

**AMGeL**

**“The Intra-Operative Application of Amiodarone Releasing Hydrogel to Prevent Postoperative Atrial Fibrillation in Patients Undergoing Lung Transplantation.”  
Clinical Investigation Plan (CIP)**

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**PRINCIPAL INVESTIGATOR SIGNATURE PAGE**

The Intra-Operative Application of Amiodarone Releasing Hydrogel to Prevent Postoperative Atrial Fibrillation in Patients Undergoing Lung Transplantation (AMGeL)  
Version #1

I have read and agree to adhere to the clinical investigational plan and all regulatory requirements applicable in conducting this clinical study.

**Principal Investigator**

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Signature: \_\_\_\_\_

Date: \_\_\_\_\_

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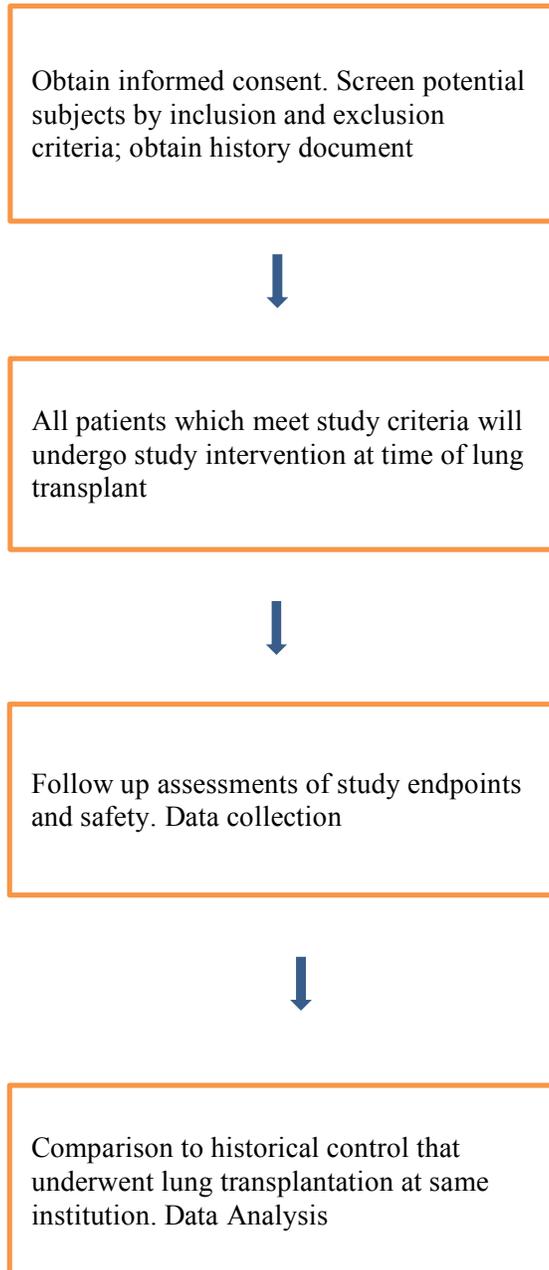
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## 1.0 SYNOPSIS

Title:	The Intra-Operative Application of Amiodarone Releasing Hydrogel to Prevent Postoperative Atrial Fibrillation in Patients Undergoing Lung Transplantation
Acronym:	AMGeL
Purpose:	The purpose of the study is to evaluate the intraoperative application of an amiodarone containing hydrogel for prevention of post-operative atrial fibrillation in lung transplant patients.
Objectives:	<p>Primary Objective: The purpose of the study is to evaluate the intraoperative application of an amiodarone containing hydrogel for prevention of post-operative atrial fibrillation in lung transplant patients.</p> <p>Secondary Objective: Demonstrate safety and effectiveness of the amiodarone hydrogel application during lung transplantation in preventing atrial arrhythmias during first year of transplantation.</p>
Endpoints:	<p>Primary Endpoint will evaluate: --Development of post-operative atrial fibrillation during initial hospitalization</p> <p>Secondary Endpoints to be evaluated: --Length of Stay initial hospital stay -Development of post-operative atrial fibrillation during first year post transplant -Thirty-day survival -One-year Survival</p>
Design:	<p>In Lung Transplant patients, we propose use of amiodarone hydrogel during surgery will result in reduced rates of post-op atrial fibrillation.</p> <p>The expected total duration of the study is 24 months.</p> <p>The clinical study will be conducted in 1 center in the United States.</p> <p>20 subjects will be enrolled in this study.</p> <p>The enrolled subjects will be compared to the historical controls who did not receive the amiodarone gel therapy during lung transplant surgery.</p> <p>Subjects will be followed for 1 year.</p>
Drug used:	Amiodarone Hydrogel in Coseal
Study Population	Male and female patients, age 18 years and older with end stage Lung Disease who require Lung Transplant.
Inclusion/Exclusion Criteria	<p>Inclusion Criteria</p> <ol style="list-style-type: none"> <li>1) Subject or legal representative has signed Informed Consent Form (ICF)</li> <li>2) Undergoing lung transplant at the Jewish Hospital</li> <li>3) Age <math>\geq</math> 18 years</li> </ol>

	<p>4) Subjects willing and able to comply with the follow up requirements of the study</p> <p>Exclusion Criteria</p> <ol style="list-style-type: none"> <li>1) Patients with previous history of atrial fibrillation.</li> <li>2) Patients with previously documented allergy or adverse reaction to amiodarone.</li> <li>3) Patients with previous ablation for atrial fibrillation</li> <li>4) Patients with an implantable pacemaker.</li> </ol> <p style="text-align: center;">•</p>
<p>Data Collection</p>	<p>Subjects will be evaluated and enrolled for receiving the amiodarone gel during their waiting period for lung transplantation.</p> <p>Patients who consent to be part of the study will receive the amiodarone gel during the surgery for lung transplantation. The amiodarone gel will be sprayed just after transplanting the lung(s). Patients will then be followed in-hospital until discharge and data regarding the primary study end-point will be captured.</p> <p>Patient study visit follow-up will occur post-operatively as per standard of care after lung transplantation. Patients' follow-up is generally comprised of routine history and physical examination. These will provide sufficient data to address the secondary study end-points. All follow up data will be collected from the subject's medical records.</p> <p style="text-align: center;">•</p>

### 1.1 STUDY FLOW CHART



## 1.2 STUDY CONTACTS

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## 2.0 BACKGROUND AND JUSTIFICATION FOR CLINICAL STUDY

Approximately 1900 transplants are performed in the US annually. Lung transplantation remains the gold standard treatment for patients with end stage lung disease. This includes patients with range of etiologies such as Idiopathic Pulmonary Fibrosis, COPD and Cystic Fibrosis. One of the more common post-operative complications in patients undergoing lung transplantation is the development of atrial fibrillation. Recent studies have demonstrated that approximately 1/3 of patients will develop atrial fibrillation during their post-operative course. While it is uncertain if the development of post-operative atrial fibrillation affects survival, it does significantly increase length of hospital stay. Importantly, a portion of the patients that develop atrial fibrillation post-operatively will require cardioversion prior to discharge.

Currently one of the main stays of treatment for post-operative atrial fibrillation is systemic (oral or intravenous) amiodarone, which is a class III antiarrhythmic agent. While this particular drug is effective, it does carry the risk of several known complications. Due to the drug's pharmacokinetics, amiodarone concentrates in organs with high lipid content such as the thyroid, liver and lung. Amiodarone has several known adverse effects on the lung ranging from acute respiratory distress syndrome to more chronic disease such as Interstitial pulmonary fibrosis. Amiodarone can have detrimental effects on the liver which in rare cases could lead to cirrhosis. Additionally, amiodarone can cause thyrotoxicosis as early as a few weeks after the initiation of amiodarone.

The adverse events listed above are related to the cumulative dose of amiodarone. Typically, when amiodarone is initiated, patients receive a loading dose of 600-800mg daily until the cumulative dose reaches 10 grams, after which patients will receive 200mg daily as a maintenance dose. Minimizing the cumulative dose of amiodarone by using a local application, could mitigate the potential adverse drug toxicities. In a previous study, the application of an amiodarone releasing hydrogel performed intraoperatively was shown to significantly decrease the rates of post-operative atrial fibrillation in patients undergoing coronary artery bypass. Currently for patients undergoing lung transplantation, there is not a safe and effective measure available to prevent post-operative atrial fibrillation.

We aim to study the intraoperative application of an amiodarone containing hydrogel for prevention of post-operative atrial fibrillation in lung transplant patients.

In patients undergoing lung transplantation, post-operative atrial fibrillation is common and leads to prolonged hospital course and increased healthcare expenditures. Amiodarone is a main stay of therapy for atrial fibrillation, however this drug does have potential serious complications when administered systemically. The local application of amiodarone, could potentially decrease the rates of atrial fibrillation, while avoiding the systemic complications. This has the potential to decrease length of stay and decrease additional procedures (ie. Cardioversion) in patients undergoing lung transplantation.

### **3.0 RISKS AND BENEFITS OF THE CLINICAL STUDY**

#### **3.1 DESCRIPTION OF SUBJECT POPULATION**

Male and female patients, age 18 years and older with end stage lung disease requiring lung transplantation and are currently on the lung transplant waiting list are the population for this research.

#### **3.2 ANTICIPATED CLINICAL BENEFITS**

Lung transplant patients have approximately 30% risk of developing atrial arrhythmias post-operatively. Currently, there is no preventive treatment strategy to reduce this burden. By conducting this study, we anticipate to demonstrate that amiodarone application through a hydrogel during the surgery is a safe and effective treatment strategy for the prevention of atrial arrhythmias.

#### **3.3 ANTICIPATED ADVERSE EVENTS AND ADVERSE DRUG EFFECTS**

##### **3.3.1 ANTICIPATED ADVERSE EVENTS AND ADVERSE DRUG EFFECTS SECONDARY TO AMIODARONE HYDROGEL APPLICATION**

Currently, the only additional risk incurred by participating in the described in this clinical investigation plan is temporary bradycardia (slow heart rate). In a previous study, by Feng et al, in patients undergoing coronary artery bypass surgery, a similar intervention using amiodarone gel was assessed and the only complication noted in those patients was bradycardia. This complication was temporary and was not clinically significant. In the above study this was a common complication (greater than 10%), however it was not serious and did not require any additional treatment.

If bradycardia is severe enough to be symptomatic, transvenous pacing may be required, in order to maintain a normal heart rate. The risks from this procedure include but are not limited to: death, femoral hematoma, arrhythmias, fever, cardiac tamponade, deep venous thrombosis, and sepsis.

Animal studies and a previous human study did not demonstrate any evidence that the local application of an amiodarone gel to the heart could result in tissue damage. However, tissue damage has been reported if leaks from the vein occur when using intravenous amiodarone

A one-time dose of amiodarone will be used in the preparation of the amiodarone hydrogel. While, the dose used in this study is extremely low, there are several known side effects of amiodarone use, which typically occur when amiodarone is administered systemically for an extended period of time. These potential side effects include: nausea, vomiting, photosensitivity, fatigue, dizziness, paraesthesias, constipation, anorexia, visual disturbances, liver damage, pulmonary fibrosis, hypo or hyperthyroidism, insomnia, headache, sleep disturbances, congestive heart failure, cardiac arrhythmias, SA node dysfunction, abdominal pain, hepatic disorders, flushing, abnormal taste and smell, edema, abnormal salivation and coagulation abnormalities.

##### **3.3.2 ANTICIPATED ADVERSE EVENTS AND ADVERSE DRUG EFFECTS SECONDARY TO LUNG TRANSPLANT**

There are numerous risk to patients undergoing lung transplantation which include but are not limited to: death, hemorrhage, infection, viral infections, arrhythmias, rejection of transplant lung, bronchial anastomotic dehiscence, pulmonary edema, pneumothorax, hemothorax, empyema, pulmonary embolism, post transplant lymphoproliferative disorder, recurrence of primary disease and bronchogenic carcinoma.

#### **3.4 RESIDUAL RISKS ASSOCIATED WITH THE DRUG UNDER INVESTIGATION, AS IDENTIFIED IN THE RISK ANALYSIS REPORT**

Due to the short half-life and one time application of the amiodarone gel, no long term residual risk is anticipated.

### **3.5 RISKS ASSOCIATED WITH PARTICIPATION IN THE CLINICAL STUDY**

The potential risks including anticipated adverse events and possible interactions with amiodarone gel application are expected to be similar to those already reported.

### **3.6 STEPS THAT WILL BE TAKEN TO CONTROL OR MITIGATE THE RISKS**

Mitigations and treatment for all adverse events will be per the current practice standards/standards of care as determined by the investigator. Subject risk from study participation will be mitigated by ensuring that only experienced personnel will be involved in the care of research subjects. The study staff will undergo product, application and study training prior to initiating study activities, and all subjects will be closely monitored throughout the study duration, at pre-specified time points to assess their clinical status.

### **3.7 RISK-TO-BENEFIT RATIONALE**

The potential benefit to patients who undergo the intraoperative application of an amiodarone containing hydrogel at the time of lung transplantation is a reduction in post-operative atrial fibrillation. Currently 1/3 of lung transplant patients develop atrial fibrillation during the post-operative course following lung transplantation. The development of atrial fibrillation significantly increases length of stay and cost of hospitalization for patients following lung transplantation. In a previous study in patients undergoing cardiac surgery, the application of an amiodarone gel significantly reduced the incidence of post-operative atrial fibrillation. The potential benefit of the reduction of atrial fibrillation outweighs the small risk of a transient episode of bradycardia, which was seen in previous studies.

## **4.0 STUDY DESIGN**

### **4.1 PURPOSE**

The purpose of the study is to evaluate the intraoperative application of an amiodarone containing hydrogel for prevention of post-operative atrial fibrillation in lung transplant patients.

### **4.2 STUDY DESIGN AND SCOPE**

This study will prospectively evaluate the use of an amiodarone releasing hydrogel applied to the pulmonary veins and atria at the time of lung transplantation. This study will include patients undergoing lung transplantation at Jewish Hospital, Louisville KY. The prospective group will be compared to historical controls from the same institution. We will access medical records and database entries for those patients undergoing lung transplantation after January 1st 2005 in order to obtain matched controls for analysis. Informed consent will be obtained from the prospective cohort prior to patient enrollment. This pilot study will be used to obtain preliminary data in order to proceed with a larger randomized, controlled trial.

#### **4.2.1 Intraoperative Application**

The Amiodarone Hydrogel will be prepared per study protocol (see attached). CoSeal Surgical Sealant (Baxter Healthcare) consists of 2 formulations of synthetic polyethylene glycols, a dilute hydrogen chloride solution along with a sodium phosphate/sodium carbonate solution. These separate solutions are mixed at the time of application to form a hydrogel. Amiodarone hydrochloride powder (1mg/kg) will be mixed with CoSeal at the time of application to form an amiodarone containing hydrogel. The dosing of amiodarone is based on previous study using amiodarone hydrogel in post-operative coronary artery bypass patients. This hydrogel will be delivered utilizing a CO2 driver along the pulmonary vein and arterial anastomoses, and to the surface right and left atria.

#### **4.2.2 Data Collection**

Data from the prospective cohort will be collected and stored in a HIPAA compliant, encrypted and secured database. A detailed preoperative history will be obtained from the patients including: age, gender, reason for transplant, pre-transplant oxygen requirement, previous myocardial infarction, previous sternotomy, previous arrhythmia, smoking history, diabetes, stroke, hypertension. Intraoperative patient characteristics obtained will include: single lung transplant, double lung transplant, cardiopulmonary use, and ischemic time. Post-operative

patient characteristics will include: ICU duration, length of stay, post-operative atrial fibrillation during first week post-transplant, atrial fibrillation at time of discharge, atrial fibrillation at time of post-operative follow up, atrial fibrillation requiring cardioversion, atrial fibrillation requiring new anti-arrhythmic medication, asymptotic bradycardia and bradycardia requiring temporary pacemaker. Data will be collected from the subject's medical records immediately following their visits.

#### **4.2.3 Number of subjects required to be included in the study**

Enrollment will include at least 20 patients undergoing lung transplant. The subjects will be evaluated with the historic controls (50).

#### **4.2.4 Estimated time needed to enroll this subject population**

Enrollment is expected to occur over a 24-month period with the total duration of the study continuing up to 30 months, dependent on the rate of enrollment and the regulatory timeline.

### **4.3 OBJECTIVES**

#### **4.3.1 Primary Objective**

Demonstrate safety and effectiveness of the amiodarone hydrogel application during lung transplantation in preventing atrial arrhythmias during index hospital stay.

#### **4.3.2 Secondary Objective**

Demonstrate safety and effectiveness of the amiodarone hydrogel application during lung transplantation in preventing atrial arrhythmias during first year of transplantation.

### **4.4. ENDPOINTS**

#### **4.4.1 Primary Endpoint**

-Development of post-operative atrial fibrillation during initial hospitalization

#### **4.4.2 Secondary Endpoints**

- Length of Stay
- Development of post-operative atrial fibrillation during first year post transplant
- Thirty-day survival
- One-year Survival

### **4.5 INCLUSION AND EXCLUSION CRITERIA**

A subject, who meets all of the inclusion criteria, and none of the exclusion criteria, is eligible to participate in this study.

All subjects enrolled in the clinical study (including those withdrawn from the clinical study or lost to follow-up) will be accounted for and documented, assigning an identification code linked to their names, alternative identification or contact information.

A log with enrollment information will be kept up to date throughout the clinical study by the principal investigator or his/her authorized designee. To ensure subject privacy and confidentiality of data this log must be maintained throughout the clinical study at the clinical site.

To participate in this clinical study, the subject must meet all of the following inclusion criteria and none of the exclusion criteria:

#### Inclusion Criteria

- Subject or legal representative has signed Informed Consent Form (ICF)
- Undergoing lung transplant at the Jewish Hospital - Patients undergoing single or double lung transplantation at Jewish Hospital (Louisville, KY). Indications for transplantation will include: Idiopathic Pulmonary Fibrosis, COPD and Cystic Fibrosis. Patients requiring cardiopulmonary bypass (CPB) along with those not requiring CPB will be included
- Age  $\geq$  18 years
- Subjects willing and able to comply with the follow up requirements of the study

#### Exclusion Criteria

- Patients with previous history of atrial fibrillation
- Patients with previously document allergy or adverse reaction to amiodarone
- Patients with previous ablation for atrial fibrillation
- Patients with an implantable pacemaker
- Patients who are pregnant

## 4.6 SUBJECT POPULATION

### 4.6.1 Subject Screening

All subjects listed for lung transplant at the investigational site will be screened by a member of the investigational team previously trained on the CIP and delegated to do so.

Subjects who do not meet the inclusion/exclusion criteria will not be eligible to participate in this study.

Subjects meeting the inclusion/exclusion criteria will be fully informed about the study and invited to participate in the study. In case the subject agrees to participate, a duly signed and dated Subject Informed Consent Form/Authorization will be obtained.

### 4.6.2 Point of Enrollment

Subjects are considered in screening for the study when the subject has provided written Subject Informed Consent. (Refer to section 4.7 for the Informed Consent Process). Subjects are considered enrolled when they have the study intervention.

## 4.7 INFORMED CONSENT PROCESS

### 4.7.1 General process

Prior to enrolling in the clinical study and conducting study-specific procedures, all subjects will be consented, as required by applicable regulations and the center's IRB. The consent form must be signed and dated by the subject and by an investigator and the person obtaining the consent if not the investigator.

The principal investigator or his/her authorized designee will conduct the Informed Consent Process. This process will include a verbal discussion with the subject on all aspects of the clinical study that are relevant to the subject's decision to participate in the clinical study.

The subject shall be provided with the informed consent form that is written in a language that is understandable to the subject and has been approved by the center's IRB. Failure to obtain informed consent from a subject prior to study enrollment should be reported to the reviewing center's IRB consistent with the center's IRB reporting requirements.

## 5.0 DRUG UNDER INVESTIGATION

### 5.1 DRUG DESCRIPTION

Amiodarone is a class III antiarrhythmic, which works by a prolongation of the myocardial cell action potential duration and refractory period and noncompetitive  $\alpha$ - and  $\beta$ -adrenergic inhibition.

### 5.2 INTENDED INDICATION

The intended indication is to use the intraoperative application of an amiodarone containing hydrogel in patients undergoing lung transplantation in order to decrease post-operative atrial fibrillation.

### 5.3 AMIODARONE HYDROGEL

The Amiodarone Hydrogel will be prepared per study protocol (see attached). CoSeal Surgical Sealant (Baxter Healthcare) consists of 2 formulations of synthetic polyethylene glycols, a dilute hydrogen chloride solution along with a sodium phosphate/sodium carbonate solution. These separate solutions are mixed at the time of application to form a hydrogel. Amiodarone hydrochloride powder (1mg/kg) will be mixed with CoSeal at the time of application to form an amiodarone containing hydrogel. The dosing of amiodarone is based on previous study using amiodarone hydrogel in post-operative coronary artery bypass patients. This hydrogel will be delivered utilizing a CO2 driver along the pulmonary vein and arterial anastomoses, and to the surface right and left atria.

Table 1. Summary of Proposed Drugs/Drugs

Drug Component	Model/Type	Investigational or Market Released
Amiodarone	Amiodarone	1985 Market Release
CoSeal	CoSeal	2003 Market Release

### 5.4 DRUG ACCOUNTABILITY

The Principal Investigator or an authorized designee will maintain separate drug accountability logs documenting the use of each of the products above. For Amiodarone, only lot/batch/serial number or unique code, dates of dispensation, subject identification, date of use, expiration date, and final disposition of drug will be documented. For the CoSeal, a dedicated study accountability log will document the date of receipt, the identification of each drug (batch number, serial number or unique code), the subject identification, the date of use, the location, the expiration date and final disposition.

### 5.5 DRUG HANDLING AND STORAGE

All products will be stored, according to the labeling. Please refer to the product labeling for additional information on drug handling and storage.

## 6.0 PROCEDURES

A subject is considered to have successfully completed the study upon completion of the 1-year visit

	Screening Visit	Baseline Data Collection	Lung Transplant and hospital follow up	Standard of Care Follow up
Consent Process	X			
Data collection from medical records		X	X	X
Confirm Eligibility	X	X	X	
Application of Amiodarone gel			X	

### 6.1 PROCEDURES

The clinical study will be conducted in accordance with the CIP. All parties participating in the conduct of the clinical study will be qualified by education, training, or experience to perform their tasks and this training will be documented appropriately.

The clinical study will not commence until approval from the IRB and relevant regulatory authorities are obtained.

### 6.2 Visit Schedule

#### 6.2.1 Screening

Study personnel will screen all patients listed on the lung transplant waiting list to determine subject eligibility for the study.

Potential subjects will be contacted to explain the study and determine if they would be interested in participating.

#### 6.2.2 Consent

If potential subjects are interested in participating in the study; they will meet with a study team to discuss the study and sign consent. No study procedures or data collection will occur before a consent form is signed.

#### 6.2.3 Baseline data collection

Data will be collected from the subject's medical records including medical/surgical history, physical exam, current medications, laboratory assessments, electrocardiogram results, pulmonary function test, CT scan results. These tests are conducted as standard of care for subjects undergoing lung transplant.

#### 6.2.4 Prior to lung transplant

When a consented subject is informed that they are scheduled for a lung transplant, the study team will review their medical record to confirm they are still eligible to participate in the study. If they meet any of the exclusion criteria since the initial consent was signed, they will be considered a screen failure and will not undergo the study procedure.

#### 6.2.5 During Lung Transplant Surgery

During the lung transplant surgery the amiodarone-containing hydrogel will be delivered utilizing a CO2 driver along the pulmonary vein and arterial anastomoses, and to the surface of the right and left atria.

### **6.2.6 Follow up data collection**

Data will be collected from the subject's medical records during their standard of care visits post transplant. Standard of care visits include weekly Clinic visits for 1-month post discharge following lung transplantation. Patients will then have monthly regularly scheduled clinic appointments for the first year after transplantation.

In case the subject was already consented to participate in the study, but becomes ineligible by a change in status so that they no longer meet inclusion/exclusion criteria, the following actions will be taken.

- If study procedure/drug implant has not occurred:
- Document enrollment information (name of the study, date of consent and inclusion/exclusion) in the hospital records; complete the Enrollment and Withdrawal Forms. The form must be authorized / approved by the principal or delegated investigator.
- Inform the subject about the screen failure.
- The EC/IRB and CA should be notified appropriately about any deviations with regards to obtaining the informed consent (if applicable).

### **6.3 EARLY TERMINATION**

The study team will attempt to collect all relevant information for the study subjects who withdraw from the study early (including CRF Study Completion Form). The following information will be collected:

- Updated medical and surgical history
- Assessment of AEs that occurred since the last visit
- Abbreviated physical examination (only significant changes since Enrollment) including vital signs (temperature, heart rate, respiratory rate, blood pressure), and weight
- Medication Review

All reasonable efforts will be made to retain subjects in the clinical trial until its completion. Subjects lost to follow-up will be withdrawn only after a minimum of two documented phone calls are made by personnel at the study center to the patient or emergency contact.

### **6.4 CRITERIA AND PROCEDURES FOR SUBJECT WITHDRAWAL OR DISCONTINUATION**

Subjects must be informed about their right to withdraw from the study at any time and for any reason without sanction, penalty or loss of benefits to which the subject is otherwise entitled and withdrawal from the study will not jeopardize their future medical care or relationship with the investigator. Subjects will be asked to specify the reason for the termination, but have the right not to answer.

The investigator may decide to withdraw a subject from the study at any time with reasonable rationale. The subject's future care will not be influenced by a decision, voluntary or otherwise, to withdraw from the study. All reasonable efforts should be made to retain the subject in the clinical study until completion of the study.

Reasons for subject's withdrawal include, but are not limited to:

- Subject refuses to continue participating in the study
- Subject does not meet the inclusion/exclusion criteria and does not require additional follow-up for safety reasons.
- Subject is deceased (cause must be documented)
- Subject's non-compliance
- Subject's participation is terminated by the PI or investigator, although the subject consented, since participation is no longer medically appropriate
- Subject is 'lost to follow up': Subject does not adhere to the scheduled follow up visits but has not explicitly requested to be withdrawn from the clinical study. Site personnel should at all times make

all reasonable efforts to locate and communicate with the subject in order to achieve subject compliance to the scheduled follow up visits:

1. A subject will be considered 'Lost to Follow Up' after a minimum of 2 phone calls of a physician or delegate at the investigational site to the subject or contact. These 2 phone calls need to be documented in the subject's hospital records.

Note: If a subject misses one or more of the scheduled follow up visits (inclusive of the assigned visit windows), this will be considered as a missed visit. The subject may therefore still return for subsequent visits and will not be excluded from the study.

If a subject withdraws from the clinical study, the site will record the subject's reasons for withdrawal (if available), on a Withdrawal CRF.

When subject withdrawal from the clinical study is due to a study related adverse event the subject will be followed until resolution of that adverse event or determination that the subject's condition is stable. The status of the subject's condition should be documented at the time of withdrawal.

## **7.0 RISK**

There are numerous risks when undergoing lung transplantation. Subjects will be informed of these risks and sign a separate surgery consent. Currently the only identified potential risk incurred by participating in this study is temporary bradycardia (slow heart rate). In a previous study in patients undergoing coronary artery bypass surgery, a similar intervention using amiodarone gel was assessed and the only complication noted in those patients was temporary, not clinically significant bradycardia. In the previous study this was a common complication (greater than 10%), however it was not serious and did not require any additional treatment.

If bradycardia is severe enough to be symptomatic, transvenous pacing may be required, in order to maintain a normal heart rate. The risks from this procedure include but are not limited to: death, femoral hematoma, arrhythmias, fever, cardiac tamponade, deep venous thrombosis, and sepsis.

Animal studies and a previous human study did not demonstrate any evidence that the local application of an amiodarone gel to the heart could result in tissue damage. However, tissue damage has been reported if amiodarone leaks from the vein when using intravenous amiodarone.

A one-time dose of amiodarone will be used in the preparation of the amiodarone hydrogel. While, the dose used in this study is extremely low, there are several known side effects of amiodarone use, which typically occur when amiodarone is administered systemically for an extended period of time. These potential side effects include: nausea, vomiting, photosensitivity, fatigue, dizziness, paraesthesias, constipation, anorexia, visual disturbances, liver damage, pulmonary fibrosis, hypo or hyperthyroidism, insomnia, headache, sleep disturbances, congestive heart failure, cardiac arrhythmias, SA node dysfunction, abdominal pain, hepatic disorders, flushing, abnormal taste and smell, edema, abnormal salivation and coagulation abnormalities.

Any serious, related, and unanticipated adverse events will be reported to the IRB within 5 working days of awareness of the event. All drug related, serious, unanticipated adverse drug reactions will be reported to the company and FDA within 15 working days of the event.

## **8.0 COMPLIANCE TO CIP**

### **8.1 STATEMENTS OF COMPLIANCE**

The study will be performed in accordance with the most current versions of the FDA regulations, and any regional and/or national regulations, as appropriate.

The investigator will not start enrolling subjects or requesting informed consent from any subject prior to obtaining FDA and IRB approval.

## 8.2 ADHERENCE TO THE CLINICAL INVESTIGATION PLAN

A deviation is defined as an event where the clinical investigator, site personnel, sponsor or sponsor representative did not conduct the clinical study according to the Clinical Investigational Plan, IRB requirements or the Investigator Agreement. The investigator is not allowed to deviate from the CIP, except as specified under emergency circumstances.

In some cases, failure to comply with the CIP may be considered failure to protect the rights, safety and well being of subjects, since the non-compliance exposes subjects to unreasonable risks. For example, failure to adhere to the inclusion/exclusion criteria: these criteria are specifically defined by the investigator/manufacturer to exclude subjects for whom the drug is not beneficial and the use involves unreasonable risks. This may be considered failure to protect the rights, safety and well being of the enrolled subject. Similarly, failure to perform safety assessments intended to detect adverse events may be considered failure to protect the rights, safety and well being of the enrolled subject. Investigators should seek minimization of such risks by adhering to the CIP.

Simultaneously, in the event that adhering to the CIP might expose the subject to unreasonable risks, the investigator is also required to protect the rights, safety and well being of the subject by intentionally deviating from the requirements of the CIP, so that subjects are not exposed to unreasonable risks.

It is the responsibility of the investigator to provide adequate medical care to a subject enrolled in a study.

Regulations require that the PI maintain accurate, complete, and current records, including documents showing the date of and reason for every deviation from the Clinical Investigational Plan. Relevant information for each deviation will be documented on a Deviation Case Report Form.

Regulations require Investigators obtain approval from IRB before initiating changes in or deviations from the protocol, except when necessary to protect the life or physical well being of a subject in an emergency. Under emergency circumstances, deviations from the CIP to protect the rights, safety and well being of human subjects may proceed without prior approval of the IRB. Such deviations shall be documented and reported to the IRB as soon as possible, but no later than 5 working days.

## 9.0 ADVERSE EVENT, ADVERSE DRUG EFFECT, DRUG DEFICIENCY

### 9.1 DEFINITIONS

#### 9.1.1 Investigational drug

Any chemical

- Intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the specific purpose(s) of
  - Diagnosis, prevention, monitoring, treatments or alleviation of disease,
  - Diagnosis, monitoring, treatment, alleviation of, or compensation for, an injury,
  - Investigation, replacement, modification, or support of the anatomy or of a physiological process,
  - Supporting or sustaining life,
  - Control of conception,
  - Disinfection of medical drugs and
- Which does not achieve its primary intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its intended function by such means

### 9.1.2 Adverse Event (AE)

- **Adverse Drug Reaction (ADR):** All noxious and unintended responses to a medicinal product related to any dose should be considered an adverse drug reaction. There must be evidence to suggest a causal relationship between the medicinal product and the adverse event, i.e. the relationship cannot be ruled out.
- **Adverse Event (AE):** Any unfavorable and unintended sign (including laboratory findings), symptom or disease that occurs to a subject while enrolled in a clinical investigation. Medical conditions that exist at study enrollment are not considered an AE unless condition worsens after enrollment.
  - **Serious Adverse Event (SAE) or Serious Adverse Drug Reaction (SADR):** Any untoward medical occurrence that at any dose:

1. Results in death
2. Is life threatening
3. Requires inpatient hospitalization or prolongation of current hospitalization related to the use of the study materials
4. Results in persistent or significant disability/incapacity
5. Results in a congenital abnormality or birth defect
6. Requires a medical or surgical intervention to prevent a permanent impairment of a body function or permanent damage to a body structure.

- **Unanticipated Adverse Event (UAE) / Unexpected Adverse Drug Reaction (UADR)/or Other Unexpected Problems:** Unexpected (in terms of nature, severity, or frequency) means that:

1. The event and/or reaction was not previously described in the research procedures included in the protocol-related documents, such as the protocol, or consent document, or in other relevant sources of information, such as product labeling or package inserts.

OR

2. The event and/or reaction was not previously described given the characteristics of the participant or the participant population being studied such as natural progression of any underlying disease, disorder or condition of the participant experiencing the adverse event/reaction, and the participants predisposing risk factor profile for the adverse event/reaction.

- **Relatedness to study drug or participation in the research.** The investigator will determine the causality of the AE or SAE (definitely not related, probably not related (unlikely), possibly related, probably related, definitely related).
- **Problem** suggests that the research places subject or others at a greater risk of harm (physical, psychological, economic, or social harm) than was previously known or recognized.
- **Unanticipated / unexpected problems involving risks to participants or others** are defined as meeting all of three of the following criteria:
  1. The event is unanticipated because it is not included in the currently approved research study documents, package insert, or study protocol or the event exceeds the described frequency or severity, or it is unexpected that it would occur given the study population described in the research. AND
  2. The event is definitely related, probably related or possibly related to procedures involved in the research. AND
  3. The event suggests that the research places the participants or others at a greater risk of harm than previously thought.

## 9.2 REPORTING OF ADVERSE EVENTS/REACTIONS

Adverse events are generally detected in two ways:

**Clinical:** Symptoms reported by the subject or signs detected on examination.

**Ancillary testing:** abnormalities of vital signs, laboratory tests, and other diagnostic procedures (other than outcome measures: the results of which are not being captured as AEs).

### Assessment of Clinical Adverse Events

The subject's medical record will be accessed to determine the occurrence of any adverse events. The study team will review the medical records in a timely manner to determine adverse events and enable timely reporting:

1. Type of event
2. Date of onset and resolution (duration)
3. Severity (mild, moderate, severe)
4. Seriousness (does the event meet the above definition for an SAE)
5. Causality, relation to investigational product and disease
6. Action taken regarding investigational product
7. Outcome

### Relatedness of Adverse Event to Investigational Product

The relationship of the AE to the investigational product should be specified by the Site, using the following definitions:

1. **Definitely Not Related:** Concomitant illness, accident or event with no reasonable association with treatment.
2. **Unlikely (probably not related):** The reaction has little or no temporal sequence from administration of the investigational product, and/or a more likely alternative etiology exists.
3. **Possibly Related:** The reaction follows a reasonably temporal sequence from administration of the investigational product and follows a known response pattern to the suspected investigational product; the reaction could have been produced by the investigational product or could have been produced by the subject's clinical state or by other modes of therapy administered to the subject. (suspected ADR)
4. **Probably Related:** The reaction follows a reasonably temporal sequence from administration of investigational product; is confirmed by discontinuation of the investigational product or by re-challenge; and cannot be reasonably explained by the known characteristics of the subject's clinical state. (suspected ADR)
5. **Definitely Related:** The reaction follows a reasonable temporal sequence from administration of investigational product; that follows a known or expected response pattern to the investigational product; and that is confirmed by improvement on stopping or reducing the dosage of the investigational product, and reappearance of the reaction on repeated exposure. (suspected ADR)

## 9.3 PROCEDURE FOR ASSESSING, RECORDING, AND REPORTING ADVERSE EVENTS, DRUG DEFICIENCIES/COMPLAINTS, ADVERSE DRUG EFFECTS, SERIOUS ADVERSE EVENTS, AND SERIOUS ADVERSE DRUG EFFECTS:

Safety surveillance within this study and the safety reporting both performed by the investigator, starts after the subject is enrolled in this study (date of signature of the informed consent) and has undergone the study intervention. The safety surveillance and the safety reporting will continue until the last investigational visit has

been performed, the subject is deceased, the subject/investigator concludes his/her participation in the study, or the subject/investigator withdraws the subject from the study.

All adverse event data including deaths will be collected throughout the clinical study and will be recorded on a dedicated case report form.

Records relating to the subject's subsequent medical course will be maintained at the site until the overall outcome has been ascertained and the record retention period for the site has expired. Adverse events related to the study intervention will be monitored until they are adequately resolved. The status of the subject's condition will be documented at each visit.

It is the responsibility of the Investigator or Sub-Investigator(s) to perform periodic assessments of all AEs as well as identifying SAEs. The AE and SAE reporting period for this study is from the study intervention through study termination. Any AEs, ADEs, SAEs and SADEs that occur during the study will be treated by established standards of care that will protect the life and safety of the subjects.

If at the time the Investigator completes an initial SAE form and the SAE has not resolved, the Investigator will complete a follow-up report as soon as the event resolves (or upon receipt of significant information if the event is still ongoing).

All AEs and ADRs will be reported in the subjects' research record. Any serious, related, and unanticipated adverse events will be reported to the IRB within 5 working days of awareness of the event. All drug related, serious, unanticipated adverse drug reactions will be reported to the company and FDA within 15 working days of the event.

## **10.0 SUBJECT DEATH**

### **10.1.1 Procedure for recording and reporting subject death**

All subject deaths will be collected throughout the clinical study and will be recorded on a dedicated case report form.

## **11.0 DATA MANAGEMENT**

The investigative team will manage the data. The investigative team will capture the data in the RedCap database provided by the university. RedCap is a secure method of capturing and storing the data.

The Sponsor/Investigator will be responsible for compiling and submitting all required reports to governmental agencies.

The privacy of each subject and confidentiality of his/her information will be preserved in reports and when publishing any data. Confidentiality of data will be observed by all parties involved at all times throughout the clinical study. All data will be secured against unauthorized access.

### **11.1 DOCUMENT AND DATA CONTROL**

#### **11.1.1 Traceability of documents and data**

The investigator will ensure accuracy, completeness, legibility, and timeliness of the data reported on the CRFs and in all required reports.

#### **11.1.2 Recording data**

Source documents will be created and maintained by the investigational site team throughout the clinical study.

The data reported on the CRFs will be derived from, and be consistent with, these source documents, and any discrepancies will be explained in writing.

## 12.0 MONITORING

Monitoring will occur through routine internal data review. This monitoring is designed to identify missing and inconsistent data, data outliers, and potential protocol deviations that may be indicative of non-compliance.

## 13.0 REGULATORY INSPECTIONS

An investigator who has authority to grant access will permit authorized governmental agency employees, at reasonable times and in reasonable manner, to enter and inspect any establishment where drugs are held (including any establishment where drugs are used or where records or results are kept).

An investigator, or any person acting on behalf of such a person with respect to the study, will permit authorized governmental agency employees, at reasonable times and in reasonable manner, to inspect and copy all records relating to the study.

An investigator will permit authorized governmental agency employees to inspect and copy records that identify subjects, upon notice that governmental agency has reason to suspect that adequate informed consent was not obtained, or that reports required to be submitted by the investigator have not been submitted or are incomplete, inaccurate, false or misleading.

## 14.0 STATISTICAL CONSIDERATIONS

### 14.1 STATISTICAL DESIGN, HYPOTHESES, METHOD AND ANALYTICAL PROCEDURES

This clinical study will provide data to support the safety, preliminary efficacy, and performance of the use of the Amiodarone hydrogel in preventing atrial arrhythmia during lung transplantation. The study has a treatment arm and a control arm. The control arm is the historic controls and will use the previously treated lung transplant patients at the facility. The treatment arm will use investigational amiodarone hydrogel. The study sample size calculation is based on typical regulatory criteria for a feasibility study to assess for safety and preliminary effectiveness hence it is not based on a power analysis to show statistically significant difference between the groups. However, the reported rate of early atrial fibrillation post lung transplantation is approximately 30% and assuming that the use of amiodarone gel will result in prevention of atrial fibrillation in 90% patients a sample size of 20 in each arm may have sufficient power to answer the question of preliminary effectiveness and safety.

Endpoint analysis will be on “as-treated” basis as historical control data will be used. Patients who will dropout or withdraw from the study before reaching the primary end-point will be excluded from the study and replaced by new enrollees to have at least 20 patients enrolled the study arm. The primary end-point analysis will be based on the study groups as per the protocol (treatment group vs. control groups). Subjects, who withdraw consent, will not be included in analyses.

All clinically relevant baseline and follow up variables will be tabulated. Means, medians, proportions and 95% confidence intervals will be reported. Comparisons of data collected at baseline and at follow-up will be analyzed as follows: categorical variables will be tested using contingency tables analyses (exact or chi-square approximations), and continuous variables will be tested using unpaired Student’s t-test or Wilcoxon rank-sum test, depending on variable distribution. The post-transplant AFIB was evaluated between study and control groups for overall occurrence, AFIB lasting < 24 hours and AFIB lasting > 24 hours. All the data were analyzed using SAS 9.4 software (SAS Inc., Cary, NC).

## 15.0 DOCUMENT RETENTION

The investigator will maintain all clinical study documents from prior, during and (as specified) after the clinical study on file at the site for a minimum of 5 years after the termination of this study, or longer as per local laws, or when it is no longer needed, whichever is later.

All original subject files must be stored for the longest possible time permitted by the regulations at the hospital, research institute, or practice in question. All data and documents will be made available on request of the relevant authorities in case of an audit.

## 16.0 AMENDMENTS TO CLINICAL INVESTIGATIONAL PLAN

Study related documents such as, the package inserts, Report of Prior Investigations (RPI) CIP, CRFs, Informed Consent form and other subject information, or other clinical study documents will be amended as needed throughout the clinical study, and a justification statement will be included with each amended section of a document.

The amendments to the CIP and the subject's Informed Consent will be notified to, or approved by, the IRB and regulatory authorities, if required. The version number and date of amendments will be documented.

The amendment will identify the changes made, the reason for the changes and whether the implementation of the amendment is mandatory or optional to implement the amendment.

Any amendment affecting the subject requires that the subject be informed of the changes and a new consent be signed and dated by the investigator at the subject's next follow up.

Changes to, or formal clarifications of, the CIP will be documented in writing and provided to the investigators. This information will be incorporated when an amendment occurs.

## 17.0 INVESTIGATION SUSPENSION OR TERMINATION

### 17.1 PREMATURE TERMINATION OF THE WHOLE CLINICAL STUDY

The Sponsor/Investigator reserves the right to stop the study at any stage, with appropriate written notice.

Possible reasons for early termination of the study by the investigator may include, but are not limited to:

- The drug/therapy fails to perform as intended
- Occurrence of USADE which cannot be prevented in future cases
- Request from Regulatory bodies
- Concern for subject safety and welfare
- Failure to secure subject Informed Consent prior to any investigational activity
- Failure to report unanticipated adverse drug effects to IRB
- Inability to successfully implement this CIP
- Violation of the Declaration of Helsinki 2008 (refer to Appendix C)
- Violation of applicable national or local laws and regulations

The study will be terminated according to applicable regulations.

If suspicion of an unacceptable risk to subjects arises during the clinical study or when so instructed by the IRB or regulatory authority, the study may be suspended as appropriate while the risk is assessed. The Sponsor/Investigator will terminate the clinical study if an unacceptable risk is confirmed.

### 17.2 RESUMING THE STUDY AFTER TEMPORARY SUSPENSION

When the Sponsor/Investigator concludes an analysis of the reasons for the suspension, implements the necessary corrective actions, and decides to lift the temporary suspension, concurrence from the IRB and FDA will be obtained before the clinical study resumes.

If subjects have been informed of the suspension, the Principal Investigator or authorized designee will inform them of the reasons for resumption.

### 17.3 STUDY CONCLUSION

The study will be concluded when all follow up has been completed, all data has been collected and the IRB and FDA have been notified of the completion of the study. A final report will be generated and submitted to FDA and the IRB with a request to close the study.

### 18.0 PUBLICATION POLICY

The results of the clinical study will be submitted, whether positive or negative for publication.

The investigator and study site will have ultimate decision making over publication of the data.

For more information on publication guidelines, please refer to the International Committee of Medical Journal Editors (ICMJE) on [www.icmje.org](http://www.icmje.org).

Upon receiving IND approval from the FDA, this clinical study will be registered on ClinicalTrials.gov. A full report of the pre-specified outcomes, including any negative outcomes, will be made public through the ClinicalTrials.gov website no later than 12 months after study completion, as required by Section 801 of the FDA Amendments Act. If this clinical study is terminated early, the Sponsor will make every effort to hasten the release of the pre-specified outcomes through the ClinicalTrials.gov website.

### 19.0 BIBLIOGRAPHY

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5. Papiris, S.A., et al., *Amiodarone: review of pulmonary effects and toxicity*. Drug Saf, 2010. **33**(7): p. 539-58.
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## APPENDIX A: ABBREVIATIONS

Select or add abbreviations used

Abbreviation	Term
COPD	Chronic Obstructive Pulmonary Disease
Mg	Milligram
CPB	Cardiopulmonary Bypass
CO2	Carbon Dioxide
HIPPA	Health Insurance Portability and Accountability Act
ICU	Intensive Care Unit
IRB	Institutional Review Board
Kg	Kilogram
PTT	Partial thromboplastin time
PT	Prothrombin time
eGFR	Estimated Glomerular filtration rate
BNP	B-type Natriuretic Peptide
CRP	C-reactive Protein
LDH	Lactate Dehydrogenase
AST	Aspartate Aminotransferase
ALT	Alanine Aminotransferase
CT	Computerized Tomography

**APPENDIX B: CIP REVISION HISTORY**

Revision History				
Amendment Number	Version	Date	Rationale	Details
Not Applicable	1	06/06/17	First draft of CIP	NA

**Appendix C: DECLARATION OF HELSINKI**

The most current version of the document will be followed.

## Appendix D: SAMPLE INFORMED CONSENT

### INFORMED CONSENT AND RESEARCH AUTHORIZATION

The Intra-Operative Application of Amiodarone Releasing Hydrogel to Prevent Postoperative Atrial Fibrillation in Patients Undergoing Lung Transplantation

Industry Contracts number: CCDN171355

Funding Agency name & address: Baxter Healthcare Corporation  
One Baxter Parkway  
Deerfield, Illinois 60015

Investigator(s): Principal Investigator: Victor H. van Berkel, MD, PhD.  
Department of Cardiovascular and Thoracic Surgery  
201 Abraham Flexner Way, Suite 1200  
Louisville, KY 40202

Co-Investigator: Matthew P. Fox, MD  
Department of Cardiovascular and Thoracic Surgery  
201 Abraham Flexner Way, Suite 1200  
Louisville KY 40202

Co-Investigator: William M Whited, MD  
Department of Cardiovascular and Thoracic Surgery  
201 Abraham Flexner Way, Suite 1200  
Louisville, KY 40202

Site(s) where study is to be conducted: Jewish Hospital  
200 Abraham Flexner Way  
Louisville, KY 40202

ULP Cardiothoracic Surgery Clinic  
Heart and Lung Building  
201 Abraham Flexner Way, 12<sup>th</sup> floor  
Louisville, KY 40202

Phone number for subjects to call for questions: 502-588-7600

#### Introduction and Background Information

You are invited to take part in a research study because you have been diagnosed with an end stage lung disease requiring lung transplantation. The transplant surgery may result in an irregular heart rhythm call atrial fibrillation after the operation. This study is being conducted to determine if there may be an a treatment to reduce the chances of the irregular heart rhythm in post surgery. This study is being conducted under the direction of Victor van Berkel, MD, PhD, Matthew Fox, MD and William Whited, MD at the University of Louisville. About 20 local subjects will be invited to take part in this research.

## Purpose

The purpose of this study is to test a new method to decrease rates of atrial fibrillation after lung transplantation. Approximately one-third of patients will develop atrial fibrillation after lung transplantation. Atrial fibrillation is a type of irregular heart rhythm or arrhythmia in which the heart does not pump effectively. This can lead to problems, such as stroke, palpitations (irregular heart beats that you can feel) and prolonged hospital stays. The purpose of this study is to determine if the application of a medication (amiodarone) containing gel to the heart at the time of lung transplant will decrease the rates of atrial fibrillation in patients undergoing lung transplantation.

## Procedures

Your participation in this study will last for 1 year. If you consent to participate you will have the following procedures:

### Screening and enrollment

You will meet with a member of the study team to discuss the study. After you have discussed the study and had time to ask any questions, if you agree to be in the study, you will sign this consent form. This will take approximately 1 hour of your time.

After you have signed the consent form, the study team will collect information from your medical records.

### Lung transplant

When you are notified that you will be undergoing a lung transplant, the study team will review your medical records to make sure you still qualify to be in the study. If something has changed and you no longer qualify, you will not receive the gel application during your surgery.

If you still qualify for the study, during your lung transplant surgery you will receive one application of a medication (amiodarone) containing gel. The gel will be applied to your heart during your operation.

### After Surgery

The remainder of your hospitalization and follow up care will not be different from standard of care in any additional ways. The study team will collect information from your medical records.

### Follow up visits

You will return to the clinic for your standard care visits. The study team will collect information from your medical records.

## Potential Risks

In a previous study in patients undergoing coronary artery bypass surgery, a similar intervention, amiodarone gel was assessed and the only complication noted in those patients was bradycardia (a slow heart beat). This complication was temporary and was not clinically significant. In the above study this was a common complication (greater than 10%), however it was not serious and did not require any additional treatment.

There may also be other procedures required as part of the study. If bradycardia is severe enough to be symptomatic, transvenous pacing (a bedside procedure where a temporary pacemaker is placed into the heart through a vein in your neck) may be required, in order to maintain a normal heart rate. The risk from this procedure include but are not limited to:

- Death

- Femoral hematoma - bruising
- Arrhythmias – irregular heartbeat
- Fever
- Cardiac tamponade-pressure on the heart that occurs when blood or fluid builds up in the space between the heart muscle and the outer covering sac of the heart.
- Deep venous thrombosis – blood clot
- Sepsis – bacterial infection

Animal studies and a previous human study did not demonstrate any evidence that the local application of an amiodarone gel to the heart could result in tissue damage. However, tissue damage is reported if amiodarone leaks from the vein when using intravenous(in the blood vessels) amiodarone.

A one-time dose of amiodarone will be used in the preparation of the amiodarone hydrogel. While, the dose used in this study is extremely low, there are several known side effects of amiodarone use. These side effects typically occur when amiodarone is administered systemically (either by mouth or in the vein) for an extended period of time. These potential side effects include:

Most Common side effects (occur in up to 33% of subjects)

- nausea
- vomiting

Common side effects (occur in 4-9% of subjects)

- sensitivity to light
- tiredness
- dizziness
- feelings of “pins and needles” (paraesthesias)
- constipation
- anorexia (loss of the urge to eat)
- visual disturbances
- liver damage
- pulmonary fibrosis (lung damage)

Less Common (occurs in 1-3% of subjects)

- hypo or hyperthyroidism (changes in the level of thyroid hormone)
- insomnia
- headache
- sleep disturbances
- heart problems (congestive heart failure, cardiac arrhythmias, SA node dysfunction)
- abdominal pain
- liver disorders
- flushing
- abnormal taste and smell
- swelling (edema)
- abnormal salivation
- blood clotting abnormalities.

In addition, you may suffer harms that we have not seen before.

### Possible Pregnancy Risks

You should discuss pregnancy risks with your doctor before signing this consent form. Women who are pregnant or breast feeding may not participate in this research study. If you are pregnant or become pregnant, your unborn child may suffer harms that we have not seen before

Before starting this research study, females able to have children will have a pregnancy test. Talk to your doctor about the best method of birth control to use while you are in this study. It is important that you call your study doctor at 502-588-7600 right away if you become pregnant or father a child during the course of this study.

We do not know the effects of an Amiodarone containing gel on an unborn baby if it is applied to the parents of that baby. There is a risk that your unborn baby could be harmed if you become pregnant during your participation in the study. (If you ask, your study doctor will discuss the possible risks to your unborn child and your options should you become pregnant while in this study.)

### Benefits

The possible benefits of this study include: decreased rates of atrial fibrillation resulting in a possible shorter hospital stay.

You may not benefit by participating in this study. The information collected may not benefit you directly; however, the information may be helpful to others.

### Alternatives

Instead of taking part in this study, you could choose to not participate. Not participating in this study, will not affect your care during or after your lung transplantation.

### Research Related Injury

If you are injured by being in this research study, the study funding agency, BAXTER, will pay for any reasonable and necessary expenses incurred for diagnostic and therapeutic medical treatment, including hospitalization determined to be a direct result of administration of the gel. If you are injured, there is no money set aside for lost wages, discomfort, disability, etc. You do not give up your legal rights by signing this form. If you think you have a research related injury, please call your study doctor (Victor van Berkel MD, PhD (502) 588-7600).

### Payment

You will not be paid for your time, inconvenience, or expenses while you are in this study.

### Costs

You will not be billed for the Amiodarone gel. You or your insurance company will be billed for all office visits, tests, medications and procedures that are part of your routine medical care outside of this research study. You will be responsible for paying your co-pay that is associated with any office visit, test, medication or procedure. Some insurance companies will not pay for medical bills for people who participate in a research study. It is your responsibility to find out what costs, if any, your insurance company will cover before taking part in the study. If you need help finding out what your insurance company will cover, please ask your study doctor for

assistance. If your insurance company does not pay for your bills associated with this study, you will be responsible for paying them.

If you are injured, there may be additional costs to you for participating in this research study.

#### HIPAA Research Authorization

The Health Insurance Portability and Accountability Act of 1996 (HIPAA) provides federal safeguards for your protected health information (PHI). Examples of PHI are your name, address, and birth date together with your health information. PHI may also include your medical history, results of health exams and lab tests, drugs taken and results of this research study. Your PHI may not be used or shared without your agreement, unless it meets one of the HIPAA exceptions.

State and federal privacy laws protect your health information. In most cases, health information that identifies you can be used or shared by the research team only if you give your permission by signing this form.

If you sign this form your health information will be used and shared to answer the research questions described in this document and to make sure that the research was done correctly. The time period when information can be used or shared ends when all activities related to this study are completed.

Your access to your health information will be limited during this study. When the study is over, you will have the right to see your health information related to this research.

You do not have to sign this form. If you do not sign this form you may not participate in the study and health information that identifies you will not be shared with the research team.

#### **Site(s) where health information about you will be used or shared for this research:**

In our research, the research team will look at and may share information about you and your health. Federal law requires that health care providers and researchers protect the privacy and security of health information that identifies you. We may ask for your health information from the following:

##### Affiliated Sites:

Jewish Hospital (Kentucky One Health)

##### Faculty Practice Group Sites:

University of Louisville Physicians (ULP) Cardiothoracic Surgery Clinic

Protected health information (PHI) that will be used or shared for research

Consultation reports  
Discharge summaries

Healthcare provider orders  
History and physical exams  
Laboratory, x-ray, and other tests  
Records of your operation(s)  
Medical progress notes  
Photos, videotapes, or digital or other images  
Records about the study drug and other drugs you may be taking

#### Revocation of Research Authorization

You may cancel the permission you have given to use and share your protected health information at any time. This means you can tell us to stop using and sharing your protected health information. If you cancel your permission:

We will stop collecting information about you.  
You may not withdraw information that we had before you told us to stop.  
We may already have used it or shared it.  
We may need it to complete the research.  
Staff may ask your permission to follow-up with you if there is a medical reason to do so.

To cancel your permission, you will be requested to complete a written “Revocation of Research Authorization” form located at the end of this document. You may also obtain a copy from your study doctor, designated personnel or from the Human Subjects Protections Program Office website (<https://louisville.edu/research/humansubjects/templates/biomedical-forms>).

#### Information Available on ClinicalTrials.gov

A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

#### Confidentiality

Total privacy cannot be guaranteed. We will protect your privacy to the extent permitted by law. If the results from this study are published, your name will not be made public. Once your information leaves our institution, we cannot promise that others will keep it private.

Your information may be shared with the following:

The funding agency Baxter Healthcare

Organizations that provide funding at any time for the conduct of the research.

The University of Louisville Institutional Review Board, Human Subjects Protection Program Office, Privacy Office, others involved in research administration and compliance at the University, and others contracted by the University for ensuring human subjects safety or research compliance

The local research team

People who are responsible for research, compliance and HIPAA oversight at the institutions where the research is conducted

People responsible for billing, sending and receiving payments related to your participation in the study

Government agencies, such as:

Office for Human Research Protections

Office of Civil Rights

Food and Drug Administration

Those responsible for data safety monitoring related to the study

### **Security**

The data collected about you will be kept private and secure by being stored on an encrypted computer, located in a secure, locked office.

### **Voluntary Participation**

Taking part in this study is completely voluntary. You may choose not to take part at all. If you decide not to be in this study, you won't be penalized or lose any benefits for which you qualify. If you decide to be in this study, you may change your mind and stop taking part at any time. If you decide to stop taking part, you won't be penalized or lose any benefits for which you qualify. You will be told about any new information learned during the study that could affect your decision to continue in the study.

### **Termination**

Your study doctor or the study sponsor has the right to stop this study at any point. Your study doctor may take you out of this study with or without your okay. **Reasons this may happen include:**

Cancellation of your lung transplant

The study doctor believes it is not in your best interest

You do not come for follow up visits

### **Participation in Other Research Studies**

You may not take part in this study if you are currently in another research study. It is important to let your doctor know if you are in another research study.

### **Contact Persons**

If you have any questions, concerns, or complaints about the research study, please contact William M Whited, MD (502) 588-7600

### **Research Subject's Rights**

If you have any questions about your rights as a research subject, you may call the Human Subjects Protection Program Office at (502) 852-5188. You may discuss any questions about your rights as a research subject, in private, with a member of the Institutional Review Board (IRB). You may also call this number if you have other questions about the research, and you cannot reach the study doctor, or want to talk to someone else. The IRB is an independent committee made up of people from the University community, staff of the institutions, as well as people from the community not connected with these institutions. The IRB has approved the participation of human subjects in this research study.

### **Concerns and Complaints**

If you have concerns or complaints about the research or research staff and you do not wish to give your name, you may call the toll free number 1-877-852-1167. This is a 24 hour hot line answered by people who do not work at the University of Louisville.

### **Acknowledgment and Signatures**

This informed consent document is not a contract. This document tells you what will happen during the study if you choose to take part. Your signature indicates that this study has been explained to you, that your questions have been answered, and that you agree to take part in the study. You are not giving up any legal rights to which you are entitled by signing this informed consent document. You will be given a copy of this consent form to keep for your records.

\_\_\_\_\_  
Subject Name (Please Print)  
Signed

\_\_\_\_\_  
Signature of Subject

\_\_\_\_\_  
Date

\_\_\_\_\_  
Printed Name of Legally Authorized Representative (if applicable)

\_\_\_\_\_  
Signature of Legally Authorized Representative

\_\_\_\_\_  
Date Signed

\_\_\_\_\_  
Authorized Representative

\_\_\_\_\_  
Authorized Representative

\_\_\_\_\_  
Authority of Legally Authorized Representative to act on behalf of Subject

\*Authority to act on behalf of another includes, but is not limited to parent, guardian, or durable power of attorney for health care.

\_\_\_\_\_  
Printed Name of Person Explaining Consent Form  
Date Signed

\_\_\_\_\_  
Signature of Person Explaining

\_\_\_\_\_  
Consent Form (if other than the Investigator)

\_\_\_\_\_  
Printed Name of Investigator  
Signed

\_\_\_\_\_  
Signature of Investigator

\_\_\_\_\_  
Date

List of Investigators:

Phone Numbers:

Victor H. van Berkel, MD, PhD

(502) 588-7600

Matthew P. Fox, MD

(502) 588-7600

William M. Whited, MD

(502) 588-7600

CONFIDENTIAL  
June, 26, 2020

Study Document No: 1, Ver. 1  
Study Name: Amiodarone Gel for Lung Transplant

REVOCAION OF AUTHORIZATION FOR USE AND DISCLOSURE OF YOUR HEALTH INFORMATION FOR RESEARCH

Return To:

PI Address: 201 Abraham Flexner Way, Suite  
1200 Louisville KY, 40202  
PI Phone: (502) 588-7600

Institutional Review Board  
MedCenter One, Suite 200  
501 E. Broadway  
Louisville, KY 40202

Do not sign this letter unless you are withdrawing from this research. You will be sent confirmation that this notice was received.

To Whom It May Concern:

I would like to discontinue my participation in the research study noted above. I understand that health information already collected will continue to be used as discussed in the Authorization I signed when joining the study.

Your options are (*choose one*):

Withdraw from Study & Discontinue Authorization:

Discontinue my authorization for the future use and disclosure of protected health information. In some instances, the research team may need to use your information even after you discontinue your authorization, for example, to notify you or government agencies of any health or safety concerns that were identified as part of your study participation.

Withdraw from Study, but Continue Authorization:

Allow the research team to continue collecting information from me and my personal health information. This would be done only as needed to support the goals of the study and would not be used for purposes other than those already described in the research authorization.

\_\_\_\_\_  
Printed Name and Signature of Subject

\_\_\_\_\_  
Date Signed

\_\_\_\_\_  
Signature of Subject's Legal Representative (if subject is unable to sign)

\_\_\_\_\_  
Date Signed

\_\_\_\_\_  
Printed Name of Subject's Legal Representative

\_\_\_\_\_  
Birthdate of Subject

\_\_\_\_\_  
Relationship of Legal Representative to Subject

\_\_\_\_\_  
Subject's Address  
Number

\_\_\_\_\_  
Subject's Phone

Optional:

I am ending my participation in this study because:

---

---

**Appendix E: CASE REPORT FORMS**

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Page 1 of 4

## Demographic Information

Record ID	_____
Last Name	_____
First Name	_____
Date of Birth	_____
Date of Consent	_____
Upload Consent	_____
Transplant Date	_____
Age	_____
Gender	<input type="radio"/> Male <input type="radio"/> Female
Medical Record Number	_____
Health Insurance ID	_____
Height (cm)	_____
Weight (kg)	_____
Body Mass Index	_____

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## Pre-operative Information

Oxygen Requirement \_\_\_\_\_

Indication for Transplant

- COPD
- IPF
- CF
- PPH
- Other

Previous Arrhythmia

- None
- Atrial Fibrillation
- Other Arrhythmia

Previous Pacemaker

- Yes
- No

Previous ICD

- Yes
- No

Prev Other Heart Rhythm Intervention

- Yes
- No  
(includes but not limited to cardioversion, other therapies)

Previous Myocardial Infarction

- Yes
- No

Previous CABG

- Yes
- No

Previous PCI

- Yes
- No

Diabetes

- Yes
- No

Hypertension

- Yes
- No

Cerebrovascular Disease

- Yes
- No

Smoking History > 20 pack years

- Yes
- No

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## Intra-operative Information

Type of Lung Transplant

- Right Single Lung
- Left Single Lung
- Double Lung

Cardiopulmonary Bypass

- Yes
- No

Ischemia Time (hour)

\_\_\_\_\_

Amiodarone Gel Usage (ml)

\_\_\_\_\_

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## Post-operative Information

ICU Length of Stay (hour)

\_\_\_\_\_

Atrial Fibrillation at discharge

- Yes
- No

Treatment for A Fib

- None
- Amiodarone IV
- Amiodarone Oral
- Cardioversion (inc chemical CV)
- Rhythm device (pacemaker/ICD) placement
- Other

A Fib resolved at discharge

- Yes
- No

Bradycardia

- None
- Yes - not treated
- Yes - required pacing

Discharge Status

- Alive
- Dead

Discharge Date

\_\_\_\_\_  
(death date if patient died in hospital)

Atrila Fibrillation at 1 week

- Yes
- No

## Appendix F: PREPARATION AND APPLICATION INSTRUCTIONS

### Standard Operating Procedure for the Preparation and Intra-Operative Application of Amiodarone Releasing Hydrogel

#### PREPARATION OF AMIODARONE HYDROGEL

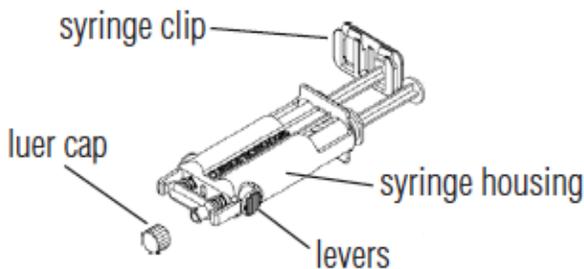
##### Materials:

Amiodarone HCl  
Coseal Surgical Sealant

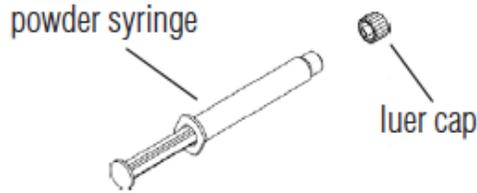
##### Procedure:

Based on the patient's body weight at the time of surgery 1mg/kg of amiodarone will be obtained from the Jewish Hospital Pharmacy. Amiodarone will be stored per pharmacy protocol until time of request. The amiodarone will be delivered to the operating room (OR) by an OR nurse and placed in a sterile fashion onto the OR back table.

A standard 4 mL application of Coseal will be obtained from the research-dedicated supply. The application will be opened and placed on the OR back table. Coseal in packs with 1 powder syringe, and 2 liquid syringes in an assembly shown below to allow mixing.

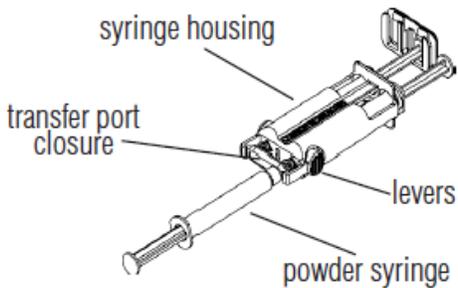


The powdered syringe and the amiodarone (powdered form) will be mixed. The plunger to the syringe, which houses the Coseal powder, is removed.

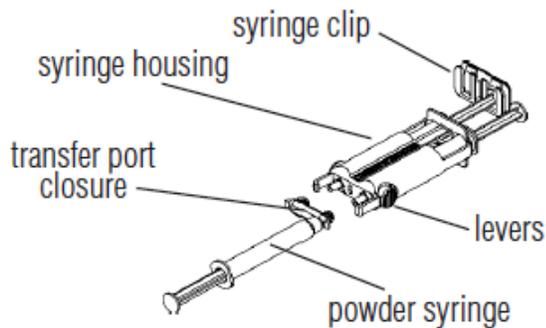


Next, the amiodarone is poured into the syringe using a funnel. The plunger is placed back onto the syringe.

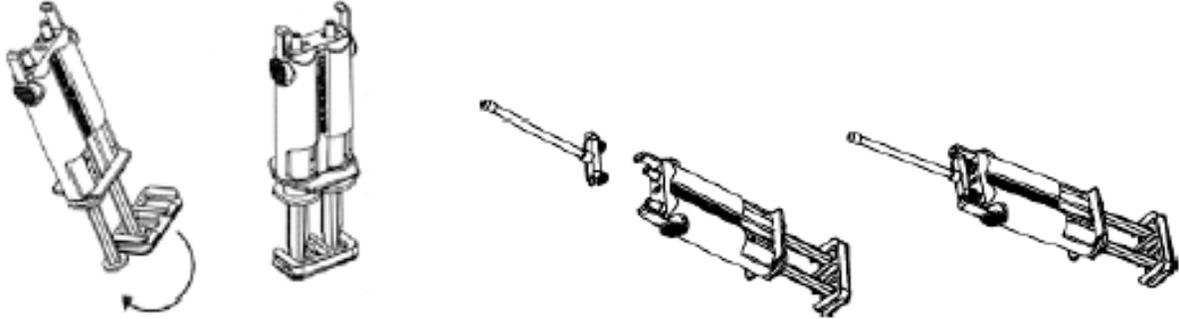
The syringe, which now contains amiodarone and Coseal powder mixture, is connected to the transfer port on syringe housing containing the solutions.



Transfer the liquid into the powder by depressing the plunger syringe housing. The contents will be mixed back and forth until the powder is completely dissolved. Push the entire contents back into the syringe contained in the syringe housing. Remove empty powdered syringe.



Holding syringe housing upright depress plunger until all air is removed. Secure applicator tip onto housing.



## APPLICATION OF AMIODARONE CONTAINING HYDROGEL

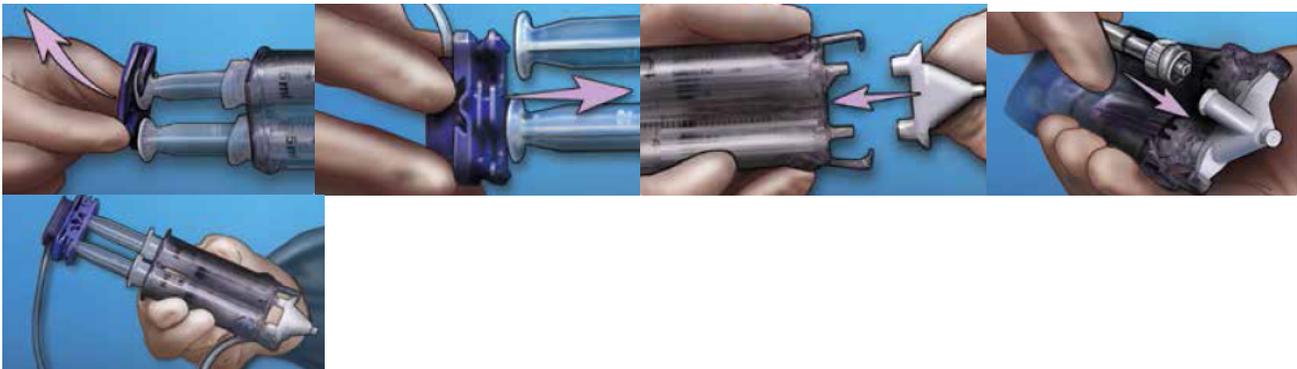
### Materials:

Amiodarone containing hydrogel as prepared above  
Coseal Spray Set

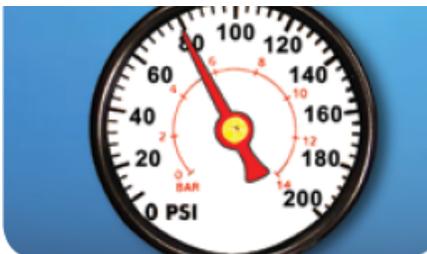
### Procedure:

Amiodarone hydrogel will be applied to the pulmonary vein anastomoses along with the left and right atria of the heart.

Attach syringe housing to pressure tubing from spray set.



Adjust pressure settings according to manufacturer's specifications.



Set wall unit pressure between 3.5  
and 7 bar (51-100 psi).

Remove excess blood and fluid from area of application.

Hold applicator tip approx. 10 cm from application site. Depress plunger on syringe housing to begin application. This will be applied by primary surgeon performing lung transplantation.



<b>Distance</b>	5 cm	10 cm	15 cm
<b>Pressure</b>	1 bar/15 psi	1.5 bar/22 psi	2 bar/29 psi

Apply hydrogel in a uniform fashion to desired area.

Allow 60 seconds for hydrogel to dry.

Lot number of Coseal and Amiodarone to be recorded in brief operative report and stored in medical record. The lot/batch numbers of the issued drug and study product will be recorded in the Research Amiodarone accountability log and Coseal Accountability Log respectively.