Esophageal Temperature Dynamics and Injury During Pulmonary Vein Isolation with Temperature-Controlled Very-High-Power Short-Duration Lesions Using the Novel Q-DOT Micro Ablation Catheter

Short Title: Esophageal Temperature During PVI

Protocol Number: STUDY00002707

National Clinical Trial (NCT) Identified Number: *pending*

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Sponsor: Cedars-Sinai Smidt Heart Institute

Funded by: Biosense-Webster, Inc.

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10 August 2023

Summary of Changes from Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale

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STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP), applicable United States (US) Code of Federal Regulations (CFR), and the Cedars-Sinai and Biosense-Webster Terms and Conditions of Award. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Investigational New Drug (IND) or Investigational Device Exemption (IDE) sponsor, funding agency and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

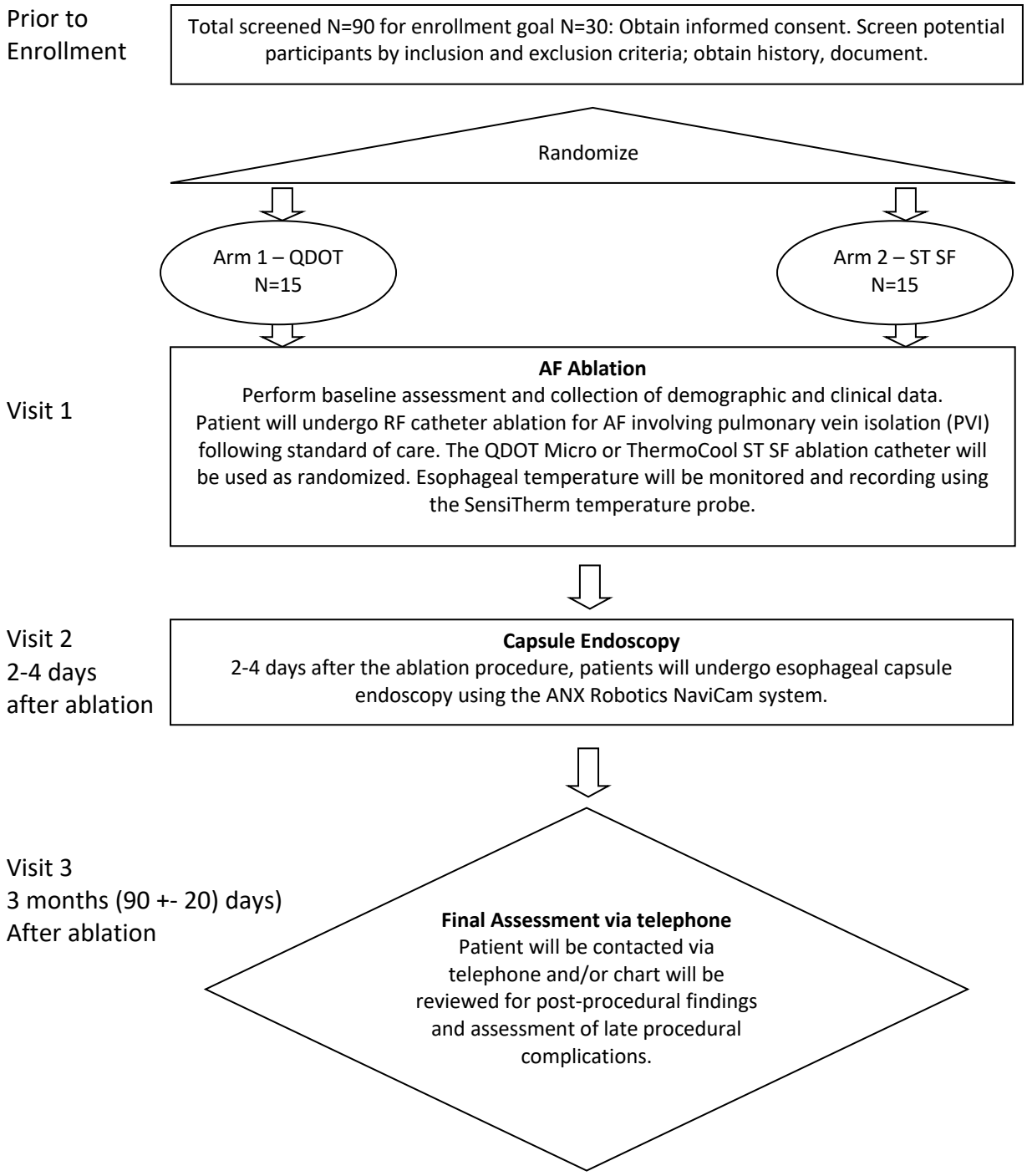
The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	Esophageal Temperature Dynamics and Injury During Pulmonary Vein Isolation with Temperature-Controlled Very-High-Power Short-Duration Lesions Using the Novel Q-DOT Micro Ablation Catheter
Study Description:	This is a prospective randomized controlled trial, studying patients undergoing ablation involving pulmonary vein isolation for paroxysmal atrial fibrillation. Patients will be assigned to undergo conventional high-power short-duration ablation or temperature-controlled very-high-power short-duration ablation, and esophageal outcomes including temperature changes during ablation and esophageal injury as assessed by post-procedure capsule endoscopy will be compared between the groups. The hypothesis is that very-high-power short-duration ablation will lead to lower rises in esophageal temperature and lower rates of esophageal findings during capsule endoscopy.
Objectives:	Primary objective: To assess for differences in changes in esophageal outcomes during posterior wall ablation between the two arms. Secondary objectives: To assess for short and long-term procedural complications. To assess for procedural efficacy as measured by number of lesions, RF time, and procedure time to achieve PVI, and first pass pulmonary vein isolation.
Endpoints:	Primary endpoint: Maximal change in esophageal temperature during posterior wall isolation. Secondary endpoints: Presence of esophageal thermal injury seen on post-procedure capsule endoscopy. Presence of procedural complications, number of lesions, RF time, and procedure time to achieve PVI, achievement of first pass isolation.
Study Population:	Adults aged 18 or more years of age who are undergoing first-time RF ablation for paroxysmal atrial fibrillation involving pulmonary vein isolation.
Phase:	N/a
Description of Sites/Facilities Enrolling Participants:	Patient will be enrolled at Cedars-Sinai Medical Center.
Description of Study Intervention:	Patients will be randomized to undergo ablation using one of two FDA approved ablation catheters (ThermoCool ST SF or QDOT Micro). They will undergo esophageal temperature monitoring during the ablation procedure using a SensiTherm esophageal temperature probe. 2-4 days after the procedure, they will undergo esophageal capsule endoscopy using the ANX Robotica NaviCam capsule endoscopy system.
Study Duration:	Projected study duration is 12 months.
Participant Duration:	3 months.

1.2 SCHEMA


Prior to Enrollment
Total screened N=90 for enrollment goal N=30: Obtain informed consent. Screen potential participants by inclusion and exclusion criteria; obtain history, document.
Randomize
Arm 1 – QDOT
N=15
Arm 2 – ST SF
N=15
Visit 1
AF Ablation
Perform baseline assessment and collection of demographic and clinical data. Patient will undergo RF catheter ablation for AF involving pulmonary vein isolation (PVI) following standard of care. The QDOT Micro or ThermoCool ST SF ablation catheter will be used as randomized. Esophageal temperature will be monitored and recording using the SensiTherm temperature probe.
Visit 2
2-4 days
after ablation
Capsule Endoscopy
2-4 days after the ablation procedure, patients will undergo esophageal capsule endoscopy using the ANX Robotics NaviCam system.
Visit 3
3 months (90 +- 20) days)
After ablation
Final Assessment via telephone
Patient will be contacted via telephone and/or chart will be reviewed for post-procedural findings and assessment of late procedural complications.

1.3 SCHEDULE OF ACTIVITIES (SOA)

Procedures	Screening Day -60 to -1	Enrollment/AF ablation Visit 1, Day 0	Capsule Endoscopy Day 2-4	Final assessment via telephone, Day 90+-10
Informed consent	X			
Demographics	X			
Medical history	X			
Randomization	X			
AF ablation		X		
Capsule Endoscopy			X	
Medication Review	X			
Adverse event review and evaluation	X	X	X	X
Complete Case Report Forms (CRFs)	X	X	X	X

2 INTRODUCTION

2.1 BACKGROUND

Atrioesophageal fistula is a rare but life-threatening complication of ablation for atrial fibrillation, and is primarily caused by thermal injury to the esophagus as a result of posterior left atrial ablation in close proximity to the esophagus. Esophageal temperature monitoring is frequently used to monitor risk of thermal injury to the esophagus, and although esophageal temperature monitoring has not been shown to reduce the risk of esophageal injury directly,[1,2] observational studies have shown that the degree of esophageal temperature rise does correlate to the severity of esophageal thermal injury.[3,4] A variety of methods have been studied to prevent esophageal injury, including high-power short duration lesions,[5,6] esophageal deviation,[7] closed loop esophageal cooling,[8] and positioning of ablation lesions to avoid the esophagus on multimodality imaging,[9] all with variable success.

Given the ongoing interest in high-power, short-duration ablation to improve safety and reduce procedure times, the Q-DOT Micro ablation catheter (Biosense Webster, Inc.) has recently been developed with the ability to deliver temperature-controlled, very-high-power (up to 90W), short-duration RF ablation lesions. Initial studies of the catheter have shown clinical feasibility, efficacy, and safety.[10,11] More recent studies including the Q-FFICIENCY[12] trial and POWER PLUS[13] trial have demonstrated comparable efficacy, reduced procedures times, and complication rates comparable to other catheters.

To date, detailed analysis of esophageal temperature dynamics and subsequent risk for esophageal injury during posterior wall ablation for AF ablation using temperature-controlled very-high-power, short-duration ablation with the Q-DOT Micro catheter as compared with conventional ablation catheters has not been fully assessed.

2.2 RISK/BENEFIT ASSESSMENT

2.2.1 KNOWN POTENTIAL RISKS

All invasive ablation procedures have risk. We do not anticipate additional ablation procedural risks stemming from participation in this study, as standard of care will be followed and only FDA approved medical devices are to be used.

In addition to standard of care, capsule endoscopy will be performed as part of this study. Although capsule endoscopy is a very safe procedure, there is a small risk of capsule retention and bowel obstruction that could necessitate a procedure or surgery to remove the capsule.

There is a small risk that patient information could be released unintentionally to unauthorized personnel. As noted above, this risk will be minimized by storing patient information in a secure, password-protected database and using a linking code for demographic information; only the principal investigator and co-investigators will have access to the databases.

2.2.2 KNOWN POTENTIAL BENEFITS

We do not anticipate any personal benefits from participation in this trial.

2.2.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

Participation in this trial will only involve small risks, the primary increased risk being capsule endoscopy. This test is necessary as one of the main endpoints of the trial is esophageal injury that needs to be assessed with endoscopy. Capsule endoscopy was chosen rather than convention endoscopy or nasal endoscopy to minimize subject risk.

3 OBJECTIVES AND ENDPOINTS

The overall objective of the study is to study the effect of different ablation power strategies on esophageal temperatures during posterior wall RF ablation during catheter ablation for paroxysmal atrial fibrillation involving pulmonary vein isolation. This prospective study will compare esophageal temperatures during conventional high-power short-duration ablation to temperature-controlled very-high-power short-duration ablation using the novel Q-DOT Micro catheter.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
To assess esophageal temperature dynamics during AF ablation using two different ablation catheters during ablation of the posterior wall.	Change in esophageal temperature during posterior wall ablation, defined by maximal temperature minus baseline esophageal temperature before the start of posterior wall ablation, as well as time to maximal esophageal temperature after start of ablation lesions.	Very-high power short duration lesions may lead to lower increases in esophageal temperature due to a different balance of resistive vs conductive heating during RF ablation.
Secondary		
To assess for esophageal thermal injury after AF ablation when using two different ablation catheters during ablation of the posterior wall.	Presence of stigmata of esophageal thermal injury as assessed by capsule endoscopy performed 2-4 days after the ablation procedure.	Very-high power short duration lesions may lead to less esophageal thermal injury, again due to a different balance of resistive vs conductive heating leading to less far field heating.
To assess for post-procedural complications related to esophageal thermal injury.	Presence of procedural complications related to esophageal injury including atrial-esophageal (AE) fistula, as assess at 90 day follow-up via chart review and/or telephone follow-up.	The most serious complication of esophageal thermal injury is AE fistula, a rare but life-threatening complication of AF ablation. Though we do not expect any instances of this during the study, it will be important to assess for.
To assess for ablation acute procedural efficacy.	Acute procedural efficacy as assessed by number of lesions, RF time, and procedure time to achieve PVI, and achievement of first pass isolation.	Very-high power short duration lesions may lead to increased procedural efficacy and shorter procedure times.

4 STUDY DESIGN

4.1 OVERALL DESIGN

A randomized, prospective, open-label, post-market, single-site, pilot study trial of patients undergoing first-time RF ablation involving pulmonary vein isolation for treatment of paroxysmal atrial fibrillation at a single center will be performed to assess for differences in esophageal temperature dynamics and thermal injury using two different ablation catheters, as well as post procedural complications and outcomes of acute procedural efficacy.

After obtaining consent, patients will be assigned to undergo ablation using either a high-power short-duration ablation strategy (40-50W, ST SF arm) or a temperature-controlled, very-high-power (up to 90W), short-duration ablation strategy (QDOT arm). During posterior wall ablation, esophageal temperatures will be monitored using a multipolar temperature monitoring probe (Abbott SensiTherm). Post-procedurally, patients will undergo esophageal capsule endoscopy to assess for evidence of thermal injury to the esophagus. Patient will then undergo 90-day follow-up via chart review and/or telephone call to assess for post-procedural complications, particularly related to esophageal thermal injury.

We hypothesize that patient undergoing temperature-controlled very-high-power short-duration ablation will have less esophageal heating and thermal injury as compared to high-power short-duration.

Patients will be recruited to the study and informed consent will be obtained.

Electronic case report forms (CRFs) will be completed which will collect data on demographic and clinical characteristics including: patient MRN, age, sex, date of birth, race/ethnicity, date of procedure, type of arrhythmia and proposed treatment strategy, medications at the time of enrollment, relevant laboratory data including serum Na, K, creatinine, Mg, Hgb, pro-BNP, echocardiographic measurements including left ventricular ejection fraction and size and left atrial size, and medical history including history of cardiac conditions (i.e. coronary artery disease, heart failure, arrhythmias) and other relevant medical history.

A linking code will be used for the demographic information above to minimize the risk of inadvertent release of PHI during the study.

The data for the prospective study will be obtained over 12 months with a goal to enroll 30 patients.

Patients will be followed for three months post-procedurally primarily to assess for late procedural complications (e.g. atrioesophageal fistula). This will be done through chart review of the EMR, and/or telephone calls to study participants if needed.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

This study is designed as a randomized open-label device trial. Currently, the differences in esophageal temperature between the two ablation strategies is not known. Due to differences in the ablation catheter design and use, it would be impractical for the study to be blinded. We are aiming to show that the intervention (QDOT) arm is superior, so therefore a non-inferiority design would not be appropriate.

4.3 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed the ablation procedure and capsule endoscopy, and completed 90-day follow-up via chart-review and/or telephone.

The end of the study is defined as completion of the last visit or procedure shown in the SoA in the trial globally.

5 STUDY POPULATION

This study will enroll 30 patients undergoing first-time RF catheter ablation for treatment of paroxysmal atrial fibrillation that will involve pulmonary vein isolation (PVI) and meet the inclusion and exclusion criteria for participation in this study.

5.1 INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Provision of signed and dated informed consent form
2. Stated willingness to comply with all study procedures and availability for the duration of the study
3. Male or female, aged greater than or equal to 18 years
4. Diagnosed with paroxysmal atrial fibrillation
5. Undergoing RF catheter ablation for treatment of paroxysmal atrial fibrillation that will involve circumferential point-by-point radiofrequency ablation pulmonary vein isolation with no additional left atrial posterior wall ablation planned

5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Patients who have undergone prior left atrial ablation procedures.
2. Patients where the use of the Q-DOT Micro ablation catheter in QMODE+ (i.e. temperature-controlled very-high-power short-duration ablation) is felt to be unsafe.
3. Patients who have contraindications to capsule endoscopy, or GI conditions that may increase the risks of capsule endoscopy (e.g. esophageal strictures, inflammatory bowel disease, etc)
4. Any records flagged “break the glass” or “research opt out.”

5.3 LIFESTYLE CONSIDERATIONS

No lifestyle considerations are anticipated for participation in this study.

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

This study will enroll 30 patients total, and we anticipate 90 patients will need to be screened to enroll this number. The projected study duration will be 12 months, and therefore we expect to screen 6-10 patients and enroll 2-3 patients per month. This is feasible based on the number of AF ablation performed at the medical center per month.

AF ablation is primarily performed as an outpatient/ambulatory procedure, and therefore the subjects will be enrolled based on referrals from faculty electrophysiologists and review of faculty electrophysiologists' schedules for patients undergoing AF ablation. They will be screened over the phone by study staff, and informed consent and the baseline visit will be done at the time of the AF ablation procedure.

Participants will be given a $100 incentive stipend for participation in this study, to help cover additional costs that may be accrued as a result of undergoing capsule endoscopy (travel, parking, etc.).

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION ADMINISTRATION

6.1.1 ABLATION PROCEDURE

Enrolled patients will undergo RF catheter ablation for treatment of paroxysmal atrial fibrillation following standard of care. Circumferential point-by-point radiofrequency pulmonary vein isolation will be performed for all patients, with additional lesions sets (e.g. cavo-tricuspid isthmus ablation) made at the discretion of the operator. Patient should not be planned to undergo additional posterior wall ablation outside of ablation required for PVI. Patients will be assigned to undergo ablation with one of two ablation strategies assigned for posterior wall ablation during PVI: a high-power short-duration ablation strategy using the ThermoCool SmartTouch SF ablation catheter (ST SF arm), or a temperature-controlled, very-high-power short-duration ablation strategy using the QDOT Micro ablation catheter (QDOT arm).

For the ST SF arm, ablation on the posterior wall will be performed using a power of 40 to 50W, with ablation duration at the discretion of the operator. Ablation endpoints including but not limited to ablation time, impedance changes, and Visitag Surpoint tag index may be used.

For the QDOT arm, ablation on the posterior wall will be performed in the QMODE+ mode, with temperature-controlled ablation lesions delivered at a maximum of 90W for 4 seconds.

The Biosense Webster Carto3 system will be used for electroanatomic mapping. 3 mm Visitags will be used for ablation lesions. Esophageal temperature monitoring will be performed using a multipolar temperature probe (Abbott SensiTherm). Baseline esophageal temperature will be recorded just prior to the start of posterior wall ablation based on the pole with the highest temperature, and the peak temperature during each posterior wall ablation lesion will be recorded also based on the pole with the highest temperature. Time to peak temperature after each ablation lesions will be recorded. Full esophageal temperature data/plots (maximum and from each pole) will be exported from the

SensiTherm console at the completion of the case for additional analyses. During ablation lesions where temperature rises >1° C are seen, the operator will be instructed to wait for the temperature to return to within 1° C of baseline or wait 60 seconds before performing another lesion within 10 mm of this lesion on the posterior wall. Fluoroscopy and electroanatomic mapping will be used to ensure the ablation catheter and temperature probe are in sufficient vertical proximity. Additional fluoroscopic images will be taken in RAO 45 and LAO 45 views to allow for post-procedure 3D reconstruction of the distance between the ablation catheter and the temperature probe. Additional data will be collected on acute procedural outcomes including number of lesions and RF time to achieve PVI, procedure duration, achievement of first pass isolation in each set of pulmonary veins (adjudicated by the operator), and presence of acute procedural complications.

All patients will be prescribed a daily proton-pump inhibitor (if they are not already taking or contraindicated) per usual protocol after RF AF ablation.

6.1.2 POST-PROCEDURE CAPSULE ENDOSCOPY

Patient will undergo esophageal capsule endoscopy using the ANX Robotica NaviCam system 2-4 days after the ablation procedure. The capsule endoscopy will be interpreted by gastroenterologists with expertise in capsule endoscopy, who will be blinded to the ablation treatment strategy used.

6.2 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

The study will be randomized in a 1:1 fashion between the two study groups. Due to differences in the operation of the two different ablation catheters being compared, the trial will be open label and no blinding will be performed, with the exception of the blinding of the interpreters of the capsule endoscopy who will be blinded to the ablation strategy used.

6.3 STUDY INTERVENTION COMPLIANCE

Informed consent will be obtained from patients at the start of the study, with particular attention to ensure compliance with the post-procedure capsule endoscopy and 90-day follow-up.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

If at any time during the ablation procedure use of the randomized ablation catheter is felt to be unsafe or suboptimal by the operator, use of the catheter can be discontinued. Discontinuation from the randomized ablation catheter does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

The data to be collected at the time of study intervention discontinuation will include the following:

- Reason for discontinuation from the study
- Relevant temperature and other procedural parameters

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request.
An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Significant study intervention non-compliance (e.g. failure to complete capsule endoscopy)
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- Disease progression which requires discontinuation of the study intervention (e.g. progression to persistent atrial fibrillation before the ablation procedure)
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

The reason for participant discontinuation or withdrawal from the study will be recorded on the Case Report Form (CRF). Subjects who sign the informed consent form and are randomized but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, and are randomized and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will also be replaced.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for the capsule endoscopy and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit within the 2-4 day post-procedural time-frame, and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

As described above, the efficacy assessments for the study will be the primary and secondary endpoints: changes in esophageal temperature during posterior wall ablation, stigmata of esophageal thermal injury on capsule endoscopy, presence of post-procedural complications particularly related to esophageal thermal injury, and measures of acute procedural efficacy.

8.2 SAFETY AND OTHER ASSESSMENTS

Presence of procedural complications will be assessed and recording in each subject's chart.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).]

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".]

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (dechallenge) should be clinically plausible. The event must be

pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.

- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- **Potentially Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

8.3.3.3 EXPECTEDNESS

The principal investigator will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The principal investigator will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.3.5 ADVERSE EVENT REPORTING

All adverse events occurring on this study will be reported to the IRB according to the IRB policy.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

The study investigator shall submit notification of the serious adverse event to the study sponsor and to the reviewing Institutional Review Board (IRB) as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect.

8.3.7 REPORTING EVENTS TO PARTICIPANTS

Study-related adverse events will be reported to the individual study participant who undergoes the adverse event as soon as it is recognized by the study staff.

8.3.8 EVENTS OF SPECIAL INTEREST

Not applicable.

8.3.9 REPORTING OF PREGNANCY

Not applicated.

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

This definition could include an unanticipated adverse device effect, any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects (21 CFR 812.3(s)).

8.4.2 UNANTICIPATED PROBLEM REPORTING

The investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB) and to the Data Coordinating Center (DCC)/lead principal investigator (PI). The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) will be reported to the IRB and to the DCC/study sponsor within 10 days of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and to the DCC/study sponsor within 10 days of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and the Office for Human Research Protections (OHRP) within 10 days of the IRB's receipt of the report of the problem from the investigator.

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

Not applicable.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

Primary Efficacy Endpoint: The first primary endpoint will be esophageal temperature dynamics during AF ablation, which will be measured by a multipolar esophageal temperature probe. We hypothesize that temperature-controlled very-high-power short-duration ablation will result in smaller increases in esophageal temperature during ablation.

Secondary Efficacy Endpoint 1: The second primary endpoint will be esophageal thermal injury after AF ablation, which will be measured by assessing for stigmata of esophageal thermal injury on post-procedure capsule endoscopy.

Secondary Efficacy Endpoint 2: The secondary endpoint will be post-procedural complications related to esophageal thermal injury. We do not anticipate any events will occur during the trial as these are very rare, but these events will be assessed for.

9.2 SAMPLE SIZE DETERMINATION

Sample size determination was based on power calculations for a 75% power. This was based on a 1 degree difference in the primary outcome defined as a significant effect. The estimated standard deviation of change in temperature is 1 degree based on review of prior procedures; therefore, the effect size is approximately 1. Using a standard 2-sided alpha of 0.05, a sample size of 30 provides 75% power.

9.3 POPULATIONS FOR ANALYSES

Though we anticipate a low-risk of any crossover occurring during the study, if crossover does occur then the analysis will be performed using intention-to-treat analysis.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

All continuous data will be expressed as mean ± SD or median (IQR) depending on normality of distribution and compared using Student's t-test or the Wilcoxon Rank-Sum test as appropriate.

Categorical data will be expressed as n (%) and compared using Fisher's exact test.

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

Univariate analysis of the primary endpoints will be performed using Student's t-test and Fisher's exact test. Linear regression for the primary endpoint will be used to assess for confounding risk factors.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Secondary endpoints will be compared between the groups using t-tests and Fisher's exact test as appropriate. Multiple logistic regression will be performed for presence of stigmata of esophageal thermal injury with potential confounding risk factors.

9.4.4 SAFETY ANALYSES

Not applicable.

9.4.5 BASELINE DESCRIPTIVE STATISTICS

Not applicable.

9.4.6 PLANNED INTERIM ANALYSES

Not applicable.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting

intervention/administering study intervention. The following consent materials are submitted with this protocol: Informed consent form.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to <study participants, investigator, funding agency, the Investigational New Drug (IND) or Investigational Device Exemption (IDE) sponsor and regulatory authorities>. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and/or Food and Drug Administration (FDA).

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants.

Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), regulatory agencies or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study team will permit access to such records.

The study participant's contact information will be securely stored for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Not applicable.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator/Medical Monitor
Eric D Braunstein, MD
Cedars-Sinai Smidt Heart Institute
127 S San Vicente Blvd, Suite A3600
310-248-6679
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10.1.6 SAFETY OVERSIGHT

As all devices and interventions being used in the study are FDA approved and in routine clinical use, safety oversight for the study will be performed by the principal investigator.

10.1.7 CLINICAL MONITORING

Not applicable.

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

Not applicable.

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into RedCap, a 21 CFR Part 11-compliant data capture system. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

10.1.9.2 STUDY RECORDS RETENTION

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an International Conference on Harminosation (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

10.1.10 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations within 10 working days of identification of the protocol deviation, or within 10 working days of the scheduled protocol-required activity. All deviations must be addressed in study source documents, reported to the principal investigator. Protocol deviations must be sent to the reviewing Institutional Review Board (IRB) per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

10.1.11 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers 2 years after the completion of the primary endpoint by contacting principal investigator.

10.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.2 ABBREVIATIONS

The list below includes abbreviations utilized in this template. However, this list should be customized for each protocol (i.e., abbreviations not used should be removed and new abbreviations used should be added to this list).

AE	Adverse Event
ANCOVA	Analysis of Covariance
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
DRE	Disease-Related Event
EC	Ethics Committee
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFR	Federal Financial Report
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ISO	International Organization for Standardization
ITT	Intention-To-Treat
LSMEANS	Least-squares Means
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
MSDS	Material Safety Data Sheet
NCT	National Clinical Trial
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee

SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States

10.3 PROTOCOL AMENDMENT HISTORY

The table below is intended to capture changes of IRB-approved versions of the protocol, including a description of the change and rationale. A Summary of Changes table for the current amendment is located in the Protocol Title Page.

Version	Date	Description of Change	Brief Rationale

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