Clinical trial results:
A Multi-Center, Open-Label Study Evaluating Safety and Clinical Outcomes in Hunter Syndrome subjects 5 Years of Age and Younger Receiving Idursulfase Enzyme Replacement Therapy

Summary

EudraCT number	2007-006044-22
Trial protocol	PL
Global end of trial date	08 July 2011

Results information

Result version number	v1 (current)
This version publication date	04 September 2018
First version publication date	24 June 2015

Trial information

Trial identification

Sponsor protocol code	HGT-ELA-038

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00607386
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Shire Human Genetic Therapies, Inc. (Shire HGT)
Sponsor organisation address	300 Shire Way, Lexington , MA 02421, United States,
Public contact	Arian Pano, Shire HGT, apano@shire.com
Scientific contact	Arian Pano, Shire HGT, apano@shire.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	08 July 2011
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	08 July 2011
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the safety of once-weekly dosing of idursulfase (Elaprase®) 0.5 milligram per kilogram (mg/kg) administered by intravenous (IV) infusion for male Hunter syndrome subjects less than or equal to (<=) 5 years old.

Protection of trial subjects:

The 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 practice and applicable regulatory requirements. Known instances of nonconformance were documented and were not considered to have an impact on the overall conclusions of this study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	31 December 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	Brazil: 15
Country: Number of subjects enrolled	Poland: 12
Country: Number of subjects enrolled	Taiwan: 3
Worldwide total number of subjects	30
EEA total number of subjects	12

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	4
Children (2-11 years)	26
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 30 subjects were enrolled of which 28 subjects received study drug.

Period 1

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

Arms

Arm title	Idursulfase

Arm description:

Open-label treatment with idursulfase

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

Dosage and administration details:

Idursulfase was administered every week at a dose of 0.5 mg/kg by continuous IV infusion over a minimum of 3 hours. The dose of drug was calculated based on the subject's weight at each visit. Subjects received their first treatment at Week 1 and every week thereafter for 1 year up to a maximum of 52 infusions for the duration of the study.

Number of subjects in period 1	Idursulfase
Started	28
Completed	27
Not completed	1
Physician decision	1

Baseline characteristics

Reporting groups[1]	
Reporting group title	Idursulfase
Reporting group description:	
Open-label treatment with idursulfase	

Notes:

[1] - The number of subjects reported to be in the baseline period is not equal to the worldwide number of subjects enrolled in the trial. It is expected that these numbers will be the same.
Justification: Not all the enrolled subjects were treated with study drug. As baseline included only treated subjects, the worldwide number enrolled in the trial differs with the number of subjects reported in the baseline period.

Reporting group values	Idursulfase	Total	
Number of subjects	28	28	
Age categorical			
Units: Subjects			
Age Continuous			
Units: years			
arithmetic mean	4		
standard deviation	± 1.62	-	
Gender Categorical			
Units: subjects			
Male	28	28	
Baseline Normalized Urinary Glycosaminoglycan (GAG) Level			
Units: micorgram/milligram creatinine			
arithmetic mean	738.3		
standard deviation	± 165.21	-	

End points

End points reporting groups

Reporting group title	Idursulfase
Reporting group description:	
Open-label treatment with idursulfase	
Subject analysis set title	Pharmacokinetic (PK) Population
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
All enrolled subjects who had at least one serum concentration measurement available.	
Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis
Subject analysis set description:	
All enrolled subjects who received at least one study dose (or any portion of a dose) of idursulfase.	

Primary: Safety Evaluation

End point title	Safety Evaluation[1]
End point description:	
An adverse event (AE) was defined as any untoward medical occurrence in a clinical investigation participant administered as a pharmaceutical product that did not necessarily have a causal relationship with this treatment. A serious adverse event (SAE) was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. Number of subjects with AEs occurred after start of study treatment until 30 days after the last infusion of idursulfase, were reported.	
End point type	Primary
End point timeframe:	
From the start of study treatment until 30 days after the last infusion of idursulfase	

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: Descriptive statistics were done, no inferential statistical analyses were performed.

End point values	Idursulfase			
Subject group type	Reporting group			
Number of subjects analysed	28[2]			
Units: subjects				
number (not applicable)				
Experienced at least one adverse event (AE)	28			
Deaths	0			
Discontinued due to an AE	0			
Experienced at least one drug-related AE	16			
Experienced at least one serious AE (SAE)	13			
Experienced at least one severe AE	2			
Experienced at least one infusion-related AE	16			

Notes:

[2] - Safety population.

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change from Baseline to Week 53 in Normalized Urinary Glycosaminoglycan (GAG) Levels

End point title	Mean Change from Baseline to Week 53 in Normalized Urinary Glycosaminoglycan (GAG) Levels

End point description:

Analysis of urinary GAG levels was performed at baseline, Week 18, Week 36, and Week 53 as an assessment of the pharmacodynamic effects of Elaprase (idursulfase). In the categories listed below, 'N' signifies the number of subjects evaluable for the timepoint.

End point type	Secondary

End point timeframe:

Baseline, Weeks 18, 36 and 53

End point values	Idursulfase			
Subject group type	Reporting group			
Number of subjects analysed	28[3]			
Units: microgram/milligram creatinine				
arithmetic mean (standard deviation)				
Baseline (N=28)	738.3 (± 165.21)			
Change at Week 18 (N=27)	-368 (± 165.44)			
Change at Week 36 (N=27)	-400.3 (± 180.27)			
Change at Week 53 (N=27)	-402.4 (± 162.13)			

Notes:

[3] - Safety population.

Statistical analyses

No statistical analyses for this end point

Secondary: Single- and Repeat-Dose Pharmacokinetics - Maximum Observed Serum Concentration (Cmax)

End point title	Single- and Repeat-Dose Pharmacokinetics - Maximum Observed Serum Concentration (Cmax)

End point description:

In the categories listed below, “N” signifies the number of subjects evaluable for the timepoint.

End point type	Secondary

End point timeframe:

Weeks 1 and 27

End point values	Idursulfase			
Subject group type	Reporting group			
Number of subjects analysed	27[4]			
Units: nanogram per milliliter				
arithmetic mean (standard deviation)				
Week 1 (N=27) Week 27 (N=19)	1333 (± 817) 1032 (± 590)			

Notes:

[4] - PK population.

Statistical analyses

No statistical analyses for this end point

Secondary: Single- and Repeat-Dose Pharmacokinetics - Time of Maximum Observed Serum Concentration (Tmax)

End point title	Single- and Repeat-Dose Pharmacokinetics - Time of Maximum Observed Serum Concentration (Tmax)

End point description:

In the categories listed below, "N" signifies the number of subjects evaluable for the timepoint.

End point type	Secondary

End point timeframe:

Weeks 1 and 27

End point values	Idursulfase			
Subject group type	Reporting group			
Number of subjects analysed	27[5]			
Units: minutes				
arithmetic mean (standard deviation)				
Week 1 (N=27) Week 27 (N=19)	163 (± 28) 167 (± 32)			

Notes:

[5] - PK population.

Statistical analyses

No statistical analyses for this end point

Secondary: Single- and Repeat-Dose Pharmacokinetics - Area Under the Serum Concentration-Time Curve from Time 0 to the Final Time Point with a Concentration of at Least Lower Limit of Quantitation (AUClast)

End point title	Single- and Repeat-Dose Pharmacokinetics - Area Under the Serum Concentration-Time Curve from Time 0 to the Final Time Point with a Concentration of at Least Lower Limit of Quantitation (AUClast)

End point description:

In the categories listed below, "N" signifies the number of subjects evaluable for the timepoint.

End point type	Secondary

End point timeframe:

Weeks 1 and 27

End point values	Idursulfase			
Subject group type	Reporting group			
Number of subjects analysed	27[6]			
Units: minute*nanogram per milliliter				
arithmetic mean (standard deviation)				
Week 1 (N=27)	196526 (± 71779)			
Week 27 (N=19)	174869 (± 109118)			

Notes:

[6] - PK population.

Statistical analyses

No statistical analyses for this end point

Secondary: Single- and Repeat-Dose Pharmacokinetics - Area Under the Serum Concentration-Time Curve from Time 0 to Infinity (AUCinf)

End point title	Single- and Repeat-Dose Pharmacokinetics - Area Under the Serum Concentration-Time Curve from Time 0 to Infinity (AUCinf)

End point description:

In the categories listed below, "N" signifies the number of subjects evaluable for the timepoint.

End point type	Secondary

End point timeframe:

Weeks 1 and 27

End point values	Idursulfase			
Subject group type	Reporting group			
Number of subjects analysed	26[7]			
Units: minute*nanogram per milliliter				
arithmetic mean (standard deviation)				
Week 1 (N=26)	224343 (± 76944)			
Week 27 (N=18)	201130 (± 117575)			

Notes:

[7] - PK population with evaluable subjects for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Single- and Repeat-Dose Pharmacokinetics - Elimination Half-Life (t1/2)

End point title	Single- and Repeat-Dose Pharmacokinetics - Elimination Half-Life (t1/2)

End point description:

t1/2 refers to the elimination of the drug. It is the time taken for the blood plasma concentration to reach half the concentration in the terminal phase of elimination. It is expressed in hours and derived from the terminal slope of the concentration versus time curve. In the categories listed below, "N" signifies the number of subjects evaluable for the timepoint.

End point type	Secondary

End point timeframe:

Weeks 1 and 27

End point values	Idursulfase			
Subject group type	Reporting group			
Number of subjects analysed	26[8]			
Units: minutes				
arithmetic mean (standard deviation)				
Week 1 (N=26)	160 (± 69)			
Week 27 (N=18)	109 (± 43)			

Notes:

[8] - PK population with evaluable subjects for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Single- and Repeat-Dose Pharmacokinetics - Mean Residence Time from Time 0 to Infinity (MRTinf)

End point title	Single- and Repeat-Dose Pharmacokinetics - Mean Residence Time from Time 0 to Infinity (MRTinf)

End point description:

MRTinf is an average duration of the drug in the body from time zero to infinity, and is expressed in minutes. In the categories listed below, "N" signifies the number of subjects evaluable for the timepoint.

End point type	Secondary

End point timeframe:

Weeks 1 and 27

End point values	Idursulfase			
Subject group type	Reporting group			
Number of subjects analysed	26[9]			
Units: minutes				
arithmetic mean (standard deviation)				
Week 1 (N=26)	153 (± 96)			
Week 27 (N=18)	127 (± 23)			

Notes:

[9] - PK population with evaluable subjects for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Single- and Repeat-Dose Pharmacokinetics - Clearance (CL)

End point title	Single- and Repeat-Dose Pharmacokinetics - Clearance (CL)

End point description:

Clearance of a drug is a measure of the rate at which a drug is metabolized or eliminated by normal biological processes. In the categories listed below, "N" signifies the number of subjects evaluable for the timepoint.

End point type	Secondary

End point timeframe:

Weeks 1 and 27

End point values	Idursulfase			
Subject group type	Reporting group			
Number of subjects analysed	26[10]			
Units: milliliter/minute/kilogram				
arithmetic mean (standard deviation)				
Week 1 (N=26)	2.4 (± 0.7)			
Week 27 (N=18)	4.7 (± 5)			

Notes:

[10] - PK population with evaluable subjects for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Single- and Repeat-Dose Pharmacokinetics - Volume of Distribution at Steady State (Vss)

End point title	Single- and Repeat-Dose Pharmacokinetics - Volume of Distribution at Steady State (Vss)

End point description:

Volume of distribution is defined as the theoretical volume in which the total amount of drug would need to be uniformly distributed to produce the desired blood concentration of a drug. Vss is the apparent volume of distribution at steady-state. In the categories listed below, "N" signifies the number of subjects evaluable for the timepoint.

End point type	Secondary

End point timeframe:

Weeks 1 and 27

End point values	Idursulfase			
Subject group type	Reporting group			
Number of subjects analysed	26[11]			
Units: milliliter per kilogram				
arithmetic mean (standard deviation)				
Week 1 (N=26) Week 27 (N=18)	394 (± 423) 551 (± 528)			

Notes:

[11] - PK population with evaluable subjects for this endpoint.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From the start of study treatment until 30 days after the last infusion of idursulfase	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	10.1

Reporting groups	
Reporting group title	Idursulfase
Reporting group description:	
Open-label treatment with idursulfase	

Serious adverse events	Idursulfase		
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 28 (46.43%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Atonic seizures			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Microcytic anaemia			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Irritability			

subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Catheter site haematoma			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Oedema peripheral			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	3 / 28 (10.71%)		
occurrences causally related to treatment / all	6 / 6		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Food poisoning			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypoxia			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bronchospasm			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Pulmonary hypertension				
subjects affected / exposed	1 / 28 (3.57%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory distress				
subjects affected / exposed	2 / 28 (7.14%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
Skin hypertrophy				
subjects affected / exposed	1 / 28 (3.57%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Rash				
subjects affected / exposed	1 / 28 (3.57%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Urticaria				
subjects affected / exposed	1 / 28 (3.57%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Muscle contracture				
subjects affected / exposed	1 / 28 (3.57%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Bronchopneumonia				
subjects affected / exposed	3 / 28 (10.71%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal infection				

subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ear infection			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Otitis media			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory tract infection			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Viral pharyngitis			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Upper respiratory tract infection			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 3.57 %

Non-serious adverse events	Idursulfase		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	28 / 28 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Hypertension			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Hyperaemia			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	2		
Haemorrhage			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
General disorders and administration site conditions			
Catheter site haemorrhage			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Chest pain			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Fatigue			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Oedema peripheral			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Malaise			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	2		

Pyrexia			
subjects affected / exposed	25 / 28 (89.29%)		
occurrences (all)	59		
Respiratory, thoracic and mediastinal disorders			
Allergic cough			
subjects affected / exposed	3 / 28 (10.71%)		
occurrences (all)	3		
Asthma			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Choking			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Bronchospasm			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	3		
Dyspnoea			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Hypoxia			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Cough			
subjects affected / exposed	16 / 28 (57.14%)		
occurrences (all)	45		
Nasal congestion			
subjects affected / exposed	6 / 28 (21.43%)		
occurrences (all)	9		
Pharyngolaryngeal pain			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Lung infiltration			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Pulmonary hypertension			

subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Respiratory disorder			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Sleep apnoea syndrome			
subjects affected / exposed	3 / 28 (10.71%)		
occurrences (all)	3		
Rhinorrhoea			
subjects affected / exposed	3 / 28 (10.71%)		
occurrences (all)	4		
Psychiatric disorders			
Bipolar disorder			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Crying			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Insomnia			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Agitation			
subjects affected / exposed	4 / 28 (14.29%)		
occurrences (all)	5		
Sleep disorder			
subjects affected / exposed	3 / 28 (10.71%)		
occurrences (all)	3		
Learning disorder			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Investigations			
Cardiac murmur			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Hepatic enzyme abnormal			

subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Gamma-Glutamyltransferase increased			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Alanine aminotransferase increased			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Electrocardiogram repolarisation abnormality			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Monocyte count decreased			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Lymphocyte morphology abnormal			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Burns second degree			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Contusion			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Fall			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Head injury			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Mouth injury			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Limb injury			

subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Procedural pain			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Sunburn			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Congenital, familial and genetic disorders			
Hip dysplasia			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Cardiac disorders			
Cardiomyopathy			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Aortic valve incompetence			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Cyanosis			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Right ventricular hypertrophy			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Left ventricular hypertrophy			
subjects affected / exposed	4 / 28 (14.29%)		
occurrences (all)	4		
Sinus bradycardia			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Ventricular extrasystoles			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Nervous system disorders			

Epilepsy			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Headache			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Hypoaesthesia			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Tremor			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Somnolence			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Eosinophilia			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Iron deficiency anaemia			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Splenomegaly			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Ear and labyrinth disorders			
Cerumen impaction			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	2		
Conductive deafness			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Deafness			
subjects affected / exposed	4 / 28 (14.29%)		
occurrences (all)	4		
Ear pain			

subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Hearing impaired			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Hypoacusis			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Otorrhoea			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Eye disorders			
Conjunctivitis			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Hypermetropia			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	2		
Anal fissure			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	2		
Constipation			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	3		
Dental caries			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Diarrhoea			
subjects affected / exposed	7 / 28 (25.00%)		
occurrences (all)	35		
Faeces hard			

subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	2		
Nausea			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	2		
Gingivitis			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Pruritus ani			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Stomatitis			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Toothache			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Umbilical hernia			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	10 / 28 (35.71%)		
occurrences (all)	12		
Skin and subcutaneous tissue disorders			
Dermatitis allergic			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	2		
Dermatitis			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Dermatitis atopic			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Heat rash			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	4		

Eczema				
subjects affected / exposed	2 / 28 (7.14%)			
occurrences (all)	2			
Dermatitis diaper				
subjects affected / exposed	2 / 28 (7.14%)			
occurrences (all)	3			
Erythema				
subjects affected / exposed	2 / 28 (7.14%)			
occurrences (all)	2			
Intertrigo				
subjects affected / exposed	1 / 28 (3.57%)			
occurrences (all)	1			
Palmar-Plantar erythrodysaesthesia syndrome				
subjects affected / exposed	1 / 28 (3.57%)			
occurrences (all)	1			
Pruritus				
subjects affected / exposed	1 / 28 (3.57%)			
occurrences (all)	1			
Rash				
subjects affected / exposed	6 / 28 (21.43%)			
occurrences (all)	11			
Petechiae				
subjects affected / exposed	2 / 28 (7.14%)			
occurrences (all)	2			
Rash generalised				
subjects affected / exposed	1 / 28 (3.57%)			
occurrences (all)	1			
Rash maculo-papular				
subjects affected / exposed	2 / 28 (7.14%)			
occurrences (all)	2			
Rash papular				
subjects affected / exposed	2 / 28 (7.14%)			
occurrences (all)	2			
Skin hypopigmentation				

subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Skin lesion			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Urticaria			
subjects affected / exposed	3 / 28 (10.71%)		
occurrences (all)	4		
Urticaria papular			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Renal and urinary disorders			
Enuresis			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Lordosis			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Muscle contracture			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Arthralgia			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	2		
Infections and infestations			
Abscess limb			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Body tinea			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Bronchitis			
subjects affected / exposed	4 / 28 (14.29%)		
occurrences (all)	4		
Bronchopneumonia			

subjects affected / exposed	3 / 28 (10.71%)			
occurrences (all)	4			
Catheter site infection				
subjects affected / exposed	1 / 28 (3.57%)			
occurrences (all)	1			
Candidiasis				
subjects affected / exposed	1 / 28 (3.57%)			
occurrences (all)	1			
Ear infection				
subjects affected / exposed	1 / 28 (3.57%)			
occurrences (all)	1			
Gastroenteritis viral				
subjects affected / exposed	2 / 28 (7.14%)			
occurrences (all)	2			
Gastrointestinal infection				
subjects affected / exposed	2 / 28 (7.14%)			
occurrences (all)	2			
Gastroenteritis				
subjects affected / exposed	6 / 28 (21.43%)			
occurrences (all)	7			
Herpes virus infection				
subjects affected / exposed	2 / 28 (7.14%)			
occurrences (all)	2			
Influenza				
subjects affected / exposed	2 / 28 (7.14%)			
occurrences (all)	2			
Herpes zoster				
subjects affected / exposed	1 / 28 (3.57%)			
occurrences (all)	1			
Lice infestation				
subjects affected / exposed	1 / 28 (3.57%)			
occurrences (all)	1			
Laryngitis				
subjects affected / exposed	2 / 28 (7.14%)			
occurrences (all)	2			
Nasopharyngitis				

subjects affected / exposed	2 / 28 (7.14%)			
occurrences (all)	2			
Oral candidiasis				
subjects affected / exposed	1 / 28 (3.57%)			
occurrences (all)	1			
Otitis externa				
subjects affected / exposed	3 / 28 (10.71%)			
occurrences (all)	5			
Otitis media acute				
subjects affected / exposed	7 / 28 (25.00%)			
occurrences (all)	10			
Otitis media				
subjects affected / exposed	2 / 28 (7.14%)			
occurrences (all)	3			
Pharyngitis				
subjects affected / exposed	7 / 28 (25.00%)			
occurrences (all)	18			
Rash pustular				
subjects affected / exposed	1 / 28 (3.57%)			
occurrences (all)	1			
Otitis media chronic				
subjects affected / exposed	1 / 28 (3.57%)			
occurrences (all)	1			
Respiratory tract infection				
subjects affected / exposed	12 / 28 (42.86%)			
occurrences (all)	36			
Pneumonia				
subjects affected / exposed	3 / 28 (10.71%)			
occurrences (all)	3			
Rhinitis				
subjects affected / exposed	11 / 28 (39.29%)			
occurrences (all)	20			
Sinusitis				
subjects affected / exposed	5 / 28 (17.86%)			
occurrences (all)	6			
Tinea versicolour				

subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Tonsillitis bacterial			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	2		
Tonsillitis			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Upper respiratory tract infection			
subjects affected / exposed	18 / 28 (64.29%)		
occurrences (all)	42		
Viral diarrhoea			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	2		
Upper respiratory tract infection bacterial			
subjects affected / exposed	6 / 28 (21.43%)		
occurrences (all)	13		
Varicella			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Viral pharyngitis			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Viral upper respiratory tract infection			
subjects affected / exposed	9 / 28 (32.14%)		
occurrences (all)	17		
Viral infection			
subjects affected / exposed	3 / 28 (10.71%)		
occurrences (all)	4		
Metabolism and nutrition disorders			
Obesity			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Hypercalcaemia			

subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Hyperuricaemia			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported