



## Clinical trial results:

### Pre-Clinical Phase 0 Microdose Study to evaluate the effect of Melphalan, Bortezomib and Dexamethasone on cellular gene-expression.

#### Summary

EudraCT number	2011-003791-37
Trial protocol	DK
Global end of trial date	31 December 2015

#### Results information

Result version number	v1 (current)
This version publication date	14 October 2017
First version publication date	14 October 2017
Summary attachment (see zip file)	Phase 0 study on microdose melphalan in multiple myeloma (EudraCT 2011-003791-37 - phase 0 study in multiple myeloma.pdf)

#### Trial information

##### Trial identification

Sponsor protocol code	KFE2011.06
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##### Additional study identifiers

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

Notes:

#### Sponsors

Sponsor organisation name	Aalborg University Hospital
Sponsor organisation address	Mølleparkvej 4, Aalborg, Denmark, 9000
Public contact	Clinical Research Unit, Henrik Gregersen, Department of Haematology, Aalborg University Hospital, 45 99326320, lit@rn.dk
Scientific contact	Clinical Research Unit, Henrik Gregersen, Department of Haematology, Aalborg University Hospital, 45 99326320, lit@rn.dk

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**

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Analysis stage	Final
Date of interim/final analysis	09 September 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 December 2015
Global end of trial reached?	Yes
Global end of trial date	31 December 2015
Was the trial ended prematurely?	No

Notes:

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**General information about the trial**

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Main objective of the trial:

To identify the specific genes that is up- or downregulated in patients who receive a microdose of either Melphalan (Alkeran)

Protection of trial subjects:

Use of antiemetic

Background therapy:

Four series of VCD

Evidence for comparator:

No

Actual start date of recruitment	01 October 2013
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	Denmark: 6
Worldwide total number of subjects	6
EEA total number of subjects	6

Notes:

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**Subjects enrolled per age group**

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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)	2
From 65 to 84 years	4
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Six patients with newly diagnosed multiple myeloma were included in the study

### Pre-assignment

Screening details:

Treatment demanding multiple myeloma according to the IMWW criteria in patients eligible for high-dose melphalan

### Period 1

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

### Arms

<b>Arm title</b>	Microdose melphalan
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Arm description:

All patient received micro-dose melphalan

Arm type	Experimental
Investigational medicinal product name	melphalan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous bolus use

Dosage and administration details:

2 mg/sqm

<b>Number of subjects in period 1</b>	Microdose melphalan
Started	6
Completed	6

## Baseline characteristics

### Reporting groups

Reporting group title

Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	6	6	
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)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	2	2	
From 65-84 years	4	4	
85 years and over	0	0	
Gender categorical			
Units: Subjects			
Female	2	2	
Male	4	4	

## End points

### End points reporting groups

Reporting group title	Microdose melphalan
Reporting group description: All patient received micro-dose melphalan	
Subject analysis set title	study is to identify specific genes
Subject analysis set type	Full analysis
Subject analysis set description: study is to identify specific genes	

**Primary: was to identify specific genes that might be up- or downregulated in the mononuclear cells (MNC) in the peripheral blood in multiple myeloma patients who receive a microdose of melphalan.**

End point title	was to identify specific genes that might be up- or downregulated in the mononuclear cells (MNC) in the peripheral blood in multiple myeloma patients who receive a microdose of melphalan. <sup>[1]</sup>
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End point description:

Results: No genes showed significant changes during the microdosis time period, when analyzed using multiple test correction. However, the genes showing most significance using un-adjusted p-values showed a small but systematic changes in a three dimensional PCA plot illustrating that the total composition of MNCs experience changes in immediate response to melphalan and that the effect is gradually lost after 120 minutes post microdose injection. However, one should be cautious interpreting these results, due to the pre-selection of significant genes. There were no clear patterns using SOMs. Finally, an analysis restricted to REGS genes and genes commonly associated with sleep patterns were conducted<sup>2</sup>. None of these showed significant changes over time and did not cluster the data patient or time wise.

End point type	Primary
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End point timeframe:

Two hours after infusion of microdose melphalan

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: . Detection of the genes with significant change over time was conducted by linear models, where significance was determined on the basis of un-adjusted p-values and p-values adjusted for multiple testing. The analysis on the significant genes included unsupervised clustering and it was assessed whether clustering based on time or patient occurred. Detection of patterns across time by inspecting the PCA trajectories over time of all the significant genes, in both 2 and 3-dimensions were conduct

End point values	Microdose melphalan			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: Genes	6			

Attachments (see zip file)	abstract/phase0_report_1.docx
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### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information<sup>[1]</sup>

Timeframe for reporting adverse events:

No adverse events reported

Assessment type	Systematic
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### Dictionary used

Dictionary name	SNOMED CT
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Dictionary version	Sep 2015
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### Reporting groups

Reporting group title	Any adverse event
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Reporting group description:

Any adverse event

Serious adverse events	Any adverse event		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 6 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	Any adverse event		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 6 (0.00%)		

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: No adverse or serious adverse events were observed in any patient in the study

## **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**

None reported