



Clinical trial results:

Short-term endothelin A receptor blockade in patients with on-pump coronary artery bypass grafting

Summary

EudraCT number	2010-023552-90
Trial protocol	AT
Global end of trial date	15 October 2015

Results information

Result version number	v1 (current)
This version publication date	06 August 2020
First version publication date	06 August 2020

Trial information

Trial identification

Sponsor protocol code	BQ123CPBP17022012
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01658410
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Medical University of Vienna
Sponsor organisation address	Spitalgasse 23, Vienna, Austria, 1090
Public contact	Prof. Dr. Martin Andreas, Medical University of Vienna, +43 14040069660, martin.andreas@meduniwien.ac.at
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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	24 June 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 October 2015
Global end of trial reached?	Yes
Global end of trial date	15 October 2015
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial was to assess the effect of BQ-123 on enzymatic infarct size (CK-MB area under the curve).

Protection of trial subjects:

The trial was conducted according to the principles of Good Clinical Practice and the Declaration of Helsinki and in agreement with the Austrian laws and regulation. The Ethics Committee of the Medical University of Vienna approved the trial. As BQ-123 was applied during cardiac surgery for the first time, the study was divided into a "pilot phase" and a "main trial" in order to improve safety. During the "pilot phase", which was intended to precede the "main trial", 30 subjects were randomized to receive either the placebo or half (3.75 µmol in the first and last cardioplegia, in total 7.5 µmol) of the in the "main trial" planned BQ-123 dose. Catecholamines given at the time of termination of surgery were the safety endpoint. Further safety measures included the performance of liver function tests after BQ-123 administration, postoperative blood pressure measurements and the assessment of postoperative catecholamine requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	24 October 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Scientific research, Efficacy
Long term follow-up duration	6 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 36
Worldwide total number of subjects	36
EEA total number of subjects	36

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)	15
From 65 to 84 years	21
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients who were scheduled for on-pump coronary artery bypass grafting at the Medical University of Vienna were assessed for eligibility. A sample size of a total of 120 subjects was calculated ("pilot trial": 30 subjects; "main trial": 90 subjects). The trial was discontinued after the "pilot phase".

Pre-assignment

Screening details:

A total of 36 patients signed the informed consent to participate in the trial. Of them, 30 subjects were randomized.

Pre-assignment period milestones

Number of subjects started	36
Number of subjects completed	30

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Consent withdrawn by subject: 1
Reason: Number of subjects	Organizational reason: 1
Reason: Number of subjects	Physician decision: 1
Reason: Number of subjects	Exclusion criterion: 3

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	BQ-123

Arm description:

BQ-123 (7.5 µmol) dissolved in 0.9% NaCl was added to the blood cardioplegic solution used during cardiopulmonary bypass

Arm type	Experimental
Investigational medicinal product name	BQ-123 Sodium Salt
Investigational medicinal product code	
Other name	Cyclo(D-trp-D-asp-L-pro-D-val-L-leu) sodium salt
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Intracoronary use

Dosage and administration details:

Subjects received a total of 7.5 µmol BQ-123 dissolved in 50ml 0.9% NaCl added to the blood cardioplegic solution used during cardiopulmonary bypass (3.75 µmol BQ-123 in the first cardioplegia and 3.75 µmol BQ-123 in the last cardioplegia).

Arm title	Placebo
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Arm description:

0.9% NaCl was added to the blood cardioplegic solution used during cardiopulmonary bypass

Arm type	Placebo
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Investigational medicinal product name	0,9% Sodium chloride solution
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intracoronary use

Dosage and administration details:

Subjects received 0,9% NaCL added to the blood cardioplegic solution used during cardiopulmonary bypass.

Number of subjects in period 1^[1]	BQ-123	Placebo
Started	15	15
Completed	15	14
Not completed	0	1
Lost to follow-up	-	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: 36 subjects were enrolled in the trial. Of them, 6 patients were excluded from the trial prior to randomization and drug administration. Reasons for exclusion from the trial included the following: consent withdrawn by subject (1 patient), organizational reason (1 patient), physician decision (1 patient), and exclusion criterion (3 patients).

Baseline characteristics

Reporting groups

Reporting group title	BQ-123
Reporting group description: BQ-123 (7.5 µmol) dissolved in 0.9% NaCl was added to the blood cardioplegic solution used during cardiopulmonary bypass	
Reporting group title	Placebo
Reporting group description: 0.9% NaCl was added to the blood cardioplegic solution used during cardiopulmonary bypass	

Reporting group values	BQ-123	Placebo	Total
Number of subjects	15	15	30
Age categorical 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)	8	5	13
From 65-84 years	7	10	17
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	65.8	67.4	-
standard deviation	± 10.6	± 9.4	
Gender categorical Units: Subjects			
Female	2	5	7
Male	13	10	23
New York Heart Association (NYHA) functional class Units: Subjects			
NYHA functional class I	3	3	6
NYHA functional class II	8	7	15
NYHA functional class III	4	5	9
NYHA functional class IV	0	0	0
Angina pectoris Units: Subjects			
No angina pectoris	4	2	6
Stable angina pectoris	8	9	17
Unstable angina pectoris	2	3	5
Atypical angina pectoris	1	1	2
Number of bypass grafts (intraoperative) Units: Subjects			

1 graft	0	1	1
2 grafts	3	2	5
3 grafts	10	8	18
4 grafts	2	4	6
Height Units: cm arithmetic mean standard deviation	174.7 ± 9.7	170.5 ± 10.8	-
Weight Units: kg arithmetic mean standard deviation	90.5 ± 9.7	80.1 ± 14.1	-
Body mass index Units: kg/m2 arithmetic mean standard deviation	29.7 ± 3.1	27.5 ± 4.0	-
EuroScore II Units: Percentage arithmetic mean standard deviation	1.4 ± 0.8	1.8 ± 1.1	-
Left ventricular ejection fraction (cardiac magnetic resonance imaging) Units: Percentage arithmetic mean standard deviation	63.3 ± 12.1	59.7 ± 11.2	-
Aortic cross-clamp time Units: Minutes arithmetic mean standard deviation	76.9 ± 31.9	88.4 ± 35.2	-
Extracorporeal circulation time Units: Minutes arithmetic mean standard deviation	130.3 ± 39.5	146.8 ± 63.3	-

End points

End points reporting groups

Reporting group title	BQ-123
Reporting group description: BQ-123 (7.5 µmol) dissolved in 0.9% NaCl was added to the blood cardioplegic solution used during cardiopulmonary bypass	
Reporting group title	Placebo
Reporting group description: 0.9% NaCl was added to the blood cardioplegic solution used during cardiopulmonary bypass	

Primary: Area under the curve (AUC) of myocard specific creatinephosphokinase-MB isoform (CK-MB)

End point title	Area under the curve (AUC) of myocard specific creatinephosphokinase-MB isoform (CK-MB)
End point description: Only patients with no missing value were included in the statistical analysis.	
End point type	Primary
End point timeframe: CK-MB levels were measured was measured 4, 12, 24, 48 and 72 hours after the operation.	

End point values	BQ-123	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	5		
Units: U/l*hours				
arithmetic mean (standard deviation)	2562.9 (± 1120.4)	2366.6 (± 1299.6)		

Statistical analyses

Statistical analysis title	AUC of CK-MB
Comparison groups	BQ-123 v Placebo
Number of subjects included in analysis	12
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.785
Method	t-test, 2-sided

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events occurring within 6 months after the surgery are reported.

Adverse event reporting additional description:

Non-serious adverse events were assessed by retrospective medical chart review. This retrospective medical chart review was conducted several years after the study was stopped.

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	23.0
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Reporting groups

Reporting group title	BQ-123
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Reporting group description:

BQ-123 (7.5 µmol) dissolved in NaCl 0.9% was added to the blood cardioplegic solution used during cardiopulmonary bypass

Reporting group title	Placebo
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Reporting group description:

NaCl 0.9% was added to the blood cardioplegic solution used during cardiopulmonary bypass

Serious adverse events	BQ-123	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 15 (40.00%)	4 / 15 (26.67%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Blood electrolytes abnormal			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac failure acute			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 15 (6.67%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary vascular graft occlusion			
alternative assessment type: Systematic			

subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asystole			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac procedure complication			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (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			
General physical health deterioration			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
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			
Anaemia			
alternative assessment type: Systematic			

subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Pancreatitis			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Postoperative wound infection			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	BQ-123	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 15 (93.33%)	15 / 15 (100.00%)	
Vascular disorders			
Thrombophlebitis			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Epistaxis			
subjects affected / exposed	1 / 15 (6.67%)	3 / 15 (20.00%)	
occurrences (all)	1	3	
Hemodynamic instability			

subjects affected / exposed	1 / 15 (6.67%)	2 / 15 (13.33%)	
occurrences (all)	1	2	
Lymphoedema			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Chronic venous insufficiency			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Weakness			
subjects affected / exposed	4 / 15 (26.67%)	1 / 15 (6.67%)	
occurrences (all)	4	1	
Sensation of heat			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Heavy sweating			
subjects affected / exposed	1 / 15 (6.67%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Tiredness			
subjects affected / exposed	2 / 15 (13.33%)	0 / 15 (0.00%)	
occurrences (all)	2	0	
Fever			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Hoarseness			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Pleural effusion			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Cold			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Pneumonia			

subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	1 / 15 (6.67%) 1	
Psychiatric disorders			
Panic attack			
subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	1 / 15 (6.67%) 1	
Acute stress disorder			
subjects affected / exposed occurrences (all)	3 / 15 (20.00%) 3	1 / 15 (6.67%) 1	
Hallucination, visual			
subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	1 / 15 (6.67%) 1	
Disorientation			
subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	1 / 15 (6.67%) 1	
Investigations			
Pancreatic enzymes increased			
subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	1 / 15 (6.67%) 1	
Deranged liver function tests			
subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	1 / 15 (6.67%) 1	
C-reactive protein abnormal			
subjects affected / exposed occurrences (all)	3 / 15 (20.00%) 3	1 / 15 (6.67%) 1	
Blood culture positive			
subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	1 / 15 (6.67%) 1	
Catheter culture positive			
subjects affected / exposed occurrences (all)	2 / 15 (13.33%) 2	2 / 15 (13.33%) 2	
Abnormal EEG			
subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	1 / 15 (6.67%) 1	
Injury, poisoning and procedural complications			

Radial nerve compression subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	1 / 15 (6.67%) 1	
Anaemia postoperative subjects affected / exposed occurrences (all)	6 / 15 (40.00%) 6	6 / 15 (40.00%) 6	
Postoperative wound infection subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	2 / 15 (13.33%) 2	
Incision site impaired healing subjects affected / exposed occurrences (all)	2 / 15 (13.33%) 2	1 / 15 (6.67%) 1	
Intraoperative hemorrhage subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	1 / 15 (6.67%) 1	
Postpericardiotomy syndrome subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	1 / 15 (6.67%) 1	
Fall subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	0 / 15 (0.00%) 0	
Surgical emphysema subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	0 / 15 (0.00%) 0	
Cardiac disorders			
Pericardial effusion subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	1 / 15 (6.67%) 1	
Atrial fibrillation subjects affected / exposed occurrences (all)	7 / 15 (46.67%) 7	4 / 15 (26.67%) 4	
Arrhythmia subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	4 / 15 (26.67%) 4	
Dyspnea exacerbated			

subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	1 / 15 (6.67%) 1	
Nervous system disorders			
Lightheadedness			
subjects affected / exposed	0 / 15 (0.00%)	2 / 15 (13.33%)	
occurrences (all)	0	2	
Carpal tunnel syndrome			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Benign paroxysmal positional vertigo			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Dysaesthesia of upper extremity			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Eye disorders			
Retinal vascular occlusion			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Ache stomach			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Haematochezia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Proctitis			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Colonic polyp			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			

Localized rash subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	1 / 15 (6.67%) 1	
Decubitus subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	0 / 15 (0.00%) 0	
Renal and urinary disorders Urinary tract infection bacterial subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	2 / 15 (13.33%) 2	
Impaired renal function subjects affected / exposed occurrences (all)	2 / 15 (13.33%) 2	0 / 15 (0.00%) 0	
Endocrine disorders Hyperparathyroidism subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	0 / 15 (0.00%) 0	
Musculoskeletal and connective tissue disorders Intervertebral disc protrusion subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	1 / 15 (6.67%) 1	
Metabolism and nutrition disorders Hyperkalaemia subjects affected / exposed occurrences (all)	2 / 15 (13.33%) 2	1 / 15 (6.67%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 April 2012	<p>The primary endpoint of the study was changed from "coronary artery bypass graft blood flow assessed by Doppler flow probe measurement 15 minutes after protamine administration" to "area under the curve (AUC) of myocard specific creatinephosphokinase-MB isoform (CK-MB)".</p> <p>A new calculation of the required sample size was performed based on the primary endpoint AUC of CK-MB evaluated 2, 4, 12, 24, 48 and 72 hours after the operation.</p> <p>A sample size of 45 patients in each group was calculated. As this medication was applied during cardiac surgery for the first time, a pilot phase with 30 participants (15 treated with half dose BQ-123 and 15 placebo) was additionally implemented.</p> <p>The performance of a proteomic analysis of blood and plasma samples was added to the protocol.</p> <p>Exclusion criteria were changed to:</p> <ul style="list-style-type: none">• Significant liver disease (transaminases and/or gamma-GT > 3 fold upper limit)• Glomerular filtration rate < 40mL/h• History of severe congestive heart failure (left ventricular ejection fraction < 35%)• Current atrial fibrillation• Significant valvular heart disease requiring valve replacement• Primary myocardial disease• Acute coronary syndrome or cardiogenic shock (sRR < 90mmHg or need for inotropic support)• Women with child-bearing potential• Subjects with contraindications for CMR (cardiac magnetic resonance)• Inability to read, understand and sign the informed consent• Life expectancy <1y• Prior organ transplantation• Participation in a clinical trial using an investigational medical product

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
15 October 2015	The study was stopped after finishing the "pilot phase". The "main trial" was never started.	-

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Preop. CK-MB levels were not measured. Postop. CK-MB levels couldn't be measured in all samples (17.8% of the data are missing). Non-serious adverse events were assessed by retrospective medical chart review several years after the study was stopped.

Notes:

