



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 Cardioplexol™ 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™ 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. Multiple 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 occurrences (all) | 2 / 119 (1.68%) 2 | 2 / 129 (1.55%) 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 | 3 / 119 (2.52%) | 1 / 129 (0.78%) | |
| occurrences (all) | 3 | 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