Clinical trial results:
Pharmacokinetics of a Single Dose of Ceftaroline fosamil in Children Ages Birth to Younger Than 12 Years With Suspected or Confirmed Infection

Summary

EudraCT number	2011-002198-44
Trial protocol	Outside EU/EEA
Global end of trial date	04 February 2013

Results information

Result version number	v1 (current)
This version publication date	09 August 2018
First version publication date	09 August 2018

Trial information

Trial identification

Sponsor protocol code	P903-21

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01298843
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Cerexa, Inc (a subsidiary of Allergan, plc)
Sponsor organisation address	185 Hudson Street, Plaza 5, Jersey City, United States, NJ 07302-3908
Public contact	Clinical Trial Registry Team, Cerexa, Inc (a subsidiary of Allergan, plc), +1 877-277-8566, IR-CTRegistration@allergan.com
Scientific contact	Clinical Trial Registry Team, Cerexa, Inc (a subsidiary of Allergan, plc), +1 877-277-8566, IR-CTRegistration@allergan.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000769-PIP01-09
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	21 November 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 February 2013
Global end of trial reached?	Yes
Global end of trial date	04 February 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evalutate the single-dose pharmacokinetic profile, safety and tolerability of ceftaroline fosamil administered by intravenous infusion in children with ages from birth to younger than 12 years

Protection of trial subjects:

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with good clinical practices and applicable regulatory requirements. Written informed consent from parent or legally acceptable representative and verbal informed assent from subject (if age appropriate and according to local requirements) were obtained before initiating study-related assessments or procedures.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 April 2011
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 States: 53
Worldwide total number of subjects	53
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	11
Newborns (0-27 days)	12
Infants and toddlers (28 days-23 months)	12
Children (2-11 years)	18
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:

A total of 53 (male and female) subjects between the chronological ages of 0 and 11 years with confirmed or suspected infections were enrolled in the study.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1 (≥ 6 years to < 12 years)

Arm description:

10 subjects from age group ≥ 6 years to < 12 years were randomised to receive 10 mg/kg (up to 600 mg for subjects ≥ 60 kg) ceftaroline fosamil as a 1-hour infusion on Study Day 1.

Arm type	Experimental
Investigational medicinal product name	Ceftaroline fosamil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

10 mg/kg (up to 600 mg for subjects ≥ 60 kg) of ceftaroline fosamil was administered as a single 1-hour infusion.

Arm title	Cohort 2 (≥ 24 months to < 6 years)

Arm description:

8 subjects from age group ≥ 24 months to < 6 years were randomised to receive 15 mg/kg ceftaroline fosamil as a 1.5-hour infusion on Study Day 1.

Arm type	Experimental
Investigational medicinal product name	Ceftaroline fosamil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

15 mg/kg of ceftaroline fosamil was administered as a 1.5-hour infusion.

Arm title	Cohort 3 (≥ 28 days to < 24 months)

Arm description:

12 subjects [young infants and toddlers ages ≥ 28 days to < 24 months (with equal representation of subjects aged 28 days to < 12 months and 12 months to < 24 months)] were randomised to receive 12 mg/kg ceftaroline fosamil as a single 1-hour infusion (age ≥ 5 months) and 8 mg/kg ceftaroline fosamil as a single 1-hour infusion (age 28 days to 5 months) on Study Day 1, respectively.

Arm type	Experimental

Investigational medicinal product name	Ceftaroline fosamil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Age ≥ 5 months: 12 mg/kg of ceftaroline fosamil was administered as a single 1-hour infusion. Age 28 days to 5 months: 8 mg/kg of ceftaroline fosamil was administered as a single 1-hour infusion.

Arm title	Cohort 4 (≥ 38 weeks to < 28 days)

Arm description:

12 subjects [term (gestational age ≥ 38 weeks) neonates ages < 28 days (stratified within the group as 0 to 14 days and > 14 days to < 28 days)] were randomised to receive 8 mg/kg ceftaroline fosamil as a 1-hour infusion on Study Day 1.

Arm type	Experimental
Investigational medicinal product name	Ceftaroline fosamil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

8 mg/kg of ceftaroline fosamil was administered as a single 1-hour infusion.

Arm title	Cohort 5 (32 - 37 weeks to < 28 days)

Arm description:

11 subjects [preterm (gestational age 32 to 37 weeks) neonates ages < 28 days (stratified within the group as 0 to 14 days and > 14 days to < 28 days)] were randomised to receive 8 mg/kg ceftaroline fosamil as a 1-hour infusion on Study Day 1.

Arm type	Experimental
Investigational medicinal product name	Ceftaroline fosamil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

8 mg/kg of ceftaroline fosamil was administered as a single 1-hour infusion.

Number of subjects in period 1	Cohort 1 (≥ 6 years to < 12 years)	Cohort 2 (≥ 24 months to < 6 years)	Cohort 3 (≥ 28 days to < 24 months)
Started	10	8	12
Completed	10	8	12
Not completed	0	0	0
Lost to follow-up	-	-	-

Number of subjects in period 1	Cohort 4 (≥ 38 weeks to < 28 days)	Cohort 5 (32 - 37 weeks to < 28 days)
Started	12	11
Completed	11	11
Not completed	1	0
Lost to follow-up	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Cohort 1 (≥ 6 years to < 12 years)
Reporting group description:	
10 subjects from age group ≥ 6 years to < 12 years were randomised to receive 10 mg/kg (up to 600 mg for subjects ≥ 60 kg) ceftaroline fosamil as a 1-hour infusion on Study Day 1.	
Reporting group title	Cohort 2 (≥ 24 months to < 6 years)
Reporting group description:	
8 subjects from age group ≥ 24 months to < 6 years were randomised to receive 15 mg/kg ceftaroline fosamil as a 1.5-hour infusion on Study Day 1.	
Reporting group title	Cohort 3 (≥ 28 days to < 24 months)
Reporting group description:	
12 subjects [young infants and toddlers ages ≥ 28 days to < 24 months (with equal representation of subjects aged 28 days to < 12 months and 12 months to < 24 months)] were randomised to receive 12 mg/kg ceftaroline fosamil as a single 1-hour infusion (age ≥ 5 months) and 8 mg/kg ceftaroline fosamil as a single 1-hour infusion (age 28 days to 5 months) on Study Day 1, respectively.	
Reporting group title	Cohort 4 (≥ 38 weeks to < 28 days)
Reporting group description:	
12 subjects [term (gestational age ≥ 38 weeks) neonates ages < 28 days (stratified within the group as 0 to 14 days and > 14 days to < 28 days)] were randomised to receive 8 mg/kg ceftaroline fosamil as a 1-hour infusion on Study Day 1.	
Reporting group title	Cohort 5 (32 - 37 weeks to < 28 days)
Reporting group description:	
11 subjects [preterm (gestational age 32 to 37 weeks) neonates ages < 28 days (stratified within the group as 0 to 14 days and > 14 days to < 28 days)] were randomised to receive 8 mg/kg ceftaroline fosamil as a 1-hour infusion on Study Day 1.	

Reporting group values	Cohort 1 (≥ 6 years to < 12 years)	Cohort 2 (≥ 24 months to < 6 years)	Cohort 3 (≥ 28 days to < 24 months)
Number of subjects	10	8	12
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	12
Children (2-11 years)	10	8	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	5	4	2
Male	5	4	10

Reporting group values	Cohort 4 (≥ 38 weeks to < 28 days)	Cohort 5 (32 - 37 weeks to < 28 days)	Total
Number of subjects	12	11	53

Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	11	11
Newborns (0-27 days)	12	0	12
Infants and toddlers (28 days-23 months)	0	0	12
Children (2-11 years)	0	0	18
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	6	2	19
Male	6	9	34

End points

End points reporting groups

Reporting group title	Cohort 1 (≥ 6 years to < 12 years)
Reporting group description:	
10 subjects from age group ≥ 6 years to < 12 years were randomised to receive 10 mg/kg (up to 600 mg for subjects ≥ 60 kg) ceftaroline fosamil as a 1-hour infusion on Study Day 1.	
Reporting group title	Cohort 2 (≥ 24 months to < 6 years)
Reporting group description:	
8 subjects from age group ≥ 24 months to < 6 years were randomised to receive 15 mg/kg ceftaroline fosamil as a 1.5-hour infusion on Study Day 1.	
Reporting group title	Cohort 3 (≥ 28 days to < 24 months)
Reporting group description:	
12 subjects [young infants and toddlers ages ≥ 28 days to < 24 months (with equal representation of subjects aged 28 days to < 12 months and 12 months to < 24 months)] were randomised to receive 12 mg/kg ceftaroline fosamil as a single 1-hour infusion (age ≥ 5 months) and 8 mg/kg ceftaroline fosamil as a single 1-hour infusion (age 28 days to 5 months) on Study Day 1, respectively.	
Reporting group title	Cohort 4 (≥ 38 weeks to < 28 days)
Reporting group description:	
12 subjects [term (gestational age ≥ 38 weeks) neonates ages < 28 days (stratified within the group as 0 to 14 days and > 14 days to < 28 days)] were randomised to receive 8 mg/kg ceftaroline fosamil as a 1-hour infusion on Study Day 1.	
Reporting group title	Cohort 5 (32 - 37 weeks to < 28 days)
Reporting group description:	
11 subjects [preterm (gestational age 32 to 37 weeks) neonates ages < 28 days (stratified within the group as 0 to 14 days and > 14 days to < 28 days)] were randomised to receive 8 mg/kg ceftaroline fosamil as a 1-hour infusion on Study Day 1.	

Primary: Mean Ceftaroline Plasma Concentrations

End point title	Mean Ceftaroline Plasma Concentrations[1]
End point description:	
End point type	Primary
End point timeframe:	
Mean Ceftaroline Plasma Concentrations were measured from the end of infusion (± 5 minutes) to 5 to 7 hours after end of infusion.	
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: The primary objective of this study is to evaluate the safety and tolerability of ceftaroline in children and it is not powered for inferential statistical analysis.	

End point values	Cohort 1 (≥ 6 years to < 12 years)	Cohort 2 (≥ 24 months to < 6 years)	Cohort 3 (≥ 28 days to < 24 months)	Cohort 4 (≥ 38 weeks to < 28 days)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	8	12	12[2]
Units: ng/mL				
arithmetic mean (standard deviation)				
At end of infusion (± 5 minutes)	18325.08 (± 3563.06)	23052.72 (± 5485.06)	16938.9 (± 3693.24)	10530.69 (± 2529.54)
15 to 45 minutes from end of infusion	12114.21 (± 3157.54)	14860.3 (± 3448.84)	12549.92 (± 2861.96)	9782.58 (± 2013.87)

3 to 4 hours from end of infusion	2769.49 (± 890.7)	3626.51 (± 1663.57)	3286.77 (± 1215.47)	4600.61 (± 819.13)
5 to 7 hours from end of infusion	1138.3 (± 489.43)	1600.83 (± 641.75)	1573.37 (± 688.59)	2687.71 (± 623.84)

Notes:

[2] - Mean Ceftaroline Plasma Concentrations 15 to 45 min from end of infusion are based on 11 subjects.

End point values	Cohort 5 (32 - 37 weeks to < 28 days)			
Subject group type	Reporting group			
Number of subjects analysed	11[3]			
Units: ng/mL				
arithmetic mean (standard deviation)				
At end of infusion (± 5 minutes)	11091.64 (± 1505.9)			
15 to 45 minutes from end of infusion	10348.61 (± 1064.83)			
3 to 4 hours from end of infusion	5061.97 (± 1668.45)			
5 to 7 hours from end of infusion	3115.87 (± 1350.72)			

Notes:

[3] - Mean Ceftaroline Plasma Concentrations at end of infusion and 15 to 45 min are based on 9 subjects.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 14 days (Study Day 15) after ceftaroline fosamil administration.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.1

Reporting groups

Reporting group title	Cohort 1 (≥ 6 years to < 12 years)

Reporting group description:

Subjects from age group ≥ 6 years to < 12 years received 10 mg/kg (up to 600 mg for subjects ≥ 60 kg) ceftaroline fosamil as a 1-hour infusion.

Reporting group title	Cohort 2 (≥ 24 months to < 6 years)

Reporting group description:

Subjects from age group ≥ 24 months to < 6 years received 15 mg/kg ceftaroline fosamil as a 1.5-hour infusion.

Reporting group title	Cohort 3 (≥ 28 days to < 24 months)

Reporting group description:

Young infants and toddlers ages ≥ 28 days to < 24 months (with equal representation of subjects aged 28 days to < 12 months and 12 months to < 24 months) received 12 mg/kg ceftaroline fosamil as a single 1-hour infusion (age ≥ 5 months) and 8 mg/kg ceftaroline fosamil as a single 1-hour infusion (age 28 days to 5 months), respectively.

Reporting group title	Cohort 4 (≥ 38 weeks to < 28 days)

Reporting group description:

Term (gestational age ≥ 38 weeks) neonates ages < 28 days (stratified within the group as 0 to 14 days and > 14 days to < 28 days) received 8 mg/kg ceftaroline fosamil as a 1-hour infusion.

Reporting group title	Cohort 5 (32 - 37 weeks to < 28 days)

Reporting group description:

Preterm (gestational age 32 to 37 weeks) neonates ages < 28 days (stratified within the group as 0 to 14 days and > 14 days to < 28 days) received 8 mg/kg ceftaroline fosamil as a 1-hour infusion.

Serious adverse events	Cohort 1 (≥ 6 years to < 12 years)	Cohort 2 (≥ 24 months to < 6 years)	Cohort 3 (≥ 28 days to < 24 months)
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 10 (10.00%)	0 / 8 (0.00%)	1 / 12 (8.33%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Nervous system disorders			
Tremor			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Blood and lymphatic system disorders			
Anaemia neonatal			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Rash			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 10 (10.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Cohort 4 (≥ 38 weeks to < 28 days)	Cohort 5 (32 - 37 weeks to < 28 days)	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 12 (0.00%)	1 / 11 (9.09%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Nervous system disorders			
Tremor			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia neonatal			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 12 (0.00%)	1 / 11 (9.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Cohort 1 (≥ 6 years to < 12 years)	Cohort 2 (≥ 24 months to < 6 years)	Cohort 3 (≥ 28 days to < 24 months)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 10 (30.00%)	0 / 8 (0.00%)	7 / 12 (58.33%)
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Prothrombin time prolonged			
subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Activated partial thromboplastin time prolonged			
subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Blood phosphorus increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Gamma-glutamyltransferase increased			

subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
International normalised ratio increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Neutrophil count decreased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Excoriation			
subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Overdose			
subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Procedural pain			
subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Congenital, familial and genetic disorders			
Coarctation of the aorta			
subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Nervous system disorders			
Tremor			
subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Anaemia neonatal			
subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Coagulopathy			

subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Device occlusion			
subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Infusion site pain			
subjects affected / exposed	1 / 10 (10.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Pain			
subjects affected / exposed	1 / 10 (10.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Pyrexia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 10 (10.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Diarrhoea			
subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Nausea			
subjects affected / exposed	1 / 10 (10.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Perianal erythema			
subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Atelectasis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0

Respiratory acidosis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Tachypnoea			
subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Rash			
subjects affected / exposed	1 / 10 (10.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Bronchiolitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Candidiasis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Alkalosis hypochloraemic			
subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Hypoalbuminaemia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Cohort 4 (≥ 38 weeks to < 28 days)	Cohort 5 (32 - 37 weeks to < 28 days)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 12 (58.33%)	6 / 11 (54.55%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 12 (16.67%)	0 / 11 (0.00%)	
occurrences (all)	2	0	
Aspartate aminotransferase increased			

subjects affected / exposed	2 / 12 (16.67%)	0 / 11 (0.00%)	
occurrences (all)	2	0	
Blood creatine phosphokinase increased			
subjects affected / exposed	2 / 12 (16.67%)	0 / 11 (0.00%)	
occurrences (all)	2	0	
Blood lactate dehydrogenase increased			
subjects affected / exposed	2 / 12 (16.67%)	0 / 11 (0.00%)	
occurrences (all)	2	0	
Prothrombin time prolonged			
subjects affected / exposed	2 / 12 (16.67%)	0 / 11 (0.00%)	
occurrences (all)	2	0	
Activated partial thromboplastin time prolonged			
subjects affected / exposed	1 / 12 (8.33%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Blood phosphorus increased			
subjects affected / exposed	0 / 12 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
International normalised ratio increased			
subjects affected / exposed	1 / 12 (8.33%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Neutrophil count decreased			
subjects affected / exposed	0 / 12 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Excoriation			
subjects affected / exposed	1 / 12 (8.33%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Overdose			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	

Procedural pain			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
Congenital, familial and genetic disorders			
Coarctation of the aorta			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
Nervous system disorders			
Tremor			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Anaemia neonatal			
subjects affected / exposed	0 / 12 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Coagulopathy			
subjects affected / exposed	1 / 12 (8.33%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Device occlusion			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
Infusion site pain			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
Pain			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
Pyrexia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
Diarrhoea			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
Nausea			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
Perianal erythema			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	1 / 12 (8.33%)	1 / 11 (9.09%)	
occurrences (all)	1	1	
Respiratory, thoracic and mediastinal disorders			
Atelectasis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Respiratory acidosis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Tachypnoea			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	1 / 12 (8.33%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Rash			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
Infections and infestations			
Bronchiolitis			

subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
Candidiasis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Alkalosis hypochloraemic			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
Hypoalbuminaemia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 11 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 November 2010	The following changes were implemented with Amendment 1: changes to trial objective(s), dosage determination, clarifications regarding sample collection, vital sign assessment, exclusion criteria and other clarifications.
12 July 2011	The following changes were implemented with Amendment 2: changes to subject disposition, enrolment, inclusion and exclusion criteria and other clarifications.
16 August 2011	The following changes were implemented with Amendment 3: corrections to 'bedside' Schwartz formula.
14 December 2011	The following changes were implemented with Amendment 4: updated study drug information to be consistent with the current version of the Investigator's Brochure.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported