Clinical trial results:
INTRAMYOCARDIAL TRANSPLANTATION OF BONE MARROW STEM CELLS FOR IMPROVEMENT OF POST-INFARCT MYOCARDIAL REGENERATION IN ADDITION TO CABG SURGERY: a controlled prospective, randomized, double blinded multicenter trial

Summary

EudraCT number	2006-006404-11
Trial protocol	DE
Global end of trial date	04 September 2017

Results information

Result version number	v1 (current)
This version publication date	26 August 2018
First version publication date	26 August 2018

Trial information

Trial identification

Sponsor protocol code	PERFECT001(M-2006-144)

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00950274
WHO universal trial number (UTN)	-
Other trial identifiers	German Clinical Trials Register: DRKS00000213

Notes:

Sponsors

Sponsor organisation name	Miltenyi Biotec GmbH
Sponsor organisation address	Friedrich-Ebert-Straße 68, Bergisch Gladbach, Germany, 51429
Public contact	Clinical Trials Information, Miltenyi Biotec GmbH, petrah@miltenyibiotec.de
Scientific contact	Clinical Trials Information, Miltenyi Biotec GmbH, petrah@miltenyibiotec.de

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	04 September 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	04 September 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Determine whether injection of autologously derived bone marrow stem cells yielded a functional benefit in addition to the coronary artery bypass graft (CABG) operation as determined by left ventricular heart function (left ventricular ejection fraction [LVEF] determined with magnetic resonance imaging [MRI]).

Protection of trial subjects:

1. Recording of AEs
2. Assessment of Major adverse cardiovascular events (cardiac death, myocardial infarction, secondary intervention/reoperation, ventricular arrhythmia) and tachycardial supraventricular arrhythmia >160 bpm (Holter ECG).
3. Laboratory tests (post-operative check and specific tests for cell preparation)
4. Unwanted tissue changes (tumors) will be monitored by MRI and/or echocardiography
5. Vital signs (blood pressure and pulse)
6. Physical examination, 12-lead ECG

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 October 2009
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	2 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 82
Worldwide total number of subjects	82
EEA total number of subjects	82

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)	0

Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	46
From 65 to 84 years	36
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details: -

Pre-assignment period milestones

Number of subjects started	119[1]
Number of subjects completed	82

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Consent withdrawn by subject: 1
Reason: Number of subjects	Adverse event, serious fatal: 1
Reason: Number of subjects	not eligible for enrolment: 35

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 119 patients were screened but only 82 patients were randomized to active treatment or placebo.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	placebo group

Arm description:

saline and serum injected intramyocardially during CABG surgery

Arm type	Placebo
Investigational medicinal product name	placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Intracardiac use

Dosage and administration details:

The placebo consisted in 5 mL of physiological saline and 10% of autologous serum. The placebo was injected intramyocardially (divided in 15 injections or more) during coronary artery bypass graft (CABG) surgery.

Arm title	CD133+ treatment group

Arm description:

CD133+ cells injected intramyocardially during CABG surgery

Arm type	Experimental

Investigational medicinal product name	CD133+ autologous bone marrow stem cells
Investigational medicinal product code	
Other name	CD133+ enriched bone marrow stem cells
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Intracardiac use

Dosage and administration details:

The CD133+ cell preparation consisted in 5 mL of CD133+ cells (500,000-5,000,000 cells) suspended in physiological saline and 10% of autologous serum. The product (CD133+ cells) was injected intramyocardially (divided in 15 injections or more) during coronary artery bypass graft (CABG) surgery.

Number of subjects in period 1	placebo group	CD133+ treatment group
Started	40	42
Completed	36	32
Not completed	4	10
Consent withdrawn by subject	-	2
Adverse event, non-fatal	-	5
Body size does not alow MRI anymore	1	-
Pacemaker implantation	1	-
Cell preparation not eligible for treatment	-	3
Protocol deviation	2	-

Baseline characteristics

Reporting groups	
Reporting group title	placebo group
Reporting group description:	
saline and serum injected intramyocardially during CABG surgery	
Reporting group title	CD133+ treatment group
Reporting group description:	
CD133+ cells injected intramyocardially during CABG surgery	

Reporting group values	placebo group	CD133+ treatment group	Total
Number of subjects	40	42	82
Age categorical			
18 years ≤ Age < 80 years			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Adults/Seniors (18-85 years)	0	0	0
18 years ≤ Age < 80 years	40	42	82
Age continuous			
Units: years			
arithmetic mean	62.9	63	
standard deviation	± 8.49	± 8.72	-
Gender categorical			
Units: Subjects			
Female	6	5	11
Male	34	37	71

Subject analysis sets	
Subject analysis set title	Full Analysis Set (FAS/ITT)
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
A full analysis set (FAS) following the principle of intent-to-treat (ITT) had to include every patient randomized and compare the patients per group to which they were randomly allocated, regardless of patients' compliance, or withdrawal from the study. Confirmatory analyses on primary efficacy end-point was to be performed on the FAS patients. This ITT analysis was to be considered as the primary one.	
Subject analysis set title	Safety Analysis Set (SAS)
Subject analysis set type	Safety analysis
Subject analysis set description:	
The safety population had to comprise all patients randomized into the study and treated. Safety	

evaluations were to be performed on the safety population (SAS). All comparisons were to be executed per the group, to which the patients were randomized.

Subject analysis set title	Per Protocol Set (PPS)
Subject analysis set type	Per protocol

Subject analysis set description:

The per protocol set (PPS) was defined as a subset of the FAS/ITT patients who were compliant with the study protocol. The PPS sample had to consist of all patients from the FAS/ITT group without any major protocol violation. A secondary efficacy analysis of the primary endpoint had to be performed based upon the PPS, to assess the sensitivity of the analysis to the choice of analysis population.

Subject analysis set title	Safety Analysis Set II (SASII)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

In case treatment application violations were regarded as major violations during the blinded review meeting, and it was decided to analyse safety issues separately, two additional safety analysis sets SASII and SASIII which were not foreseen in the protocol were to be created. SASII had to consist of all patients who were treated correctly with 15 injections.

Subject analysis set title	Safety Analysis Set III (SASIII)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

In case treatment application violations were regarded as major violations during the blinded review meeting, and it was decided to analyse safety issues separately, two additional safety analysis sets SASII and SASIII which were not foreseen in the protocol were to be created. SASIII had to consist of all patients who were treated with more than 15 injections.

Subject analysis set title	Insufficient CD 133+ Analysis Set (I-cd133+-AS)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients who received the cellular product or Placebo but were excluded from per protocol analysis set post-hoc because of cell count insufficiency were to be evaluated separately. This "Insufficient CD133+ Analysis Set"-Population (silent drop-outs) had to include every patient with a randomization number and a CD133+ cell count from 0.5x106> CD133+ cell count ≥ 0.1x106. All comparisons in the I-CD133+- AS Population were to be executed per the group, to which the patients were randomized.

Reporting group values	Full Analysis Set (FAS/ITT)	Safety Analysis Set (SAS)	Per Protocol Set (PPS)
Number of subjects	82	77	58
Age categorical			
18 years ≤ Age < 80 years			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Adults/Seniors (18-85 years)			
18 years ≤ Age < 80 years	82	77	58
Age continuous			
Units: years			
arithmetic mean			
standard deviation	±	±	±

Gender categorical Units: Subjects			
Female Male			

Reporting group values	Safety Analysis Set II (SASII)	Safety Analysis Set III (SASIII)	Insufficient CD 133+ Analysis Set (I-cd133+-AS)
Number of subjects	42	35	3
Age categorical			
18 years ≤ Age < 80 years			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Adults/Seniors (18-85 years)			
18 years ≤ Age < 80 years	42	35	3
Age continuous Units: years			
arithmetic mean standard deviation	±	±	±
Gender categorical Units: Subjects			
Female Male			

End points

End points reporting groups

Reporting group title	placebo group
Reporting group description:	
saline and serum injected intramyocardially during CABG surgery	
Reporting group title	CD133+ treatment group
Reporting group description:	
CD133+ cells injected intramyocardially during CABG surgery	
Subject analysis set title	Full Analysis Set (FAS/ITT)
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
A full analysis set (FAS) following the principle of intent-to-treat (ITT) had to include every patient randomized and compare the patients per group to which they were randomly allocated, regardless of patients' compliance, or withdrawal from the study. Confirmatory analyses on primary efficacy end-point was to be performed on the FAS patients. This ITT analysis was to be considered as the primary one.	
Subject analysis set title	Safety Analysis Set (SAS)
Subject analysis set type	Safety analysis
Subject analysis set description:	
The safety population had to comprise all patients randomized into the study and treated. Safety evaluations were to be performed on the safety population (SAS). All comparisons were to be executed per the group, to which the patients were randomized.	
Subject analysis set title	Per Protocol Set (PPS)
Subject analysis set type	Per protocol
Subject analysis set description:	
The per protocol set (PPS) was defined as a subset of the FAS/ITT patients who were compliant with the study protocol. The PPS sample had to consist of all patients from the FAS/ITT group without any major protocol violation. A secondary efficacy analysis of the primary endpoint had to be performed based upon the PPS, to assess the sensitivity of the analysis to the choice of analysis population.	
Subject analysis set title	Safety Analysis Set II (SASII)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
In case treatment application violations were regarded as major violations during the blinded review meeting, and it was decided to analyse safety issues separately, two additional safety analysis sets SASII and SASIII which were not foreseen in the protocol were to be created. SASII had to consist of all patients who were treated correctly with 15 injections.	
Subject analysis set title	Safety Analysis Set III (SASIII)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
In case treatment application violations were regarded as major violations during the blinded review meeting, and it was decided to analyse safety issues separately, two additional safety analysis sets SASII and SASIII which were not foreseen in the protocol were to be created. SASIII had to consist of all patients who were treated with more than 15 injections.	
Subject analysis set title	Insufficient CD 133+ Analysis Set (I-cd133+-AS)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Patients who received the cellular product or Placebo but were excluded from per protocol analysis set post-hoc because of cell count insufficiency were to be evaluated separately. This "Insufficient CD133+ Analysis Set"-Population (silent drop-outs) had to include every patient with a randomization number and a CD133+ cell count from 0.5x106> CD133+ cell count ≥ 0.1x106. All comparisons in the I-CD133+- AS Population were to be executed per the group, to which the patients were randomized.	

Primary: LVEF at 6 months post-OP, measured by MRI at rest

End point title	LVEF at 6 months post-OP, measured by MRI at rest

End point description:

LVEF (left ventricular ejection fraction) at 6 months postoperatively, measured by MRI (magnetic resonance imaging) at rest and change in LVEF at 6 months post-OP compared with preoperatively (screening) and early postoperatively (discharge) as assessed by MRI. Cardiac MRI was established as the gold standard for determination of LV function (LVEF and LV volumes).

End point type	Primary

End point timeframe:

6 months postoperatively

End point values	placebo group	CD133+ treatment group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34[1]	30[2]		
Units: Percentage of LVEF				
arithmetic mean (standard error)	42.5 (± 9.65)	44.1 (± 13.78)		

Notes:

[1] - arithmetic mean calculated out of 34 subjects

[2] - arithmetic mean calculated out of 30 subjects

Statistical analyses

Statistical analysis title	Primary Analysis

Statistical analysis description:

exploratory analysis of covariance (ANCOVA) adjusting for the covariates treatment, study sites and baseline LVEF.

Comparison groups	placebo group v CD133+ treatment group
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8581 [3]
Method	ANCOVA

Notes:

[3] - =0.2855 (center)
=0.0205 (LVEF at baseline)
=0.7366 (Treatment*Center)
=0.8182 (treatment*LVEF at baseline)
=0.2760 (Center*LVEF at baseline)
=0.6660 (Treatment*Center*LVEF at baseline)

Statistical analysis title	Additional Analysis

Statistical analysis description:

mixed model analysis for repeat measures approach (MMRM) in order to compensate possible artefacts due to incomplete data groups

Comparison groups	placebo group v CD133+ treatment group

Number of subjects included in analysis	64
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.4454
Method	Mixed models analysis

Secondary: Change in LVEF at 6 month post-OP compared with preoperatively (screening) assessed by cardiac MRI scans

End point title	Change in LVEF at 6 month post-OP compared with preoperatively (screening) assessed by cardiac MRI scans

End point description:

End point type	Secondary

End point timeframe:

Baseline to 6 months post OP

End point values	placebo group	CD133+ treatment group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	30		
Units: Percentage of LVEF				
arithmetic mean (standard error)	8.0 (± 8.71)	11.4 (± 13.52)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in LVEF at 6 month post-OP compared with preoperatively (screening) assessed by echocardiography

End point title	Change in LVEF at 6 month post-OP compared with preoperatively (screening) assessed by echocardiography

End point description:

End point type	Secondary

End point timeframe:

Baseline and 6 months post OP

End point values	placebo group	CD133+ treatment group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	31		
Units: Percentage of LVEF				
arithmetic mean (standard error)	5.1 (± 10.73)	6.0 (± 7.48)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in LVEF at 6 month post-OP compared with early postoperatively (discharge) assessed by cardiac MRI scans

End point title	Change in LVEF at 6 month post-OP compared with early postoperatively (discharge) assessed by cardiac MRI scans

End point description:

End point type	Secondary

End point timeframe:

Baseline and 6 months post OP

End point values	placebo group	CD133+ treatment group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	14		
Units: Percentage of LVEF				
arithmetic mean (standard error)	4.1 (± 8.57)	8.8 (± 6.38)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in LVEF at 6 month post-OP compared with early postoperatively (discharge) assessed by echocardiography

End point title	Change in LVEF at 6 month post-OP compared with early postoperatively (discharge) assessed by echocardiography

End point description:

End point type	Secondary

End point timeframe:

Baseline and 6 months post OP

End point values	placebo group	CD133+ treatment group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	30		
Units: Percentage of LVEF				
arithmetic mean (standard error)	4.5 (± 9.70)	4.3 (± 5.82)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Adverse events collected between start of screening and end of main trial phase	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	15.0

Reporting groups	
Reporting group title	CD133+
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Serious adverse events	CD133+	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	19 / 37 (51.35%)	15 / 40 (37.50%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Thrombosis			
subjects affected / exposed	0 / 37 (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	
Surgical and medical procedures			
Implantable defibrillator insertion			
subjects affected / exposed	1 / 37 (2.70%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Impaired healing			
subjects affected / exposed	1 / 37 (2.70%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			

subjects affected / exposed	1 / 37 (2.70%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Epididymitis			
subjects affected / exposed	0 / 37 (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			
Dyspnoea			
subjects affected / exposed	1 / 37 (2.70%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	0 / 37 (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	
Pneumothorax			
subjects affected / exposed	1 / 37 (2.70%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
In-stent coronary artery restenosis			
subjects affected / exposed	0 / 37 (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	
Postoperative thoracic procedure complication			
subjects affected / exposed	1 / 37 (2.70%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			

subjects affected / exposed	0 / 37 (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	
Atrial fibrillation			
subjects affected / exposed	3 / 37 (8.11%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	0 / 37 (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	
Bradycardia			
subjects affected / exposed	1 / 37 (2.70%)	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 arrest			
subjects affected / exposed	0 / 37 (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	
Cardiac failure			
subjects affected / exposed	2 / 37 (5.41%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiovascular insufficiency			
subjects affected / exposed	1 / 37 (2.70%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracardiac thrombus			
subjects affected / exposed	1 / 37 (2.70%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			

subjects affected / exposed	1 / 37 (2.70%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	1 / 37 (2.70%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular fibrillation			
subjects affected / exposed	1 / 37 (2.70%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	0 / 37 (0.00%)	2 / 40 (5.00%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 37 (2.70%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 37 (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	
Eye disorders			
Visual impairment			
subjects affected / exposed	0 / 37 (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	
Gastrointestinal disorders			
Abdominal pain			

subjects affected / exposed	0 / 37 (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	
Skin and subcutaneous tissue disorders			
Skin haemorrhage			
subjects affected / exposed	0 / 37 (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	
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	1 / 37 (2.70%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Diabetic foot infection			
subjects affected / exposed	0 / 37 (0.00%)	2 / 40 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	0 / 37 (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	
Lung infection			
subjects affected / exposed	1 / 37 (2.70%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 37 (0.00%)	2 / 40 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound infection			
subjects affected / exposed	1 / 37 (2.70%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Sepsis			
subjects affected / exposed	0 / 37 (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	
Wound infection			
subjects affected / exposed	1 / 37 (2.70%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	CD133+	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	36 / 37 (97.30%)	40 / 40 (100.00%)	
Vascular disorders			
Haematoma			
subjects affected / exposed	2 / 37 (5.41%)	2 / 40 (5.00%)	
occurrences (all)	2	2	
Hypertension			
subjects affected / exposed	3 / 37 (8.11%)	4 / 40 (10.00%)	
occurrences (all)	3	5	
Hypertensive crisis			
subjects affected / exposed	0 / 37 (0.00%)	2 / 40 (5.00%)	
occurrences (all)	0	2	
Thrombophlebitis			
subjects affected / exposed	0 / 37 (0.00%)	2 / 40 (5.00%)	
occurrences (all)	0	2	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 37 (2.70%)	3 / 40 (7.50%)	
occurrences (all)	1	3	
Chest pain			
subjects affected / exposed	4 / 37 (10.81%)	2 / 40 (5.00%)	
occurrences (all)	5	2	
Impaired healing			

subjects affected / exposed	4 / 37 (10.81%)	3 / 40 (7.50%)	
occurrences (all)	4	3	
Oedema			
subjects affected / exposed	8 / 37 (21.62%)	12 / 40 (30.00%)	
occurrences (all)	10	15	
Oedema peripheral			
subjects affected / exposed	10 / 37 (27.03%)	14 / 40 (35.00%)	
occurrences (all)	12	16	
Pain			
subjects affected / exposed	2 / 37 (5.41%)	1 / 40 (2.50%)	
occurrences (all)	2	1	
Respiratory, thoracic and mediastinal disorders			
Atelectasis			
subjects affected / exposed	3 / 37 (8.11%)	2 / 40 (5.00%)	
occurrences (all)	3	2	
Cough			
subjects affected / exposed	9 / 37 (24.32%)	7 / 40 (17.50%)	
occurrences (all)	10	7	
Dyspnoea			
subjects affected / exposed	3 / 37 (8.11%)	3 / 40 (7.50%)	
occurrences (all)	3	3	
Dyspnoea exertional			
subjects affected / exposed	3 / 37 (8.11%)	3 / 40 (7.50%)	
occurrences (all)	3	3	
Oropharyngeal pain			
subjects affected / exposed	0 / 37 (0.00%)	2 / 40 (5.00%)	
occurrences (all)	0	2	
Pleural effusion			
subjects affected / exposed	19 / 37 (51.35%)	20 / 40 (50.00%)	
occurrences (all)	20	21	
Pneumothorax			
subjects affected / exposed	2 / 37 (5.41%)	1 / 40 (2.50%)	
occurrences (all)	3	1	
Psychiatric disorders			

Insomnia			
subjects affected / exposed	5 / 37 (13.51%)	5 / 40 (12.50%)	
occurrences (all)	6	5	
Sleep disorder			
subjects affected / exposed	4 / 37 (10.81%)	5 / 40 (12.50%)	
occurrences (all)	4	5	
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 37 (2.70%)	2 / 40 (5.00%)	
occurrences (all)	1	4	
C-reactive protein increased			
subjects affected / exposed	5 / 37 (13.51%)	3 / 40 (7.50%)	
occurrences (all)	5	4	
Electrocardiogram QT prolonged			
subjects affected / exposed	1 / 37 (2.70%)	3 / 40 (7.50%)	
occurrences (all)	1	3	
Haemoglobin decreased			
subjects affected / exposed	1 / 37 (2.70%)	2 / 40 (5.00%)	
occurrences (all)	2	2	
N-terminal prohormone brain natriuretic peptide increased			
subjects affected / exposed	3 / 37 (8.11%)	1 / 40 (2.50%)	
occurrences (all)	3	2	
Troponin T increased			
subjects affected / exposed	2 / 37 (5.41%)	0 / 40 (0.00%)	
occurrences (all)	2	0	
Urine output decreased			
subjects affected / exposed	0 / 37 (0.00%)	2 / 40 (5.00%)	
occurrences (all)	0	2	
Injury, poisoning and procedural complications			
Injury			
subjects affected / exposed	8 / 37 (21.62%)	9 / 40 (22.50%)	
occurrences (all)	9	9	
Procedural pain			
subjects affected / exposed	2 / 37 (5.41%)	1 / 40 (2.50%)	
occurrences (all)	2	1	

Wound secretion			
subjects affected / exposed	1 / 37 (2.70%)	2 / 40 (5.00%)	
occurrences (all)	1	2	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	2 / 37 (5.41%)	0 / 40 (0.00%)	
occurrences (all)	3	0	
Arrhythmia			
subjects affected / exposed	2 / 37 (5.41%)	0 / 40 (0.00%)	
occurrences (all)	2	0	
Arrhythmia supraventricular			
subjects affected / exposed	1 / 37 (2.70%)	2 / 40 (5.00%)	
occurrences (all)	1	2	
Atrial fibrillation			
subjects affected / exposed	7 / 37 (18.92%)	9 / 40 (22.50%)	
occurrences (all)	9	9	
Atrioventricular block			
subjects affected / exposed	2 / 37 (5.41%)	0 / 40 (0.00%)	
occurrences (all)	2	0	
Atrioventricular block first degree			
subjects affected / exposed	2 / 37 (5.41%)	1 / 40 (2.50%)	
occurrences (all)	2	1	
Bradycardia			
subjects affected / exposed	0 / 37 (0.00%)	5 / 40 (12.50%)	
occurrences (all)	0	6	
Bundle branch block left			
subjects affected / exposed	3 / 37 (8.11%)	1 / 40 (2.50%)	
occurrences (all)	3	1	
Pericardial effusion			
subjects affected / exposed	6 / 37 (16.22%)	7 / 40 (17.50%)	
occurrences (all)	6	7	
Supraventricular extrasystoles			
subjects affected / exposed	1 / 37 (2.70%)	2 / 40 (5.00%)	
occurrences (all)	1	2	
Supraventricular tachyarrhythmia			

subjects affected / exposed	3 / 37 (8.11%)	2 / 40 (5.00%)	
occurrences (all)	5	3	
Supraventricular tachycardia			
subjects affected / exposed	3 / 37 (8.11%)	0 / 40 (0.00%)	
occurrences (all)	3	0	
Tachycardia			
subjects affected / exposed	0 / 37 (0.00%)	2 / 40 (5.00%)	
occurrences (all)	0	2	
Ventricular arrhythmia			
subjects affected / exposed	2 / 37 (5.41%)	2 / 40 (5.00%)	
occurrences (all)	2	2	
Ventricular extrasystoles			
subjects affected / exposed	4 / 37 (10.81%)	2 / 40 (5.00%)	
occurrences (all)	4	2	
Ventricular tachycardia			
subjects affected / exposed	0 / 37 (0.00%)	2 / 40 (5.00%)	
occurrences (all)	0	2	
Nervous system disorders			
Syncope			
subjects affected / exposed	1 / 37 (2.70%)	2 / 40 (5.00%)	
occurrences (all)	1	2	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	7 / 37 (18.92%)	6 / 40 (15.00%)	
occurrences (all)	8	6	
Iron deficiency anaemia			
subjects affected / exposed	0 / 37 (0.00%)	2 / 40 (5.00%)	
occurrences (all)	0	2	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	6 / 37 (16.22%)	7 / 40 (17.50%)	
occurrences (all)	6	7	
Nausea			
subjects affected / exposed	2 / 37 (5.41%)	3 / 40 (7.50%)	
occurrences (all)	2	3	
Vomiting			

subjects affected / exposed	0 / 37 (0.00%)	3 / 40 (7.50%)	
occurrences (all)	0	3	
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
subjects affected / exposed	2 / 37 (5.41%)	0 / 40 (0.00%)	
occurrences (all)	2	0	
Scar pain			
subjects affected / exposed	3 / 37 (8.11%)	1 / 40 (2.50%)	
occurrences (all)	3	2	
Renal and urinary disorders			
Nocturia			
subjects affected / exposed	0 / 37 (0.00%)	2 / 40 (5.00%)	
occurrences (all)	0	2	
Renal failure			
subjects affected / exposed	3 / 37 (8.11%)	1 / 40 (2.50%)	
occurrences (all)	4	1	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 37 (2.70%)	6 / 40 (15.00%)	
occurrences (all)	1	6	
Joint effusion			
subjects affected / exposed	2 / 37 (5.41%)	5 / 40 (12.50%)	
occurrences (all)	2	5	
Muscle tightness			
subjects affected / exposed	3 / 37 (8.11%)	3 / 40 (7.50%)	
occurrences (all)	4	3	
Neck pain			
subjects affected / exposed	2 / 37 (5.41%)	1 / 40 (2.50%)	
occurrences (all)	2	1	
Osteoarthritis			
subjects affected / exposed	0 / 37 (0.00%)	2 / 40 (5.00%)	
occurrences (all)	0	2	
Pain in extremity			
subjects affected / exposed	1 / 37 (2.70%)	3 / 40 (7.50%)	
occurrences (all)	1	3	
Infections and infestations			

Device related infection			
subjects affected / exposed	2 / 37 (5.41%)	0 / 40 (0.00%)	
occurrences (all)	2	0	
Lung infection			
subjects affected / exposed	1 / 37 (2.70%)	2 / 40 (5.00%)	
occurrences (all)	1	2	
Nasopharyngitis			
subjects affected / exposed	1 / 37 (2.70%)	2 / 40 (5.00%)	
occurrences (all)	1	2	
Pneumonia			
subjects affected / exposed	0 / 37 (0.00%)	2 / 40 (5.00%)	
occurrences (all)	0	2	
Metabolism and nutrition disorders			
Fluid retention			
subjects affected / exposed	0 / 37 (0.00%)	2 / 40 (5.00%)	
occurrences (all)	0	2	
Hyperglycaemia			
subjects affected / exposed	0 / 37 (0.00%)	2 / 40 (5.00%)	
occurrences (all)	0	2	
Hypokalaemia			
subjects affected / exposed	5 / 37 (13.51%)	3 / 40 (7.50%)	
occurrences (all)	6	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 July 2009	Chnage of Sponsorship; change of Stem Cell Maufacturer/Central Laboratory Cell Processing; IMP: range of the amount of cells applied was expanded from 5-10x106 CD133+ cells to 1-10x106 CD133+ in order to be in accordance with the range applied in the preceding phase I/II trials; moderate revision to Inclusion and exclusion criteria, Revision of AE Section: Start of documentation changed from Assessment IIa to the date of IC (Assessment I); IC: Text regarding time given to patients for considerations changed
18 December 2009	Medical Director at sponsor changed; LVEF for inclusion changed from ≤ 35% to 25% ≤ LVEF ≤ 40%
20 December 2010	Restart of recruitment; Threshold for cell number changed to 0.5 Mio -5 Mio; EQ-5D questionnaire implemented
09 June 2011	New sites; Change of Coordinating Investigator
18 November 2011	LVEF threshold rised to ≤ 50%; prolongation of recruitment time from 2 to 3 years, totalstudy duration increased to 3.5 years
17 August 2012	Interimanalyis after 70 patients completed 6-Months follow up; study duriation extended by 1 year
27 April 2016	Recruitment Stop 12Nov2015 due to decrease in availability of eligible patients; sponsor study responsible physician changed; Core lab responsibility changed

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
08 September 2010	Voluntary hold of recruitment: Cell number of at least 1 Mio CD 133+ cells not reached in two patients. Root cause analysis done	20 December 2010

Notes:

Limitations and caveats

None reported