Abbott	Clinical Investigation Plan Cover Page

NCT Number: NCT04022954
HD Mapping Observational Study
High Density (HD) Mapping Observational Study
Study Document No: ABT-CIP-10284
Version C
Date: 6-JUN-2019

Sponsor

Abbott
5050 Nathan Lane North
Plymouth, MN 55442
USA

Clinical Investigation Plan

CRD_975
HD Mapping Observational Study

Version Number	C
Date	June 6, 2019
Planned Number of Sites and Potential Region(s)	20 sites China, Hong Kong, India, Malaysia, Japan, South Korea, and Taiwan
Clinical Investigation Type	Prospective, multi-center, single-arm, post-market observational
Sponsor	Abbott 5050 Nathan Lane North Plymouth, MN 55442 USA
Electronic Data Capture Software	Oracle Clinical
CIP Author of Current Version	[redacted]

[redacted]

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SITE PRINCIPAL INVESTIGATOR SIGNATURE PAGE

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

Site Principal Investigator

Printed name:
Signature:
Date:

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COMPLIANCE STATEMENT:

This clinical investigation will be conducted in accordance with this Clinical Investigation Plan, the Declaration of Helsinki, ISO 14155:2011 standards and the appropriate local legislation(s). The most stringent requirements, guidelines or regulations must always be followed. The conduct of the clinical investigation will be approved by the appropriate Ethics Committee (EC) of the respective clinical site and as specified by local regulations.

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Clinical Investigation Plan

1.0 INTRODUCTION

This document is the clinical investigation plan (CIP) for the High Density (HD) Mapping Observational Study. This clinical study is a prospective, multi-center, single-arm, post-market observational study intended to quantify and characterize the outcomes of radiofrequency (RF) ablation after, and the utility of, electroanatomical mapping with the market-released HD mapping catheters Inquiry™ AFocusII™ Double Loop and Advisor™ HD Grid, Sensor Enabled™ with the EnSite Cardiac Mapping System and the Ensite Automap Module in subjects with atrial fibrillation in the real-world environment of the Asian population. This clinical study is sponsored by Abbott.

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

1.1 Background and Rationale

1.1.1 Background

Atrial Fibrillation (AF) is a supraventricular arrhythmia characterized by rapid and irregular activation in the atria. AF is can be divided into two main types based on the frequency of occurrence: paroxysmal and persistent. Paroxysmal AF (PAF) is defined as AF that terminates spontaneously or with intervention within 7 days of onset. Persistent AF (PersAF) is defined as continuous AF that is sustained beyond 7 days.[1] AF is progressive from PAF to PersAF; disease progression is due to arrhythmia-induced tissue remodeling that results in changes in contractile properties, electrical properties, and tissue structure.[2] AF remains a major cause of stroke, heart failure, sudden death, and cardiovascular morbidity and is associated with increased rates of hospitalization.[3, 4] Restoration and maintenance of sinus rhythm either thru pharmacological or non-pharmacological methods is the standard of treatment.[5] Based on epidemiological studies of mainly North American and European populations, an estimated 20.9 million men and 12.6 million women suffer from AF.[6] The prevalence of AF is lower in Asians than in Westerners and is estimated to be approximately 0.7-1.1% in Asians older than 40. Despite this apparent difference in prevalence, the burden of AF in the Asia Pacific region is expected to become far greater than that in Western regions based on the increasing age and size of populations within the Asia Pacific regions.[7, 8]

Catheter ablation is an established treatment option for AF[1], although corresponding success rates in long-term sinus rhythm maintenance remain modest and could benefit from further research. Ablation strategies target the pathogenic mechanisms that initiate and perpetuate abnormal electrical activity within the heart including abnormal substrates. However, identifying and eliminating the pathogenic mechanisms is not straightforward, especially with complex arrhythmias in which the distribution of potential arrhythmogenic drivers is heterogeneous across the patient population and there remains a lack of consensus on approach to identifying and ablating mechanistic drivers.

AF is electrophysiologically characterized by fast and regular atrial activities, complex fractionated atrial electrograms, direction of wave front propagation, and low peak-to-peak voltage. Pulmonary veins are believed to be the primary trigger of AF. In cases of PersAF, triggers beyond pulmonary vein triggers may include areas of fibrosis, focal automaticity, or foci, areas of rapidly rotating reentrant circuits, or rotors, asynchronous activation of myocyte bundles identified by complex fractionated electrograms, overactive ganglionated plexi, and dissociation and interaction between epicardial and endocardial layers. [1, 9, 10] The role of such mechanisms continues to be debated along with their implication on therapeutic strategy, especially since ablation techniques aim to eliminate AF triggers or modify arrhythmogenic substrate

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Electroanatomical mapping (EAM) techniques are used to locate pathologic substrates that trigger arrhythmias including identification of local abnormal ventricular activities (LAVA), late potentials, fractionated electrogram signals, and activation mapping.[11, 12] The effectiveness of catheter ablation relies heavily on the accuracy, resolution and fidelity of mapping results. Initially, EAM relied on point-to-point annotation with a single electrode unipolar or bipolar mapping catheter contacting tissue, resulting in limited quality maps. The point-by-point acquisition process is time consuming and may miss small areas critical to the aberrant circuit. The development of linear, multielectrode mapping catheters that contact tissue such as the Inquiry™ AFocusII™ Double Loop allow for more rapid collection of data resulting in high-density maps. Maps created with these catheters may be influenced by the direction of the wavefront, catheter orientation, electrode size, interelectrode spacing, proximity to tissue and contamination by far-field signals.[12] Accurate electrogram depiction of underlying substrate is limited by adequate bipole orientation which can be challenging to achieve with these traditional linear mapping catheters.[13] Nonlinear, multielectrode, tissue contacting catheters were developed to help circumvent some of these limitations. For example, the Advisor™ HD Grid diagnostic mapping catheter was created with equi-spaced multipolar grid electrodes with known bipole spacing in orthogonal directions, thereby providing the ability to discriminate voltage differences in two directions for enhanced directionality and amplitude detection.

1.1.2 Rationale for Conducting this Clinical Investigation

EAM with HD mapping catheters has been shown to provide insight into the extent of structural disease and assist in the determination of the critical atrial targets to guide catheter ablation strategy. This allows physicians to avoid both unnecessary overtreatment that could result in increased risk of complication, procedure duration, and fluoroscopy exposure, as well as undertreatment with increased likelihood of recurrence in patients that present with complex arrhythmias. The utility of HD mapping catheters on the subsequent ablation strategies used by physicians and the outcomes of ablation would benefit from further study, particularly in the Asia Pacific region, where research in AF has been less prevalent.

2.0 CLINICAL INVESTIGATION OVERVIEW

2.1 Clinical Investigation Objective

The aim of this study is to quantify and characterize the outcomes of radiofrequency (RF) ablation after, and the utility of, electroanatomical mapping with the market-released HD mapping catheters Inquiry™ AFocusII™ Double Loop and Advisor™ HD Grid, Sensor Enabled™ with the EnSite Cardiac Mapping System and the EnSite Automap module in subjects with AF in the real-world environment of the Asian population.

This study is meant to serve as a post-market observational study. As such, no formal hypothesis testing will be performed. The objective of the study is to evaluate several procedural details related to HD mapping as well as the outcome of the radiofrequency (RF) ablation after electroanatomical mapping with HD mapping catheters.

2.2 Devices to Be Used in the Clinical Investigation

2.2.1 Names of the Devices Under Investigation

All devices used in this clinical study must have proper regulatory approval and will be used according to their indications for use and Instructions for Use (IFU)/Package Insert.

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The devices that will be used in this clinical study are summarized in Table 1. Additional commercially available tools may be used in this clinical study, per physician's discretion. All tools utilized must be done so according to the specific device indications for use and IFU/package insert.

Table 1. Clinical Study Devices

Device name	Model/Type	Manufacturer
EnSite Precision™ Cardiac Mapping System Software (SV 2.2 or later)	H702496	SJM
EnSite Velocity™ Cardiac Mapping System Software (SV 5.0 or later)**	H702495	SJM
Advisor™ HD Grid Mapping Catheter, Sensor Enabled™	D-AVHD-DF16	SJM
Advisor™ HD Grid Mapping Catheter, Sensor Enabled™ Software Kit (License entitlement to use HD Grid Catheter with EnSite Precision™ SV 2.2)	H702519	SJM
Sensor Enabled™ Diagnostic Catheter Cable	D-AVSE-CBL22	SJM
EnSite™ AutoMap Module	H702498	SJM
Inquiry™ AFocusII™ Double Loop Electrophysiology Catheter	IBI-87008	SJM
Inquiry™ AFocusII™ 24-Pin Diagnostic Connecting Cable	1924-S	SJM

** The EnSite Velocity™ Cardiac Mapping System may be available in other regions. For this clinical study, its use is restricted to China only.

2.2.2 Indication for Use

Indications for use may be found in the appropriate device IFU/Package Insert. Indications for the use of each of the HD mapping catheters and the specific EnSite Cardiac Mapping System are described below.

The Advisor™ HD Grid Mapping Catheter, Sensor Enabled™, is indicated for multiple electrode electrophysiological mapping of cardiac structures in the heart with recording or stimulation only. This catheter is intended to obtain electrograms in the atrial and ventricular regions of the heart.

The Inquiry™ AFocus™ catheters are for recording intracardiac signals and cardiac stimulation during diagnostic electrophysiological studies. The Inquiry™ AFocus™ catheters are for use in mapping atrial regions of the heart.

The EnSite Velocity™ Cardiac Mapping System is a catheter navigation and mapping system capable of displaying the three-dimensional (3D) position of conventional electrophysiology catheters, as well as displaying cardiac electrical activity as waveform traces and as dynamic 3-D isopotential maps of the cardiac chamber. The contoured surfaces of these three-dimensional maps are based on the anatomy of the patient's own cardiac chamber. The EnSite Velocity™ Cardiac Mapping System (including AutoMap) is a suggested diagnostic tool in patients for whom electrophysiology studies have been indicated. When

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used with an EnSite Velocity™ Surface Electrode Kit, the EnSite Velocity™ Cardiac Mapping System is intended to display the position of conventional electrophysiology (EP) catheters in the heart.

The EnSite Precision™ Cardiac Mapping System is a catheter navigation and mapping system capable of displaying the three-dimensional (3D) position of conventional and sensor enabled electrophysiology catheters, as well as displaying cardiac electrical activity as waveform traces and as dynamic 3D isopotential maps of the cardiac chamber. The contoured surfaces of these 3D maps are based on the anatomy of the patient's cardiac chamber. The EnSite Precision™ Cardiac Mapping System (including AutoMap) is a suggested diagnostic tool in patients for whom electrophysiology studies have been indicated. The EnSite Precision™ system interfaces to either MediGuide™ Guided Medical Positioning System or the EnSite Precision™ Module to combine and display magnetic processed patient positioning and orientation mapping information. When used with an EnSite Precision™ Surface Electrode Kit, the EnSite Precision™ Cardiac Mapping System is intended to display the position of conventional electrophysiology (EP) catheters in the heart.

2.2.3 Description of the Devices Under Investigation

Please refer to the IFU/Package Insert for additional information regarding the devices used in this clinical study, pictured in the following figures.

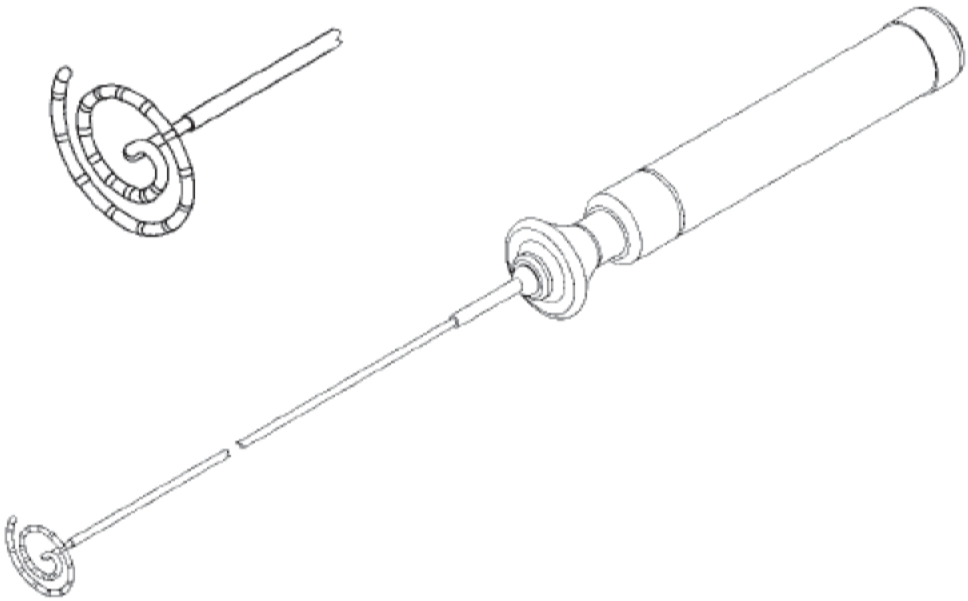

Figure 1. Inquiry™ AFocusII™ Double Loop Electrophysiology Catheter

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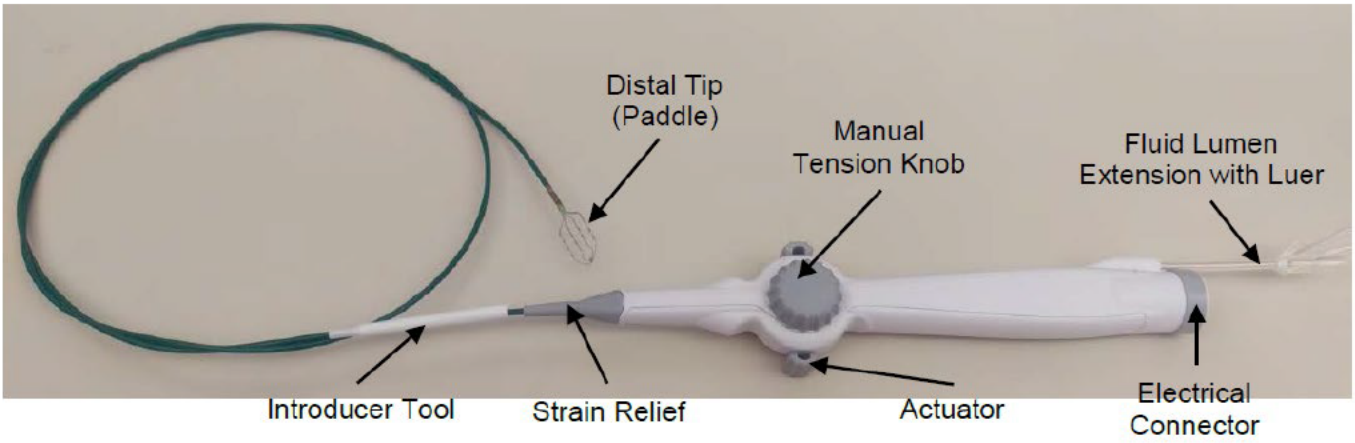

Figure 2. Advisor™ HD Grid, Sensor Enabled™ Mapping Catheter

3.0 CLINICAL INVESTIGATION DESIGN

This is a prospective, non-randomized, multi-center, single-arm, post-market observational study to characterize the outcomes of RF ablation after, and the utility of. electroanatomical mapping with the market-released HD mapping catheters Inquiry™ AFocusII™ Double Loop and Advisor™ HD Grid Mapping Catheter, Sensor Enabled™ with the EnSite Cardiac Mapping System in subjects with AF in the real-world environment of the Asian population. Approximately 200 subjects will be enrolled at up to 20 investigational sites in the Asia Pacific (APAC) region.

[redacted]

3.1 Clinical Investigation Procedures and Follow-up Schedule

Subjects will be consented for the trial prior to any data collection. Once eligibility is confirmed and a subject is consented, baseline information will be collected and the subject will undergo the RF ablation procedure per physician discretion using electroanatomical mapping with either Inquiry™ AFocusII™ Double Loop or Advisor™ HD Grid, Sensor Enabled™ depending on market release in the specific region. Subjects will be followed for 12 months post procedure. Follow-up assessments will occur in person at a clinic. The study visits will occur at baseline, procedure, pre-discharge, 6 months post ablation procedure, and 12 months post ablation procedure. The subject will be exited from the study after completion of the 12-month follow-up visit. The visit schedule and related study assessments are summarized in Figure 4 and further detail is provided in Section 6.0.

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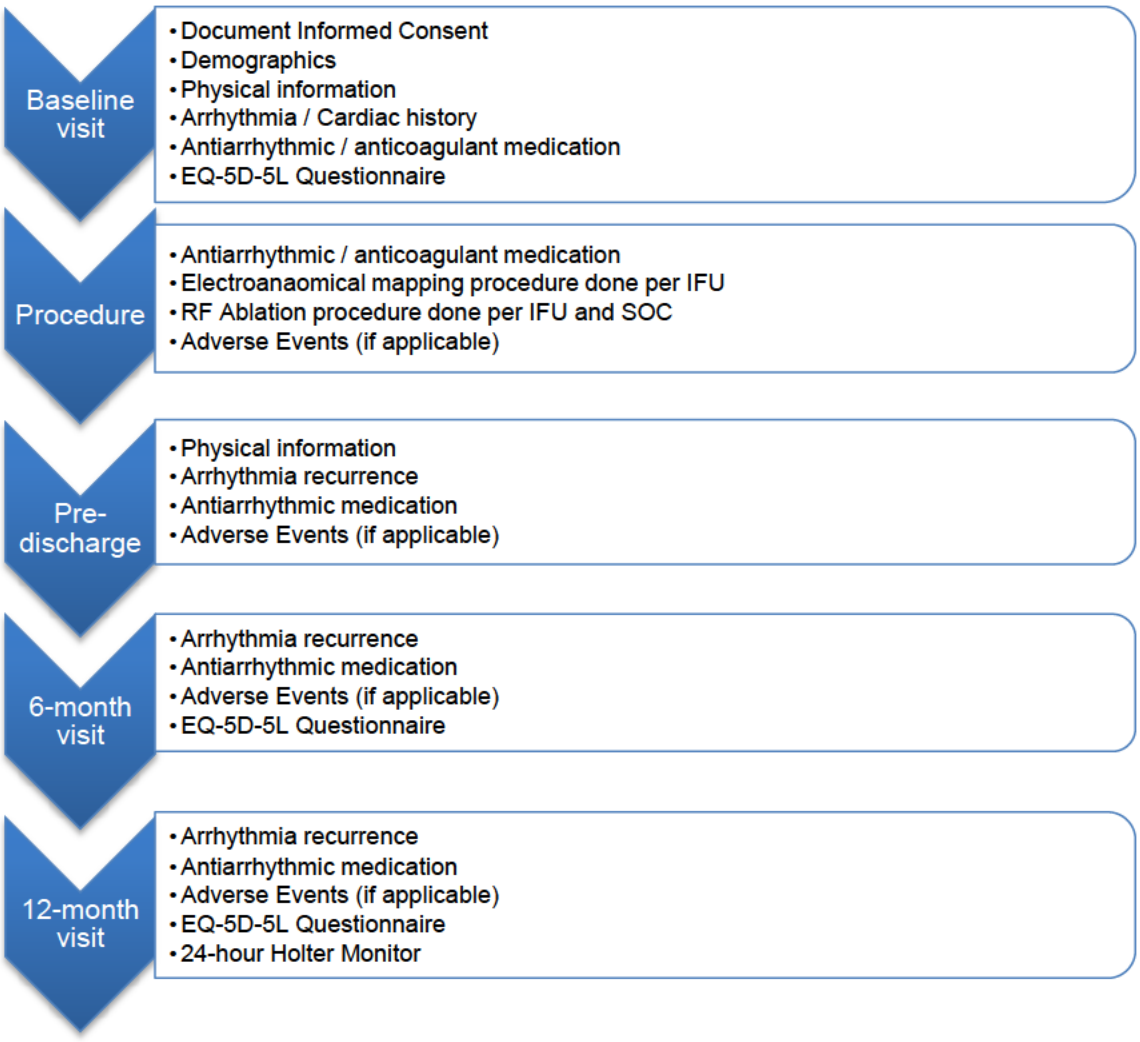

Figure 3. Clinical Investigation Flow Chart

3.2 Measures Taken to Avoid and Minimize Bias

Multiple measures will be taken to avoid bias in this clinical study. First, the HD Mapping Study is prospective, such that the outcome of the study is unknown at time of enrollment, and all subjects must meet pre-defined eligibility criteria thereby minimizing selection bias. Next, guidance will be provided to sites regarding data collection for questionnaires and post-procedure follow-up visit. Case report forms for data collection will be provided to all sites thereby minimizing inter-observer variability. Evaluation of arrhythmia recurrence via Holter monitoring will be performed by an independent core laboratory. Additionally, protocols are in place to minimize subjects lost to follow-up and collection of missing data to minimize the impact or bias caused by missing data.

3.3 Suspension or Early Termination of the Clinical Investigation

While no formal statistical rule for early termination of the clinical investigation for insufficient effectiveness of the device under investigation is defined, the Sponsor reserves the right to discontinue the clinical

investigation at any stage or reduce the follow-up period with suitable written notice to the investigator. Possible reason(s) may include, but are not limited to:

- A new unreasonable risk to the participating subjects has been identified such as an unanticipated increase in complaint rates related to the study.

Should the clinical investigation be discontinued by the Sponsor, subjects will be followed per routine hospital practice with device-related adverse events (AEs) reported to the Sponsor as per vigilance/commercial reporting requirements. All applicable clinical investigation documents shall be subject to the same retention policy as detailed in Section 11.0 of the CIP.

A Principal Investigator, Ethics Committee (EC) or regulatory authority may suspend or prematurely terminate participation in the clinical investigation at the investigational site(s) for which they are responsible. The investigators will follow the requirements specified in the Clinical Trial Agreement.

If the Sponsor suspends or prematurely terminates the clinical investigation at an individual site in the interest of safety, the Sponsor will inform all other Principal Investigators.

4.0 ENDPOINTS

4.1 Utility Endpoint

The utility of HD Mapping catheters with the EnSite Cardiac Mapping System will be quantified and characterized through the summary of the following:

- Overall procedure time: defined as time from initial catheter insertion to final catheter removal.
- Radiofrequency (RF) time: defined as duration of time RF energy is delivered
- Fluoroscopy time: defined as total time subject is exposed to fluoroscopy
- Mapping time associated with mapping arrhythmia: defined as the total cumulative mapping time and mapping time for the creation of each map (including any new or retrospective map created with Manual, AutoMap, and TurboMap mapping)
- Number of mapping points collected: defined as total number of mapping points collected for the creation of each map
- Number of mapping points used: defined as the total number of mapping points used in each map
- Number of used mapping points per minute: defined as the total number of mapping points used divided by the relative mapping time
- Substrate characteristics identified: for each type of arrhythmogenic substrate this will be defined as the frequency of substrate type identified in cases that attempted to identify the specific substrate
- Ablation strategy(s) used: defined by both the type of map used to define ablation strategy and the frequency each ablation strategy/target was used by physicians

4.2 Outcomes Endpoint

To quantify and characterize the acute- and long-term success rate of RF ablation after electroanatomical mapping with HD mapping catheters, the following will be summarized:

- Rate of acute success defined as the proportion of subjects who receive HD mapping and RF energy delivery resulting in acute termination of clinical arrhythmia, defined by termination to SR

[redacted]

(or AT if being treated for PersAF) or non-inducibility of clinical arrhythmia after ablation (cardioversion allowed prior to inducibility attempt).

- Rate of long-term success defined as the proportion of subjects who receive HD mapping and RF energy delivery with the following pre-defined procedural endpoints:

  AF (utilizing a 90-day blanking period following index ablation):

  - freedom from all atrial arrhythmias (AF/AFL/AT) greater than 30 seconds (as documented by 24-hr Holter at 12-month follow-up) and on or off class I/III antiarrhythmic drug (AAD).
  - freedom from all atrial arrhythmias (AF/AFL/AT) greater than 30 seconds (as documented by 24-hr Holter at 12-month follow-up) and off all class I/III AADs.

4.3 Additional Evaluations

- Adverse events including any device-, procedure-, or death-related events.
- Rate of repeat ablations after study procedure during 12-month follow up defined as proportion of subjects with an additional ablation procedure to treat indicated cardiac arrhythmia (outside blanking period, if applicable).
- Change in quality of life (QOL) at 6 months and 12 months after receiving HD mapping and RF ablation relative to baseline: defined as change in quality of life assessed in the validated EQ-5D-5L QOL survey.

5.0 SUBJECT SELECTION AND WITHDRAWAL

5.1 Subject Population

This clinical investigation will enroll male and female subjects from the general AF population. Subjects must meet all eligibility criteria and provide written informed consent prior to conducting any study required procedures.

5.2 Subject Screening and Informed Consent

5.2.1 Subject Screening

Potential patients presenting at the clinical sites will be fully informed about the clinical investigation, following the established Informed Consent process (described in Section 5.2.2). Once a duly dated and signed Informed Consent form is obtained, the clinical investigation-specific screening procedures may begin.

Subjects must be screened for clinical investigation eligibility by a member of the site's clinical investigation team previously trained to the CIP, and if applicable will be entered into a site-specific screening log.

If the subject does not meet all inclusion criteria, or meets any of the exclusion criteria, the subject is considered a screening failure. The Principal Investigator or the delegated clinical investigation personnel will record the screening failure in the hospital records and on a screening log as required.

[redacted]

Patients who meet all inclusion criteria and none of the exclusion criteria are eligible to participate in this clinical study. Eligible patients presenting at clinical sites will be fully informed about the clinical study and asked to sign an Informed Consent form if they wish to participate in the clinical study. These patients will also be entered into the screening log.

The following assessments may need to be performed after obtaining consent and prior to the procedure as part of the screening process:

- Pregnancy test
- Intracardiac thrombus assessment

Subject data will be collected for the clinical study after obtaining signed Informed Consent form.

5.2.2 Informed Consent

A template Informed Consent form will be provided to each site by the Sponsor under separate cover for use in this clinical study. Site-specific language will be added to the template and approved by research personnel, the Sponsor, and governing EC prior for use in the trial.

The Investigator or his/her authorized designee (if applicable) will conduct the Informed Consent process, as required by applicable regulations and the center's EC. This process will include a verbal discussion with the subject on all aspects of the clinical investigation that are relevant to the subject's decision to participate, such as details of clinical investigation procedures, anticipated benefits, and potential risks of clinical investigation participation. Subjects must be informed about their right to withdraw from the clinical investigation at any time and for any reason without sanction, penalty or loss of benefits to which the subject is otherwise entitled. Withdrawal from the clinical investigation will not jeopardize their future medical care or relationship with the investigator.

During the discussion, the Principal Investigator or his/her authorized designee will avoid any improper influence on the subject and will respect subject's legal rights. Financial incentives will not be given to the subject. Subjects may be compensated for time and travel directly related to the participation in the clinical investigation. The subject shall be provided with the Informed Consent form written in a language that is understandable to the subject and has been approved by the center's EC. The subject shall have adequate time to review, ask questions, and consider participation. The Principal Investigator or his/her authorized designee will make efforts to ensure that the subject understands the information provided. If the subject agrees to participate, the Informed Consent form must be signed and dated by the subject and thereafter by the person obtaining the consent prior to any clinical investigation-specific procedures. The signed original will be filed in the subject's hospital or research charts, and a copy will be provided to the subject.

Failure to obtain informed consent from a subject prior to clinical investigation enrollment should be reported to Sponsor within 5 working days and to the reviewing center's EC according to the EC's reporting requirements.

If, during the clinical investigation, new information becomes available that can significantly affect a subject's future health and medical care, the Principal Investigator or his/her authorized designee (if applicable) will provide this information to the subject. If relevant, the subject will be asked to confirm their continuing informed consent in writing.

Special Circumstances for Informed Consent

Incapacitated individuals, defined as persons who are mentally ill, mentally handicapped, or individuals without legal authority, are excluded from the study population.

Individuals under the age of 18 or age of legal consent are excluded from the study population.

Individuals unable to read or write are excluded from the study population.

Pregnant or breastfeeding women are excluded from the study population.

5.3 Eligibility Criteria

5.3.1 General Eligibility Criteria

Assessment for general eligibility criteria is based on medical records of the site and interview with a candidate patient. If some of the clinical and laboratory tests are not included in site standard tests, they must be done but after written informed consent is obtained. Patients must meet ALL the inclusion criteria to be considered for the clinical investigation. If ANY of the exclusion criteria are met, the patient is excluded from the clinical investigation and cannot be enrolled.

5.3.2 Inclusion Criteria

General Inclusion Criteria

1. Subject must provide written informed consent for study participation and willing and able to comply with the protocol described evaluations and follow up schedule
2. Subject must be over 18 years of age. (In Japan, the subject must be of 20 years of age or older)
3. Subject is diagnosed with AF as defined by:
   - Documented symptomatic paroxysmal AF defined as AF that terminates spontaneously or with intervention within 7 days of onset
   - Documented symptomatic persistent AF defined as continuous atrial fibrillation that is sustained beyond 7 days but less than 12 months
4. Subject is indicated for cardiac electroanatomical mapping and RF ablation procedure to treat AF
5. Subject is planned to have electroanatomical mapping performed with the HD mapping catheters under investigation

5.3.3 Exclusion Criteria

General Exclusion Criteria

1. Previous ablation or surgery in the left atria
2. Implanted left atrial appendage occluder
3. Implanted mitral or tricuspid valve replacement
4. Implanted cardiac defibrillator (ICD)
5. Participation in another clinical investigation that may confound the results of this study

[redacted]

6. Pregnant or nursing
7. Presence of other anatomic or comorbid conditions, or other medical, social, or psychological conditions that, in the investigator's opinion, could limit the subject's ability to participate in the clinical investigation or to comply with follow-up requirements, or impact the scientific soundness of the clinical investigation results.
8. Life expectancy less than 12 months

5.4 Subject Enrollment

A subject is considered enrolled in the clinical study from the moment the patient provides written informed consent, has been confirmed to meet all inclusion criteria and none of the exclusion criteria, and a HD mapping catheter (i.e. Inquiry™ AFocusII™ Double Loop or Advisor™ HD Grid Sensor Enabled™) inserted.

5.5 Subject Withdrawal

Each enrolled subject shall remain in the clinical investigation until completion of the required follow-up period; however, a subject's participation in any clinical investigation is voluntary and the subject has the right to withdraw at any time without penalty or loss of benefit. Conceivable reasons for discontinuation may include, but not be limited to, the following:

- Subject death
- Subject voluntary withdrawal
- Subject lost-to follow-up as described below

The Sponsor must be notified of the reason(s) for subject discontinuation. The site will provide this information to the Sponsor. Investigators must also report this to their respective EC as defined by their institution's procedure(s).

No additional follow–up will be required or data recorded from subjects once withdrawn from the clinical investigation, except for the status (deceased/alive).

Lost-to-Follow-up

If the subject misses two consecutive scheduled follow-up time points and the attempts at contacting the subject detailed below are unsuccessful, then the subject is considered lost-to-follow-up. Site personnel shall make all reasonable efforts to locate and communicate with the subject (and document these efforts in the source documents), including the following, at each contact time point:

- A minimum of two telephone calls on different days over the specified follow-up windows to contact the subject should be recorded in the source documentation, including date, time and initials of site personnel trying to make contact.
- If these attempts are unsuccessful, a letter (certified if applicable) should be sent to the subject.
- If a subject misses one or more non-consecutive follow-up contact time points, it will be considered a missed visit. The subject may then return for subsequent visits. If the subject misses two consecutive time points and the above-mentioned attempts at communicating with the subject are unsuccessful, the subject will be considered lost-to-follow-up.

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Note: Telephone contact with General Practitioner, non-clinical investigation cardiologist or relative without the presence of the subject or indirect documentation obtained via discharge letters will not be considered as subject contact.

[redacted]

6.0 TREATMENT AND EVALUATION OF ENDPOINTS

6.1 Baseline Visit

6.1.1 Clinical Assessments

The items listed below will be collected from each subject at the Baseline Visit. Information gathered at this visit may be used to verify eligibility of the subject for the trial.

- Documentation of the informed consent process
- Confirmation of enrollment criteria, including pregnancy test if patient is a female of child bearing potential
- Subject demographics
- Complete physical exam including height, weight, and NYHA assessment (If these assessments were performed prior to consent, they may be used if they were completed within 60-days of the ablation procedure)
- Cardiovascular disease history (most recent value prior to baseline visit)
- Arrhythmia history including documentation of AF (including paroxysmal or persistent)
- Antiarrhythmic medication – including any current class I/III AAD and dose, and history of any class I/III AAD and maximum dose
- Current anticoagulant medication

[redacted]

Record the required information on the appropriate CRFs. Any protocol deviations (refer to Section 10.5 for details) observed will also be recorded at this time.

6.1.2 Patient Reported Outcome Measures

The EQ-5D-5L[22] Questionnaire is a widely used validated questionnaire used to measure quality of life. The self-administered/electronic questionnaire consists of 6 questions. The subject is instructed to choose the option that best describes their health on the day of the assessment. The questionnaire takes approximately 5 minutes to complete.

The Site Coordinator or designee will administer the EQ-5D-5L patient-reported outcome (PRO) questionnaire. It is important the subject understands the meaning of all words and instructions in the questionnaire. The subject should be instructed to ask any questions about the questionnaire if further explanation is needed. Once the questionnaire is completed, the Site Coordinator or designee will review for completeness to verify that all questions have been answered according to the directions provided.

6.2 Index Procedure

The procedure should be performed according to the IFU/Package Insert of the specific HD mapping catheter, EnSite Cardiac Mapping System, and any other medical devices used during the procedure. Physicians performing electroanatomical mapping and ablations must be qualified operators and trained on the study. Each physician who ablates during a particular case needs to be documented on the Procedure CRF.

The following information will be collected during the Procedure Visit:

- Antiarrhythmic medications - any current class I/III AAD and dose
- Anticoagulant medications
- Subject cardiac rhythm when they enter the EP lab
- Subject cardiac rhythm during mapping
- Mapping and ablation tools used during the procedure
- Procedural characteristics (set up and timing)
- Fluoroscopy time
- Mapping time (total time to collect mapping data and time for each map created/retrospectively generated)
- Mapping points collected and used for each map created/retrospectively generated
- Mapping location(s)
- Electrode configuration used for clinical electroanatomical mapping
- Map type(s) (i.e. Voltage, LAT, CFE, etc.)
- AutoMap settings used (if applicable)
- Arrhythmogenic substrate identified
- Field Scaling use
- Ablation strategy
- AutoMark settings used (if applicable)
- Cardioversions performed during procedure
- Attempt(s) at induction of arrhythmia as applicable before and after RF delivery
- Subject rhythm after completion of procedure

Protocol deviations (refer to Section 10.6 for details) and Adverse Events (refer to Section 7.0) that were observed during the procedure, which include any device used off-label during the procedure, will also be recorded at this time.

6.2.1 Pre-procedure thrombus assessment

Thrombus assessment is required before procedure and will be performed per investigator's standard of care. If a thrombus is discovered, the procedure should be postponed and the subject placed on anticoagulation until the thrombus is resolved and confirmed by imaging. The subject may be re-consented for the study if the thrombus resolves within 90 days of detection. Baseline visit information will be verified and updated as necessary.

6.2.2 General procedural recommendations

Create a baseline geometry and map (at a minimum, collect baseline voltage map, other maps may be collected per standard of care) of the atrium using the HD mapping catheter of choice per IFU/Package Insert. Create and/or retrospectively generate the desired electroanatomical maps. Use these maps as clinically necessary to identify ablation target(s). Use ablation catheter per IFU/Package Insert to perform ablation per standard of care. Assess acute procedural success. Create post-ablation voltage map or collect additional maps and perform additional ablation if clinically necessary. Ablation to treat other arrhythmias that occur during the procedure are allowed per physician discretion and standard of care.

6.2.3 Electroanatomical mapping

The HD Mapping catheters must be used with the EnSite Cardiac Mapping System and the EnSite Automap module to generate a baseline electroanatomical map prior to the ablation procedure. Complete contact with the cardiac wall should be achieved before collecting data. Mapping will be done per investigator discretion and SOC for the particular study site. When using the HD Grid mapping catheter, it is recommended to use an HD Wave electrode configuration for catheter set-up (see Appendix X).

6.2.4 Indication Specific recommendations

If the subject presents in atypical AFL at any time during the procedure or as a result of induction, diagnostic mapping and RF ablation will be allowed. Details pertaining to the ablation of atypical AFL should be recorded in the corresponding CRF.

6.3 Pre-discharge Visit (In-hospital)

6.3.1 Clinical Assessments

Prior to discharge after the study procedure, a Pre-discharge visit will be completed. The following information will be collected from each subject:

- Arrhythmia recurrence
  - For the purposes of this clinical study recurrence of arrhythmia is deemed to have occurred only when the arrhythmia is documented on ECG, or other monitoring device used per standard of care. Atrial arrhythmias 30 seconds or longer will be collected.
- Antiarrhythmic medications - any current class I/III AAD and dose
- Adverse events if applicable
- Protocol deviations if applicable

[redacted]

6.4 Follow-up Visits

6.4.1 Clinical Assessments

A Follow-up visit will be scheduled at 6 months (180 days ± 14 days) and 12 months (360 days ± 14 days) post procedure. The scheduled visit windows are calculated from the index procedure. The visit must be completed in-clinic. The following information will be collected:

- Arrhythmia recurrence
- Antiarrhythmic medications - including any current class I/III AAD and dose
- Other monitoring device source documentation of arrhythmia if applicable
- Adverse events if applicable
- Protocol deviations if applicable
- 24-hour Holter monitor (at 12-month visit only)
  - A core laboratory will review each recording and report findings to the Sponsor.

Note: The Sponsor may request access to other patient data during the required protocol follow up visits or throughout the follow up period, which may include, but is not limited to, data from implanted device(s). Record the required information on the appropriate CRF(s). Documentation of arrhythmia (e.g. ECG printouts and/or Holter reports) where applicable, should be retrieved and submitted electronically through EDC to the Sponsor.

Sponsor representatives can be involved in providing support during the follow-up procedures.

6.4.2 Patient Reported Outcomes

The Site Coordinator or designee will administer the EQ-5D-5L questionnaire at both the 6-month and the 12-month visit. It is important the subject understands the meaning of all words and instructions in the questionnaire. The subject should be instructed to ask any questions about the questionnaire if further explanation is needed. Once the questionnaire has been completed, the Site Coordinator or designee will review for completeness to verify that all questions have been answered according to the directions provided.

6.5 Unscheduled Visits

6.5.1 Clinical Assessments

If a subject is seen by any physician for possible arrhythmia recurrence and/or arrhythmia associated symptoms outside of a regularly scheduled study visit and/or had an urgent care or emergency room visit regarding possible arrhythmia, these visits need to be documented as “Unscheduled Visits”. Minimally, the following information should be documented for an unscheduled visit:

- Monitoring device source documentation of arrhythmia if applicable
- Antiarrhythmic medication - including any current class I/III AAD and dose
- Occurrence of any repeat ablation
- Document adverse events if applicable
- Protocol deviations if applicable

6.5.2 Patient Reported Outcomes

As performed during the baseline visit, the Site Coordinator or designee will administer EQ-5D-5L questionnaire. It is important the subject understands the meaning of all words and instructions in the questionnaire. The subject should be instructed to ask any questions about the questionnaire if further explanation is needed. Once the questionnaire is completed, the Site Coordinator or designee will review for completeness to verify that all questions have been answered according to the directions provided.

6.6 Schedule of Events

The schedule of activities specific to this clinical study are described in the preceding sections and are summarized in Table 2.

Table 2. Clinical Study Specific Tests/Activities and Procedures

CIP Activity	Baseline	Procedure	Pre-Discharge	6 Month (180 days ± 14 days post procedure)	12 Month (360 days ± 14 days post procedure)	Unscheduled Visit
Informed Consent Process	X					
Eligibility Check	X	(X)				
Demographics	X					
Physical Examination	X					
Cardiovascular Disease History	X					
Arrhythmia History	X					
Anticoagulant Medication	X	X				
Antiarrhythmic Medication	X	X	X	X	X	(X)
Mapping of cardiac structures and electroanatomical map(s)		X				
RF Ablation		X				
EQ-5D-5L PRO Questionnaire	X			X	X	X
24-hour Holter-monitoring					X	(X)[a]
Other arrhythmia monitoring and source documentation			(X)	(X)	(X)	(X)
Repeat Ablation			(X)	(X)	(X)	(X)
Protocol Deviation	(X)	(X)	(X)	(X)	(X)	
Withdrawal	(X)	(X)	(X)	(X)	(X)	(X)
Adverse Events	(X)	(X)	(X)	(X)	(X)	(X)

(X) if applicable
[a] Holter monitoring during an unscheduled visit does not need to be conducted through the core laboratory

6.7 Core Laboratory

A core lab will be used for the collection, interpretation, and collation of data collected from Holter monitoring.

The core lab will provide independent review of this data by appropriately trained personnel using standardized procedures to interpret Holter monitor tracings for adjudication of atrial arrhythmias. Findings will be communicated to the investigator and to Abbott. The core lab's adjudication findings will be used for analysis.

[redacted]

7.0 Adverse Events

To comply with worldwide standards and guidelines on clinical investigation adverse event reporting, the Sponsor has adopted uniform and worldwide applicable standard definitions and reporting timelines to be used and adhered to by the investigators.

7.1 Definition

7.1.1 Adverse Event

An adverse event (AE) is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the medical device under investigation.

Note 1: This definition includes events related to the medical device under investigation or the comparator.
Note 2: This definition includes events related to the procedures involved.
Note 3: For users or other persons, this definition is restricted to events related to medical devices under investigation.

7.1.2 Serious Adverse Event

If the AE meets any of the criteria below, it is regarded as a serious adverse event (SAE).

- Led to a death,
- Led to a serious deterioration in health of the subject, that either resulted in
  - a life-threatening illness or injury, or
  - a permanent impairment of a body structure or a body function, or
  - in-patient hospitalization or prolongation of existing hospitalization, or
  - medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function.
  - chronic disease
- Led to fetal distress, fetal death or a congenital abnormality or birth defect.

Note: A planned hospitalization for pre-existing condition, or a procedure required by the CIP, without a serious deterioration in health, is not considered to be an SAE.

7.2 Device Relationship

Determination of whether there is a reasonable possibility that an investigational product or device under investigation caused or contributed to an AE is to be **determined by the Investigator** and recorded on the appropriate CRF form. Determination should be based on assessment of temporal relationships, evidence of alternative etiology, medical/biologic plausibility, and patient condition (pre-existing condition).

7.3 Adverse Event Reporting

7.3.1 Adverse Event Reporting

Safety surveillance and reporting starts as soon as the patient is enrolled in the clinical investigation. Safety surveillance and reporting will continue until the last follow-up visit has been performed, the subject is deceased, the subject concludes participation in the clinical investigation or the subject

[redacted]

withdraws from the clinical investigation. Adverse event data, including deaths, will be collected throughout the time period defined above and will be reported to the Sponsor on a CRF. Additional information with regard to an adverse event should be updated within the appropriate CRF.

Unchanged, chronic, non-worsening or pre-existing conditions are not AEs and should not be reported.

An offline form will be made available to allow the investigator to report serious adverse events (SAEs) in the event the entry cannot be made in the EDC. This does not replace the EDC reporting system. All information must still be entered in the EDC system as soon as feasible.

Non-cardiac related abnormal laboratory values will not be considered AEs unless:

1. the investigator determined that the value is clinically significant,
2. the abnormal lab value required intervention, or
3. the abnormal lab value required subject withdrawal from the clinical investigation.

For the purposes of this clinical investigation, the following events will be reported:

- Adverse events that are considered related to either the ablation catheter or the ablation procedure by the investigator
- Adverse events resulting in death

Recurrence of AF, AFL, or AT are not considered reportable adverse events unless they occur in a severity, frequency, or other manner that is significantly worse than the subject's baseline condition. These are considered lack of effectiveness and will be reported as a recurrence on the appropriate case report form.

SAE Reporting

The investigator should report all SAEs to the Sponsor as soon as possible but no later than outlined below.

Clinical Site	Reporting timelines
All Sites	SAEs must be reported to the Sponsor no later than 3 calendar days from the day the site personnel became aware of the event or as per the investigative site's local requirements, if the requirement is more stringent than those outlined.

The date the site staff became aware the event met the criteria of an SAE must be recorded in the source document. The Investigator will further report the SAE to the local IRB/EC according to the institution's IRB/EC reporting requirements.

7.3.2 Adverse Event Reporting to Country Regulatory Authorities by the Sponsor

The Sponsor will report SAEs to the country regulatory authority, per local requirements.

7.3.3 Complaints

The investigator is responsible for reporting all complaints to the Post Market Surveillance Department as they became aware of the complaint. A complaint is defined as any written, electronic or oral

[redacted]

communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness or performance of a device after it is released for distribution.

For Abbott/SJM products, the investigator must notify [redacted] as soon as possible after becoming aware of the complaint. For non-Abbott products, the investigator must notify the manufacturer of the device per that manufacturer's complaint reporting mechanisms or per the investigator's user facility procedures. This information is not collected on a CRF for the study.

8.0 STATISTICAL CONSIDERATIONS

The following section describes the statistical methods for the clinical study. The study will investigate the utility of electroanatomical mapping with HD mapping catheters and the EnSite Cardiac Mapping System as well as the outcome of subsequent RF ablation. The study is a prospective, multi-center, single-arm, unblinded observational study.

Endpoints described in Section 4.0 will be analyzed and reported using summary statistics. No hypothesis tests will be performed. Additional analysis using data collected in this study may be performed during or after completion of the 6-month and/or 12-month follow-up period for all subjects.

Nominal p-values may be presented to assess statistical significance using a significance level of 0.05. Statistical analysis will be performed using SAS version 9.3 or higher, or other analysis tools/software as necessary.

8.1 Analysis Populations

The analysis population used for all endpoints will include all subjects who have signed the Informed Consent Form and have undergone the electroanatomical mapping procedure using one of the specified HD mapping catheters and received RF ablation as specified in the protocol. If any device used during the procedure is used off-label, the subject will be excluded from non-safety related endpoint analysis and any additional evaluations.

8.2 Statistical Analysis

8.2.1 Characterization Endpoint Analysis

The endpoints will be summarized descriptively based on available data or measurements in the analysis population. No formal hypothesis testing will be performed.

In general, continuous variables will be summarized with the numbers of observations, means with standard deviations, minimums, and maximums as per the table mockups.

Categorical variables will be summarized with subject counts and percentages/rates, and where specified in the table mockups.

Survival analysis will be conducted to analyze time-to-event variables. Events occurring during the 90 days following the ablation procedure for AF subjects (90-day blanking period) will not be counted as an effectiveness outcome failure. Subjects without events will be censored at their last known event-free time

[redacted]

point. Subjects withdrawn or otherwise lost-to-follow-up during the follow-up period will be censored at their last known visit. Survival data will be presented using the Kaplan-Meier product limit method.

8.2.2 Safety Endpoints Analysis

All pre-defined adverse events will be captured. Only adverse events that occur after the HD mapping catheter has been inserted (after enrollment) will be analyzed, as defined in the safety analysis population. Tables will be created that show cardiovascular serious adverse events.

[redacted]

[redacted]

8.5 Subgroup Analysis

There are no pre-specified subgroup analyses planned for this clinical study. If more than 25% of the enrolled AF subjects are defined as paroxysmal, then the AF patient population will be split into paroxysmal AF and persistent AF and analyzed separately.

8.6 Multiplicity

No hypothesis testing will be performed; therefore, no adjustments will be made for multiplicity in the endpoint analyses.

8.7 Procedures for Accounting for Missing Data

Every effort will be made to collect all required data. All data available for the endpoints specified among the analysis population will be used. Missing data will not be imputed. Kaplan-Meier analysis will censor subjects withdrawn or otherwise lost-to-follow-up at last known visit.

[redacted].

8.9 Statistical Criteria for Termination

There are no statistical criteria for termination of this clinical investigation.

8.10 Success Criteria

Pass/Fail criteria do not apply to this study.

8.11 Deviations from Statistical Plan

Any major changes to the statistical plan discussed in the Clinical Rationale will be documented in the final report.

9.0 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The investigator/institution will permit direct access to source data/documents for the purpose of performing clinical investigation-related monitoring, audits, EC review and regulatory inspections.

Subjects providing informed consent are agreeing to allow clinical investigation monitors or regulatory authorities including foreign countries to review, in confidence, any records identifying the subjects in this clinical investigation. This information may be shared with regulatory agencies; however, Sponsor undertakes not to otherwise release the subject's personal and private information.

10.0 QUALITY CONTROL AND QUALITY ASSURANCE

10.1 Selection of Clinical Sites and Investigators

The Sponsor will select investigators qualified by training and experience to participate in the clinical investigation. Sites will be selected based upon review of a recent site assessment, if applicable, and the qualifications of the investigators who will participate in the clinical investigation.

10.2 Clinical Investigation Finances and Agreements

The clinical investigation will be financed by Abbott. Investigational sites will be compensated by Abbott for participation in the clinical investigation per the conditions of agreement between the Sponsor and the Investigational site.

10.3 CIP Amendments

Approved CIP amendments will be provided to the Investigators by the Sponsor prior to implementing the amendment. The Principal Investigator is responsible for notifying the EC or equivalent committee of the CIP amendment (administrative changes) or obtaining EC's approval of the CIP amendment (changes in subject care or safety), according to the instructions provided by the Sponsor with the CIP amendment.

Acknowledgement/approval by the EC of the CIP amendment must be documented in writing prior to implementation of the CIP amendment. Copies of this documentation must also be provided to the Sponsor.

10.4 Training

10.4.1 Site Training

All Investigators and clinical investigation personnel are required to attend Sponsor training sessions, which may be conducted at an Investigator's meeting, a site initiation visit, or other appropriate training sessions. Training of Investigators and clinical investigation personnel will include, but is not limited to, the CIP requirements, investigational device usage, electronic case report form completion and clinical investigation personnel responsibilities. All Investigators and clinical investigation personnel that are

[redacted]

trained must sign a training log (or an equivalent) upon completion of the training. Prior to signing the training log, Investigators and clinical investigation personnel must not perform any CIP-related activities that are not considered standard of care at the site.

10.5 Monitoring

It is the responsibility of the Sponsor to ensure the clinical study is conducted, recorded and reported according to the approved CIP, subsequent amendment(s), applicable regulations and guidance documents.

Centralized monitoring will occur through routine internal data review. This monitoring is designed to identify missing and inconsistent data, data outliers, and potential CIP deviations that may be indicative of site non-compliance. On-site monitoring may occur at the discretion of the Sponsor.

10.6 Deviations from CIP

The Investigator should not deviate from the CIP for any reason except in cases of medical emergencies when the deviation is necessary to protect the rights, safety and well-being of the subject or eliminate an apparent immediate hazard to the subject. In that event, the Investigator will notify Sponsor immediately by phone or in writing.

No waivers for CIP deviations will be granted by the Sponsor. All deviations must be reported to the Sponsor using the Deviation CRF. The occurrence of CIP deviations will be monitored by the Sponsor for evaluation of investigator compliance to the CIP and regulatory requirements and dealt with according to written procedures. Investigators will inform their EC or equivalent committee of all CIP deviations in accordance with their specific EC or equivalent committee reporting policies and procedures.

In the event of repeated non-compliance, as determined by the Sponsor, a Sponsor's monitor or company representative will attempt to secure compliance by one or more of the following (and not limited to):

- Visiting the investigator and/or delegate
- Telephoning the investigator and/or delegate
- Corresponding with the investigator and/or delegate

Repeated non-compliance with the signed agreement, the CIP or any other conditions of the clinical investigation may result in further escalation in accordance with the Sponsor's written procedures, including securing compliance or, at its sole discretion, Sponsor may terminate the investigator's participation in the clinical investigation.

10.7 Quality Assurance Audit

A Sponsor representative or designee may request access to all clinical investigation records, including source documentation, for inspection during a Quality Assurance audit.

In the event that an investigator is contacted by a Regulatory Agency in relation to this clinical investigation, the Investigator will notify Sponsor immediately. The Investigator and Research Coordinator must be available to respond to reasonable requests and audit queries made during the audit process. The Investigator must provide Sponsor with copies of all correspondence that may affect the review of the

current clinical investigation (e.g., Form FDA 483, Inspectional Observations, Warning Letters, Inspection Reports, etc.). Sponsor may provide any needed assistance in responding to regulatory audits.

10.8 Committees

A Publication Committee shall be established to oversee clinical investigations publications, including publication planning and authorship determinations. Publication Committee membership may include members of the Steering Committee, Principal Steering Committee, Principal Investigators, a representative of the Sponsor and a statistician. The Publication Committee will determine policy and strategies regarding individual presentations and/or publications arising from clinical investigation generated data. The committee will also review all external requests for accessing clinical investigation-related data and strategies aligning with the Sponsor's presentation and publication team expectations. The committee will also follow the Sponsor's applicable policies and Standard Operating Procedures.

11.0 DATA HANDLING AND RECORD KEEPING

Sponsor and/or its affiliates will maintain documentation of the systems and procedures used in data collection for the duration of the clinical investigation.

CRF data collection will be performed through a secure web portal and only authorized personnel will access the Electronic Data Capture (EDC) system using a unique username and password to enter, review or correct data. Passwords and electronic signatures will be strictly confidential.

The data will be subjected to consistency and validation checks within the EDC system and supplemental review by the Sponsor.

At the conclusion of the clinical investigation, completed CRF images with the date-and-time stamped electronic audit trail indicating the user, the data entered, and any reason for change (if applicable) will be provided to the investigational sites.

For the duration of the clinical investigation, the Investigator will maintain complete and accurate documentation including, but not limited to, medical records, clinical investigation progress records, laboratory reports, CRFs, signed ICFs, device accountability records (if applicable), correspondence with the IRB/EC and clinical investigation monitor/Sponsor, adverse event reports, and information regarding subject discontinuation or completion of the clinical investigation.

11.1 Protection of Personally Identifiable Information

The Sponsor respects and protects personally identifiable information collected or maintained for this clinical investigation.

The Sponsor implements technical and physical access controls to ensure that Personal Information is accessible only to and processed only on a 'need to know' basis, including periodic review of access rights, and revocation of access when an individual's employment is terminated or the individual transitions to a role that does not require access to Personal Information, and appropriate restrictions on physical access to premises, facilities, equipment, and records containing Personal Information.

The Sponsor requires the investigational sites to transfer into Sponsor's data management systems only pseudonymous Personal Information (key-coded) necessary to conduct the Clinical Investigation, such as

[redacted]

the patient's medical condition, treatment, dates of treatment, etc. The Sponsor discloses as part of the clinical investigation informed consent process that some Sponsor representatives still may see Personal Information at the participating sites for technical support of the participating physicians on the device implant or procedures, monitoring and quality control purposes. Confidentiality of Personal Information will be observed by all parties involved at all times throughout the clinical investigation. The privacy of each subject and confidentiality of his/her information will be preserved in reports and when publishing any data.

The Sponsor data management systems and processes were designed, developed, and tested according to industry standards to appropriately safeguard Confidential Information (including any Personal Information) against unauthorized access and/or interference by third parties, intrusion, theft, destruction, loss or alteration. Clinical Investigation data are encrypted in transit and at rest.

The Sponsor maintains a Privacy Incident procedure that complies in all respects with Applicable Law and industry best practices.

11.2 Data Management Plan

A Data Management Plan (DMP) will describe procedures used for data review, data cleaning, and issuing and resolving data discrepancies. If appropriate, the DMP may be updated throughout the duration of the clinical investigation. All revisions will be tracked and document controlled.

11.3 Source Documentation

Regulations and GCP require the Investigator to maintain information in the subject's original medical records that corroborates data collected on the CRFs. In order to comply with these regulatory requirements/GCP, the following information should be included in the subject record at a minimum and if applicable to the clinical investigation:

- Medical history/physical condition of the subject before involvement in the clinical investigation sufficient to verify CIP entry criteria
- Dated and signed notes on the day of entry into the clinical investigation referencing the Sponsor, CIP number, subject ID number and a statement that informed consent was obtained
- Dated and signed notes from each subject visit (for specific results of procedures and exams)
- Adverse events reported and their resolution, including supporting documents, such as discharge summaries, catheterization laboratory reports, ECGs, and lab results including documentation of site awareness of SAEs and of investigator assessment of device relationship for SAEs.
- CIP-required laboratory reports and 12-lead ECGs, reviewed and annotated for clinical significance of out of range results (if applicable).
- Notes regarding CIP-required and prescription medications taken during the clinical investigation (including start and stop dates)
- Subject's condition upon completion of or withdrawal from the clinical investigation
- Any other data required to substantiate data entered into the CRF
- Patient reported outcome measures may be completed using CRF worksheets. These serve as the source documentation.

11.4 Case Report Form Completion

Primary data collection based on source-documented hospital and/or clinic chart reviews will be performed clearly and accurately by site personnel trained on the CIP and CRF completion. The investigator will ensure accuracy, completeness, legibility and timeliness of the data reported to the Sponsor on the CRFs and in all required reports.

Data on CRFs will be collected for all subjects that are enrolled into the clinical investigation.

Only authorized site personnel will be permitted to enter the CRF data through the EDC system deployed by the Sponsor. An electronic audit trail will be used to track any subsequent changes of the entered data.

11.5 Record Retention

The Sponsor and Investigator Site will archive and retain all documents pertaining to the clinical investigation as per the applicable regulatory record retention requirements. The Investigator must obtain permission from Sponsor in writing before destroying or transferring control of any clinical investigation records.

12.0 ETHICAL CONSIDERATION

12.1 Ethics Committee Review and Approval

Ethics Committee (EC) approval for the CIP and ICF/other written information provided to the patient will be obtained by the Principal Investigator at each investigational site prior to consenting and enrolling patients in this clinical investigation. The approval letter must be received prior to the start of this clinical investigation and a copy must be provided to the Sponsor.

Any amendments to the CIP as well as associated ICF changes will be submitted to the EC and written approval obtained prior to implementation, according to each institution's EC requirements.

No changes will be made to the CIP or ICF or other written information provided to the patient without appropriate approvals, including EC, the Sponsor, and the regulatory agencies (if applicable).

Until the clinical investigation is completed, the Investigator will advise his/her EC of the progress of this clinical investigation, per EC requirements. Written approval must be obtained from the EC yearly to continue the clinical investigation, or according to each institution's EC requirements.

No investigative procedures other than those defined in this CIP will be undertaken on the enrolled subjects without the written agreement of the EC and the Sponsor.

13.0 CLINICAL INVESTIGATION CONCLUSION

The clinical investigation will be concluded when:

- All sites are closed AND
- The final report has been provided to investigators or the Sponsor has provided formal documentation of clinical investigation closure.

[redacted]

14.0 PUBLICATION POLICY

The data and results from the clinical investigation are the sole property of the Sponsor. The Sponsor shall have the right to access and use all data and results generated during the clinical investigation. The Investigators will not use this clinical investigation-related data without the written consent of the Sponsor for any purpose other than for clinical investigation completion or for generation of publication materials, as referenced in the Clinical Trial Agreement. Single-center results are not allowed to be published or presented before the multi-center results. Any proposals for publications or presentations by the investigators must be reviewed and approved by the Sponsor in a timely manner to enable Sponsor review in compliance with the Sponsor's publication policy set forth in the Clinical Trial Agreement.

The Sponsor will be responsible for determining whether to register the clinical investigation on www.clinicaltrials.gov or any other clinical trials, in accordance with the International Committee of Medical Journal Editors guidelines, or any other applicable guidelines. In the event Sponsor determines that the clinical investigation should be registered, Sponsor shall be responsible for any such registration and results posting as required by the ClinicalTrials.gov website. Institution and/or Principal Investigator(s) shall not take any action to register the clinical investigation.

15.0 RISK ANALYSIS

The risks associated with each of the HD mapping catheters and the EnSite Cardiac Mapping System can be found in the appropriate Instructions for Use. The clinical study does not require additional procedures or assessments beyond what could be considered standard of care. There are no additional risks introduced to subjects due to participation in this study.

15.1 Foreseeable Adverse Events and Anticipated Adverse Device Effects

Refer to applicable IFU/Package Insert for list of Anticipated Adverse Device Effects. There may be risks related to the devices used in this study that are unknown at present. Likewise, the exact frequency of the risk may be unknown.

15.2 Risks Associated with Participation in this Clinical Investigation

Risks to subjects enrolled in this clinical study include those risks currently associated with other commercially available electrophysiology diagnostic procedures and RF catheter ablation procedures. The risks of the procedure are related primarily to mechanical injury to the heart and vessels from catheter manipulation and thermal injury due to RF current delivery, including the risk of thromboembolism and myocardial perforation, especially for ablations in the left atrium.

For those procedures where the physician applies sedation or anesthesia, the standard risks of anesthesia also exist and include allergic reactions, pneumonia, aspiration pneumonitis, atelectasis, prolonged sedation, other medical complications and in very rare cases, death.

15.3 Steps Taken to Control or Mitigate Risks

In-depth recommendations, special precautions and instructions regarding device utilization are included in the appropriate IFU/IB/Package Insert.

[redacted]

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Physician users are expected to be aware of the known and foreseeable safety risks associated with the use of the devices including the surgical and/or non-surgical treatment of these conditions.

Risks associated with the use of the device under investigation are minimized through device design, investigator selection and training, pre-specified patient eligibility requirements and study monitoring to ensure adherence to the protocol.

[redacted]

Clinical Investigation Plan

APPENDIX I: ABBREVIATIONS AND ACRONYMS

Acronym/Abbreviation	Description
AAD	Antiarrhythmic drug
AE	Adverse event
AF	Atrial fibrillation
PAF	Paroxysmal Atrial Fibrillation
PersAF	Persistent Atrial Fibrillation
AFL	Atrial flutter
AT	Atrial tachycardia
CIP	Clinical investigation plan
CRF	Case report form
DMP	Data Management Plan
EC	Ethics Committee
ECG	Electrocardiogram
EDC	Electronic data capture
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICD	Implantable cardioverter defibrillator
ICF	Informed Consent form
IFU	Instructions for Use
LAD	Left atrial diameter
LVEF	Left ventricular ejection fraction
MI	Myocardial infarction
NYHA	New York Heart Association
PCI	Percutaneous coronary intervention
PRO	Patient Reported Outcome
PV	Pulmonary vein
PVI	Pulmonary vein isolation
QOL	Quality of Life
RF	Radiofrequency
SAE	Serious adverse event
SE	Sensor enabled
SOC	Standard of Care

Clinical Investigation Plan

APPENDIX III: SITE CONTACT INFORMATION

Contact information for each participating clinical site is available under separate cover by contacting the Sponsor.

Clinical Investigation Plan

APPENDIX VII: CASE REPORT FORMS

The Final CRFs will be kept under a separate cover and are available upon request.

Clinical Investigation Plan

APPENDIX VIII: INFORMED CONSENT FORM

A template informed consent form will be provided under a separate cover and will be available upon request.

Clinical Investigation Plan

APPENDIX IX: MONITORING PLAN

A copy of the Monitoring Plan can be obtained upon request from the Sponsor Clinical Project Manager for the clinical investigation.

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APPENDIX X: HD GRID ELECTRODE CONFIGURATIONS

HD Wave Electrode Configuration

For the purposes of this clinical study, HD Wave electrode configuration will be considered any configuration that only utilizes mapping data collected at electrodes with orthogonal bipoles. Orthogonal bipoles are defined as a pair of perpendicular bipoles originating from a single electrode with one bipole configured across two separate splines and one bipole configured along the spline. Automap settings will be set to select the 'best duplicate' at each electrode with orthogonal bipoles.

An example of HD Grid with HD Wave configuration is depicted in Figure 5. Example of HD Grid HD Wave Electrode Configuration. This HD Wave configuration utilizes bipoles both along each spline of the catheter (A, B, C, and D) and across HD Grid catheter splines (A-B, B-C, and C-D) as depicted by the dark arrows. Bipolar electrogram voltages along the splines are configured as in the along-the-spline configuration described below; using electrode pairs 1-2, 2-3, and 3-4 on each spline. Bipolar electrogram voltages across the splines are recorded using electrode pairs of the same number/position on adjacent splines (A1-B1, B1-C1, C1-D1, A2-B2, B2-C2, C3-D3, A3-B3, B3-C3, C3-D3). Automap settings will be set to select the 'best duplicate' at each electrode shown in yellow.

An alternate example of HD Grid with HD Wave configuration is depicted in Figure 6. Example of Alternative HD Grid HD Wave Electrode Configuration. Bipolar electrograms are configured as depicted by the dark arrows. Bipolar electrogram voltages along the splines are configured using the following electrode pairs and directionality: A1-A2, A2-A3, A4-A3, B1-B2, B2-B3, B3-B4, C2-C1, C3-C2, C4-C3, D1-D2, D3-D2, D4-D3. Bipolar electrogram voltages across the splines are configured using the following electrode pairs and directionality: A1-B1, B1-C1, D1-C1, A2-B2, B2-C2, C2-D2, B3-A3, C3-B3, D3-C3, A4-B4, C4-B4, D4-C4. Automap settings will be set to select the 'best duplicate' at each electrode shown in yellow.

[redacted]

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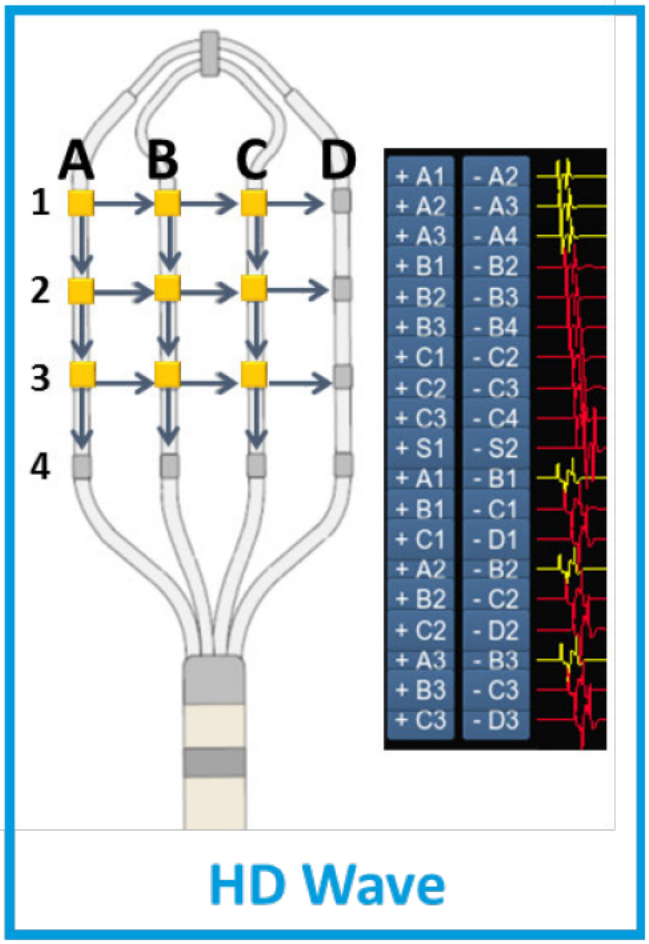

Figure 4. Example of HD Grid HD Wave Electrode Configuration

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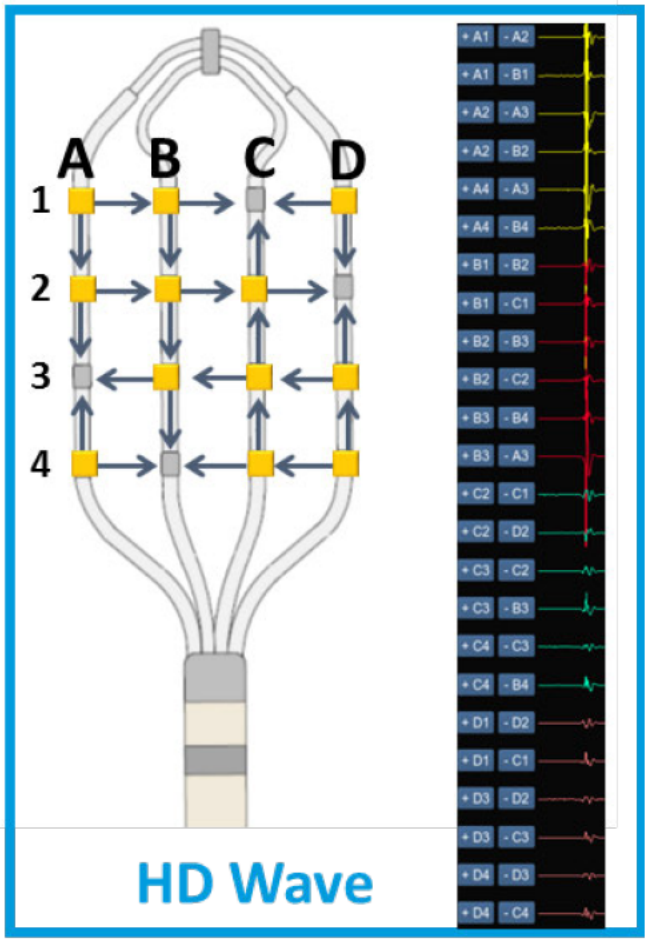

Figure 5. Example of Alternative HD Grid HD Wave Electrode Configuration.

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Clinical Investigation Plan

APPENDIX XII: CIP SUMMARY

Clinical Investigation Name and Number	HD Mapping Observational Study (CRD_975)
Objective(s)	The aim of this study is to quantify and characterize the outcomes of radiofrequency (RF) ablation after, and the utility of, electroanatomical mapping with to characterize the utility and outcomes of electroanatomical mapping with the market-released HD mapping catheters Inquiry™ AFocusII™ Double Loop and Advisor™ HD Grid, Sensor Enabled™ with the EnSite Cardiac Mapping System and Automap module in subjects with AF in the real-world environment of the Asian Population.

Device Under Investigation	• Inquiry™ AFocusII™ Double Loop EP Catheter
	• Advisor™ HD Grid Mapping Catheter, Sensor Enabled™ (HD Grid)
	• EnSite Cardiac Mapping System
	  ○ EnSite Precision™, SV 2.2 or higher **OR**
	  ○ EnSite Velocity™, SV 5.0 or higher (China only)

Number of Subjects Required for Inclusion in Clinical Investigation	Approximately 200 subjects will be enrolled in this study.
Clinical Investigation Design	Prospective, non-randomized, multi-center, single-arm, post-market observational
Endpoints	Utility Endpoint The utility of HD Mapping catheters with the EnSite Cardiac Mapping System will be quantified and characterized through the summary of the following: • Overall procedure time: defined as time from initial catheter insertion to final catheter removal. • Radiofrequency (RF) time: defined as duration of time RF energy is delivered • Fluoroscopy time: defined as total time subject is exposed to fluoroscopy • Mapping time associated with mapping arrhythmia: defined as the total cumulative mapping time and mapping time for the creation of each map (including any new or retrospective map created with Manual, AutoMap, and TurboMap mapping) • Number of mapping points collected: defined as total number of mapping points collected for the creation of each map • Number of mapping points used: defined as the total number of mapping points used in each map • Number of used mapping points per minute: defined as the total number of mapping points used divided by the relative mapping time

	• Substrate characteristics identified: for each type of arrhythmogenic substrate this will be defined as the frequency of substrate type identified in cases that attempted to identify the specific substrate • Ablation strategy(s) used: defined by both the type of map used to define ablation strategy and the frequency each ablation strategy/target was used by physicians <u>Outcomes Endpoint</u> To quantify and characterize the acute- and long-term success rate of RF ablation after electroanatomical mapping with HD mapping catheters, the following will be summarized: • Rate of acute success defined as the proportion of subjects who receive HD mapping and RF energy delivery resulting in acute termination of clinical arrhythmia, defined by termination to SR (or AT if being treated for PersAF) or non-inducibility of clinical arrhythmia after ablation (cardioversion allowed prior to inducibility attempt). • Rate of long-term success defined as the proportion of subjects who receive HD mapping and RF energy delivery with the following pre-defined procedural endpoints: AF (utilizing a 90-day blanking period following index ablation): o freedom from all atrial arrhythmias (AF/AFL/AT) greater than 30 seconds (as documented by 24-hr Holter at 12-month follow-up) and on or off class I/III antiarrhythmic drug (AAD). o freedom from all atrial arrhythmias (AF/AFL/AT) greater than 30 seconds (as documented by 24-hr Holter at 12-month follow-up) and off all class I/III AADs <u>Additional Evaluations</u> • Adverse events including any device-, procedure-, or death-related events • Rate of repeat ablations after study procedure during 12-month follow up defined as proportion of subjects without an additional ablation procedure to treat indicated cardiac arrhythmia (outside blanking period, if applicable). • Change in quality of life (QOL) at 6 months and 12 months after receiving HD mapping and RF ablation relative to baseline: defined as change in quality of life assessed in the validated EQ-5D-5L QOL survey.
Subject Follow-up	• 6 months (180 ± 14 days) • 12 months (360 ± 14 days)
Inclusion Criteria	General Inclusion Criteria:

[redacted]

Clinical Investigation Plan

	1. Subject must provide written informed consent for study participation and willing and able to comply with the protocol described evaluations and follow up schedule 2. Subject must be over 18 years of age. (In Japan, the subject must be of 20 years of age or older) 3. Subject is diagnosed with AF as defined by: • Documented symptomatic paroxysmal AF defined as AF that terminates spontaneously or with intervention within 7 days of onset • Documented symptomatic persistent AF defined as continuous atrial fibrillation that is sustained beyond 7 days but less than 12 months 4. Subject is indicated for cardiac electroanatomical mapping and RF ablation procedure to treat AF 5. Subject is planned to have electroanatomical mapping performed with the HD mapping catheters under investigation
Exclusion Criteria	General Exclusion Criteria: 1. Previous ablation or surgery in the left atria 2. Implanted left atrial appendage occluder 3. Implanted mitral or tricuspid valve replacement 4. Implanted cardiac defibrillator (ICD) 5. Participation in another clinical investigation that may confound the results of this study 6. Pregnant or nursing 7. Presence of other anatomic or comorbid conditions, or other medical, social, or psychological conditions that, in the investigator's opinion, could limit the subject's ability to participate in the clinical investigation or to comply with follow-up requirements, or impact the scientific soundness of the clinical investigation results. 8. Life expectancy less than 12 months

Clinical Investigation Plan

APPENDIX XIII: REFERENCES

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