Clinical trial results:
PHASE I/II CLINICAL TRIAL OF HAEMATOPOIETIC STEM CELL GENE THERAPY FOR THE WISKOTT-ALDRICH SYNDROME

Summary

EudraCT number	2007-004308-11
Trial protocol	GB
Global end of trial date	13 November 2019

Results information

Result version number	v1 (current)
This version publication date	04 October 2020
First version publication date	04 October 2020

Trial information

Trial identification

Sponsor protocol code	GTG002.07

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01347242
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Genethon
Sponsor organisation address	1bis, Rue de l'Internationale , EVRY, France, 91002
Public contact	Clinical Trials Information, Genethon, +33 169472900, clinical_development@genethon.fr
Scientific contact	Clinical Trials Information, Genethon, +33 169472900, clinical_development@genethon.fr

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000786-PIP01-09
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	13 November 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 November 2019
Global end of trial reached?	Yes
Global end of trial date	13 November 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of heamatopoietic stem cell gene therapy in WAS patients based on the clinical improvement in at least one of the following clinical parameters, depending on the patient's symptomatology at study entry: eczema status, frequency and severity of infections, of bruising and bleeding episodes and of autoimmune disorders and consequently to assess the number of disease-related days of hospitalisation

Protection of trial subjects:

Only male patients with WAS confirmed by DNA sequencing and with a severity score of 3 to 5 who had no suitable donor for an allogeneic HSCT were enrolled.
The cell/product target dose consisted of at least 0.5 x 10^6 cells per kg of body weight with a minimum of cells viability of 50%, transduced ex vivo with 1 x 10^8 i.g./mL of lentiviral vector to achieve ≥0.3 integrated copies per cell.
Hematopoietic cells were collected from the patient in advance of the treatment, to serve as a salvage procedure (back-up graft). Cells were collected either from bone marrow under general anaesthesia or from peripheral blood mononuclear cells recovered by leukapheresis. The bone marrow or mobilised cells were frozen and stored un-manipulated to constitute the back-up graft.
CD34+ cells were purified from bone marrow cells harvested under general anaesthesia, or from PBMCs mobilised through the use of G-CSF (possibily augmented with plerixafor to enhance mobilization) and recovered by leukapheresis, depending on the patient's clinical status. Patient conditioning was to be initiated immediately after bone marrow or PBMC collection and consisted of daily doses of busulfan (approximatively 4 mg/kg depending on age) and fludarabine (40 mg/m2) for 3 days.
If the number of CD34+ was less than 0.5 x 10^6/kg, the cells were not to be infused, and the patient was to receive the back-up harvest within 48 hours and to be withdrawn from the study.
If there was no bone marrow recovery within 6 weeks, the patient was to receive the back-up harvest.
Follow-up of patients including physical examinations and blood tests were to take place at 1 month, 6 weeks, and 3, 6, 9, 12, 18, and 24 months after infusion of transduced cells. After completion of this 2-year follow-up period, patients could participate in a long-term follow-up study for another 8 years.

Background therapy:

Allogeneic haematopoietic stem cells transplantation is a curative procedure for WAS, although success is dependent on the availability of human leukocyte antigen (HLA)-matched donors. HLA-mismatched transplantation carries an increased risk for complications, in particular for graft vs. host disease, causing increased morbidity and mortality. Long term outcome of haematopoetic stem cell transplantation (HSCT) has been analysed (Ozsahin et al, 2007). In a cohort of 137 patients treated in Europe at 17 centres between 1979-2001, overall survival in matched family donor transplants was 83%, matched unrelated donor transplants 75%, and related HLA-mismatched 50%. It is estimated that a fully matched donor can be found for about a third to one half of the patients with WAS.
As a result of existing therapeutic interventions, some patients with WAS survive into adulthood, however a significant number of patients die at less than 10 years of age from haemorrhage, infection, malignancy, or complications of HSCT.
Despite the established role of allogeneic HSCT for patients with a suitable donor, there is still a need for novel, effective, well-tolerated treatments for WAS, particularly in patients with severe disease and those who lack an HLA-matched allogeneic donor. The knowledge of the defective gene causing WAS has prompted the development of new treatment options, focusing on the infusion of autologous hematopoietic stem cells modified ex vivo by gene therapy.

Evidence for comparator:

The choice of a design with no control group was considered to be appropriate to establish a proof of concept and to investigate the safety of the investigational product in patients with severe WAS. Given

the rarity and severity of the disease as well as the lack of therapeutic alternatives, apart from an allogeneic Haemotopoietic Stem Cell Transplantation, a controlled design was considered to be neither feasible nor ethically justifiable.

Actual start date of recruitment	17 February 2010
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Ethical reason, Safety, Regulatory reason, Scientific research
Long term follow-up duration	10 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 5
Worldwide total number of subjects	5
EEA total number of subjects	5

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)	2
Children (2-11 years)	2
Adolescents (12-17 years)	0
Adults (18-64 years)	1
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were enrolled in two centers, Great Ormond Street Hospital, London, UK and Royal Free Hospital, London, UK, from February the 17th, 2010 to October the 17th, 2017.

Pre-assignment

Screening details:

Male patients with WAS confirmed by DNA sequencing and with a severity score of 3 to 5 who had no suitable donor for an allogeneic Haematopoietic stem cell transplantation.

Pre-assignment period milestones

Number of subjects started	5
Number of subjects completed	5

Period 1

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

Arms

Arm title	Treatment

Arm description:

Single arm
Single infusion of patient specific test-product administered, followed by a 2-year follow-up period.

Arm type	Experimental
Investigational medicinal product name	Autologous CD34+ cells transduced with the w1.6_hWASP_WPRE lentiviral vector Wiskott-Aldrich Syndrome
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intravenous use

Dosage and administration details:

A single cell/product target dose was used i.e. patients were to receive at least 0.5 x 106 CD34+ cells per kg of body weight transduced ex vivo with 1 x 108 i.g./mL of vector to achieve ≥ 0.3 copy integrated per cell

Patients received the investigational product as a single intravenous infusion of a total volume of 50-100 mL over 30-45 minutes.

Number of subjects in period 1	Treatment
Started	5
Completed	5

Baseline characteristics

Reporting groups	
Reporting group title	Treatment
Reporting group description:	
Single arm Single infusion of patient specific test-product administered, followed by a 2-year follow-up period.	

Reporting group values	Treatment	Total	
Number of subjects	5	5	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	2	2	
Children (2-11 years)	2	2	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	1	1	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	9.2		
standard deviation	± 11.78	-	
Gender categorical			
All patients having WAS disease are male			
Units: Subjects			
Female	0	0	
Male	5	5	
Type of mutation (DNA, Protein), and exon affected Units: Subjects			
exon 9 mutation	2	2	
no exon 9 mutation	3	3	
WAS protein status Units: Subjects			
absent	4	4	
present	1	1	
WAS Clinical score Units: Subjects			
zero	0	0	
one	0	0	
two	0	0	
three	1	1	
four	2	2	
five	2	2	

End points

End points reporting groups

Reporting group title	Treatment

Reporting group description:

Single arm
Single infusion of patient specific test-product administered, followed by a 2-year follow-up period.

Primary: Improvement in at least one of the following clinical conditions: eczema, infection, bruising/bleeding, autoimmune disorders, disease-related days of hospitalisation

End point title	Improvement in at least one of the following clinical conditions: eczema, infection, bruising/bleeding, autoimmune disorders, disease-related days of hospitalisation[1]

End point description:

Efficacy primary endpoint: Improvement at 24 months in at least one of the following clinical conditions depending on the patient's clinical symptomatology at study entry:
- Improvement in the eczema status at 24 months as compared with the baseline status at study entry
- Reduction in the frequency and severity of infection episodes, bruising and bleeding episodes evaluated by clinical examination, at 24 months as compared with the baseline status and the patient's historical data collected over the 24 months prior to study entry
- Reduction in the frequency and severity of autoimmune disorders at 24 months as compared with the baseline status at study entry
- Reduction in the number of disease-related days of hospitalisation as compared with the patient's historical data collected over the 24 months prior to study entry

End point type	Primary

End point timeframe:

24 months

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: As there is only one treatment group in this study, no comparisons were done, and thus descriptive statistics were used to summarize results.

End point values	Treatment			
Subject group type	Reporting group			
Number of subjects analysed	5[2]			
Units: participants				
number (not applicable)	5			

Notes:

[2] - Descriptive statistical analysis, small sample size (n=5)
Primary endpoint achieved all 5 patients.

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary: efficacy of heamatopoietic stem cell gene therapy on microthrombocytopenia and other heamatological parameters

End point title	Secondary: efficacy of heamatopoietic stem cell gene therapy on microthrombocytopenia and other heamatological parameters

End point description:

Secondary endpoints
- Improvement of microthrombocytopenia at 3, 6, 12, and 24 months as compared with the baseline status at study entry
- Decrease in the number and volume of platelet transfusions at 24 months as compared with the patient's historical data collected over the 24 months prior to study entry
- Evidence of sustained engraftment of WASP-expressing transduced cells at 6 weeks and 1, 3, 6, 9, 12, 18, and 24 months
- Reconstitution of humoral and cell-mediated immunity at 9, 12, 18, and 24

End point type	Secondary

End point timeframe:

3, 6, 12, 24 months after treatment.

End point values	Treatment			
Subject group type	Reporting group			
Number of subjects analysed	5[3]			
Units: participants				
number (not applicable)	5			

Notes:

[3] - Descriptive statistical analysis, small sample size (n=5)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From 17 February 2010 to 13 November 2019	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.0
Reporting groups	
Reporting group title	Treatment
Reporting group description: Single infusion of patient-specific test product, followed by a 2-year follow-up period	

Serious adverse events	Treatment		
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 5 (100.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Head injury			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Thermal burn			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Traumatic haemorrhage			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	3 / 5 (60.00%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Pain			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Haematochezia			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Vasculitic rash			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Nephrotic syndrome			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Joint swelling			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Device related infection			
subjects affected / exposed	2 / 5 (40.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Catheter site cellulitis			

subjects affected / exposed	1 / 5 (20.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Catheter site infection			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Herpes zoster			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Laryngitis			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lower respiratory tract infection			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Treatment		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 5 (100.00%)		
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	2		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	5 / 5 (100.00%)		
occurrences (all)	9		
Mucosal inflammation			
subjects affected / exposed	3 / 5 (60.00%)		
occurrences (all)	3		
Catheter site pain			
subjects affected / exposed	2 / 5 (40.00%)		
occurrences (all)	2		
Catheter site bruise			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Catheter site swelling			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Fatigue			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Inflammation			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Pain			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Immune system disorders			
Food allergy			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Reproductive system and breast			

disorders Genital rash subjects affected / exposed occurrences (all)	 2 / 5 (40.00%) 2		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Oropharyngeal pain subjects affected / exposed occurrences (all) Epistaxis subjects affected / exposed occurrences (all) Pharyngeal haemorrhage subjects affected / exposed occurrences (all) Rales subjects affected / exposed occurrences (all) Respiratory disorder subjects affected / exposed occurrences (all) Respiratory distress subjects affected / exposed occurrences (all)	 3 / 5 (60.00%) 6 2 / 5 (40.00%) 2 1 / 5 (20.00%) 1 1 / 5 (20.00%) 2 1 / 5 (20.00%) 1 1 / 5 (20.00%) 1 1 / 5 (20.00%) 1		
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all) Panic attack subjects affected / exposed occurrences (all)	 1 / 5 (20.00%) 1 1 / 5 (20.00%) 1		
Investigations Adenovirus test positive			

subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Blood urine present			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
C-reactive protein increased			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Haemoglobin decreased			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Norovirus test positive			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Platelet count decreased			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Sapovirus test positive			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	3		
Head injury			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	3		
Refractoriness to platelet transfusion			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Thermal burn			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	3		
Traumatic haemorrhage			

subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1		
Cardiac disorders Bradycardia subjects affected / exposed occurrences (all)	 1 / 5 (20.00%) 2		
Blood and lymphatic system disorders Neutropenia subjects affected / exposed occurrences (all) Anaemia subjects affected / exposed occurrences (all) Febrile neutropenia subjects affected / exposed occurrences (all) Lymphadenopathy subjects affected / exposed occurrences (all) Lymphopenia subjects affected / exposed occurrences (all)	 3 / 5 (60.00%) 4 1 / 5 (20.00%) 1 1 / 5 (20.00%) 1 1 / 5 (20.00%) 1 1 / 5 (20.00%) 1		
Ear and labyrinth disorders Ear haemorrhage subjects affected / exposed occurrences (all)	 1 / 5 (20.00%) 1		
Eye disorders Eye discharge subjects affected / exposed occurrences (all) Eye inflammation subjects affected / exposed occurrences (all)	 1 / 5 (20.00%) 1 1 / 5 (20.00%) 1		
Gastrointestinal disorders Vomiting subjects affected / exposed occurrences (all)	 5 / 5 (100.00%) 16		

Diarrhoea subjects affected / exposed occurrences (all)	3 / 5 (60.00%) 6		
Abdominal pain subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1		
Abdominal pain upper subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1		
Anal fissure subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1		
Constipation subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1		
Haematochezia subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1		
Mouth ulceration subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1		
Rectal haemorrhage subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1		
Teething subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1		
Hepatobiliary disorders Hepatomegaly subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1		
Skin and subcutaneous tissue disorders Alopecia areata subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1		
Eczema			

subjects affected / exposed	2 / 5 (40.00%)		
occurrences (all)	2		
Blood blister			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Dermatitis diaper			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Drug eruption			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Pruritus			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Skin exfoliation			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Skin lesion			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Skin mass			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Skin ulcer			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Vasculitic rash			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Renal and urinary disorders			
Nephrotic syndrome			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	2 / 5 (40.00%)		
occurrences (all)	3		
Back pain			
subjects affected / exposed	2 / 5 (40.00%)		
occurrences (all)	2		
Joint swelling			
subjects affected / exposed	2 / 5 (40.00%)		
occurrences (all)	6		
Pain in extremity			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Musculoskeletal pain			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Infections and infestations			
Rhinitis			
subjects affected / exposed	3 / 5 (60.00%)		
occurrences (all)	5		
Conjunctivitis			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	2		
Ear infection			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Device related infection			
subjects affected / exposed	2 / 5 (40.00%)		
occurrences (all)	2		
Influenza			
subjects affected / exposed	2 / 5 (40.00%)		
occurrences (all)	2		
Oral candidiasis			
subjects affected / exposed	2 / 5 (40.00%)		
occurrences (all)	2		
Rhinovirus infection			

subjects affected / exposed	2 / 5 (40.00%)			
occurrences (all)	2			
Varicella				
subjects affected / exposed	2 / 5 (40.00%)			
occurrences (all)	2			
Adenovirus infection				
subjects affected / exposed	1 / 5 (20.00%)			
occurrences (all)	1			
Bronchitis				
subjects affected / exposed	1 / 5 (20.00%)			
occurrences (all)	1			
Campylobacter infection				
subjects affected / exposed	1 / 5 (20.00%)			
occurrences (all)	1			
Catheter site cellulitis				
subjects affected / exposed	1 / 5 (20.00%)			
occurrences (all)	1			
Catheter site infection				
subjects affected / exposed	1 / 5 (20.00%)			
occurrences (all)	2			
Coronavirus infection				
subjects affected / exposed	1 / 5 (20.00%)			
occurrences (all)	1			
Cytomegalovirus infection				
subjects affected / exposed	1 / 5 (20.00%)			
occurrences (all)	1			
Cytomegalovirus viraemia				
subjects affected / exposed	1 / 5 (20.00%)			
occurrences (all)	1			
Eczema herpeticum				
subjects affected / exposed	1 / 5 (20.00%)			
occurrences (all)	1			
Eczema infected				
subjects affected / exposed	1 / 5 (20.00%)			
occurrences (all)	1			
Eye infection				

subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Herpes zoster			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Laryngitis			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	3		
Lower respiratory tract infection			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	2		
Molluscum contagiosum			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Oral herpes			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Parainfluenzae virus infection			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Respiratory tract infection viral			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Tooth infection			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Upper respiratory tract infection			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	4		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		

Feeding disorder subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1		
Hypoglycaemia subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1		
Hypokalaemia subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 3		
Hypophagia subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 February 2010	The protocol was revised to add evidence of sponsor insurance or indemnity.
20 August 2010	Modification of the clinical study protocol further to the deletion of the freezing and cryopreservation of transduced cells in the manufacturing process of the IMP: - Clarification of the inclusion and exclusion criteria - Modification of the conditioning regimen - Modification of the final total cell number required for engraftment - Adaptation of the primary endpoint Modification of the requirements for collecting and storing patient serum samples for RCL analysis Addition of criteria for assessing the severity of the AEs
09 May 2014	Adaptation of the clinical study protocol to comply under the Paediatric Investigation Plan approved by the Peadiatric Committee of the EMA on 17 September 2013: - Modification of the primary and secondary objectives - Modification of the inclusion criteria - Modification of the clinical monitoring during post-infusion period - Clarifications regarding the collection and analysis of AE data
23 October 2015	Protocol was revised to allow the physician to collect stem cells either from bone marrow harvest or peripheral blood for patients younger than 2 years old. Dose regimen of G-CSF was adapted to take into account the younger population including patients under 2 years old.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Small sample size (n=5), One arm non comparative study, Descriptive statistical analyses only

Notes: