Clinical trial results:
A Phase I, Randomised, Open-Label, Multi-National Study to Evaluate the Pharmacokinetics of Repeated Once-Daily Intravenous Doses of Esomeprazole in Paediatric Patients 0 to 17 Years Old, Inclusive

Summary

EudraCT number	2007-000628-41
Trial protocol	SE HU BE Outside EU/EEA
Global end of trial date	23 February 2010

Results information

Result version number	v1 (current)
This version publication date	01 February 2017
First version publication date	06 August 2015

Trial information

Trial identification

Sponsor protocol code	D9615C00021

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	AstraZeneca LP
Sponsor organisation address	1800 Concord Pike, Wilmington, DE, United States, 19850
Public contact	AZ Clinical Trial Transparency group, AstraZeneca R&D, ClinicalTrialTransparency@astrazeneca.com
Scientific contact	Kurt Brown, MD, AstraZeneca LP, 1 302-885-0954,

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000331-PIP01-08
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 February 2010
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 February 2010
Global end of trial reached?	Yes
Global end of trial date	23 February 2010
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to evaluate the pharmacokinetics of repeated doses of esomeprazole given as a once daily (qd) injection over 3 minutes in pediatric patients 0 to 17 years old, inclusive, by assessment of the total area under the plasma concentration versus time curve within a dosing interval (AUC_{τ}) on Day 4 of the study based on population PK modeling.

Protection of trial subjects:

This study was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with International Conference on Harmonisation (ICH)/Good Clinical Practice (GCP) and applicable regulatory requirements and the AstraZeneca policy on Bioethics. The final clinical study protocol (CSP), including the final version of the Informed Consent Form, was approved by an Institutional Review Board (IRB) associated with each study center.
The principal investigator at each center was to ensure that the patient and patient's parent/guardian was given full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study. The patient and the patient's parent/guardian were also to be notified that they were free to discontinue his/her child from the study at any time. The patient and patient's parent/guardian were to be given the opportunity to ask questions and were allowed time to consider the information provided.
The patient's signed and dated assent (if appropriate) and the patient's parent/guardian's signed and dated informed consent had to be obtained before conducting any procedure specifically for the study. Patients could be discontinued from study treatment and assessments at any time at the discretion of the investigator(s).

Background therapy:

The study included patients who were considered, in the judgment of the investigator, to be a candidate for acid suppression therapy.
Concomitant use of other PPIs were allowed up to but not including the day of randomization.

Evidence for comparator:

No comparator

Actual start date of recruitment	13 October 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	Australia: 15
Country: Number of subjects enrolled	Hungary: 10
Country: Number of subjects enrolled	Sweden: 7
Country: Number of subjects enrolled	United States: 27
Worldwide total number of subjects	59
EEA total number of subjects	17

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	4
Newborns (0-27 days)	3
Infants and toddlers (28 days-23 months)	11
Children (2-11 years)	23
Adolescents (12-17 years)	18
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

First subject enrolled: 13 October 2007
Last subject last visit: 20 October 2009

Pre-assignment

Screening details:

62 patients screened , 3 patients failed to be eligible (did not meet inclusion/exclusion criteria) and were not randomized.
Of the 59 randomised subjects, two subjects (1 newborn gestational age 32 weeks, and 1 adolscent 13 years old) were never dosed.
Note:
Safety population N=57
PK evaluable N=50;

Period 1

Period 1 title	Randomized Dosing period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Subject

Blinding implementation details:

Single Blind

Arms

Are arms mutually exclusive?	Yes
Arm title	0 - 1 month, 0.5 mg/kg

Arm description:

Zero to one month old subjects dosed at 0.5 mg/kg

Arm type	Experimental
Investigational medicinal product name	Esomeprazole sodium
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for injection
Routes of administration	Intravenous use

Dosage and administration details:

IV administration

Arm title	1 - 11 months, 1 mg/kg

Arm description:

1 to 11 month old subjects dosed at 1 mg/kg

Arm type	Experimental
Investigational medicinal product name	Esomeprazole sodium
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for injection
Routes of administration	Intravenous use

Dosage and administration details:

IV administration

Arm title	1 - 5 years, 10 mg

Arm description: 1 to 5 year olds dosed at 10 mg	
Arm type	Experimental
Investigational medicinal product name	Esomeprazole sodium
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for injection
Routes of administration	Intravenous use
Dosage and administration details: IV administration	
Arm title	6 - 11 years, 10 mg
Arm description: 6 to 11 year old subjects dosed at 10 mg	
Arm type	Experimental
Investigational medicinal product name	Esomeprazole sodium
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for injection
Routes of administration	Intravenous use
Dosage and administration details: IV administration	
Arm title	6 - 11 years, 20 mg
Arm description: 6 to 11 year olds dosed at 20 mg	
Arm type	Experimental
Investigational medicinal product name	Esomeprazole sodium
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for injection
Routes of administration	Intravenous use
Dosage and administration details: IV administration	
Arm title	12 - 17 years, 20 mg
Arm description: 12 to 17 year olds dosed at 20 mg	
Arm type	Experimental
Investigational medicinal product name	Esomeprazole sodium
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for injection
Routes of administration	Intravenous use
Dosage and administration details: IV administration	
Arm title	12 - 17 years, 40 mg
Arm description: 12 to 17 year olds dosed at 40 mg	
Arm type	Experimental

Investigational medicinal product name	Esomeprazole sodium
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for injection
Routes of administration	Intravenous use

Dosage and administration details:

IV administration

Number of subjects in period 1[1]	0 - 1 month, 0.5 mg/kg	1 - 11 months, 1 mg/kg	1 - 5 years, 10 mg
Started	6	9	8
Completed	6	8	7
Not completed	0	1	1
Adverse event, non-fatal	-	-	1
Not specified	-	1	-

Number of subjects in period 1[1]	6 - 11 years, 10 mg	6 - 11 years, 20 mg	12 - 17 years, 20 mg
Started	8	9	8
Completed	8	7	6
Not completed	0	2	2
Adverse event, non-fatal	-	1	-
Not specified	-	1	2

Number of subjects in period 1[1]	12 - 17 years, 40 mg
Started	9
Completed	8
Not completed	1
Adverse event, non-fatal	-
Not specified	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Of the 59 randomised subjects, two subjects (1 newborn gestational age 32 weeks, and 1 adolscent 13 years old) were never dosed. Thus, the number of subjects in the baseline period (ITT) is 57 while the worldwide number enrolled is 59.

Period 2

Period 2 title	Pharmacokinetic Evaluation
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Subject

Blinding implementation details:

Single Blind

Arms

Are arms mutually exclusive?	Yes
Arm title	0 - 1 month, 0.5 mg/kg

Arm description:

Zero to one month old subjects dosed at 0.5 mg/kg

Arm type	Experimental
Investigational medicinal product name	Esomeprazole sodium
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for injection
Routes of administration	Intravenous use

Dosage and administration details:

IV administration

Arm title	1 - 11 months, 1 mg/kg

Arm description:

1 to 11 month old subjects dosed at 1 mg/kg

Arm type	Experimental
Investigational medicinal product name	Esomeprazole sodium
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for injection
Routes of administration	Intravenous use

Dosage and administration details:

IV

Arm title	1 - 5 years, 10 mg

Arm description:

1 to 5 year olds dosed at 10 mg

Arm type	Experimental
Investigational medicinal product name	Esomeprazole sodium
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

IV

Arm title	6 - 11 years, 10 mg

Arm description:

6 to 11 year old subjects dosed at 10 mg

Arm type	Experimental
Investigational medicinal product name	Esomeprazole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for injection
Routes of administration	Intravenous use

Dosage and administration details:

IV

Arm title	6 - 11 years, 20 mg

Arm description:

6 to 11 year olds dosed at 20 mg

Arm type	Experimental

Investigational medicinal product name	Esomeprazole sodium
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for injection
Routes of administration	Intravenous use

Dosage and administration details:
IV

Arm title	12 - 17 years, 20 mg

Arm description:
12 to 17 year olds dosed at 20 mg

Arm type	Experimental
Investigational medicinal product name	Esomeprazole sodium
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for injection
Routes of administration	Intravenous use

Dosage and administration details:
IV

Arm title	12 - 17 years, 40 mg

Arm description:
12 to 17 year olds dosed at 40 mg

Arm type	Experimental
Investigational medicinal product name	Esomeprazole sodium
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for injection
Routes of administration	Intravenous use

Dosage and administration details:
IV

Number of subjects in period 2	0 - 1 month, 0.5 mg/kg	1 - 11 months, 1 mg/kg	1 - 5 years, 10 mg
Started	6	7	7
Completed	6	7	7

Number of subjects in period 2	6 - 11 years, 10 mg	6 - 11 years, 20 mg	12 - 17 years, 20 mg
Started	8	8	6
Completed	8	8	6

Number of subjects in period 2	12 - 17 years, 40 mg
Started	8
Completed	8

Baseline characteristics

Reporting groups	
Reporting group title	0 - 1 month, 0.5 mg/kg
Reporting group description:	
Zero to one month old subjects dosed at 0.5 mg/kg	
Reporting group title	1 - 11 months, 1 mg/kg
Reporting group description:	
1 to 11 month old subjects dosed at 1 mg/kg	
Reporting group title	1 - 5 years, 10 mg
Reporting group description:	
1 to 5 year olds dosed at 10 mg	
Reporting group title	6 - 11 years, 10 mg
Reporting group description:	
6 to 11 year old subjects dosed at 10 mg	
Reporting group title	6 - 11 years, 20 mg
Reporting group description:	
6 to 11 year olds dosed at 20 mg	
Reporting group title	12 - 17 years, 20 mg
Reporting group description:	
12 to 17 year olds dosed at 20 mg	
Reporting group title	12 - 17 years, 40 mg
Reporting group description:	
12 to 17 year olds dosed at 40 mg	

Reporting group values	0 - 1 month, 0.5 mg/kg	1 - 11 months, 1 mg/kg	1 - 5 years, 10 mg
Number of subjects	6	9	8
Age Categorical			
Subjects in Pharmacokinetic data set			
Units: Subjects			
Newborns (0-27 days)	4	0	0
Infants and toddlers (28 days-23 months)	2	9	2
Children (2-11 years)	0	0	6
Adolescents (12-17 years)	0	0	0
Age Continuous			
Median Age in months or year depending on treatment arm classification			
Units: years			
median	4	5	2
full range (min-max)	2 to 36	1 to 7	1 to 5
Gender Categorical			
Units: Subjects			
Male	4	6	5
Female	2	3	3

Reporting group values	6 - 11 years, 10 mg	6 - 11 years, 20 mg	12 - 17 years, 20 mg
Number of subjects	8	9	8

Age Categorical			
Subjects in Pharmacokinetic data set			
Units: Subjects			
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	8	9	0
Adolescents (12-17 years)	0	0	8
Age Continuous			
Median Age in months or year depending on treatment arm classification			
Units: years			
median	7.5	8	15.5
full range (min-max)	6 to 11	6 to 11	13 to 17
Gender Categorical			
Units: Subjects			
Male	5	5	5
Female	3	4	3

Reporting group values	12 - 17 years, 40 mg	Total	
Number of subjects	9	57	
Age Categorical			
Subjects in Pharmacokinetic data set			
Units: Subjects			
Newborns (0-27 days)	0	4	
Infants and toddlers (28 days-23 months)	0	13	
Children (2-11 years)	0	23	
Adolescents (12-17 years)	9	17	
Age Continuous			
Median Age in months or year depending on treatment arm classification			
Units: years			
median	15.5		
full range (min-max)	13 to 17	-	
Gender Categorical			
Units: Subjects			
Male	3	33	
Female	6	24	

Subject analysis sets

Subject analysis set title	Safety Analysis Set
Subject analysis set type	Safety analysis

Subject analysis set description:

All subjects that received at least one dose of study drug

Reporting group values	Safety Analysis Set		
Number of subjects	57		
Age Categorical			
Subjects in Pharmacokinetic data set			
Units: Subjects			
Newborns (0-27 days)	4		

Infants and toddlers (28 days-23 months)	13		
Children (2-11 years)	23		
Adolescents (12-17 years)	17		
Age Continuous			
Median Age in months or year depending on treatment arm classification			
Units: years			
median	6		
full range (min-max)	1 to 17		
Gender Categorical			
Units: Subjects			
Male	33		
Female	24		

End points

End points reporting groups

Reporting group title	0 - 1 month, 0.5 mg/kg
Reporting group description:	
Zero to one month old subjects dosed at 0.5 mg/kg	
Reporting group title	1 - 11 months, 1 mg/kg
Reporting group description:	
1 to 11 month old subjects dosed at 1 mg/kg	
Reporting group title	1 - 5 years, 10 mg
Reporting group description:	
1 to 5 year olds dosed at 10 mg	
Reporting group title	6 - 11 years, 10 mg
Reporting group description:	
6 to 11 year old subjects dosed at 10 mg	
Reporting group title	6 - 11 years, 20 mg
Reporting group description:	
6 to 11 year olds dosed at 20 mg	
Reporting group title	12 - 17 years, 20 mg
Reporting group description:	
12 to 17 year olds dosed at 20 mg	
Reporting group title	12 - 17 years, 40 mg
Reporting group description:	
12 to 17 year olds dosed at 40 mg	
Reporting group title	0 - 1 month, 0.5 mg/kg
Reporting group description:	
Zero to one month old subjects dosed at 0.5 mg/kg	
Reporting group title	1 - 11 months, 1 mg/kg
Reporting group description:	
1 to 11 month old subjects dosed at 1 mg/kg	
Reporting group title	1 - 5 years, 10 mg
Reporting group description:	
1 to 5 year olds dosed at 10 mg	
Reporting group title	6 - 11 years, 10 mg
Reporting group description:	
6 to 11 year old subjects dosed at 10 mg	
Reporting group title	6 - 11 years, 20 mg
Reporting group description:	
6 to 11 year olds dosed at 20 mg	
Reporting group title	12 - 17 years, 20 mg
Reporting group description:	
12 to 17 year olds dosed at 20 mg	
Reporting group title	12 - 17 years, 40 mg
Reporting group description:	
12 to 17 year olds dosed at 40 mg	
Subject analysis set title	Safety Analysis Set
Subject analysis set type	Safety analysis
Subject analysis set description:	
All subjects that received at least one dose of study drug	

Primary: AUCT

End point title	AUCT[1]

End point description:

Area Under the Curve (AUC) of esomeprazole

End point type	Primary

End point timeframe:

Day 4 steady state

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: NSAE includes those events that occurred in at least 2 patients during the study

End point values	0 - 1 month, 0.5 mg/kg	1 - 11 months, 1 mg/kg	1 - 5 years, 10 mg	6 - 11 years, 10 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	7	7	8
Units: µmol*h/L				
geometric mean (full range (min-max))	7.5 (4.5 to 20.5)	10.5 (4.5 to 22.2)	7.9 (2.9 to 16.6)	6.9 (3.5 to 10.9)

End point values	6 - 11 years, 20 mg	12 - 17 years, 20 mg	12 - 17 years, 40 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	6	8	
Units: µmol*h/L				
geometric mean (full range (min-max))	14.4 (7.2 to 42.3)	8.1 (4.7 to 15.9)	17.6 (13.1 to 19.8)	

Statistical analyses

No statistical analyses for this end point

Secondary: Css,max

End point title	Css,max

End point description:

End point type	Secondary

End point timeframe:

Day 4 steady state

End point values	0 - 1 month, 0.5 mg/kg	1 - 11 months, 1 mg/kg	1 - 5 years, 10 mg	6 - 11 years, 10 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	7	7	8
Units: µmol/L				
geometric mean (full range (min-max))	3.71 (2.73 to 5.77)	8.68 (4.51 to 14)	9.37 (4.4 to 17.2)	5.6 (3.13 to 13.2)

End point values	6 - 11 years, 20 mg	12 - 17 years, 20 mg	12 - 17 years, 40 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	6	8	
Units: µmol/L				
geometric mean (full range (min-max))	8.83 (3.36 to 29.4)	7.1 (4.76 to 9.02)	10.5 (7.82 to 14.2)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From first dosing to day 5	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	12.0

Reporting groups	
Reporting group title	0 - 1 month, 0.5 mg/kg
Reporting group description: Zero to one month old subjects dosed at 0.5 mg/kg	
Reporting group title	1 - 11 months, 1 mg/kg
Reporting group description: 1 to 11 month old subjects dosed at 1 mg/kg	
Reporting group title	1 - 5 years, 10 mg
Reporting group description: 1 to 5 year olds dosed at 10 mg	
Reporting group title	6 - 11 years, 10 mg
Reporting group description: 6 to 11 year old subjects dosed at 10 mg	
Reporting group title	6 - 11 years, 20 mg
Reporting group description: 6 to 11 year olds dosed at 20 mg	
Reporting group title	12 - 17 years, 20 mg
Reporting group description: 12 to 17 year olds dosed at 20 mg	
Reporting group title	12 - 17 years, 40 mg
Reporting group description: 12 to 17 year olds dosed at 40 mg	

Serious adverse events	0 - 1 month, 0.5 mg/kg	1 - 11 months, 1 mg/kg	1 - 5 years, 10 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 6 (33.33%)	0 / 9 (0.00%)	1 / 8 (12.50%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Gastrointestinal disorders			
Gastroenteritis	Additional description: Gastroenteritis with abdominal pain, dehydration, nausea, and vomiting		
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	0 / 8 (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
Colitis ulcerative	Additional description: Ulcerative colitis flare		

subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	0 / 8 (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
Respiratory, thoracic and mediastinal disorders			
Bronchial hyper-reactivity	Additional description: Reactive airway disease (secondary to Influenza A)		
subjects affected / exposed	1 / 6 (16.67%)	0 / 9 (0.00%)	0 / 8 (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
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute respiratory failuree			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	0 / 8 (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
Infections and infestations			
Candida sepsis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 9 (0.00%)	0 / 8 (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	6 - 11 years, 10 mg	6 - 11 years, 20 mg	12 - 17 years, 20 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 8 (12.50%)	1 / 9 (11.11%)	0 / 8 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Gastrointestinal disorders			
Gastroenteritis	Additional description: Gastroenteritis with abdominal pain, dehydration, nausea, and vomiting		
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 8 (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
Colitis ulcerative	Additional description: Ulcerative colitis flare		

subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	0 / 8 (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
Respiratory, thoracic and mediastinal disorders			
Bronchial hyper-reactivity	Additional description: Reactive airway disease (secondary to Influenza A)		
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 8 (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
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 8 (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
Acute respiratory failuree			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Candida sepsis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 8 (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

Serious adverse events	12 - 17 years, 40 mg		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 9 (11.11%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Gastrointestinal disorders			
Gastroenteritis	Additional description: Gastroenteritis with abdominal pain, dehydration, nausea, and vomiting		
subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Colitis ulcerative	Additional description: Ulcerative colitis flare		

subjects affected / exposed	0 / 9 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Bronchial hyper-reactivity	Additional description: Reactive airway disease (secondary to Influenza A)		
subjects affected / exposed	0 / 9 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Acute respiratory failuree			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Candida sepsis			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	0 - 1 month, 0.5 mg/kg	1 - 11 months, 1 mg/kg	1 - 5 years, 10 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 6 (33.33%)	5 / 9 (55.56%)	7 / 8 (87.50%)
Cardiac disorders			
Tachycardia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 9 (0.00%)	1 / 8 (12.50%)
occurrences (all)	1	0	1
Blood and lymphatic system disorders			
Anemia			

subjects affected / exposed	1 / 6 (16.67%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Catheter related complication			
subjects affected / exposed	0 / 6 (0.00%)	1 / 9 (11.11%)	1 / 8 (12.50%)
occurrences (all)	0	2	1
Infusion site extravasation			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 6 (0.00%)	2 / 9 (22.22%)	2 / 8 (25.00%)
occurrences (all)	0	2	2
Abdominal distension			
subjects affected / exposed	0 / 6 (0.00%)	2 / 9 (22.22%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Abdominal pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	2 / 8 (25.00%)
occurrences (all)	0	0	2
Diarrhea			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Gastroesophageal reflux disease			
subjects affected / exposed	0 / 6 (0.00%)	1 / 9 (11.11%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Nausea			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	2
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Erythema			

subjects affected / exposed	0 / 6 (0.00%)	3 / 9 (33.33%)	0 / 8 (0.00%)
occurrences (all)	0	3	0
Rash			
subjects affected / exposed	0 / 6 (0.00%)	1 / 9 (11.11%)	1 / 8 (12.50%)
occurrences (all)	0	1	1
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Pyrexia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 9 (11.11%)	1 / 8 (12.50%)
occurrences (all)	0	1	1
Pneumonia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 9 (11.11%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
Hypokalemia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 9 (0.00%)	1 / 8 (12.50%)
occurrences (all)	1	0	1
Hyponatremia			
subjects affected / exposed	0 / 6 (0.00%)	2 / 9 (22.22%)	0 / 8 (0.00%)
occurrences (all)	0	2	0

Non-serious adverse events	6 - 11 years, 10 mg	6 - 11 years, 20 mg	12 - 17 years, 20 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 8 (62.50%)	2 / 9 (22.22%)	5 / 8 (62.50%)
Cardiac disorders			
Tachycardia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Blood and lymphatic system disorders			

Anemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Catheter related complication			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Infusion site extravasation			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	1 / 8 (12.50%)
occurrences (all)	1	0	1
Abdominal distension			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Abdominal pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Diarrhea			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Gastroesophageal reflux disease			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Nausea			
subjects affected / exposed	1 / 8 (12.50%)	1 / 9 (11.11%)	0 / 8 (0.00%)
occurrences (all)	1	1	0
Vomiting			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	2 / 8 (25.00%)
occurrences (all)	0	0	2

Erythema			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Rash			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	2 / 8 (25.00%)
occurrences (all)	0	0	2
Infections and infestations			
Pyrexia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	2 / 8 (25.00%)
occurrences (all)	0	1	2
Pneumonia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
Hypokalemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Hyponatremia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	12 - 17 years, 40 mg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 9 (55.56%)		
Cardiac disorders			
Tachycardia			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Blood and lymphatic system disorders			

Anemia			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Catheter related complication			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Infusion site extravasation			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Abdominal distension			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Abdominal pain			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Diarrhea			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Gastroesophageal reflux disease			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Nausea			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Vomiting			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		

Erythema			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Rash			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Infections and infestations			
Pyrexia			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Pneumonia			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Metabolism and nutrition disorders			
Hypokalemia			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Hyponatremia			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 June 2007	Incorporating multiple changes to CSP in response to FDA comments
29 January 2008	New centers added to help meet enrollment goals; amendment to exclusion criteria
18 December 2008	Broadening of some inclusion/exclusion criteria

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported