



## Clinical trial results:

### In vivo expansion and efficacy of adoptive natural killer cell-based immunotherapy for high-risk myeloid diseases

#### Summary

EudraCT number	2011-003181-32
Trial protocol	SE
Global end of trial date	30 June 2015

#### Results information

Result version number	v1 (current)
This version publication date	13 December 2021
First version publication date	13 December 2021
Summary attachment (see zip file)	journal article (Bjorklund et al ClinCanRes 2018.pdf)

#### Trial information

##### Trial identification

Sponsor protocol code	CIMNK1001
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##### Additional study identifiers

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

Notes:

#### Sponsors

Sponsor organisation name	Karolinska Univeristy Hospital
Sponsor organisation address	Hälsövägen 13, Huddinge, Sweden, 14157
Public contact	Andreas Björklund, Center for Hematology, Karolinska University Hospital, +46 (0)78112312, andreas.bjorklund@ki.se
Scientific contact	Andreas Björklund, Center for Hematology, Karolinska University Hospital, +46 (0)78112312, andreas.bjorklund@ki.se

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:

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**Results analysis stage**

Analysis stage	Final
Date of interim/final analysis	30 June 2017
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	30 June 2015
Was the trial ended prematurely?	No

Notes:

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**General information about the trial**

Main objective of the trial:

To determine the safety and in vivo expansion of allogeneic NK cells following titrated intermediate intensity conditioning regimens.

Protection of trial subjects:

Treatment was performed at a single trial site, a university hospital hematology in-patient ward, and thereafter carefully followed at a single outpatient ward to track, monitor and treat all types of complications.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 June 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

Country: Number of subjects enrolled	Sweden: 18
Worldwide total number of subjects	18
EEA total number of subjects	18

Notes:

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**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)	10
From 65 to 84 years	8
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Patients with chemotherapy refractory AML or MDS and not eligible for allogeneic stem cell transplantation were recruited at the Hematology clinic at Karolinska University Hospital between June 2012 and Feb 2015.

### Pre-assignment

Screening details:

20 patients were screened whereof 2 failed inclusion due to rapid deterioration of the original disease.

### Pre-assignment period milestones

Number of subjects started	18
Number of subjects completed	18

### Period 1

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

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Primary

Arm description: -

Arm type	main study arm
Investigational medicinal product name	NK cells
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

All available cells from one leucapheresis product

<b>Arm title</b>	Re-treatment
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Arm description: -

Arm type	Retreatment
No investigational medicinal product assigned in this arm	

Number of subjects in period 1	Primary	Re-treatment
Started	16	2
Completed	16	2



## Baseline characteristics

### Reporting groups

Reporting group title	Primary
Reporting group description: -	
Reporting group title	Re-treatment
Reporting group description: -	

Reporting group values	Primary	Re-treatment	Total
Number of subjects	16	2	18
Age categorical Units: Subjects			
Adults (18-64 years)	9	1	10
From 65-84 years	7	1	8
Age continuous Units: years			
median	63	54	
standard deviation	± 11	± 18	-
Gender categorical Units: Subjects			
Female	6	0	6
Male	10	2	12
Disease type Units: Subjects			
Primary AML	3	1	4
MDS-AML	8	0	8
MDS	5	1	6

## End points

### End points reporting groups

Reporting group title	Primary
Reporting group description: -	
Reporting group title	Re-treatment
Reporting group description: -	

### Primary: Safety

End point title	Safety <sup>[1]</sup>
End point description: Stopping Rules for excessive toxicity: > 20% grade 4 non-hematologic and non-infectious toxicity using the NCI toxicity tables (except for fevers alone), severe persistent neutropenia (more than 35 days and not due to hematological disease) or grade III/IV GvHD enrollment to the trial will be suspended and the study re-evaluated.	
End point type	Primary
End point timeframe: 0-3 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: This was a pilot study to assess feasibility and safety, therefore no pre-defined statistical analysis was included in the protocol.

End point values	Primary	Re-treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	2		
Units: Adverse Events				
Grade 4-5 non-hematologic, non-infectious toxicity	2	0		
Neutropenia day 35 & absent hematological disease	0	0		
Grade III/IV acute GVHD	0	0		

### Statistical analyses

No statistical analyses for this end point

### Primary: In Vivo Expansion

End point title	In Vivo Expansion <sup>[2]</sup>
End point description:	
End point type	Primary
End point timeframe: Within 14 days	

Notes:

[2] - 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: This was a pilot study to assess feasibility and safety, therefore no pre-defined statistical analysis was included in the protocol.

End point values	Primary	Re-treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	2		
Units: >100 NK cells/ul	0	0		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Response Evaluation

End point title	Response Evaluation
End point description:	
End point type	Secondary
End point timeframe:	
Within 12 weeks	

End point values	Primary	Re-treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	2		
Units: Subjects				
Objective response <12 w	6	0		
CR <12w	4	0		
PR <12w	1	0		
SD <12w	1	0		

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Within 12 weeks

Adverse event reporting additional description:

NCI CTCAE grade 1-2

Assessment type	Systematic
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### Dictionary used

Dictionary name	NCI CTCAE
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Dictionary version	4.03
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### Reporting groups

Reporting group title	Overall trial
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Reporting group description: -

Serious adverse events	Overall trial		
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 18 (72.22%)		
number of deaths (all causes)	2		
number of deaths resulting from adverse events	2		
Investigations			
ALT increased	Additional description: NCI CTCAE grade 3-4		
subjects affected / exposed	1 / 18 (5.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
AST increased	Additional description: NCI CTCAE grade 3-4		
subjects affected / exposed	1 / 18 (5.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypoxia	Additional description: NCI CTCAE grade 3		
subjects affected / exposed	1 / 18 (5.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Chills	Additional description: NCI CTCAE grade 3-4		



subjects affected / exposed	1 / 18 (5.56%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Cytokine release syndrome (inkl. HLH)	Additional description: NCI CTCAE grade 4-5		
subjects affected / exposed	2 / 18 (11.11%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	1 / 1		
Gastrointestinal disorders			
Nausea	Additional description: NCI CTCAE grade 3-4		
subjects affected / exposed	2 / 18 (11.11%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Rash maculo-papular	Additional description: NCI CTCAE grade 3-4		
subjects affected / exposed	1 / 18 (5.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Febrile neutropenia	Additional description: NCI CTCAE grade 3-4		
subjects affected / exposed	6 / 18 (33.33%)		
occurrences causally related to treatment / all	0 / 7		
deaths causally related to treatment / all	0 / 0		
Lung Infection	Additional description: NCI CTCAE grade 3-4		
subjects affected / exposed	4 / 18 (22.22%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Catheter-related Infection	Additional description: NCI CTCAE grade 3-4		
subjects affected / exposed	4 / 18 (22.22%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Sepsis	Additional description: NCI CTCAE grade 4		

subjects affected / exposed	3 / 18 (16.67%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Peripheral nerve infection	Additional description: NCI CTCAE grade 3-4		
subjects affected / exposed	1 / 18 (5.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Encephalitis Infection	Additional description: NCI CTCAE grade 5		
subjects affected / exposed	1 / 18 (5.56%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		

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

Non-serious adverse events	Overall trial		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 18 (100.00%)		
Investigations			
Fever	Additional description: NCI CTCAE grade 1-2		
subjects affected / exposed	6 / 18 (33.33%)		
occurrences (all)	6		
ALT increased	Additional description: NCI CTCAE grade 1-2		
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
AST increased	Additional description: NCI CTCAE grade 1-2		
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Hypokalemia	Additional description: NCI CTCAE grade 1-2		
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Hypomagnesemia	Additional description: NCI CTCAE grade 1-2		
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
INR increased	Additional description: NCI CTCAE grade 1-2		

subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Creatinine increased	Additional description: NCI CTCAE grade 1-2		
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Cardiac disorders			
Sinus tachycardia	Additional description: NCI CTCAE grade 1-2		
subjects affected / exposed	2 / 18 (11.11%)		
occurrences (all)	2		
Nervous system disorders			
Insomnia	Additional description: NCI CTCAE grade 1-2		
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Headache	Additional description: NCI CTCAE grade 1-2		
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Oral hemorrhage	Additional description: NCI CTCAE grade 1-2		
subjects affected / exposed	4 / 18 (22.22%)		
occurrences (all)	4		
Purpura	Additional description: NCI CTCAE grade 1-2		
subjects affected / exposed	4 / 18 (22.22%)		
occurrences (all)	4		
Hemolysis	Additional description: NCI CTCAE grade 1-2		
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Eye disorders			
Vitreous Hemorrhage	Additional description: NCI CTCAE grade 1-2		
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Gastrointestinal disorders			
Nausea	Additional description: NCI CTCAE grade 1-2		
subjects affected / exposed	8 / 18 (44.44%)		
occurrences (all)	8		
Vomiting	Additional description: NCI CTCAE grade 1-2		
subjects affected / exposed	4 / 18 (22.22%)		
occurrences (all)	4		

Diarrhea subjects affected / exposed occurrences (all)	Additional description: NCI CTCAE grade 1-2		
	3 / 18 (16.67%)		
	3		
Oral pain subjects affected / exposed occurrences (all)	Additional description: NCI CTCAE grade 1-2		
	1 / 18 (5.56%)		
	1		
Abdominal pain subjects affected / exposed occurrences (all)	Additional description: NCI CTCAE grade 1-2		
	1 / 18 (5.56%)		
	1		
Skin and subcutaneous tissue disorders Rash maculo-papular subjects affected / exposed occurrences (all)	Additional description: NCI CTCAE grade 1-2		
	5 / 18 (27.78%)		
	5		
Node in breast subjects affected / exposed occurrences (all)	Additional description: NCI CTCAE grade 1-2		
	1 / 18 (5.56%)		
	1		
Urticaria subjects affected / exposed occurrences (all)	Additional description: NCI CTCAE grade 1-2		
	1 / 18 (5.56%)		
	1		
Oedema limb subjects affected / exposed occurrences (all)	Additional description: NCI CTCAE grade 1-2		
	1 / 18 (5.56%)		
	1		
Psychiatric disorders Fatigue subjects affected / exposed occurrences (all)	Additional description: NCI CTCAE grade 1-2		
	1 / 18 (5.56%)		
	1		
Musculoskeletal and connective tissue disorders Bone pain subjects affected / exposed occurrences (all)	Additional description: NCI CTCAE grade 1-2		
	2 / 18 (11.11%)		
	2		
Pain in extremity subjects affected / exposed occurrences (all)	Additional description: NCI CTCAE grade 1-2		
	2 / 18 (11.11%)		
	2		
Non-cardiac chest pain subjects affected / exposed occurrences (all)	Additional description: NCI CTCAE grade 1-2		
	1 / 18 (5.56%)		
	1		

Infections and infestations			
Lung Infection	Additional description: NCI CTCAE grade 1-2		
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Peripheral nerve infection	Additional description: NCI CTCAE grade 1-2		
subjects affected / exposed	2 / 18 (11.11%)		
occurrences (all)	2		
Soft tissue infection	Additional description: NCI CTCAE grade 1-2		
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Skin infection	Additional description: NCI CTCAE grade 1-2		
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Urinary tract infection	Additional description: NCI CTCAE grade 1-2		
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Anorectal infection	Additional description: NCI CTCAE grade 1-2		
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	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? Yes

Date	Interruption	Restart date
26 February 2013	Inclusion halted due to SUSAR-evaluation after a heavily pretreated patient died. 10 days after NK infusion the patient caught Influenza-A, H1N1, that were followed by a secondary HLH, thereafter the patients condition deteriorated and he was diagnosed with a HHV-6 encephalitis. A bone marrow examination also confirmed an active leukemia at the time of death. The patient did not have an NK cell expansion. Since HHV-6 is uncommon outside allogeneic stem cell transplantation this complication had a possible relation to the study treatment, but not directly coupled to the infused NK cell product.	01 March 2013

Notes:

### Limitations and caveats

None reported

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/29444931>