



## Clinical trial results:

**A Phase I/II study to investigate the safety of Adenovirus specific T cells given to high-risk paediatric patients post allogeneic haematopoietic stem cell transplant (allo-HSCT) to treat reactivation of adenovirus.**

### Summary

EudraCT number	2011-001788-36
Trial protocol	GB
Global end of trial date	31 December 2016

### Results information

Result version number	v1 (current)
This version publication date	25 March 2017
First version publication date	25 March 2017

### Trial information

#### Trial identification

Sponsor protocol code	CM-2011-02
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#### Additional study identifiers

ISRCTN number	ISRCTN22322271
ClinicalTrials.gov id (NCT number)	NCT01822093
WHO universal trial number (UTN)	-

Notes:

### Sponsors

Sponsor organisation name	Cell Medica Ltd.
Sponsor organisation address	1 Canal side studios, 8-14 st Pancras way, London, United Kingdom, NW1 0QG
Public contact	Medical and Scientific Affairs, Cell Medica Ltd., 44 02075544070, medical@cellmedica.co.uk
Scientific contact	Medical and Scientific Affairs, Cell Medica Ltd., 44 02075544070, medical@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	31 December 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 December 2016
Global end of trial reached?	Yes
Global end of trial date	31 December 2016
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the safety of ADV-specific T cells.

Protection of trial subjects:

The protocol was designed and the study was conducted in accordance with guidelines for ICH GCP adopted by the European Union under Directive 2005/28/EC which requires that clinical studies are conducted in accordance with ethical Principles outlined in the declaration of Helsinki.

Appropriate consent was obtained from all patients and donors before any protocol related procedures were performed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 November 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	6 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 8
Worldwide total number of subjects	8
EEA total number of subjects	8

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)	2
Children (2-11 years)	5
Adolescents (12-17 years)	1
Adults (18-64 years)	0
From 65 to 84 years	0

85 years and over	0
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## Subject disposition

### Recruitment

Recruitment details:

Enrolment period: November 2012 - July 2016

### Pre-assignment

Screening details:

Paediatric patients that develop ADV infection post allo-HSCT.

Patients must meet all inclusion/exclusion criteria and provide consent.

### Pre-assignment period milestones

Number of subjects started	8
Number of subjects completed	8

### Period 1

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

### Arms

Arm title	Cytovir ADV
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Arm description:

Cytovir ADV Dose 1 (1x10<sup>4</sup>/Kg total CD3+ lymphocytes)

Cytovir ADV Dose 2 (Maximum target dose 1x10<sup>5</sup>/Kg total CD3+ lymphocytes)

Arm type	Experimental
Investigational medicinal product name	Cytovir ADV
Investigational medicinal product code	
Other name	ADV specific T cells
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Cytovir ADV should be administered at the earliest possible opportunity following identification of ADV infection but not before 28 days post-allo-HSCT.

A single dose of 1x10<sup>4</sup>/kg total CD3+ lymphocytes will be infused. There is the option for a secondary maximum target dose of 1x10<sup>5</sup>/kg total CD3+ lymphocytes, if the patient has significant ADV viraemia requiring antiviral therapy at  $\geq 4$  weeks after the first infusion.

Number of subjects in period 1	Cytovir ADV
Started	8
Completed	6
Not completed	2
Adverse event, non-fatal	1
Lost to follow-up	1



## Baseline characteristics

### Reporting groups

Reporting group title	Treatment
Reporting group description: -	

Reporting group values	Treatment	Total	
Number of subjects	8	8	
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)	2	2	
Children (2-11 years)	5	5	
Adolescents (12-17 years)	1	1	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
Units: years			
median	5		
full range (min-max)	1 to 13	-	
Gender categorical			
Units: Subjects			
Female	3	3	
Male	5	5	
Dosages of Cytovir ADV infused			
Units: Subjects			
Dose 1	7	7	
Dose 1 & 2	1	1	

### Subject analysis sets

Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis
Subject analysis set description:	
All patients who received at least one dose of Cytovir ADV.	
Subject analysis set title	Per Protocol Analysis Set
Subject analysis set type	Per protocol
Subject analysis set description:	
All patients in the Full Analysis set who completed study assessments up to and including Day 180 (6 months)	

<b>Reporting group values</b>	Full Analysis Set	Per Protocol Analysis Set	
Number of subjects	8	4	
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)	2	0	
Children (2-11 years)	5	3	
Adolescents (12-17 years)	1	1	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
median	5		
full range (min-max)	1 to 13		
Gender categorical Units: Subjects			
Female	3	2	
Male	5	2	
Dosages of Cytovir ADV infused Units: Subjects			
Dose 1	7	3	
Dose 1 & 2	1	1	

## End points

### End points reporting groups

Reporting group title	Cytovir ADV
Reporting group description:	
Cytovir ADV Dose 1 (1x10e4/Kg total CD3+ lymphocytes)	
Cytovir ADV Dose 2 (Maximum target dose 1x10e5/Kg total CD3+ lymphocytes)	
Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis
Subject analysis set description:	
All patients who received at least one dose of Cytovir ADV.	
Subject analysis set title	Per Protocol Analysis Set
Subject analysis set type	Per protocol
Subject analysis set description:	
All patients in the Full Analysis set who completed study assessments up to and including Day 180 (6 months)	

### Primary: Toxicity

End point title	Toxicity <sup>[1]</sup>
End point description:	
Incidence and severity of GvHD, cytopenias, Grade 3-4 adverse events	
End point type	Primary
End point timeframe:	
Up to 6 months following 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: No statistical analyses were planned or performed.

End point values	Cytovir ADV	Full Analysis Set		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	8	8		
Units: Number and Percentage				
Incidence and Severity of GvHD	5	5		
Incidence and Severity of Cytopaenias	8	8		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Requirement for second infusion

End point title	Requirement for second infusion
End point description:	
The number and percentage of patients receiving the second infusion of ADV specific T cells	
End point type	Secondary
End point timeframe:	
Up to 6 months following infusion	



<b>End point values</b>	Cytovir ADV			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: Patient number				
number (not applicable)				
received first dose	8			
received second dose	1			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of treatment days with other anti-infective drugs

End point title	Number of treatment days with other anti-infective drugs
End point description: The total number of days that each patient takes any relevant anti-infective medications during the study period	
End point type	Secondary
End point timeframe: Up to 6 months following infusion	

<b>End point values</b>	Full Analysis Set	Per Protocol Analysis Set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	8	4		
Units: Days				
arithmetic mean (full range (min-max))	170.4 (93 to 216)	196.3 (175 to 216)		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of treatment days with antiviral drugs

End point title	Number of treatment days with antiviral drugs
End point description: The total number of days that each patient takes any anti-viral medications during the study period	
End point type	Secondary
End point timeframe: Up to 6 months following infusion	

End point values	Full Analysis Set	Per Protocol Analysis Set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	8	2		
Units: Day				
arithmetic mean (full range (min-max))	50.8 (2 to 128)	65 (2 to 128)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of In-hospital Days

End point title	Number of In-hospital Days
End point description: The number of in-hospital days during the study period	
End point type	Secondary
End point timeframe: Up to 6 months following infusion	

End point values	Full Analysis Set	Full Analysis Set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	7	7		
Units: Days				
arithmetic mean (full range (min-max))	77.6 (14 to 195)	77.6 (14 to 195)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Incidence of AEs, including serious adverse events (SAEs)

End point title	Incidence of AEs, including serious adverse events (SAEs)
End point description: Treatment emergent Adverse Events	
End point type	Secondary
End point timeframe: Up to 6 months following infusion	

<b>End point values</b>	Cytovir ADV			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: Number of treatment-emergent AEs				
number (not applicable)				
Number of patients with treatment-emergent AEs	6			
Total number of treatment-emergent AEs	25			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Viral clearance

End point title	Viral clearance
End point description:	
Time to absence of ADV viraemia	
End point type	Secondary
End point timeframe:	
Up to 6 months following Cytovir ADV infusion	

<b>End point values</b>	Cytovir ADV	Full Analysis Set	Per Protocol Analysis Set	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	8	8	4	
Units: Days				
arithmetic mean (full range (min-max))	56.5 (15 to 127)	56.5 (15 to 127)	66 (16 to 127)	

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Up to 6 months following infusion of ADV Specific T cells

Adverse event reporting additional description:

Treatment-emergent adverse events.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.0
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### Reporting groups

Reporting group title	ADV specific T cells
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Reporting group description:

ADV specific T cells

Serious adverse events	ADV specific T cells		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 8 (50.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Graft versus host disease			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Pancreatitis			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Abscess			

subjects affected / exposed	1 / 8 (12.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Encephalitis viral			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	1 / 8 (12.50%)		
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 %

<b>Non-serious adverse events</b>	ADV specific T cells		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 8 (87.50%)		
Investigations			
Weight decreased			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	2		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	4 / 8 (50.00%)		
occurrences (all)	7		
Immune system disorders			
Acute graft versus host disease in skin			
subjects affected / exposed	2 / 8 (25.00%)		
occurrences (all)	2		
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Haematemesis			

subjects affected / exposed occurrences (all)  Vomiting subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 0  1 / 8 (12.50%) 1		
Respiratory, thoracic and mediastinal disorders Respiratory distress subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 0		
Skin and subcutaneous tissue disorders Urticaria subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 0		
Infections and infestations Device related infection subjects affected / exposed occurrences (all)  Epstein-Barr viraemia subjects affected / exposed occurrences (all)  Pneumonia subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 0  1 / 8 (12.50%) 1  1 / 8 (12.50%) 0		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 September 2012	Clarification required in protocol regarding how patient treatment is handled including additional clarity around eligibility criteria.
24 April 2013	<p>The study protocol was revised to allow some flexibility with the 2nd dose. The protocol was amended to state that the second dose is a maximum target of <math>1 \times 10^5</math> CD3+ T cells/ kg (minimum <math>1 \times 10^4</math>/ kg) in order that additional treatment options are always available should a patient require a second dose.</p> <p>The study protocol was also amended to allow immune reconstitution baseline assays to be avoided in certain circumstances (i.e. severely lymphopaenic patients).</p>
24 March 2014	Clarification of IDSMC stopping rules and safety reporting. Patients with GvHD $\geq$ grade II would be excluded from the study (or dosing delayed until it has resolved) and any cases of de novo GvHD $>$ grade II would be reported to the Independent Data Safety Monitoring Committee (IDSMC). The protocol was updated to clarify recording and reporting of expected safety events. The list of expected events was also updated.
27 August 2014	<p>Study endpoint revised.</p> <p>Secondary objective (evaluation of persistence and expansion of adoptively transferred ADV-specific T cells) changed to an exploratory endpoint.</p>

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported