Clinical trial results:
A phase I/II study evaluating safety and efficacy of autologous hematopoietic stem cells genetically modified with GLOBE lentiviral vector encoding for the human beta-globin gene for the treatment of patients affected by transfusion dependent beta-thalassemia

Summary

EudraCT number	2014-004860-39
Trial protocol	IT
Global end of trial date	25 November 2019

Results information

Result version number	v1 (current)
This version publication date	15 October 2020
First version publication date	15 October 2020

Trial information

Trial identification

Sponsor protocol code	TIGET-BTHAL

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02453477
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Ospedale San Raffaele
Sponsor organisation address	Via Olgettina 60, Milan, Italy, 20132
Public contact	TIGET Clinical Trial Office (TCTO), OSPEDALE SAN RAFFAELE, tcto@hsr.postcert.it
Scientific contact	San Raffaele Telethon Institute for Gene Therapy (SR-TIGET), OSPEDALE SAN RAFFAELE, tcto@hsr.postcert.it

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001933-PIP01-16
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	31 July 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 November 2019
Global end of trial reached?	Yes
Global end of trial date	25 November 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

1. To evaluate the safety and tolerability of autologous CD34+ cell enriched fraction that contains Hematopoietic Stem Cells (HSC) transduced with Lentiviral Vector (LV) encoding the beta-globin gene in pediatric and adult patients with transfusion dependent beta-thalassemia following a reduced toxicity conditioning regimen.
2. To evaluate the efficacy of autologous CD34+ cell enriched fraction that contains Hematopoietic Stem Cells (HSC) transduced with Lentiviral Vector (LV) encoding the beta-globin gene in pediatric and adult patients with transfusion dependent beta-thalassemia following a reduced toxicity conditioning regimen.

Protection of trial subjects:

The study was conducted in accordance with the protocol, consistent to ICH-GCP and applicable local regulatory requirements. The written informed consent with a declaration of data privacy was signed and dated by the subject or by the subject's legally acceptable representative. For pediatric subjects or subjects unable to give free consent to the trial, subject's parents or subject's legally acceptable representative signed the informed consent. An independent Data Safety Monitoring Board (DSMB) was assigned to monitor the trial.
Long-term follow-up will be conducted under a separate protocol.

Background therapy:

Regular red blood cell transfusions and iron chelator therapy

Evidence for comparator:

No acceptable comparator therapy was available.

Actual start date of recruitment	29 May 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	6 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Italy: 10
Worldwide total number of subjects	10
EEA total number of subjects	10

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)	0
Children (2-11 years)	4
Adolescents (12-17 years)	3
Adults (18-64 years)	3
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study enrolled subjects aged ≥3 and <65 years with a diagnosis of Transfusion dependent beta-thalassemia (TDBT) (any genotype). Enrolment started with adult subjects. The ensuing enrolment of older children, and then of younger children, was conducted after Data Safety Monitoring Board (DSMB) approval for both of these age groups.

Pre-assignment

Screening details:

The conditions required by the clinical protocol for subject inclusion/exclusion were assessed during the screening phase.

Period 1

Period 1 title	OTL-300 (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

This was a single-arm open-label study.

Arms

Arm title	OTL-300

Arm description:

Each subject received the Advanced therapy investigational medicinal product (ATIMP), OTL-300 (autologous CD34+ cell enriched fraction containing HSPC transduced with the GLOBE LVV encoding for the beta-globin gene), on a single occasion via intraosseous infusion.

Arm type	Experimental
Investigational medicinal product name	OTL-300 (autologous CD34+ cell enriched fraction)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intraosseous use

Dosage and administration details:

5 x 10e6 CD34+ cells/kg, with a minimum dose of 2 x 10e6 CD34+ cells/kg and a maximum dose of 20 x 10e6 CD34+ cells/kg, depending on the yield of cells.

Number of subjects in period 1[1]	OTL-300
Started	9
ATIMP infusion/Ly infusion	9
Completed	9

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: Ten subjects have been enrolled in the study. Nine subjects received the conditioning regimen, received the OTL-300 infusion, and completed the 2-year study. One younger child discontinued the study after PBSC mobilization and transduction, and did not receive the conditioning regimen or the OTL-300 infusion.

Baseline characteristics

Reporting groups

Reporting group title	OTL-300

Reporting group description:

All patients were affected by transfusion dependent beta-thalassemia. Enrolment started with adult subjects. The ensuing enrolment of older children, and then of younger children, was conducted after DSMB approval for both of these age groups. Ten subjects underwent Peripheral blood stem cell (PBSC) mobilization and harvest: four younger children, three older children, and three adults. Nine subjects received the conditioning regimen, received the OTL-300 infusion, and completed the 2-year study; these subjects comprised the modified Intention-to-Treat (mITT) Population. One younger child discontinued the study after PBSC mobilization and transduction, and did not receive the conditioning regimen or the OTL-300 infusion.
Mean age in the mITT Population was 5.7 years for younger children, 13.5 years for older children, and 33.8 years for adult subjects. The majority of subjects were male (66.7%) and all subjects were White.

Reporting group values	OTL-300	Total	
Number of subjects	9	9	
Age categorical Units: Subjects			
Younger children (3-7 years)	3	3	
Older children (8-17 years)	3	3	
Adults (≥18 years)	3	3	
Age continuous Units: years			
median	17.64		
full range (min-max)	4.6 to 35.7	-	
Gender categorical Units: Subjects			
Female	3	3	
Male	6	6	

Subject analysis sets

Subject analysis set title	mITT Population
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

mITT Population comprised of subjects received mobilization + conditioning + OTL-300 and completed the 2-year study.

Reporting group values	mITT Population		
Number of subjects	9		
Age categorical Units: Subjects			
Younger children (3-7 years)	3		
Older children (8-17 years)	3		
Adults (≥18 years)	3		
Age continuous Units: years			
median	17.64		
full range (min-max)	4.6 to 35.7		

Gender categorical Units: Subjects			
Female	3		
Male	6		

End points

End points reporting groups

Reporting group title	OTL-300

Reporting group description:

Each subject received the Advanced therapy investigational medicinal product (ATIMP), OTL-300 (autologous CD34+ cell enriched fraction containing HSPC transduced with the GLOBE LVV encoding for the beta-globin gene), on a single occasion via intraosseous infusion.

Subject analysis set title	mITT Population
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

mITT Population comprised of subjects received mobilization + conditioning + OTL-300 and completed the 2-year study.

Primary: Overall survival

End point title	Overall survival[1]

End point description:

Overall survival of all nine subjects in the mITT Population at the end of the 24-month follow up.

End point type	Primary

End point timeframe:

Day 1 -2 Years

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: No statistical analysis has been specified for this endpoint as it is a single arm study with no comparator.

End point values	OTL-300			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: percent				
number (confidence interval 95%)				
Proportion surviving at end of follow-up	100 (66.37 to 100)			
Kaplan-Meier estimate of survival	100 (100 to 100)			

Statistical analyses

No statistical analyses for this end point

Primary: Achievement of hematological engraftment

End point title	Achievement of hematological engraftment[2]

End point description:

Hematological engraftment was defined as neutrophil count >500/mm^3 and platelets >20,000/mm^3 on three consecutive blood counts (in the absence of transfusions).

End point type	Primary

End point timeframe:

by Day +60 from OTL-300 infusion

Notes:

[2] - 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: No statistical analysis has been specified for this endpoint as it is a single arm study with no comparator.

End point values	OTL-300			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: Percentage				
number (confidence interval 95%)				
Hematological engraftment (%)	100 (70.1 to 100)			

Statistical analyses

No statistical analyses for this end point

Primary: Exposure to OTL-300 Infusion

End point title	Exposure to OTL-300 Infusion[3]

End point description:

Exposure to OTL-300 Infusion was defined by the mean number of CD34+ cells infused, mean transduction efficiency and mean VCN.

End point type	Primary

End point timeframe:

0–24 months

Notes:

[3] - 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: No statistical analysis has been specified for this endpoint as it is a single arm study with no comparator.

End point values	OTL-300			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: Percent/cells				
arithmetic mean (standard deviation)				
CD34+ cells [x 10^6/kg]	18.99 (± 1.182)			
Transduction efficiency [%]	59.4 (± 10.74)			
VCN [copies/cell]	0.93 (± 0.269)			

Statistical analyses

No statistical analyses for this end point

Primary: Polyclonal engraftment

End point title	Polyclonal engraftment[4]

End point description:

Polyclonality of hematopoiesis was defined as >1000 unique integration sites retrieved from peripheral blood and/or bone marrow cells when available.

End point type	Primary

End point timeframe:

Polyclonal engraftment evaluated by integration analysis at 6, 12, 18, 24 months after OTL-300 infusion.

Notes:

[4] - 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: No statistical analysis has been specified for this endpoint as it is a single arm study with no comparator.

End point values	OTL-300			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: Percent				
median (confidence interval 95%)				
6 months	100 (70.1 to 100)			
12 months	88.9 (56.5 to 98.0)			
18 months	77.8 (45.3 to 93.7)			
24 months	100 (70.1 to 100)			
Any time	100 (70.1 to 100)			

Statistical analyses

No statistical analyses for this end point

Primary: Transfusion Independence

End point title	Transfusion Independence[5]

End point description:

Transfusion independence was defined as less than or equal to one transfusion in the previous 6 months.

End point type	Primary

End point timeframe:

Transfusion independence at 12 and 24 months after OTL-300 infusion.

Notes:

[5] - 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: No statistical analysis has been specified for this endpoint as it is a single arm study with no comparator.

End point values	OTL-300			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: percent				
number (confidence interval 95%)				
Transfusion Independence (Overall)/12 months/N=9	55.6 (26.7 to 81.1)			
Transfusion Independence (Overall)/24 months/N=9	44.4 (18.9 to 73.3)			
Transfusion Independence (3–7 yrs)/12 months/N=3	66.7 (20.8 to 93.9)			
Transfusion Independence (3–7 yrs)/24 months/N=3	66.7 (20.8 to 93.9)			
Transfusion Independence (8–17 yrs)/12 months/N=3	66.7 (20.8 to 93.9)			
Transfusion Independence (8–17 yrs)/24 months/N=3	66.7 (20.8 to 93.9)			
Transfusion Independence (≥18 yrs)/12 months/N=3	33.3 (6.1 to 79.2)			
Transfusion Independence (≥18 yrs)/24 months/N=3	0 (0 to 56.1)			

Statistical analyses

No statistical analyses for this end point

Primary: Achievement of adequate Hb in transfusion independent subjects

End point title	Achievement of adequate Hb in transfusion independent subjects[6]

End point description:

Achievement of adequate hemoglobin in transfusion independent subjects defined as Hb >9 g/dL (adult) or >10 g/dL (child).

End point type	Primary

End point timeframe:

Achievement of adequate hemoglobin in transfusion independent subjects measured at 9, 12, 18 and 24 months.

Notes:

[6] - 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: No statistical analysis has been specified for this endpoint as it is a single arm study with no comparator.

End point values	OTL-300			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: percent				
number (not applicable)				
Adequate Hb level (3-7 yrs)/12 months/N=2	0			
Adequate Hb level (3-7 yrs)/24 months/N=2	0			
Adequate Hb level (8-17 yrs)/12 months/N=2	100			

Adequate Hb level (8-17 yrs)/24 months/N=2	100			
Adequate Hb level (>=18 yrs)/12 months/N=1	0			
Adequate Hb level (>=18 yrs)/24 months/N=0	0			

Statistical analyses

No statistical analyses for this end point

Primary: Transfusion Frequency

End point title	Transfusion Frequency[7]

End point description:

Reduction in transfusion frequency from baseline.

End point type	Primary

End point timeframe:

Baseline transfusion frequency is presented for the 6-month period from Month -7 to Month -1. Post-treatment transfusion frequency is presented for the last 6 months of the study (Month 19 to Month 24).

Notes:

[7] - 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: Application of Poisson generalized linear mixed-model repeated measures was used to compare transfusion frequency after OTL-300 infusion with Pre-Treatment. Comparing 19 to 24 months vs. Pre-Treatment for the overall population (N=9), this indicated a significant decrease in Least Squares Mean annualized transfusion frequency (ratio versus Pre-Treatment = 0.13; p<0.001).

End point values	OTL-300			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: Annualized Transfusion Frequency				
median (full range (min-max))				
Transfusion Frequency (Overall)/Pre-treatment/N=9	19.96 (14.0 to 33.9)			
Transfusion Frequency (Overall)/19–24 months/N=9	10.19 (0 to 24.4)			
Transfusion Frequency (3–7 yrs)/Pre-treatment/N=3	17.96 (14.0 to 25.9)			
Transfusion Frequency (3–7 yrs)/19–24 months/N=3	0 (0 to 12.6)			
Transfusion Frequency (8–17 yrs)/Pre-treatment/N=3	19.96 (18.0 to 22.0)			
Transfusion Frequency (8–17 yrs)/19–24 months/N=3	0 (0 to 20.5)			
Transfusion Frequency (≥18 yrs)/Pre-treatment/N=3	27.94 (18.0 to 33.9)			
Transfusion Frequency (≥18 yrs)/19–24 months/N=3	11.85 (10.2 to 24.4)			

Statistical analyses

No statistical analyses for this end point

Primary: Transfusion Volume

End point title	Transfusion Volume[8]

End point description:

Reduction in annualised transfusion volume from baseline.

End point type	Primary

End point timeframe:

Baseline transfusion volume is presented for the 6-month period from Month -7 to Month -1. Post-treatment transfusion volume is presented for the last 6 months of the study (Month 19 to Month 24).

Notes:

[8] - 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: Application of Poisson generalized linear mixed-model repeated measures was used to compare transfusion volume after OTL-300 infusion with Pre-Treatment. Comparing 19 to 24 months vs. Pre-Treatment for the overall population (N=9), this indicated a significant decrease in Least Squares Mean annualized transfusion volume (ratio versus Pre-Treatment = 0.02; p<0.001).

End point values	OTL-300			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: Annualized Transfusion Volume mL/kg/year				
median (full range (min-max))				
Transfusion Volume (Overall)/Pre-treatment/N=9	257.41 (190.4 to 346.4)			
Transfusion Volume (Overall)/ 19–24 months/N=9	85.99 (0 to 237.9)			
Transfusion Volume (3–7 yrs)/Pre-treatment/N=3	297.56 (190.4 to 346.4)			
Transfusion Volume (3–7 yrs)/ 19–24 months/N=3	0 (0 to 231.8)			
Transfusion Volume (8–17 yrs)/Pre-treatment/N=3	248.48 (239.6 to 257.4)			
Transfusion Volume (8–17 yrs)/19–24 months/N=3	0 (0 to 234.4)			
Transfusion Volume (≥18 yrs)/Pre-treatment/N=3	266.51 (196.8 to 285.9)			
Transfusion Volume (≥18 yrs)/19–24 months/N=3	93.22 (86.0 to 237.9)			

Statistical analyses

No statistical analyses for this end point

Primary: Engraftment of genetically corrected cells in bone marrow

End point title	Engraftment of genetically corrected cells in bone marrow[9]

End point description:

Adequate engraftment is defined as a vector copy number (VCN) >= 0.15 assessed on bone marrow erythroid cells (both CD36+ and glycophorin-A+).

End point type	Primary

End point timeframe:

From 6 months to 24 months

Notes:

[9] - 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: No statistical analysis has been specified for this endpoint as it is a single arm study with no comparator.

End point values	OTL-300			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: percent				
number (confidence interval 95%)				
Engraftment (Overall)/6 months/N=9	100 (70.1 to 100)			
Engraftment (Overall)/12 months/N=9	77.8 (45.3 to 93.7)			
Engraftment (Overall)/24 months/N=9	77.8 (45.3 to 93.7)			
Engraftment (3-7 yrs)/6 months/N=3	100 (43.9 to 100)			
Engraftment (3-7 yrs)/12 months/N=3	66.7 (20.8 to 93.9)			
Engraftment (3-7 yrs)/24 months/N=3	66.7 (20.8 to 93.9)			
Engraftment (8-17 yrs)/6 months/N=3	100 (43.9 to 100)			
Engraftment (8-17 yrs)/12 months/N=3	66.7 (20.8 to 93.9)			
Engraftment (8-17 yrs)/24 months/N=3	66.7 (20.8 to 93.9)			
Engraftment (>=18 yrs)/6 months/N=3	100 (43.9 to 100)			
Engraftment (>=18 yrs)/12 months/N=3	100 (43.9 to 100)			
Engraftment (>=18 yrs)/18 months/N=3	100 (43.9 to 100)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the start of mobilization until Month 24.

Adverse event reporting additional description:

All AEs were identified using Medical Dictionary for Regulatory Activities (MedDRA version 21.1) terms and for each event the following parameters were recorded: intensity or severity (see below); onset date; stop date; causality assessment with study drug (related/not related); action taken; outcome.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups

Reporting group title	OTL-300

Reporting group description: -

Serious adverse events	OTL-300		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 9 (44.44%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Pancreatitis acute			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Mycobacterium fortuitum infection			

subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Device related infection			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	OTL-300		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 9 (100.00%)		
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	5 / 9 (55.56%)		
occurrences (all)	9		
Asthenia			
subjects affected / exposed	4 / 9 (44.44%)		
occurrences (all)	5		
Oedema peripheral			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	7		
Axillary pain			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Catheter site erythema			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Catheter site pain			

subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Fatigue			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Influenza like illness			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Injection site pain			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Injection site swelling			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Reproductive system and breast disorders			
Balanoposthitis			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Perineal erythema			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Testicular pain			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	2		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Cough			
subjects affected / exposed	3 / 9 (33.33%)		
occurrences (all)	5		
Epistaxis			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Hiccups			

subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Nasal turbinate hypertrophy			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Oropharyngeal pain			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	2		
Psychiatric disorders			
Panic attack			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	2		
Investigations			
Liver iron concentration increased			
subjects affected / exposed	3 / 9 (33.33%)		
occurrences (all)	3		
Weight increased			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	2		
Blood creatinine increased			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	2		
Enterobacter test positive			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Liver iron concentration abnormal			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Staphylococcus test positive			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Urine protein/creatinine ratio increased			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Vitamin B12 decreased			

subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Joint injury			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Limb injury			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	2		
Post procedural fever			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Procedural pain			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Congenital, familial and genetic disorders			
Phimosis			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Cardiac disorders			
Tachycardia			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 9 (33.33%)		
occurrences (all)	4		
Dysaesthesia			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Syncope			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Febrile neutropenia			

subjects affected / exposed	5 / 9 (55.56%)		
occurrences (all)	5		
Lymphopenia			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	2		
Coagulopathy			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Lymphadenopathy			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Neutropenia			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Thrombocytopenia			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	6 / 9 (66.67%)		
occurrences (all)	7		
Diarrhoea			
subjects affected / exposed	5 / 9 (55.56%)		
occurrences (all)	7		
Abdominal pain			
subjects affected / exposed	4 / 9 (44.44%)		
occurrences (all)	8		
Abdominal pain upper			
subjects affected / exposed	3 / 9 (33.33%)		
occurrences (all)	5		
Nausea			

subjects affected / exposed	3 / 9 (33.33%)		
occurrences (all)	4		
Constipation			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Gingival bleeding			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Stomatitis			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Cholelithiasis			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Hepatitis			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Hyperbilirubinaemia			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Jaundice			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Rash erythematous			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	2		
Drug eruption			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Erythema			

subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Nodular rash			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Petechiae			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Pruritus			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Rash			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Rash maculo-papular			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Rash pruritic			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Urticaria			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	3 / 9 (33.33%)		
occurrences (all)	9		
Bone pain			
subjects affected / exposed	3 / 9 (33.33%)		
occurrences (all)	3		
Arthralgia			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	2		
Pain in extremity			

subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	2		
Spinal pain			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	2		
Musculoskeletal chest pain			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	2		
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	3 / 9 (33.33%)		
occurrences (all)	3		
Influenza			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	3		
Pharyngitis			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	2		
Upper respiratory tract infection			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	2		
Conjunctivitis			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Folliculitis			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Helicobacter infection			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Human bocavirus infection			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Nasal herpes			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	3		

Nasopharyngitis subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1			
Oral herpes subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1			
Periorbital infection subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1			
Rhinitis subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1			
Salmonellosis subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1			
Streptococcal infection subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1			
Streptococcal sepsis subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1			
Metabolism and nutrition disorders Vitamin D deficiency subjects affected / exposed occurrences (all)	4 / 9 (44.44%) 4			
Folate deficiency subjects affected / exposed occurrences (all)	2 / 9 (22.22%) 2			
Diabetes mellitus subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1			
Hyperferritinaemia subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1			
Hypoalbuminaemia				

subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Hypocalcaemia			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	2		
Hypokalaemia			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Hypomagnesaemia			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 November 2015	The planned assessment of globin expression by high performance liquid chromatography was removed due to the closure of the bioanalytical laboratory.
10 May 2016	• The conditioning regimen for Group 3 (aged 3–7 years) was modified to be the same as Group 2 (aged 8–17 years). This change was implemented before any subjects in Group 3 were treated. • Inclusion of two additional research endpoints (#2 and #3 in Section 8.2.3).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported