CLINICAL STUDY SYNOPSIS

1. STUDY INFORMATION

Study Title:	A Multi-Center, Open Label, Single Group, Observational Study to Investigate the Effects of Training on the Administration of Cardioplexol™.
Study and Protocol ID:	SCT-Cpx-004
EudraCT No.:	2018-002311-10
Investigation Product:	Cardioplexol™
Name of Active Ingredient:	Potassium chloride, Magnesium sulfate heptahydrate, Procaine hydrochloride, Xylitol
Indication Studied:	Cardioplegia
Developmental Phase of the Study:	Phase III, Application/Administration Training
Study Initiation Date:	19-Nov-2018
Study Completion Date:	18-Oct-2021
Sponsor:	Swiss Cardio Technologies AG Blegistrasse 1 CH – 6343 Rotkreuz ZG Switzerland
Name of EU Legal Representative:	MIT Gesundheit GmbH
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Version Number and Date	01, 09-Aug-2022

This study was conducted in compliance with Good Clinical Practices (GCP)

2. STUDY SETTING AND STUDY DESIGN

2.1 Study Setting

This study was conducted in 7 university clinics for cardiac surgery, located in three European countries (Austria, Germany Switzerland). See Appendix 1 for a detailed list of participating study centers. A total of 29 cardiac surgeons actively participated in the study.

2.2 Study Design

This was a multi-center, open label, single group, observational study designed to evaluate the effects of a Cardioplexol™ preparation and administration training program proposed to cardiac surgeons and cardiotechnicians inexperienced in the use of Cardioplexol™.

This whole study was performed in two parts. In part I, all participating surgeons were trained on site according to a predefined training schedule. In part II, the effects of the performed training were evaluated.

Part I: Training Program
The training program was addressed to all cardiac surgeons and cardiotechnicians willing to operate patients in this study. Its main aim was to increase the likelihood of a correct administration of Cardioplexol™ and consequently, to reduce the risk of Cardioplexol™ application errors.
The training program included one theoretical and one practical section. Material in electronic and paper form was distributed in advance to each candidate who was invited to get familiar with the Cardioplexol™ solution, its administration principles and particularities as well as the current clinical results. The theoretical section included a presentation, in form of a seminar of approximately 2 hours which was given by a coach who was either a representative of the sponsor itself or a designated representative. The candidates were then asked to answer individually a list of questions in order to make sure that each critical aspect of the preparation and administration was understood. In the case of mistakes, the particular points were re-discussed individually. If the participant successfully completed the theoretical section of the training program and if the coach was satisfied with his/her performance, he/she was then allowed to take part to the practical section of his/her training program.
For that practical section, each cardiac surgeon was asked to perform his/her first two surgeries with Cardioplexol™ in the presence of the training coach who monitored and, if necessary, corrected the administration procedure. Only if the coach was satisfied with the performance of the surgeon, authorization to participate in part II was given. Otherwise, a third patient had to be scheduled and operated in the presence of the coach.

Part II: Evaluation Part
Each surgeon's next consecutive 4 cases with Cardioplexol™ were performed without the presence of the coach

All activities during parts I and II were documented in an electronic Case Report Form (eCRF). All patients enrolled in parts I and II of the study followed the same schedule of five main visits:

1. *Screening visit: to determine patients' eligibility,*
2. *Pre-surgery visit: to collect baseline information,*
3. *Surgery visit: to collect surgery information as well as drug application information,*
4. *Follow-up phase: 24 hours post-surgery to collect safety information,*
5. *Follow-up phase: 30 days after surgery to collect safety and end of study information.*

Patients who satisfied all inclusion and exclusion criteria were included. Technically the conducted cardiac surgery remained unchanged as compared to other standard procedures performed in the respective centers. In brief, after exposure of the heart, the right atrium (or vena cava) and ascending aorta were cannulated with standard equipment. A standard cardiac cannula was also inserted in the aortic root, connected to a 3-way stopcock and de-aired. The Cardio-Pulmonary Bypass (CPB) was started and increased up to 100% flow rate as usual. After verifying that the cardiac cavities were correctly unloaded by the CPB, the ascending aorta was cross-clamped and Cardioplexol™ cardioplegic solution was administered. The surgical procedure was then performed as usual. For the purpose of the study, it was planned that each surgeon operates on at least 6 patients (at least 2 in part I, and 4 in part II).
Parameters regarding the correct administration (primary efficacy endpoint) were collected during the surgical procedure. Patients were evaluated with respect to safety endpoints during the surgery procedure and during the 30 post-operative days. Secondary endpoints were mainly collected during the first 24 hours following myocardial reperfusion (i.e. from the moment the aortic cross-clamp is released). A second safety follow-up visit was performed 30 days after surgery.

Inclusion Criteria:

- Male or female patients between 18 and 80 years of age;
- The patient's pre-operative evaluation indicated the need for a primary elective cardiac coronary artery bypass graft (CABG) operation and/or a cardiac valve repair/replacement;
- The operation was carried out via a full or hemi sternotomy, under cardiac arrest and under the assistance of a heart lung machine;
- Patients who provided signed written informed consent.

Exclusion Criteria:

- Pre-operative ejection fraction (EF) of less than 30%;
- Pre-operative intra-aortic balloon pump (IABP);
- Pre-operative catecholamine support;
- History of myocardial infarction within less than 7 days;
- Previous history of cardiac surgery, including the implantation of a pace maker or an implantable cardioverter defibrillator (ICD);
- Active myocarditis and/or endocarditis;
- Aortic valve insufficiency severity grade > 1;

- Under dialysis;
- Pre-operative serum creatinine value of more than 2.0 mg/dl;
- Known hematologic disorder;
- Previous therapeutic treatment with anti-vitamin K within 5 days before surgery, or with thrombin inhibitors or factor Xa inhibitors within 3 days before surgery;
- History of heparin-induced thrombocytopenia (HIT);
- Participating in a concomitant research study of an investigational product;
- Pregnant or lactating;
- Intravenous drug user, alcohol abuser, prisoner, institutionalized, or was unable to give informed consent;

Study Duration:
Study duration for each patient was approximately 37 days, 7 days screening (up to 7 days before surgery) and 30 days safety follow-up after surgery. The first patient was enrolled on 19-Nov-2018 and last follow-up took place on the 18-Oct-2021.

Number of Patients:
From a statistical point of view, for a sample size of 100, the probability of observing at least one major deviation would be 95% if the probability of a major deviation is 0.03. In other words, it would require a sample size of 100 and the observation of no major deviation, to obtain an upper bound of 0.03 on the 95% confidence interval for the probability of a major deviation. Based on these numbers it was decided that approximately 100 patients should be operated in part II to demonstrate that the training of new surgeons was successful.
The objective of the study was therefore to evaluate the performance of a minimum of 25 surgeons who would have completed the training program and operated additional patients as part of the evaluation part. This would account for a minimum of 150 patients to be operated in the study, including a minimum of 50 patients as part of the training program and 100 as part of the evaluation part.
However, because of possible drop-outs, the study protocol estimated that a total of 165 patients (55 patients in part I and 110 patients in part II) would be necessary to achieve the 100 patients of part II. This corresponds to a 10% drop out rate.

Test Product, Dose and Mode of Administration:

Indication for use: Cardioplegia solution
Mode of application: injection into the aortic root

Cardioplexol™ is composed of potassium, magnesium and xylitol (solution A, 95 mL) and procaine (solution B, 5 mL). Shortly before administration, solutions A and B are mixed (total =100 mL) and distributed in two 50 mL syringes ready to be injected. The content of the first Cardioplexol™ syringe is injected by the surgeon him/herself immediately after the aorta has been cross-clamped, and immediately followed by the content of the second syringe. Depending on the length of the surgery, a second, third, or fourth dose of Cardioplexol™ is administered.

Reference Therapy, Dose, and Mode of Administration: Not applicable

Primary Objective:

- To explore the effects of a training program on the rate of correct application of Cardioplexol™ for cardioplegic cardiac arrest during cardiac surgical interventions.

Secondary Objectives:

- 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.
- To explore the effects on duration in intensive care unit (ICU) stay and on duration of hospitalization.
- To evaluate the safety and tolerability of Cardioplexol™.

Criteria for Evaluation:

Primary Endpoint

- 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).

Secondary Efficacy Endpoints

- Evolution of troponin T (TnT) values during the first 24 hours following myocardial reperfusion.
- Evolution of creatinine kinase muscle brain (CK-MB) values during the first 24 hours following myocardial reperfusion.
- Time between the aortic cross-clamping and the complete cardiac arrest.
- Cumulative dose of catecholamines during aortic cross-clamping.
- Defibrillation rate after aorta unclamping and coronary reperfusion.
- Cumulative dose of catecholamines during the first 24 hours following coronary reperfusion.
- Duration of ICU stay.
- Mortality during the first 24 hours following coronary reperfusion.

Safety Endpoints:

- Serious and non-serious adverse events.
- Laboratory parameters.

3. STATISTICAL METHODS

Statistical evaluation of the primary endpoint, the secondary endpoints as well as the safety and tolerability variables were performed descriptively including confidence intervals using the Statistical Analysis System (SAS-System®, Version 9.4) software package.
Descriptive statistics (number of patients, arithmetic mean, standard deviation (SD), minimum, 1st quartile, median, 3rd quartile and maximum for continuous variables; number of patients, frequencies and percentages for categorical variables) are provided separately for patients included in part I (Training only Set (TOS) and Training Set (TS)), in part II (Analysis Set (AS)), as well as in the total population (Safety Set (SS)). All data are listed by patient, study part and, where applicable, by visit/time point.

Statistical Methods:
Statistical evaluation of the primary endpoint, the secondary endpoints as well as the safety and tolerability variables were performed descriptively including confidence intervals using the Statistical Analysis System (SAS-System®, Version 9.4) software package.
Descriptive statistics (number of patients, arithmetic mean, standard deviation (SD), minimum, 1st quartile, median, 3rd quartile and maximum for continuous variables; number of patients, frequencies and percentages for categorical variables) are provided separately for patients included in part I (Training only Set (TOS) and Training Set (TS)), in part II (Analysis Set (AS)), as well as in the total population (Safety Set (SS)). All data are listed by patient, study part and, where applicable, by visit/time point.

Primary Endpoint Analyses:
The primary endpoint for the AS was analyzed by using the SAS FREQ Procedure with a two-sided 95% Clopper-Pearson (exact) confidence limits.

Secondary Efficacy Analyses:
Secondary efficacy endpoints were analyzed by descriptive statistics using the TS, AS and the SS populations.

Safety Analyses:
All treatment-emergent AEs (AEs which started on or after the day of study drug application) are displayed in summary tables. The tables show the AEs at the Medical Dictionary for Regulatory Activities (MedDRA) preferred term level, the number of patients in whom the events occurred, and the rate of occurrence. AEs are grouped by MedDRA system-organ classes (Both serious and related AEs are presented separately. All AEs and SAEs which started after signing the informed consent and before the study drug application are listed only. These AEs were assessed according to the inclusion criteria, exclusion criteria and other important medical events list to decide the further participation of a patient in this study.
For each laboratory parameter, the following are displayed for each scheduled time point by the number of patients, arithmetic mean, SD, minimum, 1st quartile, median, 3rd quartile and maximum.

Medical events (AEs and medical history) are coded by using MedDRA (Version 21.0). Concomitant and previous medications are categorized using the WHO (World Health Organization) drug standardized coding dictionary and summarized by Anatomical Therapeutic Chemical (ATC) class (Version March 2019).

4. SUMMARY – CONCLUSIONS

A total of 171 patients were included in the study of which 57 (TS) were operated during part I and 100 (AS) were operated during part II of the study. The remaining 14 patients were screening failures and were not operated using Cardioplexol™.
During the study, 29 cardiac surgeons were recruited, of whom 28 (96.6%) successfully operated two patients in part I and qualified to participate in part II. Only one surgeon (study site 05) 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. In addition, two other surgeons who qualified to participate in part II did not operate any patients in part II of the study. One surgeon (study site 05) did not operate patients in part II as most of his patients did not meet the inclusion criteria of this study. Another surgeon (study site 06) did not operate patients in part II as he was partially available at the study site during the recruitment period. Both surgeons were replaced by two other surgeons by mutual agreements.

Efficacy Results:
For the Analysis Set (AS) (n = 100) 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.
The median concentration of the maximal TnT, CK-MB and creatinine values at 24 hours post coronary reperfusion for the Training Set (TS) were 0.8 ng/ml, 43 U/l and 0.9 mg/dl and for the Analysis Set (AS) 0.8 ng/ml, 44 U/l and 0.9 mg/dl respectively. The median time to cardiac arrest for TS and AS was 10 and 12 seconds. For the TS the median cumulative dose of catecholamines during surgery was 376 µg, whereas, it was 279 µg for the AS. The median cumulative catecholamine doses 24 hours post coronary reperfusion were 2418 µg and 3609 µg for TS and AS respectively. Defibrillation (internal or external) was required in 8 patients (2 in TS and 6 in AS). The median duration of ICU stay was 21 hours for the TS and the AS. There were no fatalities during the first 24 hours following coronary reperfusion (mortality 0.0%).

Safety Results:
In total, 678 adverse events (AEs) were reported from 156 patients (99.4%), among them 153 serious adverse events (SAEs) from 82 patients (52.2%) during the study. Generally, the AEs were rated as mild or moderate (616/678 AEs, 90.9% of cases) and were considered unrelated to Cardioplexol™ (662/678 AEs, 97.6%). Causality was related to Cardioplexol™ in only 17/678 AEs, 2.5%. Three patients (2 TS and 1 AS) died during the study. As expected, the mainly effected system organ classes (SOC) were Blood and lymphatic system disorders (147 AEs from 119 patients), Cardiac disorders (99 events from 63 patients), General disorders and administration site conditions (61 events from 51 patients), Injury, poisoning and procedural

complications (72 events from 57 patients) and Respiratory, thoracic and mediastinal disorders (77 events from 51 patients). The most frequently reported AEs were anemia (143 events from 119 patients), anemia postoperative (30 events from 30 patients), pain (30 events from 30 patients) atrial fibrillation (49 events from 43 patients) and pleural effusion (11 events from 10 patients). The only SAE reported in more than 10 patients was anemia (46 cases from 46 patients). All these reported AEs and SAEs can be accounted for by the surgical procedure itself rather than the administration of Cardioplexol™. This is underlined by the fact that most of these events were not seen in a causal relationship to Cardioplexol™. Therefore, Cardioplexol™ is a safe cardioplegic solution during a cardiac surgical intervention under the assistance of a heart-lung machine.

Conclusion:

Cardioplexol™ is a safe and effective cardioplegic solution during a cardiac surgical intervention under the assistance of a heart-lung machine, when it is used correctly according to the application protocol. Furthermore, training of cardiac surgeons in the correct use of Cardioplexol™ is an effective way to prevent administration errors.