



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 $\leq 2 \times 10^7$ /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 $\leq 2 \times 10^7$ /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 $\leq 1 \times 10^8$ /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 |
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| 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 $\leq 2 \times 10^7$ /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 $\leq 1 \times 10^8$ /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 $\leq 2 \times 10^7$ /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 $\leq 1 \times 10^8$ /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 $< 0.1 \times 10^9$ /L) of five or more days duration. - Infection (documented clinically or microbiologically) with Grade 4 neutropenia (absolute neutrophil count $< 0.1 \times 10^9$ /L). - Grade 4 thrombocytopenia for five or more days associated with active bleeding or requiring platelet transfusion. - Grade 3 or 4 non-haematological 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 occurrences (all) | 0 / 3 (0.00%) 0 | 2 / 4 (50.00%) 2 | |
| Lymphocyte count decreased subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 1 / 4 (25.00%) 1 | |
| Monocyte count decreased subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 1 / 4 (25.00%) 1 | |
| Injury, poisoning and procedural complications Infusion related reaction subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 1 / 4 (25.00%) 1 | |
| Vascular disorders Hypotension subjects affected / exposed occurrences (all) | 1 / 3 (33.33%) 1 | 0 / 4 (0.00%) 0 | |
| Hot flush subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 1 / 4 (25.00%) 1 | |
| Nervous system disorders Lethargy subjects affected / exposed occurrences (all) | 1 / 3 (33.33%) 2 | 0 / 4 (0.00%) 0 | |
| Hypersomnia subjects affected / exposed occurrences (all) | 1 / 3 (33.33%) 1 | 0 / 4 (0.00%) 0 | |
| Hypoaesthesia subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 1 / 4 (25.00%) 1 | |
| Dizziness subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 1 / 4 (25.00%) 1 | |
| Headache subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 1 / 4 (25.00%) 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: