Clinical trial results:
Gene therapy for SCID-X1 using a self-inactivating (SIN) gammaretroviral vector.

Summary

EudraCT number	2007-000684-16
Trial protocol	GB
Global end of trial date	14 January 2019

Results information

Result version number	v1 (current)
This version publication date	26 July 2019
First version publication date	26 July 2019

Trial information

Trial identification

Sponsor protocol code	06MI10

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01175239
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Great Ormond Street Hospital NHS Foundation Trust
Sponsor organisation address	Great Ormond Street, London, United Kingdom, WC1N 3JH
Public contact	Professor Adrian Thrasher, UCL Great Ormond Street Institute of Child Health, +44 (0)2079052660, a.thrasher@ucl.ac.uk
Scientific contact	Professor Adrian Thrasher, UCL Great Ormond Street Institute of Child Health, +44 (0)2079052660, a.thrasher@ucl.ac.uk

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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	14 January 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 January 2019
Global end of trial reached?	Yes
Global end of trial date	14 January 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

1. Treatment of SCID-X1 patients by somatic gene therapy when HLA-matched family or unrelated bone marrow donors are unavailable.
2. Successful ex vivo transduction of CD34+ haematopoietic cells from SCID-X1 patients by ex vivo gammaretrovirus-mediated gene transfer.
3. Evaluation of immunological and functional reconstitution in progeny of engrafted cells.
4. Longitudinal evaluation of clinical effect in terms of augmented immunity.
5. Evaluation of the functional performance of novel SIN gammaretroviral configuration.
6. Evaluation of the molecular characteristics of vector integration.
7. Evaluation of safety.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Council for Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy:

Bone marrow transplantation can often cure SCID-X1 particularly when an exact donor match from a brother or sister is available. However, only a third of children have a fully matched donor and the chances of success from other donor sources are not so good. For example, if a parent is used as a donor, the bone marrow is only half-matched, and more than 10% of patients will not survive beyond a year after transplant. Other survivors may also suffer from long term problems related to the toxic effect of the chemotherapy which is sometimes used to help the new bone marrow establish, and also graft versus host disease (GvHD), a condition where donor lymphocytes in the transplant recognise parts of the patient including the skin and gut as foreign and cause severe damage. Over the past decade new treatments have been developed based on our knowledge of the defective gene causing SCID-X1. We can now use genes as a type of medicine that will correct the problem in the patient’s own bone marrow cells to allow the development of a new immune system. This has been carried out effectively in over 30 patients with different forms of SCID including SCID-X1, and most of these children are living healthy lives. In some patients the gene therapy vector that carries the new gene has unfortunately caused leukaemia a few years after treatment because it has accidentally altered the way in which the growth of lymphocytes is normally controlled. Due to scientific advances, the technology now exists to reduce the risk of this side effect by changing the design of the vector. In this trial we aim to evaluate the treatment of patients with SCID-X1 with a new and safer gene therapy vector. In this study retroviral vector is designated as a critical raw material and retroviral vector transduced cells are designated as an Investigational Medicinal Product (IMP).

Evidence for comparator:

N/A

Actual start date of recruitment	12 March 2013
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	United Kingdom: 1
Worldwide total number of subjects	1
EEA total number of subjects	1

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)	1
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:

The study was conducted at Great Ormond Street Hospital Foundation Trust in London between April 2011 and January 2019.

Pre-assignment

Screening details:

This is an open labelled, non-randomised, single centre, phase I/II, cohort study involving a single infusion of autologous CD34+ cells transduced with the self-inactivating (SIN) gammaretroviral vector pSRS11.EFS.IL2RG.pre* in up to 10 patients with SCID-X1 aged 0 - 16 years old.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

N/A

Arms

Arm title	Single cohort

Arm description:

Treatment of patients with SCID-X1 by gene therapy in whom HLA-matched family or unrelated donors are unavailable.

Arm type	Experimental
Investigational medicinal product name	pSRS11.EFS.IL2RG.pre* retroviral vector transduced cells
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

The gammaretroviral vector pSRS11.EFS.IL2RG.pre* is used to modify autologous CD34+ cells. The transduction protocol has been optimised to achieve a gene transfer efficiency of 30-60% in starting cells, which is predicted to give a mean transgene copy number of 1 in developing T-cells.

Number of subjects in period 1	Single cohort
Started	1
Completed	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial
Reporting group description:	
Somatic gene therapy for boys aged 0-16 years with X-linked Severe Combined Immunodeficiency (X-SCID) in whom HLA-matched family or unrelated donors are unavailable.	

Reporting group values	Overall trial	Total	
Number of subjects	1	1	
Age categorical			
a) Patients with no HLA identical (A,B,C,DR,DQ) family donor b) Patients with HLA identical unrelated donor available within 3 months of diagnosis or c) Patients whose underlying clinical problems would be significantly compromised by chemotherapy conditioning 2. Diagnosis of classical SCID-X1 based on immunophenotype (absent, or reduced numbers of non-functional T lymphocytes and confirmed by DNA sequencing clinical genetics laboratory, GOSH) 3. Boys between the ages of 0 and 16			
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)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Boys between ages of 0-16 years	1	1	
Age continuous			
Units: years			
median	1		
standard deviation	± 1	-	
Gender categorical			
X-linked severe combined immunodeficiency (SCID-X1) is an inherited disorder that results in failure of development of the immune system. Although there are several different types of SCID, this particular type only affects boys because the genetic mistake is carried on the X-chromosome.			
Units: Subjects			
Female	0	0	
Male	1	1	

End points

End points reporting groups

Reporting group title	Single cohort

Reporting group description:

Treatment of patients with SCID-X1 by gene therapy in whom HLA-matched family or unrelated donors are unavailable.

Primary: Immunological reconstitution

End point title	Immunological reconstitution[1]

End point description:

- The gene therapy gamma chain (GTGC) lymphocyte subsets (LSS) immunophenotyping panel was carried out to show the distribution of cells and was used to detect an increase in naïve CD3+ T lymphocyte cell numbers and assess the development of normal distribution of CD4,CD8, TCRαβ, TCRγδ, CD16+CD56+ NK & c surface expression. TCR excision circles (TRECs) may be enumerated as a surrogate marker for new thymic emigrants following gene therapy.
- Whole blood Lymphocyte proliferation assays was be carried out to test function of T cells.
- Representation of TCR families by flow cytometric analysis (Vβ phenotyping), combined with CDR3 PCR spectratyping (Vβ spectratyping) also forms an important part of monitoring for both physiological and potentially pathological clonal expansions.
- Restoration of antibody production (IgA, IgM, IgG), and serological responses to vaccinations and natural infections (such as varicella) was assessed.

End point type	Primary

End point timeframe:

From consent to end of trial

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: Statistical analysis was not performed for study endpoints. No data available.

End point values	Single cohort			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: ml				
LSS	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of adverse reactions

End point title	Incidence of adverse reactions

End point description:

Adverse reactions observed by the investigator or reported by the patient/parent/guardian during the study period recorded for evaluation

End point type	Secondary

End point timeframe:

5 years post Genetherapy

End point values	Single cohort			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: Adverse reactions				
Adverse Reactions	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Molecular characterisation of gene transfer

End point title	Molecular characterisation of gene transfer

End point description:

Molecular characterisation of gene transfer in patient cells is also an important parameter for assessment of efficiency, and potentially for assessment of safety:
- Quantification of transgene copy numbers is determined on sorted cell populations by real-time PCR methodology. Detailed integration analysis maybe used to investigate specific clonal expansions.

End point type	Secondary

End point timeframe:

From treatment to end of trial

End point values	Single cohort			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: Data not analysed	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Normalisation of nutritional status, growth, and development

End point title	Normalisation of nutritional status, growth, and development

End point description:

Efficacy and safety of the gene therapy procedure will be further assessed though clinical examinations, clinical laboratory assessments. Adverse reactions observed by the investigator or reported by the patient/parent/guardian during the study period will be recorded for evaluation

End point type	Secondary

End point timeframe:

From consent to 5 years post genetherapy

End point values	Single cohort			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: Data not analysed	1			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From consent to 5 years post genetherapy

Adverse event reporting additional description:

At each scheduled visit, adverse events that might have occurred since the previous visit or assessment will be elicited from the patient/parent/guardian. The investigators will maintain a record of all adverse events/occurrences in patients participating in the clinical trial. This record will be noted in the patient's medical notes.

Assessment type	Non-systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4

Reporting groups

Reporting group title	Overall trial

Reporting group description:

Single cohort - Gene therapy for SCID-X1 using a self-inactivating (SIN) gammaretroviral vector for patients ages 0-16 years old.

Serious adverse events	Overall trial		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 1 (100.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Ear and labyrinth disorders			
Grommet insertion - Adenoids	Additional description: Hospitalisation for insertion of Grommets and removal of adenoids.		
subjects affected / exposed	1 / 1 (100.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Upper respiratory tract infection			
subjects affected / exposed	1 / 1 (100.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Overall trial		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 1 (100.00%)		
Surgical and medical procedures			
PICC line break			
subjects affected / exposed	1 / 1 (100.00%)		
occurrences (all)	1		
General disorders and administration site conditions			
Pyrexia			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 1 (100.00%)		
occurrences (all)	11		
Epistaxis			
subjects affected / exposed	1 / 1 (100.00%)		
occurrences (all)	1		
Hypokalaemia			
subjects affected / exposed	1 / 1 (100.00%)		
occurrences (all)	1		
Vomiting	Additional description: Vomiting increase		
subjects affected / exposed	1 / 1 (100.00%)		
occurrences (all)	2		
Adenovirus in NPA	Additional description: Adenovirus found in nasopharyngeal aspirate		
subjects affected / exposed	1 / 1 (100.00%)		
occurrences (all)	1		
Skin lesion	Additional description: Knee Lip and Mouth		
subjects affected / exposed	1 / 1 (100.00%)		
occurrences (all)	2		
Rash			
subjects affected / exposed	1 / 1 (100.00%)		
occurrences (all)	2		
Candida infection	Additional description: Positive candida antigen		
subjects affected / exposed	1 / 1 (100.00%)		
occurrences (all)	1		
Grommets insertion	Additional description: Bilateral grommets insertion		
subjects affected / exposed	1 / 1 (100.00%)		
occurrences (all)	1		

Adenoidectomy			
subjects affected / exposed	1 / 1 (100.00%)		
occurrences (all)	1		
Cough	Additional description: Chronic cough		
subjects affected / exposed	1 / 1 (100.00%)		
occurrences (all)	1		
Coryzal	Additional description: Chronic coryzal		
subjects affected / exposed	1 / 1 (100.00%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Viraemia	Additional description: CMV Viraemia		
subjects affected / exposed	1 / 1 (100.00%)		
occurrences (all)	1		
Gastrointestinal disorders			
Gastroenteritis	Additional description: Without infection With Rotavirus infection on second occurrence Norovirus on third occurrence		
subjects affected / exposed	1 / 1 (100.00%)		
occurrences (all)	3		
Respiratory, thoracic and mediastinal disorders			
Oxygen requirement			
subjects affected / exposed	1 / 1 (100.00%)		
occurrences (all)	1		
Small airway disease			
subjects affected / exposed	1 / 1 (100.00%)		
occurrences (all)	1		
Upper respiratory tract infection			
subjects affected / exposed	1 / 1 (100.00%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Dermatitis	Additional description: Contact dermatitis on left cheek Candida nappy rash		
subjects affected / exposed	1 / 1 (100.00%)		
occurrences (all)	2		
Blister	Additional description: Penile Blister		
subjects affected / exposed	1 / 1 (100.00%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 September 2010	The vector label previously approved by the MHRA with the initial CTA has been amended. Since the initial submission to the MHRA on the 16th March 2009, it was noted that an incorrect version of the vector labelling was submitted, therefore the final primary, secondary and tertiary container labels were sent for approval. These amended labels were approved by our QP. With this submission, we provided the labels on our IMP Label Approval Form, showing approval by the QP. Investigator Brochure version 2 amended. The substantial change was to section 8 ('guidance on risks and recognition of adverse reactions'). This section was amended to expand the information previously provided. The new text provided more detailed information on the specific risks associated with the procedure, including those associated with venepuncture, bone marrow harvest, retrovirus-mediated gene transfer, ex vivo manipulation of cells, infusion, generation of RCR and graft versus host disease.
28 September 2010	Amendment to include study-specific GP letter (version 1, dated 9th August 2010). As no GP letter was submitted for approval for this study previously, the amendment constituted implementation of a new document and was not an amendment to a previously submitted GP letter. Amendment also included non-substantial amendments to the patient information sheet and consent form.
09 February 2011	As part of the amendment the CTA was amended to remove the vector as an IMP following notification from, Dr. Elaine Godfrey that the vector was no longer classified as an IMP when used for ex vivo transduction. Subsequently, the vector was removed as a listed IMP in section D. As a result of this few minor changes were made to protocol, Investigator Brochure and Investigational Medicinal Product Dossier.
20 August 2014	This protocol was amended to incorporate the storage of a back-up graft for patients receiving conditioning. The option to condition patients prior to infusion has been included. Leukapheresis was included as an option for harvesting stem cells. Patient Information Sheets amended to reflect the changes to the treatment protocol. New back-up bone marrow harvest created for parent/guardian to consent for harvest and storage of child's bone marrow as a back-up approximately 3 months prior to gene therapy. Transduction protocol amended following in-house optimisation and validation.
27 June 2016	CD34+ cell harvest and transduction protocol amended in the IMPD. AE reporting section in the protocol updated as per updated sponsor's SOP. All AEs are recorded in both patient's notes & CRF.

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.

The recruitment target for this study was not met due to lack of patients meeting the study’s eligibility criteria and the rarity of the disease.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/25295500