
subjects affected / exposed	1 / 337 (0.30%)		
occurrences (all)	1		
Meningitis bacterial			
subjects affected / exposed	1 / 337 (0.30%)		
occurrences (all)	1		
Neonatal candida infection			
subjects affected / exposed	1 / 337 (0.30%)		
occurrences (all)	1		

Neonatal infection			
subjects affected / exposed	3 / 337 (0.89%)		
occurrences (all)	3		
Nosocomial infection			
subjects affected / exposed	4 / 337 (1.19%)		
occurrences (all)	4		
Respiratory tract infection			
subjects affected / exposed	1 / 337 (0.30%)		
occurrences (all)	1		
Rhinitis			
subjects affected / exposed	1 / 337 (0.30%)		
occurrences (all)	1		
Sepsis			
subjects affected / exposed	1 / 337 (0.30%)		
occurrences (all)	1		
Septic shock			
subjects affected / exposed	1 / 337 (0.30%)		
occurrences (all)	1		
Staphylococcal infection			
subjects affected / exposed	2 / 337 (0.59%)		
occurrences (all)	3		
Metabolism and nutrition disorders			
Acidosis			
subjects affected / exposed	1 / 337 (0.30%)		
occurrences (all)	1		
Dehydration			
subjects affected / exposed	1 / 337 (0.30%)		
occurrences (all)	1		
Glucose tolerance impaired			
subjects affected / exposed	3 / 337 (0.89%)		
occurrences (all)	3		
Hyperkalaemia			
subjects affected / exposed	1 / 337 (0.30%)		
occurrences (all)	1		
Hypernatraemia			

subjects affected / exposed	1 / 337 (0.30%)		
occurrences (all)	1		
Hyponatraemia			
subjects affected / exposed	1 / 337 (0.30%)		
occurrences (all)	1		
Metabolic acidosis			
subjects affected / exposed	3 / 337 (0.89%)		
occurrences (all)	3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 March 2012	change in consent procedures and extension of follow-up to 24 months
08 January 2013	addition of Cochin Hospital
02 April 2013	Adding of an ancillary study for Nantes's patients
04 March 2014	Prolongation of inclusion period
01 March 2016	Prolongation of inclusion period
04 October 2017	change in investigators and in coordinator
07 February 2018	final analysis carried out in 2 steps

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported