Clinical trial results:
A single arm Phase I/II study of the safety and efficacy of gene-modified WT1 TCR therapy in patients with myelodysplastic syndrome (MDS) or acute myeloid leukaemia (AML) who have failed to achieve or maintain an IWG defined response following hypomethylating agent therapy

Summary

EudraCT number	2014-003111-10
Trial protocol	DE BE
Global end of trial date	15 May 2018

Results information

Result version number	v1 (current)
This version publication date	18 January 2020
First version publication date	18 January 2020

Trial information

Trial identification

Sponsor protocol code	D-00272-CT2014002

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Cell Medica Ltd.
Sponsor organisation address	Canal Side Studios, 8-14 St Pancras Way, London, United Kingdom, NW1 0QG
Public contact	Clinical Trials Information, Cell Medica Ltd., 44 2075544070, info@cellmedica.co.uk
Scientific contact	Clinical Trials Information, Cell Medica Ltd., 44 2075544070, 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	15 May 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 May 2018
Global end of trial reached?	Yes
Global end of trial date	15 May 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To examine the safety and proportion of subjects achieving one or more IWG (2006) response criteria (within 12 months) following gene-modified WT1 TCR therapy

Protection of trial subjects:

This study was conducted in accordance with the protocol, the Declaration of Helsinki (and amendments), the International Conference on Harmonisation (ICH) Guidelines on Good Clinical Practice (GCP), and applicable local regulatory requirements and laws.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 September 2015
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: 2
Country: Number of subjects enrolled	Belgium: 1
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)	0
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was initiated at 7 centres in the UK (London, Bristol, Leeds and Cardiff), Belgium (Leuven and Bruges) and Germany (Dresden). Only 4 centres screened or recruited subjects. Three subjects failed screening.

Pre-assignment

Screening details:

The study aimed to enrol approximately 30 subjects with MDS or AML who had received hypomethylating agent therapy, and who were either relapsed or stable. Subjects who had received hypomethylating agent therapy as part of a combination regimen could be considered for eligibility at the discretion of the Sponsor.

Period 1

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

Arms

Arm title	Gene-modified WT1 TCR therapy

Arm description: -

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:

A single dose of bulk WT1 TCR-transduced T cells (≤ 2 x 10^7/kg) was intravenously administered following protocol-specified lymphodepletive conditioning regimen. Additionally, daily IL-2 subcutaneous injections (1x10^6 units/m2) were administered for 5 days concomitantly to each subject, following infusion of the ATIMP.

Number of subjects in period 1	Gene-modified WT1 TCR therapy
Started	3
Completed	0
Not completed	3
Disease progression	1
Death	2

Baseline characteristics

Reporting groups	
Reporting group title	Main study

Reporting group description: -

Reporting group values	Main study	Total	
Number of subjects	3	3	
Age categorical Units: Subjects			
From 65-84 years	3	3	
Gender categorical Units: Subjects			
Female	1	1	
Male	2	2	
Race Units: Subjects			
White	3	3	

End points

End points reporting groups

Reporting group title	Gene-modified WT1 TCR therapy

Reporting group description: -

Primary: Proportion of subjects achieving IWG response

End point title	Proportion of subjects achieving IWG response[1]

End point description:

The planned primary endpoint assessment was the proportion of subjects achieving one or more of the following IWG response criteria within 12 months of administration of WT1 TCR-transduced T cells: complete remission; partial remission; marrow complete remission; cytogenetic response; haematological improvement.

Haematological disease evaluation was conducted approximately 28 days after T cell infusion in all subjects, approximately 3 months after T cell infusion in 2 subjects and approximately 4 months after T cell infusion in one subject. Bone marrow disease evaluation was conducted at screening in all subjects and approximately 3 months after screening in 2 subjects.

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: Due to the early termination and the very small number of subjects recruited, the Sponsor decided not to complete the statistical analysis as described in the protocol.

End point values	Gene-modified WT1 TCR therapy			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: Subjects				
Achieved IWG response	0			
Did not achieve IWG response	3			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

An evaluation of the incidence of AEs was made at each study visit.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Gene-modified WT1 TCR therapy

Reporting group description: -

Serious adverse events	Gene-modified WT1 TCR therapy		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)		
number of deaths (all causes)	3		
number of deaths resulting from adverse events	0		
Investigations			
Platelet count decreased			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Febrile neutropenia	Additional description: One occurrence of the event assessed as 'possibly' relatedness to study drug		
subjects affected / exposed	2 / 3 (66.67%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Chest pain	Additional description: One occurrence of the event assessed as 'remote' relatedness to study drug		
subjects affected / exposed	1 / 3 (33.33%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Cytokine release syndrome	Additional description: Event assessed as 'possibly' relatedness to study drug		

subjects affected / exposed	1 / 3 (33.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia parainfluenzae viral			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Gene-modified WT1 TCR therapy		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Paraneoplastic syndrome			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Surgical and medical procedures			

Haematoma			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	2 / 3 (66.67%)		
occurrences (all)	2		
Chest pain			
subjects affected / exposed	2 / 3 (66.67%)		
occurrences (all)	2		
Fatigue			
subjects affected / exposed	2 / 3 (66.67%)		
occurrences (all)	4		
Pyrexia			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Malaise			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	3		
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Dyspnoea			
subjects affected / exposed	2 / 3 (66.67%)		
occurrences (all)	5		
Epistaxis			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	3		
Haemoptysis			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Oropharyngeal pain			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		

Pulmonary oedema			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Respiratory distress			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Investigations			
C-reactive protein increased			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Hyperglycaemia			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 3 (100.00%)		
occurrences (all)	6		
Dizziness			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	2		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	3		
Febrile neutropenia			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Eye disorders			
Retinal detachment			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Retinal haemorrhage			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Gastrointestinal disorders			
Constipation			

subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1 2 / 3 (66.67%) 3 1 / 3 (33.33%) 1 1 / 3 (33.33%) 1		
Skin and subcutaneous tissue disorders Hyperhidrosis subjects affected / exposed occurrences (all) Decubitus ulcer subjects affected / exposed occurrences (all) Rash subjects affected / exposed occurrences (all)	 2 / 3 (66.67%) 2 1 / 3 (33.33%) 1 1 / 3 (33.33%) 1		
Renal and urinary disorders Acute kidney injury subjects affected / exposed occurrences (all)	 1 / 3 (33.33%) 1		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all)	 1 / 3 (33.33%) 1 1 / 3 (33.33%) 1		
Infections and infestations Rhinitis subjects affected / exposed occurrences (all)	 1 / 3 (33.33%) 1		

Oral candidiasis subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 2		
Pneumonia parainfluenzae viral subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1		
Upper respiratory tract infection subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1		
Metabolism and nutrition disorders Fluid overload subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1		
Hypophosphataemia subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1		
Hypokalaemia subjects affected / exposed occurrences (all)	2 / 3 (66.67%) 4		
Decreased appetite subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 October 2014	The Protocol Amendment (Version 2.0) was developed to provide clarity and addition of the following protocol aspects: 1) Further rationale for provision of 2nd infusion of WT1 TCR-transduced T cells 2) Clarification of schedule of activities for: a. Repeat infusion, including potential for repeat leukapheresis procedure. b. Provision of separate consent for HLA and brief medical history screening c. Full trial consent to be performed at Visit 2 3) Inclusion of 24-hour in-patient hospitalisation for initial 3 subjects for infusion, including criteria for discharge 4) Clarification that protocol amendment will be submitted to Regulatory Authorities and Ethics Committees when DSMB recommends modifications to the clinical protocol 5) Clarification that an internal safety review will be held with recommendations submitted to Regulatory Authorities and Ethics Committees prior to re-start of a trial where DSMB has recommended trial suspension.
19 December 2014	The Protocol Amendment (Version 3.0) was developed to revise the starting conditioning regimen from a fludarabine-cyclophosphamide-based regimen to the lower intensity regimen of fludarabine-methylprednisolone, previously stated in the protocol. The rationale for this change is for reduction in risk and improved feasibility of clinical management of the protocol-specified population with regards to potential regimen-induced toxicities, particularly significant myelosuppression and prolonged aplasia.
24 June 2016	The Protocol Amendment (Version 4.0) was developed to expand the patient population, add WT1 transcript analysis as an exploratory endpoint, clarify the conditioning regimen and further clarifications throughout the document.
01 September 2017	The Protocol Amendment (Version 5.0) changed the Sponsor from Catapult to Cell Medica Ltd.

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: