Clinical trial results:
CMV TCR Gene Therapy: A Phase I Safety, Toxicity and Feasibility Study of Adoptive Immunotherapy with CMV TCR-transduced Donor-derived T cells for Recipients of Allogeneic Haematopoietic Stem Cell Transplantation.

Summary

EudraCT number	2008-006649-18
Trial protocol	GB
Global end of trial date	11 December 2018

Results information

Result version number	v1 (current)
This version publication date	22 August 2020
First version publication date	22 August 2020

Trial information

Trial identification

Sponsor protocol code	08/0214

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02988258
WHO universal trial number (UTN)	-
Other trial identifiers	GTAC: 169

Notes:

Sponsors

Sponsor organisation name	University College London
Sponsor organisation address	Gower Street, London, United Kingdom, W1T 7DN
Public contact	Professor Emma Morris, University College London, 44 (0)20 7794 0500, e.morris@ucl.ac.uk
Scientific contact	Professor Emma Morris, University College London, 44 (0)20 7794 0500, e.morris@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	22 January 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	11 December 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The proposed study will test the feasibility of generating donor-derived cytomegalo virus (CMV)-specific T cells via the ex vivo introduction of a CMV-specific T cell receptor using a GMP grade retroviral vector. It will also determine the safety, toxicity (side effects) and efficacy of CMV TCR-transduced T cells used for the pre-emptive treatment of CMV reactivation following HLA-matched sibling Allo-Haematopoietic Stem Cell Transplantation.

Primary Objectives:
(i) Evaluate the feasibility of retroviral-mediated TCR gene transfer to generate CMV-specific T cells from CMV seronegative donors;
(ii) Evaluate the safety, toxicity and side effects of pre-emptive CMV TCR-transduced donor-derived T cells for immunotherapy after Allo-HSCT, where donors are CMV seronegative.

Primary Endpoints:
(i) Document transduction efficiency and TCR expression on TCR-transduced T cells; (ii) Identify organ toxicities and other side effects.

Protection of trial subjects:

Antiviral drug therapy will be initiated in the following circumstances:
1. if the CMV viral load ≥3000 copies/ml or
2. if there is evidence of CMV disease.
Anti-viral therapy will be stopped when the viral load is below the level of quantification of the assay.

In the event of any adverse reactions, chlorpheniramine and hydrocortisone were to be given, as well as oxygen and salbutamol in the event of respiratory distress. Nursing and medical staff experienced in the administration of cellular blood products including donor T cell infusions and CMV-specific T cells cared for the trial patients. The site followed trial-specific SOPs and local guidelines for the administration of cellular blood products.

Background therapy:

One of the inclusion criteria is that patients were undergoing matched sibling allogeneic HSCT for an underlying haematological malignancy with a CMV seronegative donor. As part of this transplant, patients will have received conditioning treatment.

Evidence for comparator:

Not applicable

Actual start date of recruitment	18 July 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 3
Worldwide total number of subjects	3
EEA total number of subjects	3

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

Subject disposition

Recruitment

Recruitment details:

All patients were recruited from one site. Patients who met the eligibility criteria were approached at the time or prior to commencement of their pre-transplant conditioning and the protocol was discussed with them and they were given a copy of the Patient Information Sheet. The trial was opened to recruitment on 15 Jul 2013.

Pre-assignment

Screening details:

Patients were screened & enrolled onto the Study prior to HSCT and the allogeneic CMV-specific T cells were to be prepared for all participants. The CMV-specific T cells were released following a single positive CMV PCR result. At this point, patients were re-evaluated for eligibility.
3 patients enrolled - 2 treated; 1 did not reactivate CMV.

Period 1

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

Blinding implementation details:

Not applicable

Arms

Arm title	Treatment arm

Arm description:

Patients treated on trial with the IMP, CMV TCR-Transduced T Cells. This is a single arm non-randomised trial.

Arm type	Experimental
Investigational medicinal product name	CMV TCR-transduced Donor-derived T cells
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Each patient was planned to receive a single infusion of bulk CMV-TCR transduced donor-derived T cells on first CMV reactivation post allogeneic HSCT, at a dose of 10e4 T cells/kg recipient weight (cohort 1, n=3), 10e5 T cells/kg recipient weight (cohort 2, remaining patients if no excess toxicity, or protocol stopping rules) or at a de-escalation dose of 10e3 T cells/kg recipient weight (cohort 1a).
In the trial 2 patients only were dosed, in Cohort 1 at a dose of 10e4 T cells/kg.

Number of subjects in period 1	Treatment arm
Started	3
Completed	0
Not completed	3
Adverse event, serious fatal	1
Patient did not have CMV reactivation post HSCT	1
Lack of efficacy	1

Baseline characteristics

Reporting groups

Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	3	3	
Age categorical			
Age ≥ 18 years and ≤ 65 years			
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)	3	3	
From 65-84 years	0	0	
85 years and over	0	0	
Gender categorical			
Units: Subjects			
Female	3	3	
Male	0	0	

Subject analysis sets

Subject analysis set title	Treated patients
Subject analysis set type	Per protocol

Subject analysis set description:

Patients are included in the analysis set if they reactivated for CMV and were then treated with CMV TCR-transduced Donor-derived T cells.

Reporting group values	Treated patients		
Number of subjects	2		
Age categorical			
Age ≥ 18 years and ≤ 65 years			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	2		
From 65-84 years	0		

85 years and over	0		

Gender categorical Units: Subjects			
Female Male	2		

End points

End points reporting groups

Reporting group title	Treatment arm

Reporting group description:

Patients treated on trial with the IMP, CMV TCR-Transduced T Cells. This is a single arm non-randomised trial.

Subject analysis set title	Treated patients
Subject analysis set type	Per protocol

Subject analysis set description:

Patients are included in the analysis set if they reactivated for CMV and were then treated with CMV TCR-transduced Donor-derived T cells.

Primary: Organ toxicities and other side effects.

End point title	Organ toxicities and other side effects.[1]

End point description:

All AEs are captured in the Adverse Event Section rather than this Endpoint section - please refer to 'Adverse Event' section.

End point type	Primary

End point timeframe:

AEs were recorded and reported from the day of a single positive PCR result to 12 months post T cell infusion. Adverse Reactions and/or Serious Adverse Events were recorded and reported to 5 years post T cell infusion.

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: Due to the small number of subjects treated (N=2) no statistical analyses have been done as this would not be appropriate.

End point values	Treated patients			
Subject group type	Subject analysis set			
Number of subjects analysed				
Units: Number	0			

Statistical analyses

No statistical analyses for this end point

Primary: Transduction efficiency and TCR expression on TCR-transduced T cells

End point title	Transduction efficiency and TCR expression on TCR-transduced T cells[2]

End point description:

TCR expression of >5% and <70% of CMV-TCR+ cells within viable CD3+ cells was required in order to meet the specification defined in the IMPD. This is because sufficient numbers of CMV-specific T cells are required to be functionally effective following adoptive transfer.

End point type	Primary

End point timeframe:

At point of QP release of study treatment

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was specified in the protocol for this endpoint. The protocol states that the data is to be documented. The value given (18%) is the mean value of TCR expression for the 2 patients. The individual values are 12.83% and 22.5%.

End point values	Treated patients			
Subject group type	Subject analysis set			
Number of subjects analysed	2[3]			
Units: percentage	18			

Notes:

[3] - The value given is the average percentage for the product as released for each treated patient (n=2)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs were recorded and reported from the day of a single positive PCR result to 12 months post T cell infusion. Adverse Reactions and/or Serious Adverse Events were recorded and reported to 5 years post T cell infusion.

Adverse event reporting additional description:

Participants were questioned about adverse events at each study visit.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Treatment group

Reporting group description:

This group contains all those participants who received the CMV TCR-Transduced T Cells

Serious adverse events	Treatment group		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 2 (100.00%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	1		
Cardiac disorders			
Right ventricular failure			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Ear and labyrinth disorders			
Hypoacusis			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			

Pneumonia cytomegaloviral			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary hypertension			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal failure			
subjects affected / exposed	1 / 2 (50.00%)		
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	Treatment group		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 2 (100.00%)		
Vascular disorders			
Epistaxis			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Hypertension			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Hypotension			

subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Fatigue			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	2		
Swelling			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Pyrexia			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Decreased appetite			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Spinal pain			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Generalised oedema			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Reproductive system and breast disorders			
Vaginal discharge			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Vulvovaginal inflammation			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Vulvovaginal swelling			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	2 / 2 (100.00%)		
occurrences (all)	4		
Pneumonia viral			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Dyspnoea			
subjects affected / exposed	2 / 2 (100.00%)		
occurrences (all)	2		
Lower respiratory tract infection fungal			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Oropharyngeal pain			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Pulmonary hypertension			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Hypoxia			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Investigations			
Human metapneumovirus test positive			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Coronavirus test positive			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
BK polyomavirus test positive			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Blood urea increased			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Blood creatinine increased			

subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Cardiac disorders			
Tachycardia			
subjects affected / exposed	2 / 2 (100.00%)		
occurrences (all)	2		
Pericardial effusion			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	2		
Tricuspid valve incompetence			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Right ventricular hypertrophy			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Mitral valve incompetence			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 2 (100.00%)		
occurrences (all)	4		
Paraesthesia			
subjects affected / exposed	2 / 2 (100.00%)		
occurrences (all)	2		
Dizziness			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	2		
Tremor			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Febrile neutropenia			

subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	2 / 2 (100.00%)		
occurrences (all)	3		
Vomiting			
subjects affected / exposed	2 / 2 (100.00%)		
occurrences (all)	5		
Diarrhoea			
subjects affected / exposed	2 / 2 (100.00%)		
occurrences (all)	4		
Abdominal pain			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	2		
Proctalgia			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Constipation			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	3		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	2 / 2 (100.00%)		
occurrences (all)	3		
Pain of skin			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Dysuria			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Polyuria			

subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	3		
Pain in extremity			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Neck pain			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Infections and infestations			
Oral candidiasis			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Urinary tract infection			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 December 2012	The Patient & Donor Information Sheets and Consent Forms were amended mainly to change the information regarding personal identifiers that will be collected from Patient/Donor.
05 July 2013	1. Addition of new Trial Site 2. An additional blood test added at multiple time-points throughout the trial for immunological evaluations. This slightly increased the amount of blood taken from the patient. 3. Modification to the T cell transduction protocol. The changes reflected an improved production procedure, to allow a more efficient CMV-specific T Cell transduction, based on scale ups at both the manufacturer's site (GOSH) and the UCL Immunology research team. 4. New and amended product label: Different types of cryopreservation containers to be used depending on the IMP dose (cohort and weight dependent)
18 February 2014	To document a change of supplier of human albumin and that human serum (and not human serum albumin) to be used for cell culture.
26 September 2014	Temporary halt of trial in order to manufacture more vector.
24 November 2016	Amendment to: - Re-start Trial - Change IMP manufacturing site - New vector manufactured via different method - Change from human serum to Human Platelet Lysate in IMP manufacturing process - Addition of Bristol site and removal of RFH site
24 July 2018	Temporarily halt to recruitment as the original trial grant reached the end of its no cost extension.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
30 September 2014	Temporary halt of trial in order to manufacture more vector. Vector was required in order to manufacture the IMP.	01 December 2017

Notes:

Limitations and caveats

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

This trial was terminated early leading to a small number of subjects analysed. Therefore the data presented is restricted to the primary endpoints, including all AEs and SAEs. Recruitment was difficult due to strict eligibility criteria.

Notes: