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

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
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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 saftey 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	Efficacy, Scientific research
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

Arm description:

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

Arm type	Placebo

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

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	BQ-123

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

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

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

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 April 2012	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)". 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. 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. The performance of a proteomic analysis of blood and plasma samples was added to the protocol. Exclusion criteria were changed to: • 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: