



## Clinical trial results:

### Prophylactic infusion of CD4 positive donor lymphocytes early after T-cell depleted stem cell transplantation

#### Summary

EudraCT number	2008-001447-19
Trial protocol	NL
Global end of trial date	01 May 2020

#### Results information

Result version number	v1 (current)
This version publication date	30 November 2021
First version publication date	30 November 2021

#### Trial information

##### Trial identification

Sponsor protocol code	LUMCCD4PROTOCOL
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##### Additional study identifiers

ISRCTN number	ISRCTN51398568
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

##### Sponsors

Sponsor organisation name	Leids Universitair Medisch Centrum, department of hematology
Sponsor organisation address	Albinusdreef 2, Leiden, Netherlands, 2333ZA
Public contact	Dr. P van Balen, LUMC, department of hematology, 0031 715262267, P.van_Balen@lumc.nl
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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	10 November 2021
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	01 May 2020
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To evaluate whether CD4+ lymphocytes infusion given three months after T-cell depleted allogeneic SCT improves immunological recovery (number of circulating CD4+ lymphocytes) with an incidence of GvHD requiring systemic treatment not exceeding 30% of the patients.

Protection of trial subjects:

Patients are closely monitored in our outpatient clinic on a regular basis. A structured anamnesis was performed, as well as physical anamnesis and laboratory results. Furthermore bone marrow examination was performed (morphology, flow cytometry, bone marrow chimerism) at regular intervals ( after transplantation: 3 months, 4.5 months, 6 months, 9 months, 12 months). (local lab, physical exam and structured anamnesis).

Background therapy:

All patients after alloSCT are monitored and treated according to local guidelines with regards to immunosuppressive treatment, antibiotic treatment.

Evidence for comparator:

At the time of initiation of this study all patients were eligible for prophylactic DLI 6 months after alloSCT. To assess whether prophylactic CD4 DLI 3 months after alloSCT would be beneficial in addition to unmodified DLI at 6 months, we compared patients in the control group (treated according to standard protocol and eligible for prophylactic unmodified DLI 6 months after alloSCT) to the experimental arm with prophylactic CD4 DLI at 3 months (the experimental arm was also eligible to receive unmodified prophylactic DLI at 6 months).

Actual start date of recruitment	04 January 2008
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	Netherlands: 66
Worldwide total number of subjects	66
EEA total number of subjects	66

Notes:

### Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	56
From 65 to 84 years	10
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

All adult patients treated with 10/10 HLA matched alemtuzumab based T-cell depleted stem cell transplantation from a related donor in the Leiden University medical center are eligible for inclusion. Patients were recruited between and 4 January 2008 and 1 May 2020 in the department of hematology.

### Pre-assignment

Screening details:

Inclusion criteria: concomitant disease, WHO performance status of 0-2, Life expectancy longer than 3 months and providing informed consent.

Exclusion criteria: progressive disease, severe GVHD, systemic immunosuppressive treatment, pregnancy, positive HIV test

### Period 1

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

Blinding implementation details:

Patients were randomized to receive either CD4 DLI or no treatment at 3 months after alloSCT. All patients were eligible to receive unmodified DLI at 6 months.

Both patient and doctor were aware of randomization arm.

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	CD4+ donor lymphocytes infusion

Arm description:

Infusion of  $1 \times 10^6$  CD4+ T-cells/kg 3 months after alloSCT

Arm type	Experimental
Investigational medicinal product name	CD4 positive lymphocytes
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Infusion

Dosage and administration details:

$1 \times 10^6$  CD4+ T cells/kg infused once at 3 months after alloSCT

<b>Arm title</b>	Control
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Arm description:

No intervention 3 months. Patients are eligible to receive unmodified DLI 6 months after alloSCT according to standard LUMc protocol

Arm type	No intervention
No investigational medicinal product assigned in this arm	

<b>Number of subjects in period 1</b>	CD4+ donor lymfocyten infusion	Control
Started	33	33
Completed	29	31
Not completed	4	2
Adverse event, serious fatal	4	2

## Baseline characteristics

### Reporting groups

Reporting group title	CD4+ donor lymphocyten infusion
Reporting group description:	
Infusion of $1 \times 10^6$ CD4+ T-cells/kg 3 months after alloSCT	
Reporting group title	Control
Reporting group description:	
No intervention 3 months. Patients are eligible to receive unmodified DLI 6 months after alloSCT according to standard LUMc protocol	

Reporting group values	CD4+ donor lymphocyten infusion	Control	Total
Number of subjects	33	33	66
Age categorical			
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)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Units: years			
median	60.5	59.1	
inter-quartile range (Q1-Q3)	57.4 to 64.4	50.2 to 61.7	-
Gender categorical			
Units: Subjects			
Female	10	14	24
Male	23	19	42
Conditioning			
Conditioning regime for transplantation. Myeloablative conditioning consists of cyclophosphamide and TBI, while non-myeloablative conditioning consists of Fludarabine and Busulfan			
Units: Subjects			
Myeloablative	8	6	14
Non-myeloablative	25	27	52
HCT comorbidity score			
HCT comorbidity score before transplantation			
Units: Subjects			
0-2	28	28	56
3-7	5	5	10
Hematologic disease			
Hematologic disease for which a allogeneic stem cell transplantation was performed			
Units: Subjects			
CML	1	2	3
MPN	1	2	3

MDS/MPN overlap	3	1	4
MDS	3	0	3
AML	14	15	29
Multiple myeloma	5	6	11
Mature B-cell lymphoma	3	5	8
ALL/LBL	2	2	4
Leukemia with mixed phenotype	1	0	1
CD4+ T-cell count at randomization			
CD4+ T-cell count measured with flow cytometry at randomization. In patients who did receive CD4+ DLI, T-cell counts were measured before infusion.			
Units: cells/microlitre			
median	113	112	
inter-quartile range (Q1-Q3)	69 to 233	64 to 198	-

## End points

### End points reporting groups

Reporting group title	CD4+ donor lymphocytin infusion
Reporting group description: Infusion of $1 \times 10^6$ CD4+ T-cells/kg 3 months after alloSCT	
Reporting group title	Control
Reporting group description: No intervention 3 months. Patients are eligible to receive unmodified DLI 6 months after alloSCT according to standard LUMc protocol	

### Primary: CD4+ T-cell counts 6 months after alloSCT

End point title	CD4+ T-cell counts 6 months after alloSCT
End point description:	
End point type	Primary
End point timeframe: The primary endpoint (CD4+ T-cell counts) is measured 3 months after randomization (6 months after alloSCT).	

End point values	CD4+ donor lymphocytin infusion	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29 <sup>[1]</sup>	32		
Units: cells/microlitre				
median (inter-quartile range (Q1-Q3))	155 (102 to 211)	178 (132.5 to 223.2)		

Notes:

[1] - 4 patients did not survive until 3 months after alloSCT

### Statistical analyses

Statistical analysis title	CD4+ T-cell counts at 3 months
Statistical analysis description: Mann Whitney U test between CD4+ T-cell counts the two treatment arms at 3 months after inclusion	
Comparison groups	Control v CD4+ donor lymphocytin infusion
Number of subjects included in analysis	61
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.2917
Method	Wilcoxon (Mann-Whitney)

### Primary: severe GvHD



End point title	severe GvHD
End point description:	Cumulative incidence of GvHD requiring immunosuppressive treatment. We used a competing risk analysis with relapse, unmodified DLI and death as competing events.
End point type	Primary
End point timeframe:	3 months after randomization

<b>End point values</b>	CD4+ donor lymphocyten infusion	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	33		
Units: Cumulative incidence	9	9		

<b>Attachments (see zip file)</b>	competing events at 3 months.png GvHD.png
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## Statistical analyses

<b>Statistical analysis title</b>	Cumulative incidence
Statistical analysis description:	Comparing cumulative incidence of developing GvHD requiring immunosuppressive treatment with log-rank test.
Comparison groups	CD4+ donor lymphocyten infusion v Control
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.8
Method	Logrank

## Secondary: Overall survival

End point title	Overall survival
End point description:	Probability of overall survival after randomization in intention to treat analysis
End point type	Secondary
End point timeframe:	up to 5 years after randomization

End point values	CD4+ donor lymphocyten infusion	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	33		
Units: Overall survival	44	52		

<b>Attachments (see zip file)</b>	Overall survival.png
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### Statistical analyses

<b>Statistical analysis title</b>	Overall Survival
Statistical analysis description: Overall survival between two treatment arms	
Comparison groups	CD4+ donor lymphocyten infusion v Control
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.5
Method	Logrank

### Secondary: Relapse

<b>End point title</b>	Relapse
End point description: Relapse requiring systemic treatment during follow-up. Competing risk analysis with death as a competing event	
<b>End point type</b>	Secondary
End point timeframe: up to 5 years after randomization	

End point values	CD4+ donor lymphocyten infusion	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	33		
Units: Cumulative incidence	39	36		

<b>Attachments (see zip file)</b>	relapse.png
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### Statistical analyses

<b>Statistical analysis title</b>	Relapse
Statistical analysis description: Comparing relapse between two treatment arms	
Comparison groups	CD4+ donor lymphocyten infusion v Control
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.5
Method	Logrank

## Secondary: Any sign of GvHD

End point title	Any sign of GvHD
End point description: Cumulative incidence of any signs of GvHD. Patients did not need to receive immunosuppressive. We used a competing risk analysis with relapse, unmodified DLI and death as competing events.	
End point type	Secondary
End point timeframe: 3 months after randomization	

End point values	CD4+ donor lymphocyten infusion	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	33		
Units: Cumulative incidence	24	27		

<b>Attachments (see zip file)</b>	anyGvHD.png
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## Statistical analyses

<b>Statistical analysis title</b>	Cumulative incidence
Comparison groups	CD4+ donor lymphocyten infusion v Control
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.6
Method	Logrank

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Between randomization and 6 months after alloSCT

Assessment type	Non-systematic
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### Dictionary used

Dictionary name	CTCAE
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Dictionary version	4
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### Reporting groups

Reporting group title	CD4+ donor lymphocytin infusion
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Reporting group description:

All adverse events from randomization until 6 months after alloSCT

Serious adverse events: severe GvHD, relapse, death, infections requiring hospitalization

Reporting group title	Controle
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Reporting group description: -

Serious adverse events	CD4+ donor lymphocytin infusion	Controle	
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 33 (30.30%)	9 / 33 (27.27%)	
number of deaths (all causes)	4	1	
number of deaths resulting from adverse events	4	1	
Blood and lymphatic system disorders			
GVHD	Additional description: Graft versus host disease between randomization and 6 months.		
subjects affected / exposed	4 / 33 (12.12%)	3 / 33 (9.09%)	
occurrences causally related to treatment / all	4 / 4	3 / 3	
deaths causally related to treatment / all	1 / 1	0 / 0	
Relapse	Additional description: Relapse between 3 and 6 months. Fatality numbers reported until 6 months after alloSCT		
subjects affected / exposed	5 / 33 (15.15%)	6 / 33 (18.18%)	
occurrences causally related to treatment / all	5 / 5	6 / 6	
deaths causally related to treatment / all	2 / 2	1 / 1	
Immune system disorders			
Autoimmunity	Additional description: Autoimmunity between randomization and 6 months after alloSCT requiring IST		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			

Infection	Additional description: Any infection requiring hospitalization between randomization and 6 months after alloSCT		
subjects affected / exposed	2 / 33 (6.06%)	4 / 33 (12.12%)	
occurrences causally related to treatment / all	2 / 2	4 / 4	
deaths causally related to treatment / all	1 / 1	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	CD4+ donor lymphocytin infusion	Controle	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 33 (18.18%)	2 / 33 (6.06%)	
Blood and lymphatic system disorders			
GvHD without IST	Additional description: Patients that did develop signs of GvHD, but did not need systemic immunosuppressive treatment for it.		
subjects affected / exposed	5 / 33 (15.15%)	1 / 33 (3.03%)	
occurrences (all)	5	1	
Immune system disorders			
autoimmunity without immune suppression	Additional description: Any sign of autoimmunity, not requiring immunosuppressive treatment		
subjects affected / exposed	1 / 33 (3.03%)	1 / 33 (3.03%)	
occurrences (all)	1	1	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### 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.

Since all patients were eligible to receive unmodified DLI at 6 months, the reported outcomes and all AE/SAE are reported until 6 months; afterwards the adverse events are probably related to the unmodified DLI. These results are not reported here.
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Notes: