Clinical trial results:
Phase I/II clinical trial of haematopoietic stem cell gene therapy for the Wiskott-Aldrich Syndrome

Summary

EudraCT number	2009-011152-22
Trial protocol	FR
Global end of trial date	09 January 2017

Results information

Result version number	v1 (current)
This version publication date	30 June 2019
First version publication date	30 June 2019

Trial information

Trial identification

Sponsor protocol code	GTG003.08

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01347346
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	GENETHON
Sponsor organisation address	1 bis rue de l'Internationale, EVRY, France, 91002
Public contact	GERALDINE HONNET, GENETHON, 0033 169472868, clinical_development@genethon.fr
Scientific contact	GERALDINE HONNET, GENETHON, 0033 169472868, 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	20 January 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 January 2016
Global end of trial reached?	Yes
Global end of trial date	09 January 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of haematopoietic stem-cell gene therapy in Wiskott-Aldrich syndrome (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 hospitalization.

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 3 x 10^6 but not more than 15 x 10^6 CD34+ cells per kg body weight transduced ex vivo with 1 x 10^8 i.g./mL of vector to achieve an average of 1 copy integrated per cell in 30-60% of cells. CD34+ cells were purified from bone marrow cells harvested under general anaesthesia, or from PBMCs mobilised through the use of G-CSF and plerixafor and recovered by leukapheresis, depending on the patient’s body weight and clinical status. Patient conditioning was to be initiated immediately after bone marrow or PBMC collection and consisted of busulfan (4 mg/kg) and fludarabine (40 mg/m2) for 3 days.
If the number of CD34+ was less than 1 x 10^6/kg, the cells were not to be infused, and the patient was to receive a haploidentical bone-marrow graft and to be withdrawn
from the study.
If there was no bone marrow recovery within 6 weeks, the patient was to receive a haploidentical bone marrow graft.
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:

The only known cure for WAS is allogeneic haematopoietic stem cell transplantation (HSCT), using bone marrow, peripheral blood, or umbilical cord blood from a human leukocyte antigen (HLA)-matched donor. HLA-mismatched transplantation carries an increased risk for complications, in particular for graft vs. host disease, causing increased morbidity and mortality. In a cohort of 137 WAS patients treated in Europe, overall survival was 83% for matched family donor transplants, 75% for matched unrelated donor transplants, and 50% for related HLA-mismatched donors. 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 in their infancy 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	04 May 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy, Ethical reason, 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	France: 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)	1
Children (2-11 years)	3
Adolescents (12-17 years)	1
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were all enrolled in one center at Necker-Enfants Malades Hospital, Paris, France from May the 4th, 2011 (patient # FR01) to January the 6th, 2014 (FR05).

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 period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Treatment

Arm description:

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

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

Dosage and administration details:

Patient-specific test product, corresponding to autologous CD34+ cells transduced ex vivo with the w1.6_hWASP_WPRE (VSVg) lentiviral vector containing the human WAS gene in final formulation and container closure system, ready for intended medical use
Intravenous administration
Single infusion, cell/product target dose consisting of at least 3 x 10^6 but not more than 15 x 10^6 CD34+ cells per kg bodyweight transduced ex vivo with 1 x 10^8 i.g./ml of vector to achieve an average of 1 copy integrated per cell in 30-60% of cells

Number of subjects in period 1	Treatment
Started	5
Completed	4
Not completed	1
Adverse event, serious fatal	1

Baseline characteristics

Reporting groups	
Reporting group title	overall trial

Reporting group description: -

Reporting group values	overall trial	Total	
Number of subjects	5	5	
Age categorical			
The age of patients at baseline ranged from 10 months to 15 years , namely 15 yrs (FR01), 10 yrs (FR02), 10 months (FR03), 2 yrs (FR04) and 3 yrs (FR05)			
Units: Subjects			
Infants and toddlers (28 days-23 months)	1	1	
Children (2-11 years)	3	3	
Adolescents (12-17 years)	1	1	
Gender categorical Units: Subjects			
Female	0	0	
Male	5	5	

End points

End points reporting groups

Reporting group title	Treatment
Reporting group description:	
Single infusion of patient-specific test product, 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:

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 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 bruising and bleeding episodes at 24 months evaluated by clinical examination as compared with the baseline status at study entry 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.

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: Descriptive statistical analyses only, small sample size (n=5).

End point values	Treatment			
Subject group type	Reporting group			
Number of subjects analysed	4[2]			
Units: participants				
Yes	4			
No	0			

Notes:

[2] - One patient died before completing the 2-year follow-up period

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From 26 April 2011 to 20 January 2016	
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	4 / 5 (80.00%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	1		
General disorders and administration site conditions			
Mucosal inflammation			
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			
Mouth haemorrhage			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Hepatocellular injury			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			

subjects affected / exposed	1 / 5 (20.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Haemothorax				
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				
Aspergillus infection				
subjects affected / exposed	1 / 5 (20.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cytomegalovirus chorioretinitis				
subjects affected / exposed	1 / 5 (20.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis				
subjects affected / exposed	1 / 5 (20.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sinusitis				
subjects affected / exposed	1 / 5 (20.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Staphylococcal infection				
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			
Air embolism			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	2		
Chest discomfort			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Drug intolerance			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Malaise			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Mucosal inflammation			
subjects affected / exposed	3 / 5 (60.00%)		
occurrences (all)	3		
Pyrexia			
subjects affected / exposed	3 / 5 (60.00%)		
occurrences (all)	7		
Immune system disorders			
Allergy to immunoglobulin therapy			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	2		
Rhinorrhoea			

subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1		
Psychiatric disorders Sleep disorder subjects affected / exposed occurrences (all)	 1 / 5 (20.00%) 1		
Congenital, familial and genetic disorders Aplasia subjects affected / exposed occurrences (all) Phimosis subjects affected / exposed occurrences (all)	 4 / 5 (80.00%) 4 1 / 5 (20.00%) 1		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	 1 / 5 (20.00%) 1		
Blood and lymphatic system disorders Febrile bone marrow aplasia subjects affected / exposed occurrences (all) Neutropenia subjects affected / exposed occurrences (all) Pancytopenia subjects affected / exposed occurrences (all) Thrombocytopenia subjects affected / exposed occurrences (all) Thrombocytopenic purpura subjects affected / exposed occurrences (all)	 1 / 5 (20.00%) 1 1 / 5 (20.00%) 1 3 / 5 (60.00%) 3 3 / 5 (60.00%) 3 1 / 5 (20.00%) 1		
Ear and labyrinth disorders Otorrhoea			

subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	2		
Eye disorders			
Chalazion			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	2		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 5 (40.00%)		
occurrences (all)	2		
Diarrhoea			
subjects affected / exposed	3 / 5 (60.00%)		
occurrences (all)	6		
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Haemorrhoids			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	5 / 5 (100.00%)		
occurrences (all)	6		
Hepatobiliary disorders			
Cholestasis			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Hepatocellular injury			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Liver disorder			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Alopecia areata			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Dermatitis allergic			

subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Infections and infestations			
Conjunctivitis			
subjects affected / exposed	2 / 5 (40.00%)		
occurrences (all)	2		
Ear infection			
subjects affected / exposed	2 / 5 (40.00%)		
occurrences (all)	3		
Furuncle			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	2		
Gastroenteritis			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	3		
Nasopharyngitis			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Onychomycosis			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Osteomyelitis			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Pneumonia			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	2		
Rhinitis			
subjects affected / exposed	3 / 5 (60.00%)		
occurrences (all)	6		
Sepsis			

subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Sinusitis			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Urinary tract infection			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Viral infection			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 January 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 AEs
09 April 2014	Adaptation of the clinical study protocol to comply with the Paediatric Investigation Plan approved by the Paediatric Committee of the EMA on 17 Sep 2013: - modification of the primary and secondary objectives - modification of inclusion criteria - modification of the clinical monitoring during post-infusion period - clarifications regarding the collection and analysis of AE data

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:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/25898053

http://www.ncbi.nlm.nih.gov/pubmed/28716862

http://www.ncbi.nlm.nih.gov/pubmed/26672655