Clinical trial results:
WT1 TCR Gene Therapy for Leukaemia: A Phase I/II Safety and Toxicity Study

Summary

EudraCT number	2006-004950-25
Trial protocol	GB
Global end of trial date	17 April 2018

Results information

Result version number	v1 (current)
This version publication date	11 March 2020
First version publication date	11 March 2020

Trial information

Trial identification

Sponsor protocol code	D-00272-CT2014001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	ClinicalTrials.gov: NCT01621724

Notes:

Sponsors

Sponsor organisation name	Cell Medica
Sponsor organisation address	2617 Bissonnet St, Suite 300, Houston, United States, TX 77005
Public contact	Clinical Trials Information, Cell Medica, 1 7132313224, info@cellmedica.co.uk
Scientific contact	Clinical Trials Information, Cell Medica, 1 7132313224, info@cellmedica.co.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	17 April 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	17 April 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

PRIMARY OBJECTIVES
1) To determine the feasibility of TCR gene transfer in a clinical setting.
2) To identify organ toxicities or other side effects related to the re-infusion of TCR-Transduced T cells.
3) Propose a safe dose of TCR-Transduced T cells for Phase II evaluation.

Protection of trial subjects:

This study was conducted in accordance with the protocol, the International Conference on Harmonisation Guidelines on Good Clinical Practice (GCP), the Declaration of Helsinki (Edinburgh 2000) and applicable regulatory requirements. The study was conducted under a Clinical Trials Authorisation and approval from the Medicines and Healthcare products Regulatory Agency was obtained.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 September 2014
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: 7
Worldwide total number of subjects	7
EEA total number of subjects	7

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)	1

From 65 to 84 years	6
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 2 centres in the UK.

Pre-assignment

Screening details:

The study aimed to enrol up to 18 HLA-A*0201 positive patients aged between 18 and 75 years with AML or CML confirmed by morphology, histology, immunophenotyping and cytogenetics. Patients were to have a life expectancy of ≥16 weeks, a World Health Organisation (WHO) performance status of 0 to 2, and a total peripheral blood lymphocyte count of >0.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1

Arm description:

Patients in Cohort 1 received standard conditioning [fludarabine plus methylprednisolone] and the lower dose of ≤2x10^7/kg T cells

Arm type	Experimental
Investigational medicinal product name	Gene-modified Wilms' Tumour Antigen 1 (WT1) T cell receptor (TCR)-transduced autologous T cells
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intravenous use

Dosage and administration details:

Bulk transduced WT1 TCR T-lymphocytes were administered by iv infusion over 30 to 60 minutes through a large peripheral vein or centrally through a Hickman line at a dose of ≤2x10^7/kg after standard conditioning (fludarabine plus methylprednisolone). Patients were also administered 106 units/m2 interleukin-2 (IL-2) by subcutaneous injection immediately after T cell infusion and for the next 4 days.

Arm title	Cohort 2A

Arm description:

Patients in Cohort 2A received standard conditioning [fludarabine plus methylprednisolone] and the higher dose of ≤1x10^8/kg T cells

Arm type	Experimental
Investigational medicinal product name	Gene-modified Wilms' Tumour Antigen 1 (WT1) T cell receptor (TCR)-transduced autologous T cells
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intravenous use

Dosage and administration details:

Bulk transduced WT1 TCR T-lymphocytes were administered by iv infusion over 30 to 60 minutes through a large peripheral vein or centrally through a Hickman line at a dose of ≤1x10^8/kg after standard conditioning (fludarabine plus methylprednisolone). Patients were also administered 106 units/m2 interleukin-2 (IL-2) by subcutaneous injection immediately after T cell infusion and for the next 4 days.

Number of subjects in period 1	Cohort 1	Cohort 2A
Started	3	4
Completed	2	3
Not completed	1	1
Disease progression	1	-
Other	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Cohort 1
Reporting group description:	
Patients in Cohort 1 received standard conditioning [fludarabine plus methylprednisolone] and the lower dose of ≤2x10^7/kg T cells	
Reporting group title	Cohort 2A
Reporting group description:	
Patients in Cohort 2A received standard conditioning [fludarabine plus methylprednisolone] and the higher dose of ≤1x10^8/kg T cells	

Reporting group values	Cohort 1	Cohort 2A	Total
Number of subjects	3	4	7
Age categorical Units: Subjects			
Adults (18-64 years)	1	0	1
From 65-84 years	2	4	6
Age continuous Units: years			
arithmetic mean	69.7	69.5	
standard deviation	± 5.5	± 1.9	-
Gender categorical Units: Subjects			
Female	2	2	4
Male	1	2	3
Race Units: Subjects			
White	3	3	6
Black/African American	0	1	1

End points

End points reporting groups

Reporting group title	Cohort 1
Reporting group description:	
Patients in Cohort 1 received standard conditioning [fludarabine plus methylprednisolone] and the lower dose of ≤2x10^7/kg T cells	
Reporting group title	Cohort 2A
Reporting group description:	
Patients in Cohort 2A received standard conditioning [fludarabine plus methylprednisolone] and the higher dose of ≤1x10^8/kg T cells	

Primary: Dose-limiting toxicity

End point title	Dose-limiting toxicity[1]

End point description:

Dose-limiting toxicity was defined as almost certainly/probably dose-related, WT1 TCR-transduced T cell infusion related:
- Grade 4 neutropenia (absolute neutrophil count <0.1x10^9/L) of five or more days duration.
- Infection (documented clinically or microbiologically) with Grade 4 neutropenia (absolute neutrophil count <0.1x10^9/L).
-Grade 4 thrombocytopenia for five or more days associated with active bleeding or requiring platelet transfusion.
-Grade 3 or 4 non-haematologocial toxicity (excluding Grade 3 nausea and Grade 3 or 4 vomiting or diarrhoea in patients who had not received optimal treatment with anti-emetics or anti-diarrhoeal agents).
-Death

End point type	Primary

End point timeframe:

28 days

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: All analyses were exploratory, with data presented using descriptive statistics for all variables.

End point values	Cohort 1	Cohort 2A		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	4		
Units: Subjects				
Dose-limiting toxicity	0	0		
No dose-limiting toxicity	3	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Persistence of of TCR-transduced T cells

End point title	Persistence of of TCR-transduced T cells

End point description:

WT1-TCR expressing T cells in the peripheral blood post infusion were identified using a PCR assay. The persistence of TCR-transduced T cells was measured at various time points during the study. This primary end point refers to the persistence of TCR-transduced T cells at the end of the study.

End point type	Secondary

End point timeframe:

12 months

End point values	Cohort 1	Cohort 2A		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	4		
Units: Subjects				
Persistence of TCR-transduced T cells	2	2		
Absence of TCR-transduced T cells	1	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Disease response

End point title	Disease response

End point description:

Disease response to treatment from the start of the study to the end of the study. Disease response was assessed by bone marrow aspirate and trephine and/or cytogenetics and molecular studies (specific to individual cytogenetic/molecular abnormality in a given trial patient)

End point type	Secondary

End point timeframe:

12 months

End point values	Cohort 1	Cohort 2A		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	4		
Units: Subjects				
Complete response	1	3		
No response	2	1		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 28 days	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups	
Reporting group title	Cohort 1
Reporting group description: -	
Reporting group title	Cohort 2A
Reporting group description: -	

Serious adverse events	Cohort 1	Cohort 2A	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 3 (66.67%)	0 / 4 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Cohort 1	Cohort 2A	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 3 (33.33%)	4 / 4 (100.00%)	
Investigations			
Platelet count decreased			

subjects affected / exposed	0 / 3 (0.00%)	2 / 4 (50.00%)	
occurrences (all)	0	2	
Lymphocyte count decreased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Monocyte count decreased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Hot flush			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Nervous system disorders			
Lethargy			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	
occurrences (all)	2	0	
Hypersomnia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Hypoaesthesia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Dizziness			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Headache			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
General disorders and administration site conditions			

Pyrexia			
subjects affected / exposed	1 / 3 (33.33%)	3 / 4 (75.00%)	
occurrences (all)	1	3	
Injection site reaction			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Non-cardiac chest pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Fatigue			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	2	
Localised oedema			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Eye disorders			
Dry eye			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Vomiting			
subjects affected / exposed	1 / 3 (33.33%)	1 / 4 (25.00%)	
occurrences (all)	2	1	
Nausea			
subjects affected / exposed	1 / 3 (33.33%)	2 / 4 (50.00%)	
occurrences (all)	1	2	
Mouth ulceration			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Dyspepsia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			

Epistaxis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Cough			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 3 (33.33%)	1 / 4 (25.00%)	
occurrences (all)	1	1	
Rash maculo-papular			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Pruritus			
subjects affected / exposed	0 / 3 (0.00%)	2 / 4 (50.00%)	
occurrences (all)	0	2	
Skin ulcer			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Dry skin			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Bone pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	2	
Myalgia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	2	
Infections and infestations			
Nasopharyngitis			

subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Lung infection			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Folliculitis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 January 2008	Protocol V1.0 to V5.0 were submitted by a different Sponsor. No subjects were enrolled until 2014.
19 January 2012	Version 5.1
11 February 2014	Version 5.2
14 July 2014	Version 6.0
15 July 2015	Version 7.0
15 April 2016	Version 7.1
22 September 2017	Version 8.0

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.

Due to difficulties in recruitment of patients, enrolment into the study was terminated early.

Notes: