Clinical trial results:
A Single-Centre, Single Blind, Randomized, Active-Controlled Phase III Non-Inferiority Study to Investigate the Safety and Efficacy of the Cardioplegic Solution Cardioplexol when used during a Cardiac Surgical Intervention under the Assistance of a Heart-Lung Machine

Summary

EudraCT number	2011-004198-10
Trial protocol	AT
Global end of trial date	03 August 2015

Results information

Result version number	v1 (current)
This version publication date	13 October 2016
First version publication date	13 October 2016

Trial information

Trial identification

Sponsor protocol code	SCT-Cpx-003

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Swiss Cardio Technologies AG
Sponsor organisation address	Kehrsitenstrasse 2, Stansstad, Switzerland, 6362
Public contact	Hendrik Tevaearai, Swiss Cardio Technologies AG, 41 763804835, hendrik.tevaearai@swisscardiotech.com
Scientific contact	Hendrik Tevaearai, Swiss Cardio Technologies AG, 41 763804835, hendrik.tevaearai@swisscardiotech.com

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	03 August 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 August 2015
Global end of trial reached?	Yes
Global end of trial date	03 August 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To explore the effects of CardioplexolTM on the protection of cardiac cells during the "ischemic" period in order to allow a rapid and complete reversibility of the cardiac arrest when used during a cardiac surgical intervention under the assistance of a heart-lung machine.

Protection of trial subjects:

The study was conducted in compliance with the ethical principals derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practise (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy:

-

Evidence for comparator:

Cardioplexol TM was compared to a blood cardioplegia approach as originally described by Buckberg. Blood cardioplegia is considered as a reference worldwide, and served as a comparator in this study.

Actual start date of recruitment	29 May 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 264
Worldwide total number of subjects	264
EEA total number of subjects	264

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)	101

From 65 to 84 years	163
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment territory: Austria
Recruitment period: approx. 3 years
Every patient who was a candidate for an elective surgical cardiac procedure was considered to be included in the current study, providing the operation was being performed via a full sternotomy and under cardiac arrest and assistance of an extra corporeal circulation.

Pre-assignment

Screening details:

It was anticipated that 260 patients would need to be screened in order to randomize and to achieve 240 completed patients (120 per treatment group). The actual patient number screened was 280. Patients who satisfied all inclusion and no exclusion criteria were randomly assigned to one of the 2 groups "Cardioplexol™" or "Buckberg" (ratio 1:1).

Period 1

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

Blinding implementation details:

not relevant

Arms

Are arms mutually exclusive?	Yes
Arm title	Cardioplexol (Group 1)

Arm description:

After randomisation the patients underwent cardiac surgery and received the necessary volume of Cardioplexol. The necessary volume is the volume needed for cardiac arrest, which is a prerequisite for the cardiac surgery. After the cardiac arrest was achieved the patients received further doses whose number and volume depended on the duration of the cardiac surgery as well as individual factors.

Arm type	Experimental
Investigational medicinal product name	Cardioplexol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for cardioplegia
Routes of administration	Intracardiac use

Dosage and administration details:

Administration of one single dose (100 ml) of Cardioplexol (TM). Further Cardioplexol (TM) was applied in regular intervals depending on the duration of the cardiac surgery as well as individual factors.

Arm title	Buckberg (Group 2)

Arm description:

After randomisation the patients underwent cardiac surgery and received the necessary volume of Buckberg blood cardioplegia. The necessary volume is the volume needed for cardiac arrest, which is a prerequisite for the cardiac surgery. Buckberg cardioplegia consists of a cold induction solution, a cold reinfusion solution and a warm reinfusion solution (hot shot).
One patient withdrew his consent shortly before surgery and was excluded from the analysis.

Arm type	Active comparator

Investigational medicinal product name	Buckberg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for cardioplegia
Routes of administration	Intracardiac use

Dosage and administration details:

Buckberg blood cardioplegia consists of a cold induction solution for the cold induction of the cardioplegic arrest, a cold reinfusion solution for the repeated infusions every 20 minutes and a warm reinfusion solution (hot shot) for the infusion immediately before the aorta unclamping.

Number of subjects in period 1	Cardioplexol (Group 1)	Buckberg (Group 2)
Started	132	132
Completed	117	124
Not completed	15	8
Adverse event, serious fatal	1	5
not operated under study protocol	13	3
Lost to follow-up	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Cardioplexol (Group 1)

Reporting group description:

After randomisation the patients underwent cardiac surgery and received the necessary volume of Cardioplexol. The necessary volume is the volume needed for cardiac arrest, which is a prerequisite for the cardiac surgery. After the cardiac arrest was achieved the patients received further doses whose number and volume depended on the duration of the cardiac surgery as well as individual factors.

Reporting group title	Buckberg (Group 2)

Reporting group description:

After randomisation the patients underwent cardiac surgery and received the necessary volume of Buckberg blood cardioplegia. The necessary volume is the volume needed for cardiac arrest, which is a prerequisite for the cardiac surgery. Buckberg cardioplegia consists of a cold induction solution, a cold reinfusion solution and a warm reinfusion solution (hot shot).
One patient withdrew his consent shortly before surgery and was excluded from the analysis.

Reporting group values	Cardioplexol (Group 1)	Buckberg (Group 2)	Total
Number of subjects	132	132	264
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)	48	53	101
From 65-84 years	84	79	163
85 years and over	0	0	0
Age continuous Units: years			
median	69	68	
full range (min-max)	39 to 80	34 to 79	-
Gender categorical Units: Subjects			
Female	47	33	80
Male	85	99	184
Logistic EURO Score			
method of calculating predicted operative mortality for patients undergoing cardiac surgery			
Units: calculated points			
median	2.4	2.5	
inter-quartile range (Q1-Q3)	1.4 to 4	1.5 to 4.1	-

End points

End points reporting groups

Reporting group title	Cardioplexol (Group 1)

Reporting group description:

After randomisation the patients underwent cardiac surgery and received the necessary volume of Cardioplexol. The necessary volume is the volume needed for cardiac arrest, which is a prerequisite for the cardiac surgery. After the cardiac arrest was achieved the patients received further doses whose number and volume depended on the duration of the cardiac surgery as well as individual factors.

Reporting group title	Buckberg (Group 2)

Reporting group description:

After randomisation the patients underwent cardiac surgery and received the necessary volume of Buckberg blood cardioplegia. The necessary volume is the volume needed for cardiac arrest, which is a prerequisite for the cardiac surgery. Buckberg cardioplegia consists of a cold induction solution, a cold reinfusion solution and a warm reinfusion solution (hot shot).
One patient withdrew his consent shortly before surgery and was excluded from the analysis.

Primary: Max values of Trop-T during the first 24h following myocardial perfusion ITT

End point title	Max values of Trop-T during the first 24h following myocardial perfusion ITT

End point description:

Based on the data from published literature, max. of troponin T values was determined as a suitable primary endpoint reflecting a clear benefit for the patient. Measurements to evaluate maximal value of troponin-T were performed at 6, 12, and 24 hours following myocardial reperfusion. Continuous endpoints are analysed by a Student’s t-test on the log-scale and in the ITT population.

End point type	Primary

End point timeframe:

first 24 hours following myocardial perfusion

End point values	Cardioplexol (Group 1)	Buckberg (Group 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	132	132		
Units: ng/ml				
geometric mean (confidence interval 95%)	0.83 (0.73 to 0.93)	0.78 (0.7 to 0.87)		

Statistical analyses

Statistical analysis title	Cpx vs BB: max Troponin T during first 24h (ITT)

Statistical analysis description:

The primary endpoint was compared between the treatment groups by a Student’s t-test. The analysis was performed on the log-transformed values. A two-sided 95% confidence interval for the difference on the log scale (Cardioplexol-Buckberg) was calculated and then back transformed (anti log) to give a 95% confidence interval for ratio of means.
The max value was calculated from the remaining Trop T values if 1 or 2 values were missing. If no values were available, multiple imputation was used.

Comparison groups	Cardioplexol (Group 1) v Buckberg (Group 2)

Number of subjects included in analysis	264
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
P-value	= 0.49
Method	t-test, 2-sided
Parameter estimate	geometric mean ratio
Point estimate	1.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	1.25

Notes:

[1] - Pre-defined non-inferiority margin was 1.20 for the upper limit of the 95% confidence interval of the geometric mean ratio. For the primary endpoint both ITT and PP Analysis were considered equally important.

Primary: Max values of Trop-T during the first24h following myocardial perfusion PP

End point title	Max values of Trop-T during the first24h following myocardial perfusion PP

End point description:

Based on the data from published literature, max. of troponin T values was determined as a suitable primary endpoint reflecting a clear benefit for the patient. Measurements to evaluate maximal value of troponin-T were performed at 6, 12, and 24 hours following myocardial reperfusion. Continuous endpoints are analysed by a Student's t-test on the log-scale and in the PP population.

End point type	Primary

End point timeframe:

first 24 hours following myocardial perfusion

End point values	Cardioplexol (Group 1)	Buckberg (Group 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100	126		
Units: ng/ml				
geometric mean (confidence interval 95%)	0.77 (0.69 to 0.86)	0.78 (0.7 to 0.87)		

Statistical analyses

Statistical analysis title	Cpx vs BB: max Troponin T during first 24h (PP)

Statistical analysis description:

The primary endpoint was compared between the treatment groups by a Student's t-test. The analysis was performed on the log-transformed values. A two-sided 95% confidence interval for the difference on the log scale (Cardioplexol-Buckberg) was calculated and then back transformed (anti log) to give a 95% confidence interval for ratio of means.
The max value was calculated from the remaining Trop T values if 1 or 2 values were missing. If no values were available, multiple imputation was used.

Comparison groups	Cardioplexol (Group 1) v Buckberg (Group 2)

Number of subjects included in analysis	226
Analysis specification	Pre-specified
Analysis type	non-inferiority[2]
P-value	= 0.87
Method	t-test, 2-sided
Parameter estimate	geometric mean ratio
Point estimate	0.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.84
upper limit	1.16

Notes:

[2] - Pre-defined non-inferiority margin was 1.20 for the upper limit of the 95% confidence interval of the geometric mean ratio. For the primary endpoint both ITT and PP Analysis were considered equally important.

Secondary: Max value of CK-MB during the first 24h following myocardial perfusion

End point title	Max value of CK-MB during the first 24h following myocardial perfusion

End point description:

CK-MB is related to the primary endpoint troponin-T and was therefore chosen as the key secondary endpoint. Maximal value of CK-MB was analysed using a Student's t-test on the log-scale in the ITT population. Max. values of CK-MB Levels were measured at 3, 6, 12 and 24h following myocardial perfusion.

End point type	Secondary

End point timeframe:

first 24 hours following myocardial perfusion

End point values	Cardioplexol (Group 1)	Buckberg (Group 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	132	132		
Units: U/l				
geometric mean (confidence interval 95%)	56.4 (50 to 63)	53.8 (49.2 to 58.8)		

Statistical analyses

Statistical analysis title	Cpx vs BB: max CK-MB during first 24h

Statistical analysis description:

Maximal value of CK-MB was analysed using a Student's t-test on the log-scale. A two-sided 95% confidence interval for the ratio of means (Cardioplexol/Buckberg) was reported.
Missing data: The maximum value was calculated from the remaining CK-MB values if up to 3 values were missing. If no values were available, multiple imputation was used to replace the missing max value. Multiple imputations were based on selected baseline and postoperative variables. Chained equations were used.

Comparison groups	Cardioplexol (Group 1) v Buckberg (Group 2)

Number of subjects included in analysis	264
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.51
Method	t-test, 2-sided
Parameter estimate	geometric mean ratio
Point estimate	1.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.91
upper limit	1.21

Secondary: Time between aortic cross-clamping and complete cardiac arrest	
End point title	Time between aortic cross-clamping and complete cardiac arrest
End point description: no details required	
End point type	Secondary
End point timeframe: Time from aortic cross-clamping to complete cardiac arrest	

End point values	Cardioplexol (Group 1)	Buckberg (Group 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	132	132		
Units: second				
geometric mean (confidence interval 95%)	14.1 (12.1 to 16.6)	77.5 (69.3 to 86.7)		

Statistical analyses

Statistical analysis title	Time to complete cardiac arrest

Statistical analysis description:

Time between the aortic cross-clamping and the complete cardiac arrest was analysed using Student's t-tests on the log-scale in the ITT population.
If any of those values were not normally distributed after log-transformation, analysis on the normal scale (if normally distributed) or the use of non-parametric methods was planned to be included as sensitivity analyses.

Comparison groups	Buckberg (Group 2) v Cardioplexol (Group 1)

Number of subjects included in analysis	264
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	t-test, 2-sided
Parameter estimate	geometric mean ratio
Point estimate	0.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.15
upper limit	0.22

Secondary: cumulative dose of catecholamines during aortic cross-clamping

End point title	cumulative dose of catecholamines during aortic cross-clamping

End point description:

no further details required.

End point type	Secondary

End point timeframe:

time during aortic cross-clamping

End point values	Cardioplexol (Group 1)	Buckberg (Group 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	132	132		
Units: inotropic score				
geometric mean (confidence interval 95%)	759 (614 to 940)	775 (619 to 969)		

Statistical analyses

Statistical analysis title	Cpx vs BB: catecholamines during cross-clamp. time

Statistical analysis description:

Analyses was performed using Student’s t-tests on the log-scale in the ITT population.
If any of those values were not normally distributed after log-transformation, analysis on the normal scale (if normally distributed) or the use of non-parametric methods was planned to be included as sensitivity analyses.

Comparison groups	Cardioplexol (Group 1) v Buckberg (Group 2)
Number of subjects included in analysis	264
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9
Method	t-test, 2-sided
Parameter estimate	geometric mean ratio
Point estimate	0.98

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.72
upper limit	1.33

Secondary: cumulative dose of catecholamines during the first 24 hours

End point title	cumulative dose of catecholamines during the first 24 hours
End point description:	
This is an additional secondary endpoint demonstrating the overall benefit for the patients.	
End point type	Secondary
End point timeframe:	
within first 24 hours after reperfusion	

End point values	Cardioplexol (Group 1)	Buckberg (Group 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	132	132		
Units: inotropic score				
geometric mean (confidence interval 95%)	5384 (4257 to 6808)	7569 (6129 to 9349)		

Statistical analyses

Statistical analysis title	Cpx vs BB: catecholamines during first 24h
Statistical analysis description:	
Analyses was performed using Student’s t-tests on the log-scale in the ITT population. If any of those values were not normally distributed after log-transformation, analysis on the normal scale (if normally distributed) or the use of non-parametric methods was planned to be included as sensitivity analyses.	
Comparison groups	Cardioplexol (Group 1) v Buckberg (Group 2)
Number of subjects included in analysis	264
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.035
Method	t-test, 2-sided
Parameter estimate	geometric mean ratio
Point estimate	0.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.52
upper limit	0.98

Secondary: Maximal ST-elevation during the first 24 hours	
End point title	Maximal ST-elevation during the first 24 hours
End point description:	
This is an additional secondary endpoint demonstrating the overall benefit for the patients.	
End point type	Secondary
End point timeframe:	
the first 24 hours following coronary reperfusion or until ICU discharge (if discharge occurs before 24 hours)	

End point values	Cardioplexol (Group 1)	Buckberg (Group 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	132	132		
Units: mm				
arithmetic mean (confidence interval 95%)	1.7 (1.44 to 2)	1.79 (1.53 to 2.09)		

Statistical analyses

Statistical analysis title	Cpx vs BB: Max ST-elevation during first 24h
Statistical analysis description:	
Analyses was performed using Student’s t-tests on the log-scale in the ITT population. If any of those values were not normally distributed after log-transformation, analysis on the normal scale (if normally distributed) or the use of non-parametric methods was planned to be included as sensitivity analyses.	
Comparison groups	Cardioplexol (Group 1) v Buckberg (Group 2)
Number of subjects included in analysis	264
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.93
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.39
upper limit	0.36

Secondary: Defibrillation rate after aorta unclamping and coronary reperfusion	
End point title	Defibrillation rate after aorta unclamping and coronary reperfusion

End point description: no further details required.	
End point type	Secondary
End point timeframe: after aorta unclamping and coronary reperfusion	

End point values	Cardioplexol (Group 1)	Buckberg (Group 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	132	132		
Units: number of patients	20	67		

Statistical analyses

Statistical analysis title	Cpx vs BB: Defibrillation rate
Statistical analysis description: This binary secondary outcome was expressed as risk ratio within corresponding 95% confidence interval (based on a normal approximation for log risk ratio) and compared using chi square tests. Analysis is performed on ITT Population.	
Comparison groups	Cardioplexol (Group 1) v Buckberg (Group 2)
Number of subjects included in analysis	264
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Chi-squared
Parameter estimate	Risk ratio (RR)
Point estimate	0.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.18
upper limit	0.47

Secondary: Installation of an IABP

End point title	Installation of an IABP
End point description: This is an additional secondary endpoint demonstrating the overall benefit for the patients.	
End point type	Secondary
End point timeframe: during the first 24 hours following coronary reperfusion or until ICU discharge (if discharge occurs before 24 hours)	

End point values	Cardioplexol (Group 1)	Buckberg (Group 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	132	132		
Units: number of patients	3	5		

Statistical analyses

Statistical analysis title	Cpx vs BB: Installation of IABP in the first 24

Statistical analysis description:

This binary secondary outcome was expressed as risk ratio within corresponding 95% confidence interval (based on a normal approximation for log risk ratio) and compared using chi square tests. Analysis is performed on ITT poluation.

Comparison groups	Cardioplexol (Group 1) v Buckberg (Group 2)
Number of subjects included in analysis	264
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.48
Method	Chi-squared
Parameter estimate	Risk ratio (RR)
Point estimate	0.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.09
upper limit	3.08

Secondary: Mortality

End point title	Mortality

End point description:

This is an additional secondary endpoint demonstrating the overall benefit for the patients.

End point type	Secondary

End point timeframe:

during the first 24 hours following coronary reperfusion or until ICU discharge (if discharge occurs before 24 hours)

End point values	Cardioplexol (Group 1)	Buckberg (Group 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	119	129		
Units: number of patients	1	2		

Statistical analyses

Statistical analysis title	Cpx vs BB: Mortality

Statistical analysis description:

This binary secondary outcome was expressed as risk ratio within corresponding 95% confidence interval (based on a normal approximation for log risk ratio) and compared using chi square tests. Mulitple imputation was not done due to the low number of events, complete case analysis.

Comparison groups	Cardioplexol (Group 1) v Buckberg (Group 2)
Number of subjects included in analysis	248
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.61
Method	Chi-squared
Parameter estimate	Risk ratio (RR)
Point estimate	0.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.05
upper limit	5.9

Secondary: Duration of intubation

End point title	Duration of intubation

End point description:

no further details required.

End point type	Secondary

End point timeframe:

from timepoint of intubation to timepoint of extubation

End point values	Cardioplexol (Group 1)	Buckberg (Group 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	132	132		
Units: hours				
median (confidence interval 95%)	13 (12 to 14)	13.5 (12.5 to 14.5)		

Statistical analyses

Statistical analysis title	Cpx vs BB: Duration of intubation

Statistical analysis description:

This secondary endpoint was analysed using parametric accelerated failure time (AFT) models with a generalized gamma survival time distribution. Results were reported as time ratio with 95% confidence interval and p-value.

Comparison groups	Cardioplexol (Group 1) v Buckberg (Group 2)

Number of subjects included in analysis	264
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1
Method	AFT models
Parameter estimate	time ratio
Point estimate	0.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.83
upper limit	1.02

Secondary: Patients requiring catecholamines

End point title	Patients requiring catecholamines
End point description: no further details required.	
End point type	Secondary
End point timeframe: during aortic cross-clamping	

End point values	Cardioplexol (Group 1)	Buckberg (Group 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	118	129		
Units: number of patients	118	128		

Statistical analyses

Statistical analysis title	Cpx vs BB: Patients requiring catecholamines
Statistical analysis description: This binary secondary outcome was expressed as risk ratio within corresponding 95% confidence interval (based on a normal approximation for log risk ratio) and compared using chi square tests. Multiple imputation was not done due to the high number of events, complete case analysis.	
Comparison groups	Cardioplexol (Group 1) v Buckberg (Group 2)
Number of subjects included in analysis	247
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.34
Method	Chi-squared
Parameter estimate	Risk ratio (RR)
Point estimate	1.01

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.99
upper limit	1.02

Secondary: Duration of ICU stay

End point title	Duration of ICU stay

End point description:

End point type	Secondary

End point timeframe:

from timepoint of ICU admission to timepoint of ICU discharge

End point values	Cardioplexol (Group 1)	Buckberg (Group 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	132	132		
Units: hours				
median (confidence interval 95%)	37.8 (22.1 to 46.1)	44 (26.3 to 45.5)		

Statistical analyses

Statistical analysis title	Cpx vs BB: Duration of ICU stay

Statistical analysis description:

This secondary endpoint was analysed using parametric accelerated failure time (AFT) models. Patients who did not reach the endpoint because of death were censored at the time of death. Results were reported as time ratio with 95% confidence interval and p-value.

Comparison groups	Cardioplexol (Group 1) v Buckberg (Group 2)
Number of subjects included in analysis	264
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003
Method	AFT models
Parameter estimate	time ratio
Point estimate	0.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.78
upper limit	0.95

Secondary: Duration of hospitalization

End point title	Duration of hospitalization
End point description: no further description required.	
End point type	Secondary
End point timeframe: from date of hospital admission to date of hospital discharge	

End point values	Cardioplexol (Group 1)	Buckberg (Group 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	132	132		
Units: days				
median (confidence interval 95%)	10 (10 to 11)	11 (10 to 11)		

Statistical analyses

Statistical analysis title	Cpx vs BB: Duration of hospitalization
Statistical analysis description: This secondary endpoint was analysed using parametric accelerated failure time (AFT) models with a generalized gamma survival time distribution. Patients that did not reach the endpoint because of death were censored at the time of death. Patients still hospitalized at 30 days were censored at 30 days. Results were reported as time ratio with 95% confidence interval and p-value.	
Comparison groups	Cardioplexol (Group 1) v Buckberg (Group 2)
Number of subjects included in analysis	264
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.97
Method	AFT models
Parameter estimate	time ratio
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.95
upper limit	1.05

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AE collection started after signature of the informed consent form, irrespective of whether or not they may be related to the study intervention.
Investigators followed-up adverse events until resolution or the end of the study (= follow up visit)

Adverse event reporting additional description:

At each assessment, all AEs either observed by the Investigator or one of his clinical collaborators or reported by the patient spontaneously or in response to a direct question were evaluated by the Investigator. Nature of each event, date and time (where appropriate) of onset, outcome, severity and relationship to administration were established.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Cardioplexol (Group 1)

Reporting group description:

After randomisation the patients underwent cardiac surgery and received the necessary volume of Cardioplexol. The necessary volume is the volume needed for cardiac arrest, which is a prerequisite for the cardiac surgery. After the cardiac arrest was achieved the patients received further doses whose number and volume depended on the duration of the cardiac surgery as well as individual factors.

Reporting group title	Buckberg (Group 2)

Reporting group description:

After randomisation the patients underwent cardiac surgery and received the necessary volume of Buckberg blood cardioplegia. The necessary volume is the volume needed for cardiac arrest, which is a prerequisite for the cardiac surgery. Buckberg cardioplegia consists of a cold induction solution, a cold reinfusion solution and a warm reinfusion solution (hot shot).

Serious adverse events	Cardioplexol (Group 1)	Buckberg (Group 2)	
Total subjects affected by serious adverse events			
subjects affected / exposed	55 / 119 (46.22%)	59 / 129 (45.74%)	
number of deaths (all causes)	1	5	
number of deaths resulting from adverse events	1	1	
Vascular disorders			
Haematoma			
subjects affected / exposed	0 / 119 (0.00%)	2 / 129 (1.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemodynamic instability			
subjects affected / exposed	0 / 119 (0.00%)	3 / 129 (2.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Haemorrhage			
subjects affected / exposed	0 / 119 (0.00%)	1 / 129 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	1 / 119 (0.84%)	1 / 129 (0.78%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Aortic valve repair			
subjects affected / exposed	1 / 119 (0.84%)	0 / 129 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemostasis			
subjects affected / exposed	1 / 119 (0.84%)	0 / 129 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Medical device implantation			
subjects affected / exposed	0 / 119 (0.00%)	1 / 129 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sternotomy			
subjects affected / exposed	1 / 119 (0.84%)	0 / 129 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoracotomy			
subjects affected / exposed	0 / 119 (0.00%)	1 / 129 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Death			
subjects affected / exposed	1 / 119 (0.84%)	4 / 129 (3.10%)	
occurrences causally related to treatment / all	1 / 1	1 / 4	
deaths causally related to treatment / all	1 / 1	1 / 4	

Drug ineffective			
subjects affected / exposed	2 / 119 (1.68%)	1 / 129 (0.78%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impaired healing			
subjects affected / exposed	0 / 119 (0.00%)	1 / 129 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiorgan failure			
subjects affected / exposed	0 / 119 (0.00%)	1 / 129 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Systemic inflammatory response syndrome			
subjects affected / exposed	0 / 119 (0.00%)	1 / 129 (0.78%)	
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	0 / 119 (0.00%)	1 / 129 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 119 (0.84%)	3 / 129 (2.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 119 (0.84%)	0 / 129 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	2 / 119 (1.68%)	2 / 129 (1.55%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Psychiatric disorders			
Delirium			
subjects affected / exposed	0 / 119 (0.00%)	1 / 129 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reactive psychosis			
subjects affected / exposed	1 / 119 (0.84%)	1 / 129 (0.78%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood pressure decreased			
subjects affected / exposed	1 / 119 (0.84%)	0 / 129 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrocardiogram Q waves			
subjects affected / exposed	0 / 119 (0.00%)	1 / 129 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Anaemia postoperative			
subjects affected / exposed	10 / 119 (8.40%)	5 / 129 (3.88%)	
occurrences causally related to treatment / all	0 / 10	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
subjects affected / exposed	1 / 119 (0.84%)	0 / 129 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	1 / 119 (0.84%)	0 / 129 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative thoracic procedure complication			

subjects affected / exposed	1 / 119 (0.84%)	1 / 129 (0.78%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postpericardiotomy syndrome			
subjects affected / exposed	0 / 119 (0.00%)	1 / 129 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular bypass dysfunction			
subjects affected / exposed	1 / 119 (0.84%)	0 / 129 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular graft occlusion			
subjects affected / exposed	1 / 119 (0.84%)	0 / 129 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	0 / 119 (0.00%)	5 / 129 (3.88%)	
occurrences causally related to treatment / all	0 / 0	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute coronary syndrome			
subjects affected / exposed	1 / 119 (0.84%)	0 / 129 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	1 / 119 (0.84%)	0 / 129 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	0 / 119 (0.00%)	4 / 129 (3.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
atriventricular block complete			

subjects affected / exposed	0 / 119 (0.00%)	1 / 129 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 119 (0.84%)	0 / 129 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 119 (0.84%)	0 / 129 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac tamponade			
subjects affected / exposed	0 / 119 (0.00%)	2 / 129 (1.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery insufficiency			
subjects affected / exposed	0 / 119 (0.00%)	1 / 129 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
heart failure			
subjects affected / exposed	0 / 119 (0.00%)	1 / 129 (0.78%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracardiac thrombus			
subjects affected / exposed	0 / 119 (0.00%)	1 / 129 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular dysfunction			
subjects affected / exposed	0 / 119 (0.00%)	1 / 129 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			

subjects affected / exposed	3 / 119 (2.52%)	2 / 129 (1.55%)	
occurrences causally related to treatment / all	1 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	0 / 119 (0.00%)	1 / 129 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Right ventricular failure			
subjects affected / exposed	0 / 119 (0.00%)	1 / 129 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Visual field defect			
subjects affected / exposed	0 / 119 (0.00%)	1 / 129 (0.78%)	
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			
subjects affected / exposed	35 / 119 (29.41%)	37 / 129 (28.68%)	
occurrences causally related to treatment / all	0 / 35	0 / 38	
deaths causally related to treatment / all	0 / 0	0 / 0	
Heparin-induced thrombocytopenia			
subjects affected / exposed	1 / 119 (0.84%)	0 / 129 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Normochromic normocytic anaemia			
subjects affected / exposed	1 / 119 (0.84%)	0 / 129 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	0 / 119 (0.00%)	1 / 129 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Abdominal wall haematoma			
subjects affected / exposed	0 / 119 (0.00%)	1 / 129 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	0 / 119 (0.00%)	1 / 129 (0.78%)	
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 lesion			
subjects affected / exposed	1 / 119 (0.84%)	0 / 129 (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			
Actinomycotic pulmonary infection			
subjects affected / exposed	0 / 119 (0.00%)	1 / 129 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	1 / 119 (0.84%)	4 / 129 (3.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasopharyngitis			
subjects affected / exposed	0 / 119 (0.00%)	1 / 129 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 119 (0.00%)	1 / 129 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypoalbuminaemia			

subjects affected / exposed	1 / 119 (0.84%)	0 / 129 (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: 1 %

Non-serious adverse events	Cardioplexol (Group 1)	Buckberg (Group 2)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	99 / 119 (83.19%)	102 / 129 (79.07%)	
Injury, poisoning and procedural complications			
Anaemia postoperative			
subjects affected / exposed	2 / 119 (1.68%)	2 / 129 (1.55%)	
occurrences (all)	2	2	
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	19 / 119 (15.97%)	19 / 129 (14.73%)	
occurrences (all)	19	20	
Atrial fibrillation			
subjects affected / exposed	14 / 119 (11.76%)	17 / 129 (13.18%)	
occurrences (all)	14	18	
Bradycardia			
subjects affected / exposed	3 / 119 (2.52%)	4 / 129 (3.10%)	
occurrences (all)	4	4	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	10 / 119 (8.40%)	8 / 129 (6.20%)	
occurrences (all)	10	8	
Thrombocytopenia			
subjects affected / exposed	2 / 119 (1.68%)	4 / 129 (3.10%)	
occurrences (all)	2	4	
General disorders and administration site conditions			
Impaired healing			
subjects affected / exposed	4 / 119 (3.36%)	2 / 129 (1.55%)	
occurrences (all)	4	2	
Pain			

subjects affected / exposed	2 / 119 (1.68%)	2 / 129 (1.55%)	
occurrences (all)	2	2	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 119 (1.68%)	4 / 129 (3.10%)	
occurrences (all)	2	4	
Nausea			
subjects affected / exposed	3 / 119 (2.52%)	2 / 129 (1.55%)	
occurrences (all)	3	2	
Vomiting			
subjects affected / exposed	1 / 119 (0.84%)	4 / 129 (3.10%)	
occurrences (all)	1	4	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 119 (2.52%)	6 / 129 (4.65%)	
occurrences (all)	3	6	
Lung infiltration			
subjects affected / exposed	2 / 119 (1.68%)	2 / 129 (1.55%)	
occurrences (all)	2	2	
Pleural effusion			
subjects affected / exposed	6 / 119 (5.04%)	11 / 129 (8.53%)	
occurrences (all)	6	14	
Pneumothorax			
subjects affected / exposed	4 / 119 (3.36%)	3 / 129 (2.33%)	
occurrences (all)	4	3	
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	3 / 119 (2.52%)	1 / 129 (0.78%)	
occurrences (all)	3	1	
Psychiatric disorders			
Delirium			
subjects affected / exposed	2 / 119 (1.68%)	3 / 129 (2.33%)	
occurrences (all)	2	3	
Reactive psychosis			
subjects affected / exposed	2 / 119 (1.68%)	6 / 129 (4.65%)	
occurrences (all)	2	6	

Infections and infestations Infection subjects affected / exposed occurrences (all)	 3 / 119 (2.52%) 3	 1 / 129 (0.78%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported