Panoramic ECGi to guide Ablation of Non-Paroxysmal AF: Effect of Ibutilide on AF Source Location and Organization
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Panoramic ECGi to guide Ablation of Non-Paroxysmal AF: Effect of Ibutilide on AF Source Location and Organization

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Table of Contents:

PROTOCOL SUMMARY

Title:	**Panoramic ECGi to guide Ablation of Non-Paroxysmal AF: Effect of Ibutilide on AF Source Location and Organization**
Objective:	This prospective, multicenter observational study will examine the 1) Effect of Ibutilide on the number and size of the driver domains 2) Effect of ablation of Ibutilide-organized driver domains 3) Effect of PV isolation on driver domains
Design:	This is a prospective, multi-center, non-randomized, un-blinded, observational trial.
Enrollment:	Eligible subjects will be consented for participation in the trial prior to undergoing AF ablation. Patients are considered eligible if they have 1. ≥ 18 years of age. 2. 1) Symptomatic persistent AF refractory or intolerant to at least 1 class I or III antiarrhythmic medication Persistent AF - defined as Persistent: AF that is sustained > 7 days. Episodes of AF which are terminated by electrical or pharmacologic cardioversion after ≥ 48 hours of AF, but prior to 7 days, should also be classified as persistent AF episodes. 2) Planned to undergo first catheter ablation procedure (prior atrial flutter typical is allowed) 3. Ability to understand the requirements of the study and sign the informed consent form. 4. Willingness to adhere to study restrictions and comply with all post-procedural follow-up requirements 5. Projected lifespan greater than 1 year. Patients will be excluded from the trial if: 1. They have baseline prolonged QT or renal failure precluding safe used of ibutilide 2. Rheumatic heart disease, 3. Current intra-cardiac thrombus, 4. History of MI or CABG within 6 weeks; 5. Class IV HF, 6. Unable to sign consent 7. Projected lifespan of < 1 year 8. Women known to be pregnant or to have positive beta-HCG. 9. Participation in another study that would interfere with this study. 10.Unstable Angina 11. Recent cerebral ischemic events 12. Contraindication to anticoagulation 13. Prior history of polymorphic ventricular tachycardia or torsades de pointes Patients are considered enrolled once consented. Patients who do not

	undergo AF ablation within 90 days of enrolling will be considered to be screen failures. Twenty subjects are expected to be enrolled in the study.
Clinical Sites:	1. Mount Sinai Hospital, New York, NY 2. Homolka Hospital, Prague, Czech Republic
Time Course:	Expected duration of patient enrollment is approximately 8months to 1 year.
Subject Description:	Subjects will only be eligible for this study if they are ≥ 18 years of age and have a history of AF.
Primary Endpoints:	1. Acute Procedural Outcome Analysis: after performing procedures on the 20 patients 2. Clinical Outcome Analysis - Freedom from recurrent At/AF at 12 months
Additional Endpoints:	1. Effect of PV isolation on driver domains 2. Number/Size of drivers identified/ablated baseline 3. Percentage reduction of driver regions (site and size) after ibutilide 4. AF termination rate (to AT/SR) 5. Post-ablation inducibility of sustained AF (>5 mins) with isuprel 6. Post-ablation inducibility of AF with (>5mins) burst pacing 7. Total duration of RF ablation/ Fluro time/exposure/ procedure time
Follow-Up	1) Post-Ablation blanking period = 3 months 2) AAD use during blanking: Any AAD is permitted, but should be stopped by 4 weeks post-procedure. 3) Any post-blanking AT or AF episode >30 seconds would be considered as a failure 4) Patients will undergo continuous 7-14 day ambulatory monitoring at 3, 6 and 12 months
Primary Analytical Analysis:	N/A
Secondary Analytical Analysis:	N/A
Principal Investigator:	Vivek Reddy , M.D. Icahn School of Medicine at Mount Sinai One Gustave L Levy Place, Box 1030 New York, NY 10029, USA
Site, Monitoring, and Data Management Center	Electrophysiology Clinical Research Group Icahn School of Medicine at Mount Sinai One Gustave L Levy Place, Box 1030 New York, NY 10029, USA

1 CONTACT INFORMATION

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1.1 STUDY SITES & INVESTIGATORS

Site	Principal Investigator
1. Mount Sinai Hospital	Vivek Reddy, MD
2. Homolka Hospital	Petr Neuzil, MD

2 STUDY OBJECTIVE

This prospective, multicenter observational study will examine the ability of ECGi mapping to

1) Effect of Ibutilide on the number and size of the driver domains
2) Effect of ablation of Ibutilide-organized driver domains
3) Effect of PV isolation on driver domains

We hypothesize that this approach will lead to successful arrhythmia control

3 INTRODUCTION, RATIONALE

Beyond PV isolation, ablation strategies for non-paroxysmal AF remain controversial although several types of targets have been proposed: non-PV triggers, continuous fragmented atrial electrograms, ganglionated plexi, and linear lesions. In STAR AF-2, PV isolation (PVI) alone resulted in successful maintenance of SR in only 59% of patients with persistent AF.[1] This clearly reveals the need for establishing strategies to address non-PV sources of AF in non-paroxysmal AF. However, in the STAR AF-2 trial, after 18 months, the freedom from recurrent AF in patients assigned to PVI alone (59%) was not improved by the addition of either CFAE ablation (49%) or linear ablation (46%), p=0.15.[1] Thus, beyond PV isolation, there is little consensus as to what additional lesion sets one should perform.

Localized driver domains perpetuating AF have been difficult to detect with conventional techniques because of the limits of sequential temporospatial mapping, intermittent firing, and, presumably, spatial meandering of rotor-like activity. However, panoramic biatrial AF mapping using a body surface array with 252 electrodes has been used to enable activation and phase-based analysis of body surface potentials.[2] This noninvasive "ECG imaging"(ECGi) approach has been reported able to identify driver domains that, when targeted for ablation (along with PVI), can terminate AF. And most recently, the non-

randomized prospective multicenter AFACART study (8 centers, 118 patients) revealed that for persistent AF, the combination of PVI and ablation of driver domains identified by ECGi resulted in i) acute AF termination in 66% of patients, and ii) one-year freedom from recurrent atrial arrhythmias in 83%.[2]

The efficacy of an ablation strategy of targeting these driver domains will require a number of clinical studies: both large randomized studies and smaller mechanistic studies. To this latter point, we propose conducting an exploratory study of the use of panoramic ECGi in non-paroxysmal patients, in which the effect of pharmacological organization of driver domains will be evaluated, by the administration of progressive doses of Ibutilide.

4 DEVICES AND PROCEDURES

4.1 CardioInsight ECGi Mapping System

The CardioInsight mapping system is a noninvasive, single beat cardiac arrhythmia mapping system that provides 3D electroanatomic maps of the heart. It combines body surface potential measurements with cardiac anatomy to generate panoramic, bi-atrial or bi-ventricular 3D electroanatomic maps. The components include a cart, workstation, mapping amplifier, isolation transformer, monitor, manual, connection cables and a Sensor Array. The CardioInsight mapping system has market approval in the U.S.

4.2 Ablation Catheters

The AF ablation procedure will be performed using any of the following marketed catheters: (Note: the catheters listed below are FDA approved for the treatment of paroxysmal atrial fibrillation but not persistent.)

- **Biosense Thermocool SF**
- **Biosense Smart Touch SF (STSF)**

5 SCHEDULE OF TREATMENT AND TESTS

TABLE 1: SCHEDULE OF TREATMENTS AND TESTS:

	Baseline	Procedure	Discharge	3 months	6 months	12 months
Type of visit	Office	Hospital		Telephone Event Monitor	Telephone Event Monitor	Telephone Event Monitor
Informed Consent	X					
Brief History & Physical	X					
Blood Laboratory Testing: CBC, Electrolytes, BUN/Creatinine, BNP, INR, LFTs	X					
TTE	X					
CT	X					
EKG	X					
Medications	X	X	X	X	X	X
AFEQT	X					X
Holter Monitoring				X	X	X
Adverse Events		X	X	X	X	X

6 ENDPOINTS

6.1 Primary Endpoint

Primary Endpoints:	1. Acute Procedural Outcome Analysis: after performing procedures on the 20 patients 2. Clinical Outcome Analysis - Freedom from recurrent At/AF at 12 months
Additional Endpoints:	1. Effect of PV isolation on driver domains 2. Number/Size of drivers identified/ablated baseline 3. Percentage reduction of driver regions (site and size) after ibutilide 4. AF termination rate (to AT/SR) 5. Post-ablation inducibility of sustained AF (>5 mins) with isuprel 6. Post-ablation inducibility of AF with (>5mins) burst pacing 7. Total duration of RF ablation/ Fluro time/exposure/ procedure time

7 STUDY SUBJECTS

7.1 INCLUSION CRITERIA

1. ≥ 18 years of age.
2.
    1) Symptomatic persistent AF refractory or intolerant to at least 1 class I or III antiarrhythmic medication Persistent AF - defined as Persistent: AF that is sustained > 7 days. Episodes of AF which are terminated by electrical or pharmacologic cardioversion after ≥ 48 hours of AF, but prior to 7 days, should also be classified as persistent AF episodes.
    2) Planned to undergo first catheter ablation procedure (prior atrial flutter typical is allowed)

3. Ability to understand the requirements of the study and sign the informed consent form.
4. Willingness to adhere to study restrictions and comply with all post-procedural follow-up requirements
5. Projected lifespan greater than 1 year.

7.2 EXCLUSION CRITERIA

1. They have baseline prolonged QT or renal failure precluding safe used of ibutilide
2. Rheumatic heart disease,
3. Current intra-cardiac thrombus,
4. History of MI or CABG within 6 weeks;
5. Class IV HF,
6. Unable to sign consent
7. Projected lifespan of < 1 year
8. Women known to be pregnant or to have positive beta-HCG.
9. Participation in another study that would interfere with this study.
10. Unstable angina

11. Recent cerebral ischemic events
12. Contraindication to anticoagulation
13. Prior history of polymorphic ventricular tachycardia or torsades depointes.

8 SAMPLE SIZE

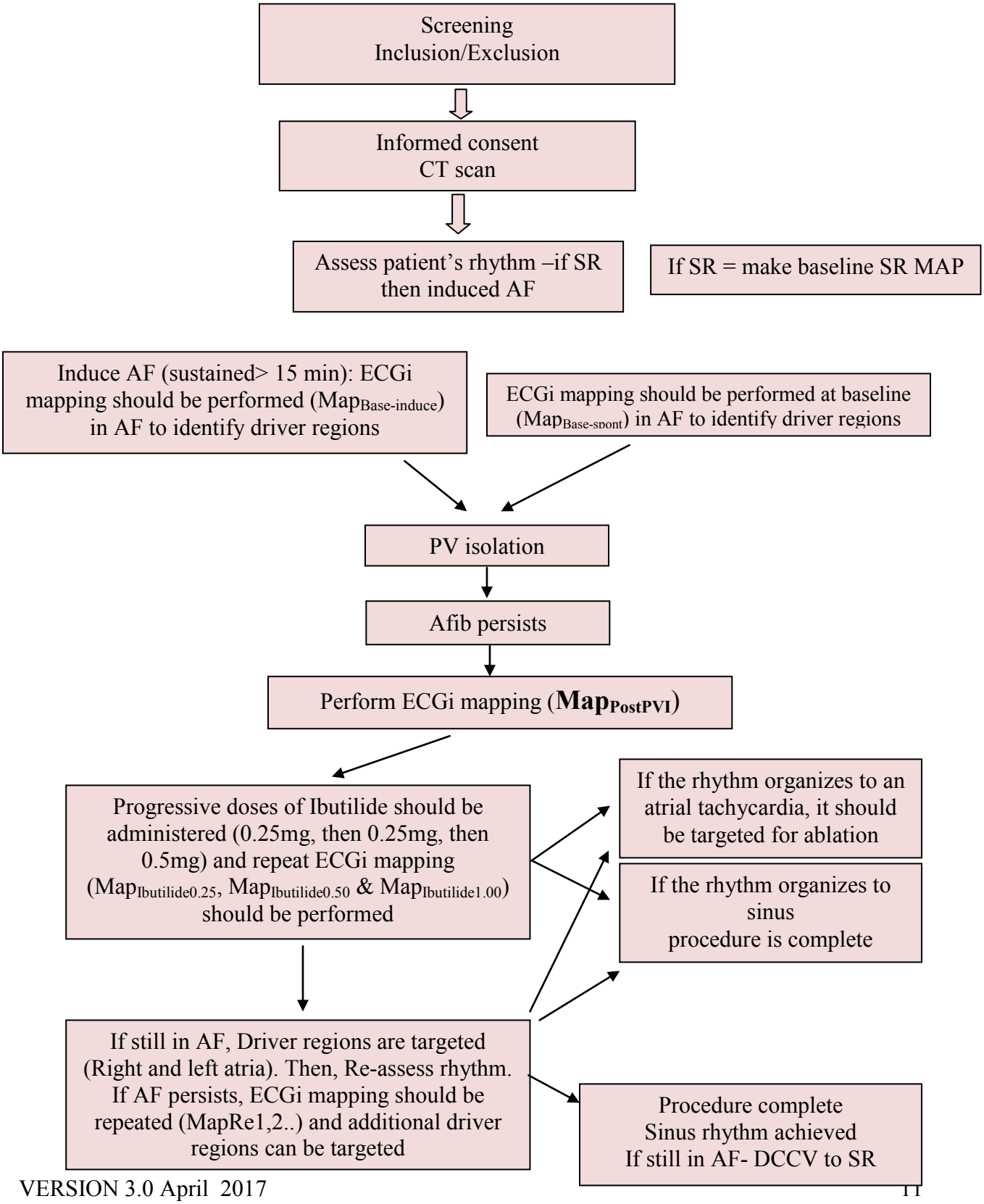
This safety and efficacy study will enroll 20 patients across 1US centers and 1 OUS center. This number has been determined on the basis of study feasibility and not by statistical means. This is a feasibility study of the mapping system (ECGi) performance in which the sample size of the clinical investigation is intended to provide preliminary estimates of safety and performance.

9 PATIENT ENROLLMENT AND WITHDRAWAL

Patients meeting the study inclusion criteria will be identified in the outpatient or inpatient setting by investigators. Patients will be followed by one of the study site primary or co-investigators.

The study will typically be described (including the risks and benefits) during the initial clinic or hospital visit. Consent will typically be obtained at the time of the initial assessment if it is clear that the patient truly understands the nature of the study. Alternatively, the patient will be encouraged to take a copy of the consent form home to contemplate whether he/she would like to be enrolled in the study (see Appendix 1 for informed consent form.) Only patients who voluntarily provide consent will be included in this study. Consent will be obtained prior to undergoing the ablation procedure. Patients will be able to withdraw from the study at any point without compromising their medical care. All data will be de-identified and protected in accordance with institutional and HIPAA guidelines, including 1) de-identification of all geographic subdivisions smaller than a state; 2) all elements of dates related to the individual; 3) telephone and fax numbers; 4) email addresses; 5) social security, medical record, health plan beneficiary, account, and certificate/license numbers; 6) vehicle identifiers; 7) device identifiers; 8) URLs and IP addresses; 9) biometric identifiers; and 10) photographic images.

Eligible subjects will be consented for participation in the trial prior to undergoing AF ablation. Patients are considered enrolled once consented. Patients who do not undergo ablation within 90 days of enrolling will be considered to be screen failures. Patients will be followed for 12 months


Screening
Inclusion/Exclusion
Informed consent
CT scan
Assess patient's rhythm –if SR then induced AF
If SR = make baseline SR MAP
Induce AF (sustained> 15 min): ECGi mapping should be performed (Map$_{Base-induce}$) in AF to identify driver regions
ECGi mapping should be performed at baseline (Map$_{Base-spont}$) in AF to identify driver regions
PV isolation
Afib persists
Perform ECGi mapping (**Map$_{PostPVI}$**)
Progressive doses of Ibutilide should be administered (0.25mg, then 0.25mg, then 0.5mg) and repeat ECGi mapping (Map$_{Ibutilide0.25}$, Map$_{Ibutilide0.50}$ & Map$_{Ibutilide1.00}$) should be performed
If the rhythm organizes to an atrial tachycardia, it should be targeted for ablation
If the rhythm organizes to sinus
procedure is complete
If still in AF, Driver regions are targeted (Right and left atria). Then, Re-assess rhythm. If AF persists, ECGi mapping should be repeated (MapRe1,2..) and additional driver regions can be targeted
Procedure complete
Sinus rhythm achieved
If still in AF- DCCV to SR

- **<u>Empiric ablation (CFAE or linear ablation) is not permitted</u>**

10 STUDY PROCEDURES

10.1. PRE-PROCEDURE EVALUATION

Patients will be consented for the study in either the inpatient or outpatient setting. The following tests and procedures will occur before the ablation as a routine part of pre-procedural medical assessment:

- Recording of patient medical history (including details of previous ablation)
- Recording of patient AF/AT recurrences
- Recording medication history (including all anti-arrhythmic drugs used and duration of use)
- Obtain β-HCG in females of child bearing age the morning of the procedure as per usual clinical practice
- Baseline assessment of arrhythmia burden and type: Office/inpatient records, ICD interrogation report
- Collect any pre-procedural echocardiograms
- Baseline laboratory, including complete blood count, standard electrolyte panel, renal function
- Consent must be obtained before the procedure.

10.2 PRE-PROCEDURE MEDICATION MANAGEMENT

Choice of pre-procedural anti-platelet and anti-thrombotic medications will be at the discretion of the primary operator. All patients will be required to have three weeks of uninterrupted anticoagulation prior to ablation. For those patients with interruptions in anticoagulation or if there is clinical concern for possible left atrial thrombus, a preprocedure transesophageal echocardiography will be performed to rule out left atrial thrombus Typically, however, these medications will be continued through the procedure. Every effort will be made to discontinue AAD prior to ablation.

10.3 PROCEDURAL DETAILS

- Patients will be brought to the electrophysiology laboratory in a fasting state
- Patients will have an ECG to determine rhythm – ie Sinus rhythm vs Atrial fibrillation
- A trained clinical specialist places 252 dry gelled ECG electrodes on the patient's torso. The CardioInsight™ Sensor Array (vest) is hooked up to the The CardioInsight™ System and body surface ECG recordings are made during the patient's arrhythmia. The patient is then sent to the

radiology department for a CT scan (no contrast) to image both the heart and electrodes on the patient's torso. A trained clinical specialist segments the CT DICOM images from the CT scan to obtain epicardial anatomy and establish heart-torso geometry. The electro grams are processed by the mapping system to produce movies of sinus rhythm activation or fibrillatory activity (both focal activity, and rotor activity) depending on presenting rhythm.

- Proper placement of vest patches will be done at this time
- Defibrillator patches will not be placed until needed

Patients will undergo electrophysiology study using a mapping system and ablation as per standard practice. Placement of trimmed patches will be placed in standardized locations

Ablation details
All patients undergoing ablation will be anticoagulated with heparin with the aim of maintaining ACT between 300 and 400 throughout the case. This will be confirmed with periodic ACT testing.
Ablation parameters are as per operator discretion and driver ablation will require adequate lesion placement as assessed by the operator in the area of interest as defined by the map. We recommend that ablation be performed with sufficient power and/or duration and guided by traditional parameters of effective lesion formation as confirmed by impedance drops. During atrial fibrillation additional parameters such as effacement of local electrograms or slowing of local atrial cycle length in the ablated area can be also used.

Other mapping and protocols
Isoprenaline challenge for trigger mapping or for induction of sustained atrial fibrillation
- The infusion can be used for doses as high at 30mcg/kg/min and should be continued for 10-30 minutes to truly assess the effect of isoprenaline. Trigger mapping requires the operators to use at least 20 mcg/kg/min or maximum tolerated dose for 10-20 minutes. When isoprenaline is used to sustain AF in cases where AF induced by pacing is nonsustained then lower doses can be used – 2-4 mcg/kg/min

AF induction and cardioversion- Induce atrial fibrillation by rapid pacing in the atrium. Once sustained AF is noted- then perform DCCV and wait to see if triggers are seen inducing atrial fibrillation.

- **<u>Presenting rhythm- Sinus- Induce AF – is sustained >15 mins</u>**
  - **Map** sinus acquired first and then **Map** $_{\textbf{induceAF}}$ will be acquired

- **<u>Presenting rhythm- Atrial fibrillation</u>**
  - **Map** $_{\textbf{spontAF}}$ will be acquired
    PV isolation is initially completed with standard approach
  - If AF persists then

↓

- Progressive doses of Ibutilide should be administered (0.25mg, then 0.25mg, then 0.5mg) and repeat ECGi mapping ($Map_{Ibutilide0.25}$, $Map_{Ibutilide0.50}$ & $Map_{Ibutilide1.00}$) should be performed. If the rhythm organizes to atrial tachycardia this will be ablated and if rhythm converts to sinus – then procedure is deemed complete.

↓

If still in AF, Driver regions are targeted
(Right and left atria)
Prior to ablation- LAA and RAA cycle length are to be measured over 10 beats
Ablation of drivers can be initiated in chamber with faster CL or
with greater number of identified drivers. Drivers can be addressed in order of importance as suggested by maps.

Periodic reassessment of TCL in LAA and RAA to be done to help direct operator to chamber of interest- e.g. if there is significant gradient between RAA and LAA such that RAA is faster then drivers can be pursued in RAA prior to completion of all driver regions of LA
All drivers are to be sequentially ablated; if rhythm is still not organized then ablation sites are visited again to ensure adequate ablation.If AF persists, ECGi mapping should be repeated (MapRe1,2.) and additional driver regions can be targeted

- **Ibutilide Dosing Guidelines**

1. Patients <60 kg – Ibutilide dosing is limited to a maximum dose of 0.50
2. Patients >60 kg are allowed to receive full dosing of ibutilide up to 1.0mg
3. All patients must receive 1g of intravenous magnesium to minimize the risk of ventricular arrhythmias associated with Ibutilide administration.
4. Hypokalemia and hypomagnesemia should be corrected before ibutilide infusion.
5. All aliquots must be administered over a minimum of 5 minutes.
6. If AF terminates during infusion the infusion must be terminated.
7. An EKG assessment must be done prior to any Ibutilide dosing and if QTc interval >500ms (unless on amiodarone) then further doses will not be administered.
8. Continuous ECG monitoring should be provided for at least 4 hours following ibutilide infusion or until QTc has returned to baseline.

10.4 POST-PROCEDURE

10.4.1 POST-PROCEDURE FOLLOW UP

- Discharge criteria decisions will be made at the discretion of the primary operator per current guidelines.
- Medication and adverse event review will be performed prior to discharge.

- Complications including vascular, stroke, heart failure, pericardial effusion, tamponade, bleeding, and death will be documented.
- The post ablation blanking period will last 3 months - any AAD is permitted but should be stopped by 4 weeks after the study procedure
- The total number of episodes of post-blanking AT or AF episode >30 seconds will be recorded
- Patients will undergo continuous 7-14 day ambulatory monitoring at 3, 6 and 12 months
- Review of medications and adverse events will be performed at the 6 and 12 month follow up

10.4.2 POST-PROCEDURE MEDICATION MANAGEMENT

- Standard cardiovascular medications are left up to the discretion of the investigator.
- Therapeutic anticoagulation beyond the requisite 2 months post-procedure time point will be at the discretion of the patient's physician.
- The post ablation blanking period will last 3 months- any AAD is permitted but should be stopped by 4 weeks after the study procedure

11 SAFETY

We anticipate no significant increase in adverse events as compared to the standard AT/AF ablation procedures. The local site primary investigator will oversee the safety of the study at his/her site. As this is a mapping tool that is non-invasive we don't anticipate any adverse events unique to the case in itself. The CT scan that is required is already part of the standard of care. A detailed tally of adverse events will be kept and they are defined as such.

Adverse Events

An adverse event is any undesirable clinical occurrence in a study patient, whether or not it is related to the study intervention. Any condition that was recorded as pre-existing is *not* an adverse event unless there is a change in the nature, severity or degree of the condition.

Serious Adverse Event

Serious adverse events are defined by FDA regulation as any experience that results in a fatality or is life threatening; results in significant or persistent disability; requires or prolongs a hospitalization; results in a congenital anomaly/birth defect; or represents other significant hazards or potentially serious harm to research subjects or others, in the opinion of the investigators. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, or convulsions that do not result in inpatient hospitalization.

Unanticipated Adverse Device Effects

An unanticipated adverse device effects (UADE) is any serious adverse effect on health or safety or any life-threatening problem 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 any other unanticipated serious problem associated with the device that relates to the rights, safety, or welfare of subjects

Event Recording

The following adverse events will be captured throughout the period of trial participation:

- Protocol-defined (as described below)
- Serious unanticipated events (serious "Other" adverse events)

Causality

The investigator will assess the relationship of an adverse event to the intervention. Causality will be defined as follows:

Probable
Adverse events that, after careful medical evaluation, are considered with a high degree of certainty to be related to the ablation procedure. The following characteristics will apply:

- A reasonable temporal relationship exists between the event and the intervention, and
- The event is a known reaction to the intervention, and cannot be explained by an alternative etiology commonly occurring in the population/individual.

Possible
Adverse events that, after careful medical evaluation, do not meet the criteria for a probable relationship to the intervention, but for which a connection cannot be ruled out with certainty. The following characteristics will apply:

- The event occurs after intervention, and
- The event is not a known reaction to intervention, but cannot be explained by a commonly occurring alternative etiology

Unlikely
Adverse events that, after careful medical evaluation, do not meet the criteria for a possible or probable relationship to intervention and for which a connection is unlikely. The following characteristics will apply:

- The event does not follow a reasonable temporal sequence from administration of the intervention, or
- May have been produced by environmental factors, and there is no apparent pattern of response to the intervention.

Reporting of Serious Adverse Events and Unanticipated Adverse Device Effects

All investigators must report both expected (protocol-defined) and unexpected SAEs. All protocol defined SAEs must be reported directly to the clinical center's IRB and the DCC within 5 business days of knowledge of the event, or as dictated by the specific IRB policy, whichever is sooner. All deaths, UADEs, and unexpected SAEs that are possibly or probably related to the Panoramic ECGi and Ibutilide ablation must be reported to the DCC and the clinical center's IRB within 24 hours of knowledge of the event, or as dictated by the specific IRB policy, whichever is sooner. All unexpected SAEs that are unlikely related to the study intervention must be reported to the DCC and the clinical center's IRB within 5 business days of knowledge of the event, or as dictated by the specific IRB policy, whichever is sooner.

The DCC will report these events to the DSMB chair within 72 hours of notification. All SAEs will be reported to the DSMB at least semi-annually, at the discretion of the DCC medical monitor.

Reporting of Unanticipated Problems

All UPs that are also SAEs, which are at least possibly related to the study intervention, must be reported to the DCC within 24 hours of knowledge of the event. All UPs that are not SAEs must be reported to the DCC within 5 calendar days of knowledge of the event, or as dictated by the specific IRB policy, whichever is sooner.

DCC Reporting to FDA

The DCC will report unexpected SAEs that are possibly or probably related to the investigational device or UADEs to FDA as appropriate. The DCC will send an initial IDE safety report communication to the FDA within 2 business days of notification from the site. The DCC will submit a follow-up safety communication to the FDA, based on source documentation or PI Report from the site, within 10 business days from notification of a UADE for this IDE trial.

DMC

To meet the study's ethical responsibility to its subjects, an independent Data Monitoring Committee (DMC) will monitor results during the study. The DMC for this trial will consist of a single cardiologist who has no formal involvement or conflict of interest with the subjects, the investigators, the sponsor or the DCC. The DMC will act in a senior advisory capacity to the DCC regarding data and safety matters throughout the duration of the study. In addition, the DMC will review interim summary results of the accumulating data every 6 months or as needed. These data include adverse events (e.g., infection, bleeding, right heart failure) and mortality. They will communicate their findings directly with the DCC. The FDA will be provided a copy of any written communication from the DMC to the study sponsor related to safety concerns, or changes to the study protocol, procedures or informed consent document. The DMC will be provided a copy of any letter from the FDA to the study sponsor related to safety concerns, or changes to the study protocol, procedures or informed consent document. The clinical centers will have no contact with the DMC regarding this trial and no voting member of the committee may participate in the study as an investigator. Non-DMC members will not be allowed during DMC closed meetings. However, the PI will only be present at the open session of the meetings to clarify questions concerning the protocol and to provide updates to the DMC regarding pertinent new trial information. However, recommendations and decisions regarding the study are solely up to the discretion of the DMC.

12 RISKS

Patient confidentiality risks associated with any research study are minimal and include: breach of confidentiality and loss of personal data.

As the protocol includes a *standard of care* AF ablation procedure, *the risks of the procedure are generic to a standard AF ablation procedure, and include the following:*

Potential Risks Associated with AF Ablation

- Death: End of Life
- Stroke (also called Cardiovascular Accident or CVA): may cause an interruption in the blood supply to a part of the brain
- Pericarditis: inflammation may occur in the outer lining of the heart (<1%).
- Cardiac perforation causing pleural effusion or tamponade: fluid build-up around the heart. A hole in your heart wall (*perforation*) could result in bleeding into the sac, called the pericardium, which surrounds your heart (*cardiac tamponade*). This may be treated by insertion of a needle, through your chest wall, into the sac and removal of the blood. This type of hole sometimes requires surgical repair
- Heart Valve injury (also called Valvular Damage/Insufficiency): an injury to a valve structure resulting in a loss and/or worsening of function (e.g., worsening of regurgitation score or prolapse) (<1%).
- Acute Pulmonary edema: fluid accumulation (build-up) in the lungs (<1%).
- Pulmonary embolism: blockage of a pulmonary artery; a blood clot from a vein may get stuck in the lungs. This is usually treated with drugs (<1%).
- Vascular access complications: an obstruction or perforation or damage to the vascular (blood vessel) system (2%).
- Arterial/venous thrombus: clot formation in the artery or vein (1.5%).
- AV fistula: an abnormal passageway (such as a hole) between an artery and a vein; this may allow blood to go between the arteries and veins and not through the entire body. This may cause some part of the body to not receive the usual amount of blood. This may heal on its own, but may require surgical repair (1.5%).
- Catheter insertion site hematoma: bleeding or bruising from the site of catheter placement. This may go away without treatment, but may require manual compression or surgical repair. If excessive bleeding at the site of the catheter placement continues, this could result in anemia requiring medical intervention (2%).
- Hypoxia: reduced oxygen supply to tissue (<1%).
- Infection, Localized or systemic: an infection may occur anywhere an incision or cut is made during the procedure (<1%).
- Peripheral venous thrombosis: blood clots in the vein (<1%).
- Phrenic nerve damage: damage to the nerve that controls the diaphragm and may affect your breathing. Symptoms may be temporary but in some cases can be permanent (respiratory arrest) (<1%).
- Pneumonia: infection of lungs or gathering of fluid in the lungs (<1%).
- Pseudoaneurysm: development of a false pouch in the vessel wall. This can be caused by movement of catheters in the blood vessels. This may heal on its own, but sometimes need surgical repair (<1%).
- Radiation injury resulting in dermatitis (skin burns): (<1%).
- Respiratory failure: damage to breathing that can be permanent (respiratory arrest) (<1%).

- Radiation exposure during the fluoroscopic imaging of the catheters during ablation: this may slightly increase the lifetime risk of developing a fatal malignancy or a genetic defect in offspring (<1%).
- Fluid overload: excessive fluid built up could result in pulmonary (lung) edema; congestive heart failure (CHF) may occur or may be exacerbated (worsened) due to delivery of sterile salt water (saline) during the procedure (these risks are specific to open irrigated ablation catheters) (1.5%).

Potential Risks Associated with Ibutilide

- Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, chest tightness, trouble breathing
- Arrhythmias, including Torsades de pointes
- Fast, pounding, or uneven heartbeat
- Headache
- Syncope
- Nausea
- Renal Failure

The protocol requires a CT scan to be performed. Routine CT scan with contrast is often performed if there is no contraindication as part of normal pre-procedural planning. For this protocol this will be performed on the day of the procedure. If the patient has impaired renal functions or has abnormal renal functions we will perform a non- contrast scan

13 STUDY MANAGEMENT

13.1 Study Data Collection and Processing

The Case Report Form (CRF) is an integral part of the study and subsequent reports. The CRF must be used to capture all study data recorded in the patient's medical record. The CRF must be kept current to reflect patient status during the course of the study. Patients will be identified by a 5-digit number and their initials. The investigator must keep a separate log of patient names and medical record numbers (or other personal identifiers) for their own reference. All study-related documents (CRFs, source medical records, regulatory binder) must be kept in a secure, locked environment with access limited to study personnel only.

The PI is responsible for ensuring the following: 1) adherence to the protocol; 2) verifying adherence to local regulations on the conduct of clinical research; and 3) ensuring completeness, accuracy, and consistency of the data entered in the CRF.

Final CRFs in human readable format must be reviewed and verified for accuracy by the study site Principal Investigator and signed-off. A copy of the final CRF will remain at the investigator's site at the completion of the study.

The CRF numbering convention is as follows:

_01_-_2__3__4_ A -B -A
_01_: Site # must be 2 digits (use leading zero) --- (sites 01-5)

_2_ _3__4_: patient screening/enrollment # (001 – 050)—must be 3 digits

A-B-A: Patient initials (if no middle initial, use dash)

Total 5 digits and initials for enrolled patients.

13.2 Confidentiality

Patient information will be kept confidential and managed according to the 1996 HIPAA guidelines. Each patient will be given a unique subject number and will be identified by this number and their initials. All data used in the analysis and reporting of this evaluation will be without identifiable reference to the patient. Data relating to the study might be made available to third parties (for example in case of an audit performed by regulatory authorities) provided the data are treated confidential and that the patient's privacy is protected.

13.3 Deviations from Protocol

The investigator will not deviate from the protocol except in medical emergencies or in unforeseen, isolated instances where minor changes are made that will not increase the patient's risk or affect the validity of the trial. In medical emergencies, prior approval for protocol deviations will not be required, but the IRB/EC must be notified within five days of the incident.

13.4 Role of the Coordinating Center

As principal investigator and study sponsor of this clinical study, Vivek Reddy, MD assumes the overall responsibility for the conduct of the study, including assurance tht the study meets national and institutional guidelines for study conduct. In this study, Vivek Reddy, MD will have certain direct responsibilities and will delegate other responsibilities to his staff at the Coordinating Center, the Icahn School of Medicine at Mount Sinai. The coordinating center will: 1) ensure adherence to the national and institutional regulations; 2) develop and distribute protocols and case report forms; 3) coordinate data organization; 4) perform statistical analyses; 5.) provide on-site and remote monitoring.

13.5 Withdrawal of Subjects

A subject may withdraw from the study at any time should they choose to do so. Additionally, subjects may be withdrawn by the investigator if deemed appropriate due to safety or compliance issues.

13.6 Economic Impact on Subjects

There are no additional costs related to involvement in this study. Since the cost of the procedure will be included within the Disease Related Group (DRG) charge, neither patient nor insurance provider will incur additional cost.

14 ETHICAL AND REGULATORY CONSIDERATIONS

14.1 Maintaining Records (21 CFR 812. 140 (B))

All clinical sites will maintain study records for two years after research termination. The Coordinating center will maintain copies of correspondence, data, shipment of devices, adverse device effects and other records related to the clinical trial.

14.2 Institutional Review Board (IRB) / Ethics Committee (EC) Information

This protocol and the informed consent must be reviewed and approved by the appropriate IRB/EC where the trial is to be conducted before enrollment of patients. Changes to the protocol that may increase the risk or present new risks to the patient, or may adversely affect the validity of the trial, must be approved in writing by the IRB/EC before the change is made.

The study site Principal Investigator(s) is responsible for submitting and obtaining initial and continuing review (at intervals not greater than once a year) of the trial by their IRB/EC.

15 CLINICAL CENTERS

The study will be conducted in up to 4 sites in the United States and 1 in Europe. Each clinical center will be required to obtain IRB/EC approval for the protocol and consent (and their revisions) in a timely fashion, to recruit patients, to collect data and enter it accurately in the electronic data capture (EDC) system, to faithfully follow the protocol and adhere to the standards of Good Clinical Practice (GCP). In addition, centers will be required to provide the DCC with the information necessary for interim, annual, and final reports, to provide source documents, data and regulatory documents for study monitors, provide prompt responses to DCC inquiries, and to participate in analyses and reporting of study results.

Investigator Profile
All cardiologists, coordinators and other investigators in the study must complete the Investigator Profile form, including hospital affiliation, address, telephone, fax, beeper and email information. The cardiologist and coordinator must email or fax their CV, Conflict of Interest Statement and Financial Disclosure Certification, and Institutional Health Insurance Portability and Accountability Act (HIPAA) Certificates to the DCC.

Qualifications and Training

Clinical investigators will be electrophysiologists with expertise in AF ablation. The certified operator will either perform the ablation on their own patient, or participate in the ablation of an enrolled patient. The clinical site Principal Investigator will be responsible for overseeing the ongoing performance of the other participating investigators at that site over the course of the study.

All clinical site investigators and coordinators will be trained by the DCC in the specifics of the protocol at a site initiation visit in advance of patient enrollment. In addition, the investigators and coordinators will undergo a separate training session to gain familiarity with the electronic data capture system.

16 DATA HANDLING

Information about patients will be kept confidential and managed according to the requirements of the United States of American Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed patient authorization informing the patient of the following:

1. What protected health information (PHI) will be collected from patients.
2. Who will have access to that information and why.
3. Who will use or disclose that information.
4. The rights of a research patient to revoke their authorization for use of their PHI.

In order to ensure patient confidentiality, all case report forms and patient information (CT / MRI, if reviewed), fluoroscopic and endoscopic images, ECGs) will be de-identified and replaced with a unique patient identifier. Information will be stored in the office of the local study coordinator, which will be kept in a secure, locked location. The research study coordinators, principal investigator and co-investigators will be the only personnel with access to this data. All data will be stored without any patient information apart from the unique three digit patient identifier. Electronic data will be encrypted and password-protected.

17 DATA ANALYSIS

Baseline clinical characteristics (e.g. age, gender, renal function) and procedural characteristics (e.g. surface intracardiac electrogram, and imaging findings) of the patients will be collected and analyzed. All continuous variables will be performed as the mean ± standard deviation, and all categorical variables as a percentage of the total study population.

REFERENCES

1) Substrate and Trigger Ablation for Reduction of Atrial Fibrillation (**STAR AF**): a randomized, multicentre, international **trial**.Verma A, Mantovan R, Macle L, De Martino G, Chen J, Morillo CA, Novak P, Calzolari V, Guerra PG, Nair G, Torrecilla EG, Khaykin Y. Eur Heart J. 2010 Jun;31(11):1344-56.
2) Knecht, S., Sohal, M., Arentz, T., Jadidi, A., Rostock, T., Deisendorfer, I.V., Cauchemez, B., Albenque, J.P., Neumann, T., Ernst, S. and Packer, D., 2015. Noninvasive mapping prior to ablation for persistent atrial fibrillation: The AFACART multicenter study (PO 06-52). Heart Rhythm, 12, p.S508