Clinical trial results:
Phase I/II, historical controlled, open-label, non-randomised, single-centre trial to assess the safety and efficacy of EF1S-ADA lentiviral vector mediated gene modification of autologus CD34+ cells from ADA-deficient individuals

Summary

EudraCT number	2010-024253-36
Trial protocol	GB
Global end of trial date	23 December 2019

Results information

Result version number	v1 (current)
This version publication date	09 July 2020
First version publication date	09 July 2020

Trial information

Trial identification

Sponsor protocol code	10MI29

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01380990
WHO universal trial number (UTN)	-
Other trial identifiers	GTAC reference: GTAC178

Notes:

Sponsors

Sponsor organisation name	Great Ormond Street Hospital for Children NHS Foundation Trust
Sponsor organisation address	30 Guilford Street, London, United Kingdom, WC1N 1EH
Public contact	Dr Claire Booth, UCL Institute of Child Health, +44 207 905 2198, C.Booth@ucl.ac.uk
Scientific contact	Dr Claire Booth, UCL Institute of Child Health, +44 207 905 2198, C.Booth@ucl.ac.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001974-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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	23 December 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	23 December 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objectives of the study were to assess the safety and efficacy of EFS-ADA LV-mediated gene therapy (OTL-101*) for the treatment of ADA-SCID subjects

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) regulations/guidelines, the general principles indicated in the Declaration of Helsinki, and all applicable regulatory requirements. Prior to initiation at each study center, the study protocol was reviewed by an Independent Ethics Committee (IEC). All subjects were to provide written informed consent prior to entering the study and before initiation of any study-related procedure (including administration of investigational product). The investigator was responsible for explaining the benefits and risks of participation in the study to each subject or the subject's legally acceptable representative and for obtaining written informed consent.

Background therapy:

Busulfan was administered intravenously as a single non-myeloablative dose prior to administration of OTL-101*. The dose of Busulfan was according to weight of the individual subject and was based on European Society for Blood and Marrow Transplantation (EBMT) guidelines for Busulfan dosing in children and a recent publication (Bartelink et al., 2012).

All subjects were receiving PEG-ADA Enzyme Replacement Therapy (ERT) prior to study participation. PEG-ADA ERT was continued until 1 month (+/- 6 days) post infusion of genetically modified cells. PEG-ADA ERT was restarted if after 180 days there was no evidence of genetically modified cell engraftment and/or failure of T cell recovery. PEG-ADA ERT could be restarted at the PI's discretion prior to that time point on clinical grounds (e.g. in the event of infections or delayed T cell reconstitution).

Evidence for comparator:

Not applicable

Actual start date of recruitment	15 November 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Regulatory reason
Long term follow-up duration	12 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 36
Worldwide total number of subjects	36
EEA total number of subjects	36

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)	28
Children (2-11 years)	7
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:

This study was conducted at a single site in the UK between 20-Nov-2012 (First Patient First Visit) and 23-Dec-2019 (Last Patient Last Visit, Compassionate Use)

Pre-assignment

Screening details:

10 subjects were treated with OTL-101* on study. 10 additional patients were treated with OTL-101* within the protocol under a Great Ormond Street Hospital (GOSH) Specials Licence, constituting the compassionate use program (CUP). 16 patients treated with hematopoietic stem cell transplant (HSCT) at GOSH, constituting the historical control group.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Gene Therapy

Arm description:

Infusion of autologous EFS-ADA LV CD34+ cells

Arm type	Experimental
Investigational medicinal product name	Autologous CD34+ hematopoietic stem and progenitor cells (HSPCs) transduced ex vivo using the EFS-ADA lentiviral vector (LV)
Investigational medicinal product code	OTL-101*
Other name	
Pharmaceutical forms	Dispersion for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received OTL-101* following harvest of CD34+ hematopoietic stem and progenitor cell (HSPCs) from leukapheresis or BM and successful transduction and release of OTL-101*. The dose for each subject consisted of at least 0.5 x 10e6 CD34+ cells/kg of body weight.

If the total infusion dose for OTL-101* was confirmed to be <0.5 x 10e6 CD34+ cells/kg, it was intended that OTL-101* be administered, followed by the back-up cells. The subject would have been withdrawn from the study.

Arm title	Historical Control Group

Arm description:

Historical data from a database of ADA-SCID patients treated with allogeneic HSCT from GOSH was collected as comparator group

Arm type	Haematopoietic Stem Cell Transplantation

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Gene Therapy	Historical Control Group
Started	20	16
Completed	19	15
Not completed	1	1
Treatment Failure	1	-
Death	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Gene Therapy
Reporting group description:	
Infusion of autologous EFS-ADA LV CD34+ cells	
Reporting group title	Historical Control Group
Reporting group description:	
Historical data from a database of ADA-SCID patients treated with allogeneic HSCT from GOSH was collected as comparator group	

Reporting group values	Gene Therapy	Historical Control Group	Total
Number of subjects	20	16	36
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	14	14	28
Children (2-11 years)	5	2	7
Adolescents (12-17 years)	1	0	1
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: months			
median	11.6	13.5	
full range (min-max)	4 to 193	1 to 118	-
Gender categorical Units: Subjects			
Female	8	0	8
Male	12	0	12
Not Reported	0	16	16

Subject analysis sets	
Subject analysis set title	HSCT Controls without MRD
Subject analysis set type	Full analysis
Subject analysis set description:	
The primary efficacy population from the HSCT historical control cohort comprises ADA-SCID patients without a medically eligible MRD who were treated with HSCT at GOSH from 2000 to 2016. An MRD refers to either a matched sibling or family donor.	
Subject analysis set title	HSCT Controls with MRD
Subject analysis set type	Full analysis
Subject analysis set description:	
Secondary efficacy population for comparison comprise ADA-SCID patients with an MRD treated with HSCT at GOSH from 2000 to 2016	
Subject analysis set title	All HSCT Controls

Subject analysis set type	Full analysis

Subject analysis set description:

Complete HSCT historical control group consisting of ADA-SCID patients with any type of donor treated with HSCT at GOSH from 2000 to 2016 (referred to as the All HSCT Controls group)

Subject analysis set title	OTL-101* On-Study Subjects
Subject analysis set type	Full analysis

Subject analysis set description:

The primary efficacy population for analysis consists of the on-study OTL-101*-treated subjects.

Subject analysis set title	OTL-101* On-Study and CUP Subjects
Subject analysis set type	Full analysis

Subject analysis set description:

The safety population consists of all OTL-101*-treated subjects (on-study and CUP). The secondary efficacy population consists of all OTL-101*-treated subjects (on-study and CUP).

Reporting group values	HSCT Controls without MRD	HSCT Controls with MRD	All HSCT Controls
Number of subjects	5	11	16
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	4	10	14
Children (2-11 years)	1	1	2
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: months			
median	17.0	4.0	13.5
full range (min-max)	12 to 118	1 to 37	1 to 118
Gender categorical Units: Subjects			
Female			
Male			
Not Reported	5	11	16

Reporting group values	OTL-101* On-Study Subjects	OTL-101* On-Study and CUP Subjects	
Number of subjects	10	20	
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)	9	14	
Children (2-11 years)	1	5	
Adolescents (12-17 years)	0	1	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	

85 years and over	0	0	

Age continuous Units: months			
median	10.2	11.6	
full range (min-max)	7 to 64	4 to 193	
Gender categorical Units: Subjects			
Female	4	8	
Male	6	12	
Not Reported	0	0	

End points

End points reporting groups

Reporting group title	Gene Therapy
Reporting group description:	
Infusion of autologous EFS-ADA LV CD34+ cells	
Reporting group title	Historical Control Group
Reporting group description:	
Historical data from a database of ADA-SCID patients treated with allogeneic HSCT from GOSH was collected as comparator group	
Subject analysis set title	HSCT Controls without MRD
Subject analysis set type	Full analysis
Subject analysis set description:	
The primary efficacy population from the HSCT historical control cohort comprises ADA-SCID patients without a medically eligible MRD who were treated with HSCT at GOSH from 2000 to 2016. An MRD refers to either a matched sibling or family donor.	
Subject analysis set title	HSCT Controls with MRD
Subject analysis set type	Full analysis
Subject analysis set description:	
Secondary efficacy population for comparison comprise ADA-SCID patients with an MRD treated with HSCT at GOSH from 2000 to 2016	
Subject analysis set title	All HSCT Controls
Subject analysis set type	Full analysis
Subject analysis set description:	
Complete HSCT historical control group consisting of ADA-SCID patients with any type of donor treated with HSCT at GOSH from 2000 to 2016 (referred to as the All HSCT Controls group)	
Subject analysis set title	OTL-101* On-Study Subjects
Subject analysis set type	Full analysis
Subject analysis set description:	
The primary efficacy population for analysis consists of the on-study OTL-101*-treated subjects.	
Subject analysis set title	OTL-101* On-Study and CUP Subjects
Subject analysis set type	Full analysis
Subject analysis set description:	
The safety population consists of all OTL-101*-treated subjects (on-study and CUP). The secondary efficacy population consists of all OTL-101*-treated subjects (on-study and CUP).	

Primary: Overall Survival (OS) of subjects treated with Investigational Medicinal Product (IMP) (1 year)

End point title	Overall Survival (OS) of subjects treated with Investigational Medicinal Product (IMP) (1 year)[1]
End point description:	
Overall survival is defined as the proportion of subjects alive at 12 months	
End point type	Primary
End point timeframe:	
12 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: If there was at least 1 event in each group, it was planned to use the log rank test to compare the difference in survival curves between each OTL-101* treatment groups and each of the HSCT control groups. However, as there was no event in any group at 12 months, this analysis was not carried out.

End point values	HSCT Controls without MRD	HSCT Controls with MRD	All HSCT Controls	OTL-101* On-Study Subjects
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	5	11	16	10
Units: percent				
number (confidence interval 95%)				
Proportion surviving at 12 months (95% CI)	100 (47.82 to 100)	100 (71.51 to 100)	100 (79.41 to 100)	100 (69.15 to 100)

End point values	OTL-101* On-Study and CUP Subjects			
Subject group type	Subject analysis set			
Number of subjects analysed	20			
Units: percent				
number (confidence interval 95%)				
Proportion surviving at 12 months (95% CI)	100 (83.16 to 100)			

Statistical analyses

No statistical analyses for this end point

Primary: Event-free survival (EvFS) of subjects treated with Investigational Medicinal Product (IMP) (1 year)

End point title	Event-free survival (EvFS) of subjects treated with Investigational Medicinal Product (IMP) (1 year)[2]

End point description:

Event-free survival is defined as the proportion of subjects alive with no "event", an "event" being the resumption of PEG-ADA ERT or the need for a rescue allogenic Hematopoietic Stem Cell Transplant (HSCT), or death.

End point type	Primary

End point timeframe:

12 months

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: If there was at least 1 event in each group, it was planned to use the log rank test to compare the difference in survival curves between each OTL-101* treatment groups and each of the HSCT control groups. However, as there was no event in any group at 12 months, this analysis was not carried out.

End point values	HSCT Controls without MRD	HSCT Controls with MRD	All HSCT Controls	OTL-101* On-Study Subjects
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	5	11	16	10
Units: percent				
number (confidence interval 95%)				
Proportion event-free at 12 months (95% CI)	100 (47.82 to 100)	100 (71.51 to 100)	100 (79.41 to 100)	100 (69.15 to 100)

End point values	OTL-101* On-Study and CUP Subjects			
Subject group type	Subject analysis set			
Number of subjects analysed	20			
Units: percent				
number (confidence interval 95%)				
Proportion event-free at 12 months (95% CI)	100 (83.16 to 100)			

Statistical analyses

No statistical analyses for this end point

Primary: Comparison of OS of subjects treated with IMP with those of patients treated with allogeneic HSCT (1 year)

End point title	Comparison of OS of subjects treated with IMP with those of patients treated with allogeneic HSCT (1 year)[3]

End point description:

Difference in OS of historical control group, "HSCT Controls without MRD", "HSCT Controls with MRD" and "All HSCT Controls group", compared to subjects treated with OTL-101* in the "OTL-101* On-Study" group and "OTL-101* On-Study and CUP Subjects" group.

End point type	Primary

End point timeframe:

12 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: If there was at least 1 event in each group, it was planned to use the log rank test to compare the difference in survival curves between each OTL-101* treatment groups and each of the HSCT control groups. However, as there was no event in any group at 12 months, this analysis was not carried out.

