Clinical trial results:
A multi-center, open label, single group, observational study to investigate the effects of training on the administration of Cardioplexol (TM)

Summary

EudraCT number	2018-002311-10
Trial protocol	AT DE
Global end of trial date	18 October 2021

Results information

Result version number	v1 (current)
This version publication date	03 November 2022
First version publication date	03 November 2022
Summary attachment (see zip file)	Clinical Study Synopsis SCT-Cpx-004 (Clinical Study Synopsis SCT-Cpx-004.pdf)

Trial information

Trial identification

Sponsor protocol code	SCT-Cpx-004

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	Blegistrasse 1, Rotkreuz ZG, Switzerland, CH – 6343
Public contact	Hendrik Tevaearai Stahel, Testa Logic GmbH, 0041 763804835, hendrik.tevaearai@gmail.com
Scientific contact	Hendrik Tevaearai Stahel, Testa Logic GmbH, 0041 763804835, hendrik.tevaearai@gmail.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	18 October 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 October 2021
Global end of trial reached?	Yes
Global end of trial date	18 October 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective is to explore the effects of a training program on the rate of correct application of Cardioplexol (TM) for cardioplegic cardiac arrest during cardiac surgical interventions.

Protection of trial subjects:

The study was performed in accordance with the ethical principles that have their origins in the Declaration of Helsinki. The planning and conduct of this clinical study followed the respective national laws of the participating country (competent authorities) and the principles and guidelines for Good Clinical Practice (GCP), Good Laboratory Practices (GLP) and Good Pharmacovigilance Practice (GVP).

Background therapy:

None

Evidence for comparator:

Not applicable. The main objective of this study was to explore the effects of a training program on the rate of correct application of Cardioplexol (TM) for cardioplegic cardiac arrest during cardiac surgical interventions. Hence, no comparator was used.

Actual start date of recruitment	19 November 2018
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: 107
Country: Number of subjects enrolled	Germany: 33
Country: Number of subjects enrolled	Switzerland: 31
Worldwide total number of subjects	171
EEA total number of subjects	140

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)	72
From 65 to 84 years	99
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 29 surgeons and 171 patients were recruited over a period of approx. 3 years in Austria, Germany and Switzerland. Every patient who was a candidate for an elective surgical cardiac procedure was included in this study, provided the operation was being performed via a full or hemi sternotomy and under cardiac arrest and assistance of ECC.

Pre-assignment

Screening details:

A total of 25 surgeons was planned to be trained, accounting for a minimum of 150 patients to be operated in the study, including 50 patients in total in part I (i.e. 2 patients per surgeon), and 100 patients in total in part II (i.e. 4 patients per surgeon). The actual number of surgeons was 29, and a total of 171 patients were screened.

Period 1

Period 1 title	Overall Trial Period
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Observational group
Arm description: -	
Arm type	Observational
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 dose of Cardioplexol (TM) was applied in regular intervals depending on the duration of the cardiac surgery as well as individual factors.

Number of subjects in period 1	Observational group
Started	171
signed informed consent	171
Completed	157
Not completed	14
Screen failure	14

Period 2

Period 2 title	Overall Trial Period _Treated patients
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Observational group

Arm description:

All operated patients.

Part I: Training Program: The training program was addressed to all cardiac surgeons and cardiotechnicians willing to operate patients in this study, and included one theoretical and one practical section. A total of 29 surgeons were recruited and 28 had successfully operated 2 patients each. One surgeon did not qualify to participate in part II of the study as he only operated one patient in part I. Hence, he was replaced by another surgeon by mutual agreement. During the training phase 57 patients were operated.

Part II: Evaluation Part: A total of 28 surgeons participated in this phase and operated 100 patients using Cardioplexol. Parameters regarding the correct administration (primary efficacy endpoint) were collected during the surgical procedure. Secondary endpoints were mainly collected during the first 24 hours following myocardial reperfusion (i.e. after aortic unclamping). A second safety follow-up visit was performed 30 days after surgery.

Arm type	Observational
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 dose of Cardioplexol (TM) was applied in regular intervals depending on the duration of the cardiac surgery as well as individual factors.

Number of subjects in period 2	Observational group
Started	157
Completed	152
Not completed	5
Adverse event, serious fatal	3
Lost to follow-up	2

Baseline characteristics

Reporting groups

Reporting group title	Overall Trial Period

Reporting group description: -

Reporting group values	Overall Trial Period	Total	
Number of subjects	171	171	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	72	72	
From 65-84 years	99	99	
85 years and over	0	0	
Age continuous Units: years			
median	67		
full range (min-max)	39 to 80	-	
Gender categorical Units: Subjects			
Female	38	38	
Male	133	133	

Subject analysis sets

Subject analysis set title	Training Set (TS)
Subject analysis set type	Full analysis

Subject analysis set description:

Statistical evaluation of the primary endpoint was done based on the Analysis Set (AS, n = 100, Phase II), whereas the evaluation of the secondary endpoints as well as the safety and tolerability variables were performed using the Full analysis (AS, n = 100) set and Safety Set (n = 157) (Training set (n = 57) and AS (n = 100).

Subject analysis set title	Analysis Set (AS)
Subject analysis set type	Full analysis

Subject analysis set description:

Statistical evaluation of the primary endpoint was done based on the Analysis Set (AS, n = 100, Phase II), whereas the evaluation of the secondary endpoints as well as the safety and tolerability variables were performed using the Full analysis (AS, n = 100) set and Safety Set (n = 157) (Training set (n = 57) and AS (n = 100).

Subject analysis set title	Safety Set (SS)
Subject analysis set type	Full analysis

Subject analysis set description:

Statistical evaluation of the primary endpoint was done based on the Analysis Set (AS, n = 100, Phase II), whereas the evaluation of the secondary endpoints as well as the safety and tolerability variables were performed using the Full analysis (AS, n = 100) set and Safety Set (n = 157) (Training set (n =

57) and AS (n = 100).

Reporting group values	Training Set (TS)	Analysis Set (AS)	Safety Set (SS)
Number of subjects	57	100	157
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)	28	39	67
From 65-84 years	29	61	90
85 years and over	0	0	0
Age continuous Units: years			
median	67	67	67
full range (min-max)	39 to 80	45 to 80	39 to 80
Gender categorical Units: Subjects			
Female	11	24	35
Male	46	76	122

End points

End points reporting groups

Reporting group title	Observational group

Reporting group description: -

Reporting group title	Observational group

Reporting group description:

All operated patients.

Part I: Training Program: The training program was addressed to all cardiac surgeons and cardiotechnicians willing to operate patients in this study, and included one theoretical and one practical section. A total of 29 surgeons were recruited and 28 had successfully operated 2 patients each. One surgeon did not qualify to participate in part II of the study as he only operated one patient in part I. Hence, he was replaced by another surgeon by mutual agreement. During the training phase 57 patients were operated.

Part II: Evaluation Part: A total of 28 surgeons participated in this phase and operated 100 patients using Cardioplexol. Parameters regarding the correct administration (primary efficacy endpoint) were collected during the surgical procedure. Secondary endpoints were mainly collected during the first 24 hours following myocardial reperfusion (i.e. after aortic unclamping). A second safety follow-up visit was performed 30 days after surgery.

Subject analysis set title	Training Set (TS)
Subject analysis set type	Full analysis

Subject analysis set description:

Statistical evaluation of the primary endpoint was done based on the Analysis Set (AS, n = 100, Phase II), whereas the evaluation of the secondary endpoints as well as the safety and tolerability variables were performed using the Full analysis (AS, n = 100) set and Safety Set (n = 157) (Training set (n = 57) and AS (n = 100).

Subject analysis set title	Analysis Set (AS)
Subject analysis set type	Full analysis

Subject analysis set description:

Statistical evaluation of the primary endpoint was done based on the Analysis Set (AS, n = 100, Phase II), whereas the evaluation of the secondary endpoints as well as the safety and tolerability variables were performed using the Full analysis (AS, n = 100) set and Safety Set (n = 157) (Training set (n = 57) and AS (n = 100).

Subject analysis set title	Safety Set (SS)
Subject analysis set type	Full analysis

Subject analysis set description:

Statistical evaluation of the primary endpoint was done based on the Analysis Set (AS, n = 100, Phase II), whereas the evaluation of the secondary endpoints as well as the safety and tolerability variables were performed using the Full analysis (AS, n = 100) set and Safety Set (n = 157) (Training set (n = 57) and AS (n = 100).

Primary: Number of major deviations from the application of Cardioplexol as determined by the pre-specified training procedure

End point title	Number of major deviations from the application of Cardioplexol as determined by the pre-specified training procedure[1]

End point description:

The primary endpoint of the study was the number of major deviations from the application of Cardioplexol as determined by the pre-specified training procedure (incorrect volume of initial dose, incorrect volume of second/third/fourth dose, incorrect duration of injection of initial dose, incorrect timing of application of initial dose, incorrect timing of application of second/third/fourth dose).
The primary endpoint for each patient was considered to be fulfilled only if the application of Cardioplexol was correct in all of the following points: correct volume of initial dose, correct volume of second/third/fourth dose, correct duration of injection of initial dose, correct timing of application of initial dose, correct timing of application of second/third/fourth dose or if a detailed explanation by the surgeon was given why she/he deviated from the pre-specified training procedures.

End point type	Primary

End point timeframe:

The variables of the primary endpoint (timing and volumes of initial, second, third and fourth doses of Cardioplexol) were documented in an intraoperative worksheet during surgery-visit.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The primary endpoint for the AS was analyzed by using the SAS FREQ Procedure with a two-sided 95% Clopper-Pearson (exact) confidence limits. No major deviation from the application of Cardioplexol as determined by the pre-specified training procedure was observed and the (95% (Clopper-Pearson (Exact)) confidence interval was [0.964; 1.000]. The performed training of surgeons, who had never used Cardioplexol before, resulted in a correct application of Cardioplexol in all100 patients of the AS.

End point values	Analysis Set (AS)			
Subject group type	Subject analysis set			
Number of subjects analysed	100			
Units: number				
No. Major deviations	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Max values of Tnt during the first 24h following myocardial perfusion

End point title	Max values of Tnt during the first 24h following myocardial perfusion

End point description:

Secondary efficacy endpoints were analyzed by descriptive statistics for the Training Set (TS), the Analysis Set (AS) and the Safety Set (SS) population.

End point type	Secondary

End point timeframe:

Measurements to evaluate maximal value of TnT were performed at 3, 6, 12, and 24 hours following myocardial reperfusion.

End point values	Training Set (TS)	Analysis Set (AS)	Safety Set (SS)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	56	100	156	
Units: nanogram(s)/millilitre				
median (full range (min-max))				
Max TnT 24 hour post reperfusion	0.83 (0.16 to 12.38)	0.81 (0.11 to 28.88)	0.82 (0.11 to 28.88)	

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Secondary efficacy endpoints were analyzed by descriptive statistics for the Training Set (TS), the Analysis Set (AS) and the Safety Set (SS) population.

End point type	Secondary

End point timeframe:

Measurements to evaluate maximal value of CK-MB were performed at 3, 6, 12, and 24 hours following myocardial reperfusion.

End point values	Training Set (TS)	Analysis Set (AS)	Safety Set (SS)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	54	98	152	
Units: unit(s)/litre				
median (full range (min-max))				
Max values of CK-MB 24h post reperfusion	43 (20 to 501)	44 (16 to 466)	43 (16 to 501)	

Statistical analyses

No statistical analyses for this end point

Secondary: Time between the aortic cross-clamping and the complete cardiac arrest.

End point title	Time between the aortic cross-clamping and the complete cardiac arrest.

End point description:

Secondary efficacy endpoints were analyzed by descriptive statistics for the Training Set (TS), the Analysis Set (AS) and the Safety Set (SS) population.

End point type	Secondary

End point timeframe:

The time between the aortic cross-clamping and the complete cardiac arrest was documented on a working sheet during surgery.

End point values	Training Set (TS)	Analysis Set (AS)	Safety Set (SS)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	55	95	150	
Units: second				
median (full range (min-max))				
Time to cardiac arrest	10 (3 to 42)	12 (0 to 360)	10 (0 to 360)	

Statistical analyses

No statistical analyses for this end point

Secondary: Cumulative dose of catecholamines during aortic cross-clamping.

End point title	Cumulative dose of catecholamines during aortic cross-clamping.

End point description:

Secondary efficacy endpoints were analyzed by descriptive statistics for the Training Set (TS), the Analysis Set (AS) and the Safety Set (SS) population.

End point type	Secondary

End point timeframe:

The cummulative dose of catecholamines during surgery was documented on a working sheet during surgery.

End point values	Training Set (TS)	Analysis Set (AS)	Safety Set (SS)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	49	75	124	
Units: microgram(s)				
median (full range (min-max))				
Cumulative catecholamine dose during surgery	376 (6 to 3029)	279 (10 to 36780)	319 (6 to 36780)	

Statistical analyses

No statistical analyses for this end point

Secondary: Defibrillation rate after aorta unclamping and coronary reperfusion

End point title	Defibrillation rate after aorta unclamping and coronary reperfusion

End point description:

Secondary efficacy endpoints were analyzed by descriptive statistics for the Training Set (TS), the Analysis Set (AS) and the Safety Set (SS) population.

End point type	Secondary

End point timeframe:

The need for defibrillation and the intesnisty of defibrillation after aortic unclamping and coronary reperfusion were documented for each concerned patient.

End point values	Training Set (TS)	Analysis Set (AS)	Safety Set (SS)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	57	100	157	
Units: number (%)				
Need for defibrillation after aorta unclamping	2	8	10	

Statistical analyses

No statistical analyses for this end point

Secondary: Cumulative dose of catecholamines during the first 24 hours following coronary reperfusion

End point title	Cumulative dose of catecholamines during the first 24 hours following coronary reperfusion

End point description:

Secondary efficacy endpoints were analyzed by descriptive statistics for the Training Set (TS), the Analysis Set (AS) and the Safety Set (SS) population.

End point type	Secondary

End point timeframe:

The cumulative dose of catecholamines during the first 24 hours following coronary reperfusion was documented for each patient.

End point values	Training Set (TS)	Analysis Set (AS)	Safety Set (SS)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	48	83	131	
Units: microgram(s)				
median (full range (min-max))				
Catecholamine doses 24 h post reperfusion	2418 (30 to 223780)	3609 (8 to 500000)	3245 (8 to 500000)	

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of ICU stay

End point title	Duration of ICU stay

End point description:

Secondary efficacy endpoints were analyzed by descriptive statistics for the Training Set (TS), the Analysis Set (AS) and the Safety Set (SS) population.

End point type	Secondary

End point timeframe:

The duration (hours) of ICU stay for each patient was documented.

End point values	Training Set (TS)	Analysis Set (AS)	Safety Set (SS)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	47	87	134	
Units: hour				
median (full range (min-max))				
Duration of ICU stay	21.5 (7 to 262)	21.4 (1.2 to 184)	21.5 (1.2 to 262)	

Statistical analyses

No statistical analyses for this end point

Secondary: Mortality during the first 24 hours following coronary reperfusion

End point title	Mortality during the first 24 hours following coronary reperfusion

End point description:

Secondary efficacy endpoints were analyzed by descriptive statistics for the Training Set (TS), the Analysis Set (AS) and the Safety Set (SS) population.

End point type	Secondary

End point timeframe:

No mortality during the first 24 hours following coronary repersufion was documented in this study.

End point values	Training Set (TS)	Analysis Set (AS)	Safety Set (SS)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	57	100	157	
Units: number				
Patient alive at 24h post perfusion	57	100	157	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All adverse events (AEs) after signature of the informed consent form were recorded irrespective of whether or not they may be related to the study intervention. Investigators followed-up AEs 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	21.0

Reporting groups

Reporting group title	Overall (Safety Set (SS))

Reporting group description:

The safety set (SS) consisted of a total of 157 patients who were operated using Cardioplexol, of whom 156 patients (99.4%) experienced at least 1 AE starting on or after the day of study drug application (treatment emergent adverse event, TEAE). In general, there were 678 treatment emergent adverse events reported (i.e. all AEs which started after or on the same day as surgery).

Serious adverse events	Overall (Safety Set (SS))		
Total subjects affected by serious adverse events			
subjects affected / exposed	82 / 157 (52.23%)		
number of deaths (all causes)	3		
number of deaths resulting from adverse events	3		
Investigations			
Myocardial necrosis marker increased			
subjects affected / exposed	4 / 157 (2.55%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Anaemia postoperative			
subjects affected / exposed	8 / 157 (5.10%)		
occurrences causally related to treatment / all	0 / 8		
deaths causally related to treatment / all	0 / 0		
Wound dehiscence			

subjects affected / exposed	4 / 157 (2.55%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Anastomotic haemorrhage				
subjects affected / exposed	3 / 157 (1.91%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Post procedural haemorrhage				
subjects affected / exposed	2 / 157 (1.27%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Postoperative delirium				
subjects affected / exposed	2 / 157 (1.27%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Weaning failure				
subjects affected / exposed	2 / 157 (1.27%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Atrial fibrillation				
subjects affected / exposed	5 / 157 (3.18%)			
occurrences causally related to treatment / all	2 / 5			
deaths causally related to treatment / all	0 / 0			
Pericardial effusion				
subjects affected / exposed	5 / 157 (3.18%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Atrioventricular block complete				
subjects affected / exposed	3 / 157 (1.91%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Acute myocardial infarction				

subjects affected / exposed	3 / 157 (1.91%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Cardiac failure			
subjects affected / exposed	2 / 157 (1.27%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Ventricular fibrillation			
subjects affected / exposed	1 / 157 (0.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Blood and lymphatic system disorders			
Anaemia	Additional description: For an existing and reportable post-operative anemia the Hb cut-off value of <110 g/L for both female and male was used. In case additional blood transfusions are needed and given in the post-operative period, this anemia will be judged as "serious".		
subjects affected / exposed	47 / 157 (29.94%)		
occurrences causally related to treatment / all	0 / 47		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Impaired healing			
subjects affected / exposed	4 / 157 (2.55%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	3 / 157 (1.91%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Acute respiratory failure			
subjects affected / exposed	2 / 157 (1.27%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 1		
Pleural effusion			

subjects affected / exposed	2 / 157 (1.27%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	2 / 157 (1.27%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	5 / 157 (3.18%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	3 / 157 (1.91%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 1		

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

Non-serious adverse events	Overall (Safety Set (SS))		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	156 / 157 (99.36%)		
Investigations			
C-reactive protein increased			
subjects affected / exposed	9 / 157 (5.73%)		
occurrences (all)	9		
Injury, poisoning and procedural complications			
Anaemia postoperative			
subjects affected / exposed	22 / 157 (14.01%)		
occurrences (all)	22		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	38 / 157 (24.20%)		
occurrences (all)	38		

Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	 73 / 157 (46.50%) 73		
General disorders and administration site conditions Pain subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all)	 30 / 157 (19.11%) 30 11 / 157 (7.01%) 11		
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all)	 15 / 157 (9.55%) 15		
Respiratory, thoracic and mediastinal disorders Pleural effusion subjects affected / exposed occurrences (all)	 28 / 157 (17.83%) 28		
Psychiatric disorders Delirium subjects affected / exposed occurrences (all) Sleep disorder subjects affected / exposed occurrences (all)	 14 / 157 (8.92%) 14 12 / 157 (7.64%) 12		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 April 2019	Due to the request of the competent authority in Germany (BfArM) several amendments were done for the previous study protocol. Exclusion criteria 11: Exclusion criteria updated to define anticoagulatory drugs more precisely Footnote 6:Specification of safety laboratory parameters added Footnote 7: More precise information on time windows were added Footnote 8: More precise information on time windows were added Footnote 9: Sponsor added this footnote to specify parameters more clearly Footnote 10: Sponsor added this footnote to specify parameters more clearly Footnote 11: More precise information on time windows were added Footnote 12: Sponsor added this footnote to specify parameters more clearly 7.7 Safety related criteria for patient's discontinuation include (but are not limited to): Safety related criteria for discontinuation were added 7.8 Any anticoagulant and any other auxiliary medicinal product: Updated to be more precise regarding anticoagulatory drugs 8.4 Premature termination or temporarily suspension: Detailed description of discontinuation criteria added 10.9 The end of the study is defined as the date of the last visit last subject (LVLS): Exact specification of end of study was added
20 January 2020	Page 9 & 24: Inclusion Criterion 3: The operation will be carried out via a full or a hemi sternotomy, under cardiac arrest and under the assistance of a heart lung machine; Page 21: The purpose of this study is to evaluate a training program addressed to all cardiac surgeons and cardiotechnicians who are unexperienced with the use of the cardioplegic solution Cardioplexol when operating patients via a full or a hemi sternotomy and who are willing to operate with Cardioplexol (TM) and aiming at increasing the efficacy of Cardioplexol (TM) administration while reducing the risk of false manipulations. Due to ongoing discussions with the participating investigators, it was realized that the wording of inclusion criterion 3 "The operation can be carried out via a full sternotomy, under cardiac arrest and under the assistance of a heart lung machine", Study Protocol, version 3.0 dated 03.04.2019, might lead to two different interpretations by the investigators. To harmonise the protocol and for better understanding inclusion criterion N°3 was updated. The update is also reflected I the objectives. The respective text can be found in the list of inclusion criteria on pages 9 and 24 of the study protocol, and further in the text on pages 21 and 24.

17 March 2021	Page 21: 1.3.4. Risks In the IB, contraindications for the use of the product are stated. These provisions were integrated in the clinical trial protocol according to the request of the authorities Swissmedic to have harmonized information in the two documents. Page 24-25: 3.1 Training Program It is described more in detail how the training of the surgeons is managed by the sponsor, as recommended by the Swiss Ethical Committee "Kantonale Ethik-kommission Zürich". Page 30: 6.2 Storage conditions In the QIMP it is indicated that after mixing, the reconstituted solution has been shown to be stable for 6 hours at 5°C. The shelf-life of the reconstituted solution is determined as 6 hours. This information was integrated in the Protocol according to the request of the authorities Swissmedic to harmonize the information of the two documents. Page 39 & 40 Chapter 8.2.1 Reporting of SAEs and AEs: 2nd and 3rd paragraphs: It is clarified that the SAE reporting obligations of the investigator should be fulfilled "without delay" as noted by the authorities BfArM and demanded in GCP-V §12 (4). Page 43-44: 3 new Sections 8.5, 8.6., 8.7 added in Chapter 8 "Safety Reporting For the sake of completeness and clarification, as recommended by the Swiss Ethical Committee "Kantonale Ethikkommission Zürich", a detailed description is given which Adverse Events are reported to Competent authorities and Ethics committees (8.5). It is also described which other safety reportings are performed (8.6 and 8.7). It is clarified that these obligations should be fulfilled "without delay" as noted by the authorities BfArM demanded in GCP-V §12 and §13 (8.5 and 8.7). Additionally, all adressees for immediate safety and protective measures are mentioned, as noted by the authorities BfArM. Page 46 Chapter 10.1 "Research Ethics Committee and Regulatory Compliance" : For the sake of completeness, an explanation is given in which international register the clinical study is registered.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported