



## Clinical trial results:

### Stamcellebehandling af patienter med kronisk kranspulsåresygdom

### MesenchYmal STROMAL CELL therapy in patients with chronic myocardial ischemia (MyStromalCell Trial)

#### Summary

EudraCT number	2009-017752-28
Trial protocol	DK
Global end of trial date	23 June 2017

#### Results information

Result version number	v1 (current)
This version publication date	29 July 2019
First version publication date	29 July 2019
Summary attachment (see zip file)	Article (SCI2017-5237063.pdf)

#### Trial information

##### Trial identification

Sponsor protocol code	MSCII
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01449032
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	Rigshospitalet
Sponsor organisation address	Blegdamsvej 9, Copenhagen, Denmark, 2100
Public contact	Jens Kastrup, Department of Cardiology, Rigshospitalet, Blegdamsvej 9, 2100 Copenhagen Ø, Denmark, jens.kastrup@regionh.dk
Scientific contact	Jens Kastrup, Department of Cardiology, Rigshospitalet, Blegdamsvej 9, 2100 Copenhagen Ø, Denmark, jens.kastrup@regionh.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:

## Results analysis stage

Analysis stage	Final
Date of interim/final analysis	23 June 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 June 2017
Global end of trial reached?	Yes
Global end of trial date	23 June 2017
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To improve myocardial perfusion and exercise capacity in patients with chronic ischemic heart disease

Protection of trial subjects:

The patients were protected according to the Declaration of Helsinki and the protocol was approved by the Danish National Ethical Committee (02-268856) and Danish Medicines Agency (2612-2867). The Good Clinical Practice Unit of the Capital Region monitored the study. All patients provided written informed consent prior entering the study.

Background therapy:

There were no test or products used in the groups beside intramyocardial injections of autologous adipose derived stromal cells stimulated with VEGF\_A165 in the active arm and intramyocardial injections of saline in the placebo group.

Liposuction was performed in all patients.

Evidence for comparator:

Adipose derived stromal cells (ASCs) are reported to be more angiogenic than mesenchymal stromal cells, which potentially favors myocardial perfusion and regeneration in patients with chronic ischemic heart disease (CIHD).

Preclinical studies have previously demonstrated the benefit of intramyocardial injection of ASCs. In mice with CIHD, ASC improved left ventricle ejection fraction (LVEF) assessed by echocardiography and 18F-FDG microPET imaging. Moreover, intramyocardially injected ASCs have demonstrated increased LVEF, wall thickness, and reduction of infarct size in rats.

A small study using an intramyocardial injection of freshly harvested adipose-derived stromal vascular fraction (SVF) cells in patients with refractory angina showed that exercise capacity in the active group remained stable during the follow-up period while there was a decrease in the placebo group. Another small study delivering freshly harvested adipose-derived SVF cells intracoronary in patients with ST-elevation myocardial infarction showed a trend towards improved LVEF. Another trial used intramyocardial injection of adipose-derived SVF cells in patients with ischemic heart failure and showed that maximum oxygen consumption on exercise treadmill testing was increased in the therapy group but not significantly different from the placebo group.

SVF consists of only 2 % ASCs. So, this study was established to investigate the effect of culture expanded ASCs in patients with CIHD.

Actual start date of recruitment	01 April 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Denmark: 61
Worldwide total number of subjects	61
EEA total number of subjects	61

Notes:

<b>Subjects enrolled per age group</b>	
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)	27
From 65 to 84 years	34
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

This trial was initiated in 2010 and the enrolment was completed in 2014. The patients were included from Denmark.

### Pre-assignment

Screening details:

In total 110 patient signed the informed consent. However, 37 patients did not meet the inclusion criteria, 10 withdrew their consent, 1 dead before randomization and 1 had limited amount of abdominal adipose tissue.

### Pre-assignment period milestones

Number of subjects started	61
Number of subjects completed	61

### Period 1

Period 1 title	Baseline period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

The patients were randomized 2:1 to ASC or placebo, in blocks of six with a computer-generated list by an unrelated study person.

### Arms

Are arms mutually exclusive?	Yes
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<b>Arm title</b>	Placebo
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Arm description:

Intramyocardial injections of saline

Arm type	Placebo
Investigational medicinal product name	Saline
Investigational medicinal product code	NA
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intracardiac use

Dosage and administration details:

Intramyocardial injections of 3 cc saline

<b>Arm title</b>	Active arm
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Arm description:

Intramyocardial injections of autologous adipose derived stromal cells

Arm type	Active comparator
Investigational medicinal product name	Adipose derived stromal cells
Investigational medicinal product code	NA
Other name	ASCs
Pharmaceutical forms	Solution for injection
Routes of administration	Intracardiac use

Dosage and administration details:

The number of adipose derived stromal cells reached after culture expansion were delivered intramyocardially in 10-15 injections of 2mL .

<b>Number of subjects in period 1</b>	Placebo	Active arm
Started	20	41
Completed	19	37
Not completed	1	4
Consent withdrawn by subject	-	1
Myocardial infarction during follow-up	-	1
Myocardial infarction during follow-up period	1	-
Adverse event, non-fatal	-	1
Dead	-	1

## Baseline characteristics

### Reporting groups

Reporting group title	Placebo
Reporting group description: Intramyocardial injections of saline	
Reporting group title	Active arm
Reporting group description: Intramyocardial injections of autologous adipose derived stromal cells	

Reporting group values	Placebo	Active arm	Total
Number of subjects	20	41	61
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			
63.5 ±8.7 years in the placebo arm 65.5 ±9.7 years in the active arm			
Units: years			
median	63.5	65.5	
standard deviation	± 8.7	± 9.7	-
Gender categorical			
Male gender placebo:20 (100); active Group: 35 (87.5)			
Units: Subjects			
Female	0	6	6
Male	20	35	55
Left ventricular ejection fraction (LVEF)			
LVEF in the placebo Group: 54±8 and in the active Group: 52±8			
Units: procent			
median	54	52	
standard deviation	± 8	± 8	-
Bicycle exercise time			
Theplacebo Group: 437 ±53s and the active group: 383 ±30s			
Units: second			
median	437	383	
standard deviation	± 53	± 30	-

## End points

### End points reporting groups

Reporting group title	Placebo
Reporting group description: Intramyocardial injections of saline	
Reporting group title	Active arm
Reporting group description: Intramyocardial injections of autologous adipose derived stromal cells	

### Primary: Bicycle exercise time

End point title	Bicycle exercise time
End point description: The mean duration of bicycle exercise test at baseline was 437 ±53s and 383 ±30s for the placebo and active groups, respectively. At 6 months follow-up, the exercise test duration of time increased to 446 ± 64s and 407 ±36s in placebo group and active group, respectively. The primary endpoint, changes in exercise test from baseline to follow-up, was increased in the placebo group by 9s (95% CI -203 to 221s) and in the active Group by 22s (95% CI -164 to 208s). However, there was no statistical significant difference between the two groups. The increase in time duration, from baseline to follow-up, was only significant in the ASC group.	
End point type	Primary
End point timeframe: 6 months follow-up after intramyocardial injections of either saline or adipose derived stromal cells	

End point values	Placebo	Active arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20 <sup>[1]</sup>	40 <sup>[2]</sup>		
Units: seconds	19	37		

Notes:

[1] - 19 were available for the primary endpoint

[2] - 37 were available at the time of primary endpoint

### Statistical analyses

Statistical analysis title	repeated measures analysis
Statistical analysis description: Repeated measure with autoregressive covariance structure is used for follow-up data due to more than two time-points.	
Comparison groups	Active arm v Placebo
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority <sup>[3]</sup>
P-value	< 0.05 <sup>[4]</sup>
Method	Reapeated measures analysis
Parameter estimate	Mean difference (net)
Point estimate	60

Confidence interval	
level	90 %
sides	2-sided
lower limit	25
upper limit	95
Variability estimate	Standard deviation
Dispersion value	35

Notes:

[3] - The primary end point is exercise tolerance testing 6 months after the treatment. With an estimated enrollment of 60 patients, the statistic power was estimated to be more than 90% for the detection of an improvement in exercise tolerance testing of 60 s in the active group compared with the placebo group, with an expected standard deviation of 35 s and a 5%  $\alpha$ -value.

[4] -  $P < 0.05$  was considered of significance



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From baseline to 6 months follow-up

Adverse event reporting additional description:

Adverse events were obtained through patient files and at the follow-up consultations

Assessment type	Systematic
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### Dictionary used

Dictionary name	GCP unit
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Dictionary version	1
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### Reporting groups

Reporting group title	Placebo
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Reporting group description:

The group recieved saline injections

Subjects in the active group, affected by serious and non-serious adverse events were 4 and 4, respectively.

Reporting group title	Active group
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Reporting group description:

The group recieved adipose derived stromal cells

Subjects in the active group, affected by serious and non-serious adverse events were 9 and 4, respectively.

Serious adverse events	Placebo	Active group	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 20 (20.00%)	9 / 40 (22.50%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
hematoma	Additional description: Hematoma at insertion site for NOGA procedure		
subjects affected / exposed	1 / 20 (5.00%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Myocardial infarction	Additional description: Myocardial infarction observed in the follow-up period		
subjects affected / exposed	1 / 20 (5.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope	Additional description: Due to side effects of medicin		

subjects affected / exposed	1 / 20 (5.00%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris	Additional description: Angina worsening		
subjects affected / exposed	3 / 20 (15.00%)	6 / 40 (15.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion	Additional description: Procedure related pericardial effusion		
subjects affected / exposed	0 / 20 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ECG changes	Additional description: After saline and stem cell therapy probably related to the procedure		
subjects affected / exposed	2 / 20 (10.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	0 / 20 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	1 / 20 (5.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Discomfort	Additional description: General discomfort		
subjects affected / exposed	0 / 20 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pneumonia			

subjects affected / exposed	1 / 20 (5.00%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash	Additional description: Rash and fever - Allergic reaction		
subjects affected / exposed	0 / 20 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	Active group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 20 (0.00%)	3 / 40 (7.50%)	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea	Additional description: A short period with feeling of breathlessness		
subjects affected / exposed	0 / 20 (0.00%)	1 / 40 (2.50%)	
occurrences (all)	0	1	
Pneumonia			
subjects affected / exposed	0 / 20 (0.00%)	1 / 40 (2.50%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Oedema peripheral	Additional description: one-sided leg/knee oedema		
subjects affected / exposed	0 / 20 (0.00%)	1 / 40 (2.50%)	
occurrences (all)	0	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.

Limitations of the study are that at the baseline; the exercise time duration is seemingly better in the placebo group compared to the ASC group and the changes seem like they are increasing constantly.
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Notes:

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/29333165>