End point values	HSCT Controls without MRD	HSCT Controls with MRD	All HSCT Controls	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	5	11	16	
Units: percent				
number (not applicable)				
Difference from OTL-101* on-study subjects	0	0	0	
Difference from OTL-101* on-study and CUP subjects	0	0	0	

Statistical analyses

No statistical analyses for this end point

Primary: Vector copy number (VCN) in Granulocyte fraction (Neutrophils)

End point title	Vector copy number (VCN) in Granulocyte fraction (Neutrophils)[4]

End point description:

Engraftment of transduced cells was assessed using vector gene marking in Granulocytes (Neutrophils)

End point type	Primary

End point timeframe:

36 months

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: As VCN was assessed for the gene therapy arm only, there is no comparator and so formal statistical analysis could not be performed.

End point values	OTL-101* On-Study Subjects	OTL-101* On-Study and CUP Subjects		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9[5]	18[6]		
Units: copies/cell				
median (full range (min-max))				
Granulocytes fraction (Neutrophils)	0.240 (0.15 to 0.79)	0.280 (0.03 to 1.60)		

Notes:

[5] - 9/10 subjects evaluated for granulocytes at Month 36

[6] - 18/20 subjects evaluated for granulocytes at Month 36

Statistical analyses

No statistical analyses for this end point

Primary: Vector copy number (VCN) in Peripheral Blood mononuclear cells (PBMCs)

End point title	Vector copy number (VCN) in Peripheral Blood mononuclear cells (PBMCs)[7]

End point description:

Engraftment of transduced cells was assessed using vector gene marking in PBMCs

End point type	Primary

End point timeframe:

36 months

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: As VCN was assessed for the gene therapy arm only, there is no comparator and so formal statistical analysis could not be performed.

End point values	OTL-101* On-Study Subjects	OTL-101* On-Study and CUP Subjects		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9[8]	18[9]		
Units: copies/cell				
median (full range (min-max))				
PBMCs	0.600 (0.20 to 1.67)	0.625 (0.20 to 1.67)		

Notes:

[8] - 9/10 subjects evaluated for PBMCs at Month 36

[9] - 18/20 subjects evaluated for PBMCs at Month 36

Statistical analyses

No statistical analyses for this end point

Primary: Vector copy number (VCN) in CD3+ T Cells

End point title	Vector copy number (VCN) in CD3+ T Cells[10]

End point description:

Engraftment of transduced cells was assessed using vector gene marking in CD3+ T Cells

End point type	Primary

End point timeframe:

36 months

Notes:

[10] - 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 VCN was assessed for the gene therapy arm only, there is no comparator and so formal statistical analysis could not be performed.

End point values	OTL-101* On-Study Subjects	OTL-101* On-Study and CUP Subjects		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	8[11]	17[12]		
Units: copies/cell				
median (full range (min-max))				
CD3+ T cells	1.065 (0.84 to 1.59)	1.160 (0.30 to 4.61)		

Notes:

[11] - 8/10 subjects evaluated for CD3+ T Cells at Month 36

[12] - 17/20 subjects evaluated for CD3+ T Cells at Month 36

Statistical analyses

No statistical analyses for this end point

Primary: Vector copy number (VCN) in CD19+ B Cells

End point title	Vector copy number (VCN) in CD19+ B Cells[13]

End point description:

Engraftment of transduced cells was assessed using vector gene marking in CD19+ B Cells

End point type	Primary

End point timeframe:

36 months

Notes:

[13] - 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 VCN was assessed for the gene therapy arm only, there is no comparator and so formal statistical analysis could not be performed.

End point values	OTL-101* On-Study Subjects	OTL-101* On-Study and CUP Subjects		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9[14]	17[15]		
Units: copies/cell				
median (full range (min-max))				
CD19+ B cells	0.880 (0.68 to 1.77)	1.190 (0.68 to 3.75)		

Notes:

[14] - 9/10 subjects evaluated for CD19+ B Cells at Month 36

[15] - 17/20 subjects evaluated for CD19+ B Cells at Month 36

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in CD3+ T cell counts (3 years)

End point title	Change from Baseline in CD3+ T cell counts (3 years)[16]

End point description:

Immune reconstitution was assessed by change in CD3+ T Cell counts over time.

End point type	Primary

End point timeframe:

36 months

Notes:

[16] - 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: Change in CD3+ T Cell counts was assessed for the gene therapy arm only. As this is a single group, there is no comparator and so statistical analysis could not be performed.

End point values	OTL-101* On-Study Subjects	OTL-101* On-Study and CUP Subjects		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	7[17]	16[18]		
Units: 10e9/L				
median (full range (min-max))				
CD3+ T Cells Change from Baseline	1.060 (0.59 to 1.47)	1.090 (-0.49 to 1.47)		

Notes:

[17] - Change from Baseline data available for 7/10 subjects

[18] - Change from Baseline data available for 16/20 subjects

Statistical analyses

No statistical analyses for this end point

Primary: ADA activity in erythrocytes

End point title	ADA activity in erythrocytes[19]

End point description:

ADA enzyme activity was assessed as a measure of successful engraftment of genetically modified HSPCs, as it marks sustained gene expression from the normal ADA transgene.

End point type	Primary

End point timeframe:

36 months

Notes:

[19] - 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: Formal statistical analysis was not performed, data was analysed using descriptive statistics.

End point values	HSCT Controls without MRD	HSCT Controls with MRD	All HSCT Controls	OTL-101* On-Study Subjects
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	4[20]	7[21]	11[22]	9[23]
Units: nmol/h/mg				
median (full range (min-max))				
ADA Activity	86.5 (39 to 115)	1.0 (0 to 27)	23.0 (0 to 115)	638.0 (220 to 3038)

Notes:

[20] - Data available for 4/5 subjects at "Over 30 Months post HSCT"

[21] - Data available for 7/11 subjects at "Over 30 Months post HSCT"

[22] - Data available for 11/16 subjects at "Over 30 Months post HSCT"

[23] - Data available for 9/10 subjects at 36 months

End point values	OTL-101* On-Study and CUP Subjects			
Subject group type	Subject analysis set			
Number of subjects analysed	18[24]			
Units: nmol/h/mg				
median (full range (min-max))				
ADA Activity	490.5 (27 to 3038)			

Notes:

[24] - Data available for 18/20 subjects at 36 months

Statistical analyses

No statistical analyses for this end point

Primary: Reduction in deoxyadenosine triphosphate (dATP) in erythrocytes

End point title	Reduction in deoxyadenosine triphosphate (dATP) in erythrocytes[25]

End point description:

Decreased dATP levels coincide with increased ADA enzyme activity, detoxification was used as a marker of correction of the defective ADA gene. The threshold for detoxification was <100 µmol/L.

End point type	Primary

End point timeframe:

36 months

Notes:

[25] - 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: Formal statistical analysis was not performed, data was analysed using descriptive statistics.

End point values	HSCT Controls without MRD	HSCT Controls with MRD	All HSCT Controls	OTL-101* On-Study Subjects
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	1[26]	6[27]	7[28]	7[29]
Units: umol/L				
median (full range (min-max))				
dATP	0.0 (0 to 0)	114.0 (23 to 192)	90.0 (0 to 192)	50.0 (50 to 50)

Notes:

[26] - Data available for 1/5 subjects at "Over 30 Months post HSCT"

[27] - Data available for 6/11 subjects at "Over 30 Months post HSCT"

[28] - Data available for 7/16 subjects at "Over 30 Months post HSCT"

[29] - Data available for 7/10 subjects at Month 36

End point values	OTL-101* On-Study and CUP Subjects			
Subject group type	Subject analysis set			
Number of subjects analysed	15[30]			
Units: umol/L				
median (full range (min-max))				
dATP	50.0 (50 to 50)			

Notes:

[30] - Data available for 15/20 subjects at Month 36

Statistical analyses

No statistical analyses for this end point

Primary: Analysis of the frequency of vector integration into known protooncogenes (3 years)

End point title	Analysis of the frequency of vector integration into known protooncogenes (3 years)[31]

End point description:

Vector Integration Site Analysis (VISA) allowed determination of the distribution of vector integration sites in each subject's genome, as well as the relative clonal abundance. VISA was to be considered abnormal for a subject if, in 2 or more instances during the course of follow-up, a single integration site was found to represent >30% of the total integration sites detected.

End point type	Primary

End point timeframe:

36 months

Notes:

[31] - 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: Vector integration analysis was assessed for the gene therapy arm only. As this is a single group, there is no comparator and so statistical analysis could not be performed.

End point values	OTL-101* On-Study Subjects	OTL-101* On-Study and CUP Subjects		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	20		
Units: percent				
number (not applicable)				
No. instances of integration >30% total sites	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Comparison of EvFS of subjects treated with IMP with those of patients treated with allogeneic HSCT (1 year)

End point title	Comparison of EvFS of subjects treated with IMP with those of patients treated with allogeneic HSCT (1 year)[32]

End point description:

Difference in EvFS of historical control group, "HSCT Controls without MRD", "HSCT Controls with MRD" and "All HSCT Controls group", compared to subjects treated with OTL-101* in the "OTL-101* On-Study" group and "OTL-101* On-Study and CUP Subjects" group.

End point type	Primary

End point timeframe:

12 months

Notes:

[32] - 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: If there was at least 1 event in each group, it was planned to use the log rank test to compare the difference in survival curves between each OTL-101* treatment groups and each of the HSCT control groups. However, as there was no event in any group at 12 months, this analysis was not carried out.

End point values	HSCT Controls without MRD	HSCT Controls with MRD	All HSCT Controls	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	5	11	16	
Units: percent				
number (not applicable)				
Difference from OTL-101* on-study subjects	0	0	0	
Difference from OTL-101* on-study and CUP subjects	0	0	0	

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in CD3+ T cell counts (1 year)

End point title	Change from Baseline in CD3+ T cell counts (1 year)

End point description:

Immune reconstitution was assessed by change in CD3+ T Cell counts over time.

End point type	Primary

End point timeframe:

12 months

End point values	OTL-101* On-Study Subjects	OTL-101* On-Study and CUP Subjects		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	8	17		
Units: 10e9/L				
geometric mean (confidence interval 95%)				
Adjusted Mean (95% CI)	3.58 (1.64 to 7.83)	3.18 (1.98 to 5.10)		

Statistical analyses

Statistical analysis title	MMRM Analysis of OTL-101* On-Study at M12

Statistical analysis description:

MMRM Analysis of Change from Baseline to Month 12 in Log-Transformed CD3+ T Cell count (OTL-101*) for "OTL-101* on-study subjects" group

Comparison groups	OTL-101* On-Study Subjects v OTL-101* On-Study and CUP Subjects
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	other[33]
P-value	= 0.002
Method	Mixed models analysis

Notes:

[33] - Model includes fixed effects for visit and Baseline, subject as random effect, with compound symmetry covariance structure. Observations with a value of 0 were imputed as 0.01. Model analyses log transformed data, so the adjusted mean refers to the geometric mean ratio between Month 12 and Baseline.

Statistical analysis title	MMRM Analysis of OTL-101* On-Study/CUP at M12

Statistical analysis description:

MMRM Analysis of Change from Baseline to Month 12 in Log-Transformed CD3+ T Cell count (OTL-101*) for "OTL-101* on-study and CUP subjects" group

Comparison groups	OTL-101* On-Study and CUP Subjects v OTL-101* On-Study Subjects
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	other[34]
P-value	< 0.001
Method	Mixed models analysis

Notes:

[34] - Model includes fixed effects for visit and Baseline, subject as random effect, with compound symmetry covariance structure. Observations with a value of 0 were imputed as 0.01. Model analyses log transformed data, so the adjusted mean refers to the geometric mean ratio between Month 12 and Baseline.

Secondary: OS of subjects treated with IMP with those of patients treated with allogeneic HSCT (3 years)

End point title	OS of subjects treated with IMP with those of patients treated with allogeneic HSCT (3 years)

End point description:

Overall survival is defined as the proportion of subjects alive at 36 months

End point type	Secondary

End point timeframe:

36 months

End point values	HSCT Controls without MRD	HSCT Controls with MRD	All HSCT Controls	OTL-101* On-Study Subjects
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	5	11	16	10
Units: percent				
number (confidence interval 95%)				
Proportion surviving at 36 months (95% CI)	100 (47.82 to 100)	88.89 (51.75 to 99.72)	92.86 (66.13 to 99.82)	100 (66.37 to 100)

End point values	OTL-101* On-Study and CUP Subjects			
Subject group type	Subject analysis set			
Number of subjects analysed	20			
Units: percent				
number (confidence interval 95%)				
Proportion surviving at 36 months (95% CI)	100 (82.35 to 100)			

Statistical analyses

No statistical analyses for this end point

Secondary: EvFS of subjects treated with IMP with those of patients treated with allogeneic HSCT (3 years)

End point title	EvFS of subjects treated with IMP with those of patients treated with allogeneic HSCT (3 years)

End point description:

Event-free survival is defined as the proportion of subjects alive with no "event", an "event" being the resumption of PEG-ADA ERT or the need for a rescue allogenic Hematopoietic Stem Cell Transplant (HSCT), or death.

End point type	Secondary

End point timeframe:

36 months

End point values	HSCT Controls without MRD	HSCT Controls with MRD	All HSCT Controls	OTL-101* On-Study Subjects
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	5	11	16	10
Units: percent				
number (confidence interval 95%)				
Proportion event-free at 36 months (95% CI)	80.00 (28.36 to 99.49)	60.00 (26.24 to 87.84)	66.67 (38.38 to 88.18)	90.00 (55.50 to 99.75)

End point values	OTL-101* On-Study and CUP Subjects			
Subject group type	Subject analysis set			
Number of subjects analysed	20			
Units: percent				
number (confidence interval 95%)				
Proportion event-free at 36 months (95% CI)	95.00 (75.13 to 99.87)			

Statistical analyses

Statistical analysis title	HSCT without MRD & OTL 101* on-study
Statistical analysis description: Comparison of "HSCT Controls without MRD" and "OTL-101* on-study subjects" groups	
Comparison groups	OTL-101* On-Study Subjects v HSCT Controls without MRD
Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.645
Method	Logrank

Statistical analysis title	HSCT without MRD & OTL 101* on-study/CUP
Statistical analysis description: Comparison of "HSCT Controls without MRD" and "OTL-101* on-study and CUP subjects" groups	
Comparison groups	HSCT Controls without MRD v OTL-101* On-Study and CUP Subjects
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.299
Method	Logrank

Statistical analysis title	HSCT with MRD & OTL 101* on-study

Statistical analysis description:	
Comparison of "HSCT Controls with MRD" and "OTL-101* on-study subjects" groups	
Comparison groups	OTL-101* On-Study Subjects v HSCT Controls with MRD
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2
Method	Logrank

Statistical analysis title	HSCT with MRD & OTL 101* on-study/CUP
Statistical analysis description:	
Comparison of "HSCT Controls with MRD" and "OTL-101* on-study and CUP subjects" groups	
Comparison groups	HSCT Controls with MRD v OTL-101* On-Study and CUP Subjects
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.028
Method	Logrank

Statistical analysis title	All HSCT & OTL 101* on-study
Statistical analysis description:	
Comparison of "All HSCT Controls" and "OTL-101* on-study subjects" groups	
Comparison groups	All HSCT Controls v OTL-101* On-Study Subjects
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.259
Method	Logrank

Statistical analysis title	All HSCT & OTL 101* on-study/CUP
Statistical analysis description:	
Comparison of "All HSCT Controls" and "OTL-101* on-study and CUP subjects" groups	
Comparison groups	All HSCT Controls v OTL-101* On-Study and CUP Subjects
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.044
Method	Logrank

Secondary: Comparison of OS of subjects treated with IMP with those of patients

treated with allogeneic HSCT (3 years)

End point title	Comparison of OS of subjects treated with IMP with those of patients treated with allogeneic HSCT (3 years)

End point description:

Difference in OS of historical control group, "HSCT Controls without MRD", "HSCT Controls with MRD" and "All HSCT Controls group", compared to subjects treated with OTL-101* in the "OTL-101* On-Study" group and "OTL-101* On-Study and CUP Subjects" group.

End point type	Secondary

End point timeframe:

36 months

End point values	HSCT Controls without MRD	HSCT Controls with MRD	All HSCT Controls	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	5	11	16	
Units: percent				
number (confidence interval 95%)				
Difference in OS from OTL-101* on-study subjects	0 (0 to 0)	11.11 (-22.41 to 48.25)	7.14 (-28.10 to 34.23)	
Difference from OTL-101* on-study and CUP subjects	0 (0 to 0)	11.11 (-10.1 to 48.25)	7.14 (-12.91 to 33.87)	

Statistical analyses

No statistical analyses for this end point

Secondary: Comparison of EvFS of subjects treated with IMP with those of patients treated with allogeneic HSCT (3 years)

End point title	Comparison of EvFS of subjects treated with IMP with those of patients treated with allogeneic HSCT (3 years)

End point description:

Difference in EvFS of historical control group, "HSCT Controls without MRD", "HSCT Controls with MRD" and "All HSCT Controls group", compared to subjects treated with OTL-101* in the "OTL-101* On-Study" group and "OTL-101* On-Study and CUP Subjects" group.

End point type	Secondary

End point timeframe:

36 months

End point values	HSCT Controls without MRD	HSCT Controls with MRD	All HSCT Controls	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	5	11	16	
Units: percent				
number (confidence interval 95%)				
Difference from OTL-101* on-study subjects	10.00 (-32.05 to 61.97)	30.00 (-10.72 to 65.87)	23.33 (-15.24 to 54.59)	

Difference from OTL-101* on-study and CUP subjects	15.00 (-13.70 to 63.54)	35.00 (2.29 to 68.45)	28.33 (2.04 to 56.36)	

Statistical analyses

No statistical analyses for this end point

Secondary: Infection Rate

End point title	Infection Rate

End point description:

The infections of interest in this study were severe infections or opportunistic infectious episodes, defined as infections requiring hospitalization or prolonging hospitalization and/or documented infections by opportunistic pathogens.

End point type	Secondary

End point timeframe:

36 months

End point values	HSCT Controls without MRD	HSCT Controls with MRD	All HSCT Controls	OTL-101* On-Study Subjects
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	5	11	16	10
Units: per person per year				
number (not applicable)				
Severe infection rate	0.13	0.17	0.16	0.14

End point values	OTL-101* On-Study and CUP Subjects			
Subject group type	Subject analysis set			
Number of subjects analysed	20			
Units: per person per year				
number (not applicable)				
Severe infection rate	0.14			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Adverse events were reported from the time of participant consent to end of trial	
Adverse event reporting additional description:	
Adverse events were analysed from OTL-101* administration to end of trial	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups	
Reporting group title	OTL-101* On-Study and CUP Subjects
Reporting group description: -	
Reporting group title	OTL-101* On-Study Subjects
Reporting group description:	
The safety population for analysis consists of the on-study OTL-101*-treated subjects.	

Serious adverse events	OTL-101* On-Study and CUP Subjects	OTL-101* On-Study Subjects	
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 20 (55.00%)	7 / 10 (70.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events		0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	6 / 20 (30.00%)	5 / 10 (50.00%)	
occurrences causally related to treatment / all	0 / 8	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Bone marrow failure			
subjects affected / exposed	1 / 20 (5.00%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Immune reconstitution inflammatory syndrome			
subjects affected / exposed	2 / 20 (10.00%)	2 / 10 (20.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 20 (5.00%)	1 / 10 (10.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 20 (5.00%)	1 / 10 (10.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 20 (5.00%)	1 / 10 (10.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			
subjects affected / exposed	1 / 20 (5.00%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Device related infection			
subjects affected / exposed	1 / 20 (5.00%)	3 / 10 (30.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related sepsis			
subjects affected / exposed	1 / 20 (5.00%)	1 / 10 (10.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis norovirus			
subjects affected / exposed	1 / 20 (5.00%)	1 / 10 (10.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			

subjects affected / exposed	1 / 20 (5.00%)	1 / 10 (10.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral candidiasis			
subjects affected / exposed	1 / 20 (5.00%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 20 (5.00%)	1 / 10 (10.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transmission of an infectious agent via product			
subjects affected / exposed	1 / 20 (5.00%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection bacterial			
subjects affected / exposed	1 / 20 (5.00%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Weight gain poor			
subjects affected / exposed	1 / 20 (5.00%)	1 / 10 (10.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	OTL-101* On-Study and CUP Subjects	OTL-101* On-Study Subjects	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 20 (100.00%)	10 / 10 (100.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Haemangioma of skin			

subjects affected / exposed	1 / 20 (5.00%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Skin papilloma			
subjects affected / exposed	1 / 20 (5.00%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 20 (5.00%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Pallor			
subjects affected / exposed	1 / 20 (5.00%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	9 / 20 (45.00%)	4 / 10 (40.00%)	
occurrences (all)	16	9	
Developmental delay			
subjects affected / exposed	1 / 20 (5.00%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
Infusion site erythema			
subjects affected / exposed	1 / 20 (5.00%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
Catheter site erythema			
subjects affected / exposed	1 / 20 (5.00%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Chest pain			
subjects affected / exposed	1 / 20 (5.00%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Hypothermia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Malaise			
subjects affected / exposed	1 / 20 (5.00%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Mucosal inflammation			

subjects affected / exposed	1 / 20 (5.00%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Hypermetropia			
subjects affected / exposed	1 / 20 (5.00%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
Amblyopia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Astigmatism			
subjects affected / exposed	1 / 20 (5.00%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Strabismus			
subjects affected / exposed	1 / 20 (5.00%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Immune system disorders			
Immune reconstitution inflammatory syndrome			
subjects affected / exposed	1 / 20 (5.00%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
Reproductive system and breast disorders			
Testicular swelling			
subjects affected / exposed	1 / 20 (5.00%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	11 / 20 (55.00%)	4 / 10 (40.00%)	
occurrences (all)	19	6	
Epistaxis			
subjects affected / exposed	2 / 20 (10.00%)	1 / 10 (10.00%)	
occurrences (all)	3	1	
Oropharyngeal pain			
subjects affected / exposed	2 / 20 (10.00%)	1 / 10 (10.00%)	
occurrences (all)	2	1	
Rhinorrhoea			
subjects affected / exposed	2 / 20 (10.00%)	0 / 10 (0.00%)	
occurrences (all)	4	0	

Wheezing			
subjects affected / exposed	2 / 20 (10.00%)	0 / 10 (0.00%)	
occurrences (all)	2	0	
Bronchial disorder			
subjects affected / exposed	1 / 20 (5.00%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Pharyngeal oedema			
subjects affected / exposed	1 / 20 (5.00%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 20 (5.00%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
Attention deficit/hyperactivity disorder			
subjects affected / exposed	1 / 20 (5.00%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Investigations			
Sapovirus test positive			
subjects affected / exposed	2 / 20 (10.00%)	1 / 10 (10.00%)	
occurrences (all)	3	2	
Norovirus test positive			
subjects affected / exposed	4 / 20 (20.00%)	1 / 10 (10.00%)	
occurrences (all)	4	1	
Adenovirus test positive			
subjects affected / exposed	2 / 20 (10.00%)	1 / 10 (10.00%)	
occurrences (all)	2	1	
Weight decreased			
subjects affected / exposed	2 / 20 (10.00%)	1 / 10 (10.00%)	
occurrences (all)	2	1	
Enterococcus test positive			
subjects affected / exposed	2 / 20 (10.00%)	0 / 10 (0.00%)	
occurrences (all)	2	0	
Acinetobacter test positive			
subjects affected / exposed	1 / 20 (5.00%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
Alanine aminotransferase increased			

subjects affected / exposed	1 / 20 (5.00%)	1 / 10 (10.00%)		
occurrences (all)	1	1		
Influenza A virus test positive				
subjects affected / exposed	1 / 20 (5.00%)	1 / 10 (10.00%)		
occurrences (all)	1	1		
Morganella test positive				
subjects affected / exposed	1 / 20 (5.00%)	1 / 10 (10.00%)		
occurrences (all)	1	1		
Aspiration bone marrow abnormal				
subjects affected / exposed	1 / 20 (5.00%)	0 / 10 (0.00%)		
occurrences (all)	1	0		
Blood creatinine increased				
subjects affected / exposed	1 / 20 (5.00%)	0 / 10 (0.00%)		
occurrences (all)	1	0		
C-reactive protein increased				
subjects affected / exposed	1 / 20 (5.00%)	0 / 10 (0.00%)		
occurrences (all)	1	0		
Chest x-ray abnormal				
subjects affected / exposed	1 / 20 (5.00%)	0 / 10 (0.00%)		
occurrences (all)	1	0		
Computerised tomogram thorax abnormal				
subjects affected / exposed	1 / 20 (5.00%)	0 / 10 (0.00%)		
occurrences (all)	1	0		
Cytomegalovirus test positive				
subjects affected / exposed	1 / 20 (5.00%)	0 / 10 (0.00%)		
occurrences (all)	1	0		
Epstein-Barr virus test positive				
subjects affected / exposed	1 / 20 (5.00%)	0 / 10 (0.00%)		
occurrences (all)	3	0		
Human metapneumovirus test positive				
subjects affected / exposed	1 / 20 (5.00%)	0 / 10 (0.00%)		
occurrences (all)	1	0		
Human rhinovirus test positive				

subjects affected / exposed	1 / 20 (5.00%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Respirovirus test positive			
subjects affected / exposed	1 / 20 (5.00%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Staphylococcus test positive			
subjects affected / exposed	1 / 20 (5.00%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Streptococcus test positive			
subjects affected / exposed	1 / 20 (5.00%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Hypophagia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	3 / 20 (15.00%)	2 / 10 (20.00%)	
occurrences (all)	3	2	
Skin abrasion			
subjects affected / exposed	2 / 20 (10.00%)	1 / 10 (10.00%)	
occurrences (all)	2	1	
Thermal burn			
subjects affected / exposed	1 / 20 (5.00%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Congenital, familial and genetic disorders			
Combined immunodeficiency			
subjects affected / exposed	1 / 20 (5.00%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
Preauricular cyst			
subjects affected / exposed	1 / 20 (5.00%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
Cardiac disorders			
Bradycardia			
subjects affected / exposed	1 / 20 (5.00%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
Nervous system disorders			

Headache			
subjects affected / exposed	2 / 20 (10.00%)	0 / 10 (0.00%)	
occurrences (all)	2	0	
Gross motor delay			
subjects affected / exposed	1 / 20 (5.00%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
Hypotonia			
subjects affected / exposed	1 / 20 (5.00%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
Speech disorder developmental			
subjects affected / exposed	1 / 20 (5.00%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
Dizziness			
subjects affected / exposed	1 / 20 (5.00%)	0 / 10 (0.00%)	
occurrences (all)	2	0	
Hypoaesthesia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	7 / 20 (35.00%)	3 / 10 (30.00%)	
occurrences (all)	9	3	
Thrombocytopenia			
subjects affected / exposed	2 / 20 (10.00%)	0 / 10 (0.00%)	
occurrences (all)	2	0	
Lymphopenia			
subjects affected / exposed	1 / 20 (5.00%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
Bone marrow failure			
subjects affected / exposed	1 / 20 (5.00%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Febrile neutropenia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Lymphadenopathy			

subjects affected / exposed	1 / 20 (5.00%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Ear and labyrinth disorders			
Deafness			
subjects affected / exposed	1 / 20 (5.00%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
Motion sickness			
subjects affected / exposed	1 / 20 (5.00%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
Deafness neurosensory			
subjects affected / exposed	1 / 20 (5.00%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Ocular hyperaemia			
subjects affected / exposed	2 / 20 (10.00%)	2 / 10 (20.00%)	
occurrences (all)	2	2	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	9 / 20 (45.00%)	4 / 10 (40.00%)	
occurrences (all)	13	5	
Diarrhoea			
subjects affected / exposed	10 / 20 (50.00%)	3 / 10 (30.00%)	
occurrences (all)	15	4	
Constipation			
subjects affected / exposed	3 / 20 (15.00%)	3 / 10 (30.00%)	
occurrences (all)	3	3	
Abdominal pain			
subjects affected / exposed	2 / 20 (10.00%)	0 / 10 (0.00%)	
occurrences (all)	3	0	
Mouth ulceration			
subjects affected / exposed	2 / 20 (10.00%)	0 / 10 (0.00%)	
occurrences (all)	2	0	
Abdominal distension			
subjects affected / exposed	1 / 20 (5.00%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
Dental caries			

subjects affected / exposed	1 / 20 (5.00%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
Gastritis			
subjects affected / exposed	1 / 20 (5.00%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
Oral mucosal erythema			
subjects affected / exposed	1 / 20 (5.00%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
Stomatitis			
subjects affected / exposed	1 / 20 (5.00%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
Tongue discolouration			
subjects affected / exposed	1 / 20 (5.00%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
Nausea			
subjects affected / exposed	1 / 20 (5.00%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Proctitis			
subjects affected / exposed	1 / 20 (5.00%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Dermatitis diaper			
subjects affected / exposed	7 / 20 (35.00%)	5 / 10 (50.00%)	
occurrences (all)	8	6	
Rash			
subjects affected / exposed	7 / 20 (35.00%)	3 / 10 (30.00%)	
occurrences (all)	10	5	
Alopecia			
subjects affected / exposed	2 / 20 (10.00%)	1 / 10 (10.00%)	
occurrences (all)	2	1	
Dry skin			
subjects affected / exposed	3 / 20 (15.00%)	0 / 10 (0.00%)	
occurrences (all)	3	0	
Blood blister			
subjects affected / exposed	1 / 20 (5.00%)	1 / 10 (10.00%)	
occurrences (all)	1	1	

Dermatitis atopic			
subjects affected / exposed	1 / 20 (5.00%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
Eczema			
subjects affected / exposed	1 / 20 (5.00%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
Exfoliative rash			
subjects affected / exposed	1 / 20 (5.00%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
Rash maculo-papular			
subjects affected / exposed	1 / 20 (5.00%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
Dermatitis acneiform			
subjects affected / exposed	1 / 20 (5.00%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Petechiae			
subjects affected / exposed	1 / 20 (5.00%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Skin lesion			
subjects affected / exposed	1 / 20 (5.00%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 20 (5.00%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Azotaemia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	1 / 20 (5.00%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	1 / 20 (5.00%)	1 / 10 (10.00%)	
occurrences (all)	1	1	

Infections and infestations			
Rhinitis			
subjects affected / exposed	9 / 20 (45.00%)	5 / 10 (50.00%)	
occurrences (all)	15	9	
Viral upper respiratory tract infection			
subjects affected / exposed	7 / 20 (35.00%)	4 / 10 (40.00%)	
occurrences (all)	12	7	
Otitis media			
subjects affected / exposed	3 / 20 (15.00%)	2 / 10 (20.00%)	
occurrences (all)	4	2	
Lower respiratory tract infection			
subjects affected / exposed	2 / 20 (10.00%)	2 / 10 (20.00%)	
occurrences (all)	2	2	
Metapneumovirus infection			
subjects affected / exposed	2 / 20 (10.00%)	2 / 10 (20.00%)	
occurrences (all)	2	2	
Viral rash			
subjects affected / exposed	2 / 20 (10.00%)	2 / 10 (20.00%)	
occurrences (all)	2	2	
Ear infection			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 20 (10.00%)	1 / 10 (10.00%)	
occurrences (all)	3	2	
Device related infection			
subjects affected / exposed	2 / 20 (10.00%)	0 / 10 (0.00%)	
occurrences (all)	2	0	
Urinary tract infection			
subjects affected / exposed	3 / 20 (15.00%)	1 / 10 (10.00%)	
occurrences (all)	3	1	
Hand-foot-and-mouth disease			
subjects affected / exposed	2 / 20 (10.00%)	1 / 10 (10.00%)	
occurrences (all)	2	1	
Influenza			
subjects affected / exposed	1 / 20 (5.00%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Varicella			

subjects affected / exposed	2 / 20 (10.00%)	1 / 10 (10.00%)	
occurrences (all)	2	1	
Upper respiratory tract infection			
subjects affected / exposed	3 / 20 (15.00%)	0 / 10 (0.00%)	
occurrences (all)	5	0	
Staphylococcal infection			
subjects affected / exposed	2 / 20 (10.00%)	0 / 10 (0.00%)	
occurrences (all)	2	0	
Adenovirus infection			
subjects affected / exposed	1 / 20 (5.00%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
Bronchiolitis			
subjects affected / exposed	1 / 20 (5.00%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
Epstein-Barr virus infection			
subjects affected / exposed	1 / 20 (5.00%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
Gastroenteritis			
subjects affected / exposed	1 / 20 (5.00%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
Impetigo			
subjects affected / exposed	1 / 20 (5.00%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
Laryngitis			
subjects affected / exposed	1 / 20 (5.00%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
Parainfluenzae virus infection			
subjects affected / exposed	1 / 20 (5.00%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
Respiratory tract infection			
subjects affected / exposed	1 / 20 (5.00%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
Tinea capitis			
subjects affected / exposed	1 / 20 (5.00%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
Tinea infection			

subjects affected / exposed	1 / 20 (5.00%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
Bronchitis			
subjects affected / exposed	1 / 20 (5.00%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Conjunctivitis			
subjects affected / exposed	1 / 20 (5.00%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Cytomegalovirus infection			
subjects affected / exposed	1 / 20 (5.00%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Gastroenteritis viral			
subjects affected / exposed	1 / 20 (5.00%)	0 / 10 (0.00%)	
occurrences (all)	2	0	
Haemophilus infection			
subjects affected / exposed	1 / 20 (5.00%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Herpes zoster			
subjects affected / exposed	1 / 20 (5.00%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Oral candidiasis			
subjects affected / exposed	1 / 20 (5.00%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Weight gain poor			
subjects affected / exposed	2 / 20 (10.00%)	1 / 10 (10.00%)	
occurrences (all)	2	1	
Abnormal loss of weight			
subjects affected / exposed	1 / 20 (5.00%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
Dehydration			
subjects affected / exposed	1 / 20 (5.00%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
Feeding intolerance			
subjects affected / exposed	1 / 20 (5.00%)	1 / 10 (10.00%)	
occurrences (all)	1	1	

Hypercalcaemia			
subjects affected / exposed	1 / 20 (5.00%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
Hypocalcaemia			
subjects affected / exposed	1 / 20 (5.00%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
Metabolic acidosis			
subjects affected / exposed	1 / 20 (5.00%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
Decreased appetite			
subjects affected / exposed	1 / 20 (5.00%)	0 / 10 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 October 2012	Changed busulfan dosage from 4 mg/kg IV to a weight-adjusted dosage after a change to EBMT guidelines for busulfan dosing in children Changed to continue PEG-ADA ERT until after the re-infusion of gene modified cells based on data from a recently published murine study and promising data from 2 patients treated on a compassionate basis
18 December 2013	Clarified inclusion criterion for patients >5 years of age
06 May 2014	Clarified procedure timing of BM harvest versus leukapheresis and storage of back-up cells Corrected to allow a back-up BM harvest to be collected 3 months before gene therapy in cases where this was necessary Clarified that inclusion criterion for subjects based on age was <5 years OR >5 years with preserved thymic function Removed exclusion criterion for evidence of infection with HIV-1&2, hepatitis B, HCV Amended GCSF dose for mobilization Changed monitoring of CD34+ cell counts from Day 4 to Day 5 Removed sequential dosing Added statistical analysis plan for the study Removed Treg analysis before gene therapy Corrected an error in follow-up time points
29 September 2015	Updated trial summary flow charts to better reflect the instructions in text Amended leukapheresis procedure to 1-2 days Clarified window of PEG-ADA ERT withdrawal Clarified inclusion criteria around age Harmonized and clarified primary and secondary objectives and endpoints Clarified withdrawal of cotrimoxazole concomitant medication Inserted flexibility on GCSF dosing Removed "ADA expression" from testing after infusion Corrected OTL-101* volume bag Removed some tests to monitor immunological reconstitution as they were not needed to demonstrate objectives and required too large a blood draw Created a more detailed subject monitoring schedule Clarified that OTL-101* cell dose specifications were based on CD34+ cells Moved reporting of AEs from patient notes to the CRF
05 August 2016	Changed trial personnel Added historical HSCT control group Moved from paper CRFs to eCRFs Updated monitoring
16 March 2017	Rewrote primary and secondary objectives and corresponding endpoints Added the CUP group
28 June 2017	Updated the schedule of assessment relating to immune reconstitution.

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.

Not applicable

Notes: