# A Prospective Pilot Study of the Combination of CardiaMend and Amiodarone for the Prevention of Postoperative Atrial Fibrillation (POAF) in Patients Undergoing Isolated Cardiac Arterial Bypass Grafting or Isolated Valve Surgery (CAMP POAF)

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**PROTOCOL: CAMP POAF—VERSION 2**

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## 1. PURPOSE AND OBJECTIVES

The purpose of this study is to evaluate the performance of HEMOBLAST ™ in reducing the risk of bleeding associated with on pump sternotomy surgeries requiring intervention.
Open heart cardiovascular procedures, such as coronary artery bypass grafting (CABG), aortic or mitral valve replacement/repair or the combination thereof comes with a degree of increased risk of bleeding.

## 2. DEVICE AND DRUG DESCRIPTION

### 2.1. CardiaMend

CardiaMend Pericardial and Epicardial Reconstruction Matrix (K210331) is an FDA cleared porous acellular matrix derived from fetal bovine dermis designed to provide soft tissue reinforcement, repair, and reconstruction of the pericardium following cardiac surgery. The device is composed of a porous network of collagen fibers that allows for cell and microvascular ingrowth, leading to integration and remodeling of the matrix by the host. The single-layer (1 ply) device is not chemically crosslinked, and consists of a naturally-woven network of collagen fibers. It is lyophilized (freeze-dried) for long term shelf stability and room temperature shipping and storage.

The single use device is supplied terminally sterilized via ethylene oxide and is available in one size ( 7 x 15 cm x 1.0 mm).

### 2.2. Amiodarone

Amiodarone hydrochloride injection, USP contains amiodarone hydrochloride, USP (C25H29I2NO3.HCl), which is approved as a class III antiarrhythmic drug. Amiodarone hydrochloride is (2-butyl-3-benzo-furanyl)[4-[2-(diethylamino)ethoxy]-3,5-diiodophenyl] - methanone hydrochloride. Amiodarone is commonly used in the treatment and prophylaxis of postoperative atrial fibrillation (POAF). This use is considered standard of care by many hospital systems. Guidelines by the American Association of Thoracic Surgeons (AATS) state that for prevention of POAF in high-risk patients undergoing cardiac surgery, preoperative amiodarone can be used to reduce the incidence of AF (Class IIA recommendation) (Frendl et al., 2014)

Amiodarone hydrochloride injection solution is a sterile, clear, pale-yellow micellar solution visually free from particulates. Each milliliter of the amiodarone formulation contains 50 mg of amiodarone hydrochloride, 20.2 mg of benzyl alcohol, 100 mg of polysorbate 80, and water for injection.

## 3. PATIENT POPULATION AND SELECTION CRITERIA

The study patient population will consist of a minimum of 30 patients meeting the following selection criteria:

### 3.1. Inclusion Criteria:

- Subject aged 20-85 years old.
- Patients able to provide written informed consent, understand, and be willing to comply with study-related procedures.
- Participants who are scheduled to undergo open-chest cardiac surgery via complete median sternotomy. Includes:

    - Coronary artery bypass graft (CABG) or valve repair/replacement, or
    - Inclusionary valve repair/replacement procedures for the primary reason for surgery include: aortic valve repair/replacement, mitral valve repair/replacement.
    - Note: Left atrial appendage (LAA) procedures are allowed if CABG and/or valve repair or replacement is the qualifying surgical procedure, but is not a qualifying surgical procedure on its own.
- In sinus rhythm at the time of office visit and prior EKG (note: continuous EKG monitoring for 48 hours is not required).

### 3.2. Exclusion Criteria:

- Subject unable to give voluntary written informed consent, is unlikely to cooperate or is legally incompetent, including subjects who are institutionalized by court or official order, or in a dependency relationship with, testing center or investigator.
- Any condition which could interfere with the subject's ability to comply with the study.
- Ongoing participation in an interventional clinical study or during the preceding 30 days.
- Female subjects who are pregnant, breastfeeding, were pregnant within the last three months, or are planning to become pregnant during the course of the study.
- Active skin or deep infection at the site of implantation.
- History of chronic wounds or wound-healing disorders.
- Known connective tissue diseases (e.g. Ehlers-Danlos syndrome, Epidermolysis bullosa, Marfan syndrome, Osteogenesis imperfecta).
- Immune-suppressed subjects, immune-deficiency subjects (properly managed diabetes mellitus is not an exclusion criterion).
- Concomitant oral or IV systemic corticosteroid therapy and/or other constant anti-inflammatory therapies.
- The subject has an implantable cardiac device (i.e., cardiac resynchronization therapy devices with and without defibrillator capabilities (CRTs and CRT-Ds), implantable cardioverter-defibrillators (ICD) and pacemakers).
- Known history of atrial fibrillation or paroxysmal atrial fibrillation.
- History of ablation for atrial fibrillation.
- Patients already receiving amiodarone as a treatment for atrial fibrillation or ventricular arrhythmias.
- Disease of the left pleura, previous intervention in the left pleural space, or chest deformity.
- Subjects with end-stage chronic-renal disease / dialysis.
- Subjects with heart failure (BNP>1000), low ejection fraction (<35%), end stage renal disease (on dialysis or creatinine >1.8).
- STS risk >5.5% for 30 day mortality.
- Patients electing to receive an ablative procedure for atrial fibrillation during the index operation.

## 4. STUDY DESIGN

This is a single-center, prospective, pilot study, enrolling adult subjects undergoing isolated cardiac arterial bypass surgery or isolated valve surgery, via complete median sternotomy. A total of up to 30 patients will be enrolled in the study.

Patients will be followed for the duration of hospitalization until discharge.

### 4.1. Patient Assignment/Randomization

All study patients will undergo a screening interview wherein their medical history will be reviewed, and inclusion/exclusion criteria verified. The patients meeting the criteria for enrollment in the study will sign the informed consent form and be assigned a patient identification number. Patient identification numbers will be generated chronologically and assigned only to patients who have met all inclusion/exclusion criteria and signed the informed consent form. Patients will be de-identified through their patient identification number, which will be stored in a secure location. The 30 patients enrolled will be attributed to the treatment (intervention).

### 4.2. Screening

- The informed consent form will be reviewed with the patient. The patient will have the study explained and an opportunity will be provided to have all questions answered prior to agreeing to consent to be enrolled in the study.
- Medical history of each patient will be reviewed, and inclusion/exclusion criteria verified.
- Patients meeting the criteria for enrollment in the study will sign the informed consent form and be assigned a patient identification number.

### 4.3. Treatment

#### 4.3.1. CardiaMend

- CardiaMend should be used according to the Instructions for Use with the exception that device hydration is performed with 3 ampules of amiodarone (150mg/3ml) instead of room temperature saline. For best results, the device should be fixed in place using a continuous or interrupted stitch (approximately 1 stitch per cm) to approximate the edge of the pericardial defect. The closed defect should not put pressure on the underlying structures. A non-absorbable monofilament suture is preferred such as 5-0 or 4-0 prolene. A small edge may be left open for drain placement and a small slit for LIMA in case of CABG.

### 4.4. Follow up and evaluation

Patients will have continuous EKG until discharge. If clinically indicated, patients will receive a monitor for home monitoring per standard of care.

### 4.5. Pregnancy

Patients may not participate in this study if they are pregnant, breastfeeding, were pregnant within the last three months or are planning a pregnancy during the course of the study. If patient is of childbearing potential (i.e., females not post-menopausal or not surgically sterile) a negative urine pregnancy test must be conducted within 24 hours of the procedure.

### 4.6. Right to Withdraw or Removal from Study

Patients are free to withdraw from this study at any time. They must inform the Investigator immediately if they intend to withdraw. Their decision to participate in this study or to withdraw from this study will not influence the availability of their future medical care and will involve no penalty or loss of benefits to which they are otherwise entitled.

The Investigator can remove a patient from this study without their consent, for any reason, including, but not limited to:

a. Investigator's judgment that any condition or circumstance may jeopardize the welfare of the patient or the integrity of the study.
b. Patient's failure to follow the instructions of the Investigator.
c. If the study is stopped by the Investigator prior to its completion.

### 5.7 Outcome Measures

#### 5.7.1 Primary

- STS SEQ. #: 6945. Incidence of POAF up to patient discharge as defined as patient experienced atrial fibrillation/flutter (AF) after OR Exit that
    - lasted longer than one hour, or
    - lasted less than one hour but required medical or procedural intervention

#### 5.7.2 Secondary

- Time until discharge
- Burden of atrial fibrillation as defined by additional treatment regimen, additional time in ICU, complications directly associated with atrial fibrillation.

## 5. RISK MANAGEMENT

The Investigator has previous experience with cardiac surgery and the treatment of postoperative complications such as POAF. All other known risks will be disclosed to the patient via the informed consent process.

## 6. ADVERSE REACTIONS

"Side effects" means anticipated reactions to treatment and typically resolve spontaneously. "Anticipated events" means reactions to treatment previously observed that may require medical intervention but are not serious in nature.

Adverse events will be recorded that are related to the procedure, device, and/or amiodarone captured in the medical history.

Adverse events will be followed until the condition resolves, stabilizes, or is otherwise explained, or the patient is lost to follow-up. Patients will be instructed that they may contact the Investigator at any time throughout the course of the study.

The Investigator will review each adverse event and assess its relationship to the study device (not related, unlikely, possible, probable, and highly probable). The following definitions will be used for rating relationship to the treatments or study device:

- Not related – The event is clearly related to other factors such as the patient's clinical state, therapeutic interventions, or concomitant medications administered to them.
- Unlikely – The event was most likely produced by other factors such as the patient's clinical state, therapeutic interventions, or a concomitant medication administered to them, and does not follow a known response pattern to the study device.
- Possible – The event follows a reasonable temporal sequence from the time the study device was used, and/or follows a known response pattern to the study treatments, but could have been produced by other factors such as the patient's clinical state, therapeutic interventions, or concomitant medications administered to them.
- Probable – The event follows a reasonable temporal sequence from the time the study device was used, and follows a known response pattern to the study device; and cannot be reasonably explained by other factors such as the patient's clinical state, therapeutic interventions, or concomitant medications administered to them.
- Highly Probable – The event follows a reasonable temporal sequence from the time the study device was used, and follows a known response pattern to the device; and cannot be reasonably explained by other factors such as the patient's clinical state, therapeutic interventions, or concomitant medications administered to them; and either occurs immediately following device use, or improves on stopping the device, or reappears on repeat exposure, or there is a positive reaction at the treatment site.

Each adverse event reported will be graded on a 3-point severity scale (Mild, Moderate, Severe).

The following definitions for rating severity will be used:

- Mild – easily tolerated, causing minimal discomfort, and not interfering with normal everyday activities.
- Moderate – sufficiently discomforting to interfere with normal everyday activities.
- Severe – incapacitating and/or preventing normal everyday activities.

**A Serious Adverse Event** is any adverse experience that results in any of the following outcomes: death, a life-threatening adverse experience, in-patient hospitalization or prolongation of hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may or may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse experience when, based upon appropriate medical judgment, they may jeopardize the patient or patient may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

If any of the above adverse events are serious as defined by the FDA Code of Federal Regulations (CFR), Title 21, special procedures will be followed. All serious adverse events will be reported within 24 hours of acknowledgment to the device manufacturer (Helios Cardio Inc.) whether or not the serious events are deemed treatment-related. All serious event reporting will adhere to 21 CFR part 812 and the IRB will be notified per IRB reporting guidelines.

The investigator will enter the SAE information into the database and submit a desk copy of the complete SAE report to the files.

Adverse events, whether serious or non-serious, will be followed until the condition is resolved, stabilized, or otherwise explained, or the patient is lost to follow-up.

Outcomes may be classified as resolved, improved, unchanged, worse, fatal, or unknown (lost to follow-up). Following the resolution of any study-associated adverse events there will be no further adverse event reports for that patient.

Complications of the procedure may include:

- Bruising, swelling
- Infection
- Bleeding
- Erythema
- Seroma
- Cyst
- Microcalcification
- Scarring
- Anesthesia toxicity
- Excessive fluid loss
- Damage to skin or nerves
- Heart block
- Death

Proper pre and post treatment safety precautions will reduce the risk of these complications. However, these conditions may or may not resolve over time.

## 7. PROTOCOL DEVIATIONS

All requests for protocol deviations by the Investigator must be approved by the IRB. If an unplanned deviation occurs, the Investigator should inform the IRB per the IRB reporting guidelines.

## 8. DATA COLLECTION AND MONITORING

The device manufacturer (Helios Cardio Inc.) will train the investigative site and may be present at initiation of device use. Case Report Forms/Notes and Investigator Binders will be reviewed for current data. The Investigator will collect data at the end of each follow-up period. The Investigator will list the study on clinicaltrials.gov as required by FDA regulations.

**Data Collection Schedule**

| Assessment | Screening/ Baseline | Procedure | Post Op (12 hours) | Post Op (24 hours) | Post Op (48 hours) | Discharge *+45 days |
|---|---|---|---|---|---|---|
| Eligibility Criteria | X | | | | | |
| Informed Consent | X | | | | | |
| Medical History/Demographics | X | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Medications | X | X | X | X | X | X |
| Surgical Procedure Information | | X | | | | |
| Daily Chest Tube Output | | | X | X | X | |
| AE assessment | | X | X | X | X | X** |
| STS CRF Form | | | | | | X* |

*STS form completed by hospital staff and entered into STS National Database per standard guidelines. Some elements of this form are to be reported for trial purposes. Staff given 45 days to obtain form and report required data.

**AEs and medications will captured until the day of discharge

## 9. CONFIDENTIALITY AND DISCLOSURE OF MEDICAL INFORMATION

As part of this study the Investigator will keep records of patient participation in the study. These study records will include personal information that the patients provide, such as age, sex, etc., the results of the study, information about response to treatments, photographs taken during the study and other medical information relating to participation in the study.

Under Federal law, the study records cannot be used or disclosed by the Investigator for research purposes unless patients sign the informed consent authorization.

Some or all of the test results will be reported to Helios Cardio Inc., the manufacturer of the CardiaMend device. Study records will be assigned a code number by the study team and the patient will not be identified by name in the study records that are sent to Helios Cardio.

However, Helios Cardio will only use the information for purposes of the study and business needs and will not disclose the study records to parties other than the FDA and similar government agencies, unless disclosure is required by law. If reports or articles are written about the study, patients will not be identified by name in them. The study records may be retained at the study facility indefinitely following the completion of the study.

## 10. LABELING

Directions for use are contained in the Instructions for Use for the study device.

## 11. CLINICAL STUDY CONDUCT

The study will be conducted in accordance with the protocol, International Conference on Harmonization (ICH) GCP guidelines, applicable regulations and guidelines governing clinical study conduct and ethical principles that have their origin in the Declaration of Helsinki. The Investigator must ensure that the study is conducted in accordance with the provisions as stated in the FDA regulations and complies with the applicable local or regional regulatory requirements.

## 12. INFORMED CONSENT

During patient screening, the Investigator or a representative on their behalf will perform the informed consent process. At the screening, all aspects of the study will be discussed with the patient. A signed informed consent form (ICF) shall be obtained from the patient, clearly indicating his/her understanding of the study requirements, as well as the possible risks involved with study participation.

## 13. DATA ANALYSIS

The initial pilot study will assess safety and the burden of atrial fibrillation vs historical controls. Length of stay and percentage of patients with atrial fibrillation will be compared to historical controls.

## 14. REPORTING FOR THE STUDY

A study summary report will be generated by the Investigator. It will include a description of the clinical conduct of the study and results, and the statistical analysis described in the data analysis section of this protocol.

## 15. RESPONSIBILITY OF THE INVESTIGATOR

The Investigator is responsible for ensuring that the clinical study is performed in accordance with the Declaration of Helsinki (revised version of Edinburgh, Scotland, 2000 including notes of clarification, Washington, 2002 and Tokyo, 2004) and FDA Good Clinical Practice Regulations (21 CFR parts 50, 56, and 812).

## 16. PROCEDURE FOR AMENDMENTS TO THE PROTOCOL

No deviations from this protocol will be permitted, except in a medical emergency. All revisions and/or amendments to the protocol must be approved in writing by the appropriate Institutional Review Board.

## 17. INSTITUTIONAL REVIEW BOARD

This protocol, informed consent forms, and any amendments to the protocol will be reviewed by the appropriate Institutional Review Board prior to initiation. The study will not be initiated without the approval from the Institutional Review Board.

## 18. TERMINATION OF STUDY

The Investigator reserves the right to discontinue the study for safety reasons at any time.

## 19. STUDY RECORDS

All records and documents pertaining to the study will be maintained in appropriate permanent files as per the ICH guidelines for Essential Documents for the Conduct of a Clinical Trial and 21 CFR 11, and will be available for inspection by the Food and Drug Administration at any time.

## 20. CONFIDENTIALITY

After the informed consent form is signed, each patient will be entered on a screening/enrollment log, which will be kept with the study records. Once a patient is consented, a unique patient identification number will be assigned. No two patients will have the same patient identification number. This patient identification number will identify the patient throughout the study and will be used for all source documents, and Data Collection Forms. The patient identification number will be held confidential so far as permitted by law. Investigative site staff, under certain circumstances, the FDA and Institutional Review Board (IRB) will be able to inspect and have access

to the patient identification number and the confidential data that it links to. Any publication or presentation of data will not contain any identifiable patient information.

## 21. DATA SECURITY

To ensure the privacy and confidentiality of data for this protocol, the data will be stored in a restricted access location at the Investigator's site. Access to the project directory containing the data will be limited to the Investigator and study staff. Information about data security awareness is promoted through user training and education, supplemented by policies and procedures. Password protection will be used for all transactions that allow viewing, editing, and analysis of data, or that provide access to data fields derived from the original source documents.

## 22. REFERENCES


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