EU Focal Impulse and Rotor Modulation Registry

Topera® E-FIRM Registry

Overview and Registry Synopsis

Overview

Protocol number The protocol number is E-FIRM-02
NCT-02386345

Revision and date Revision: E
Date: July 29th, 2014

Principal investigator(s) Principal investigators per site are listed in the table below, additional sites could be added

Site #	Institution	Investigator
01	Herzzentrum, Leipzig	[redacted]
02		
03		
04		
05		
06		
07		
08		

Ethics Committee

ECs The registry will be submitted to the EC of the PI, to the Ethics Commission of the Universität Leipzig as a leading EC and/ or the relevant ECs of the participating sites.

Confidentiality Agreement

[redacted]

Steering/ Publication Committee

- [redacted]

Sponsor

[redacted] Topera Inc., Palo Alto as sponsor for the Registry

Synopsis

Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia in man, and has an increasing population prevalence over time. Treatment is aimed at stroke prevention on the one hand, and amelioration of symptoms (palpitations, lightheadedness, dyspnea, fatigue) due to the arrhythmia. Medical therapy often fails to render a satisfactory response for the latter, prompting the search for alternative therapies. Surgical and, in the last 15 years, catheter ablation techniques have been devised to try to prevent episodes from starting. Groundbreaking work by Haïssaguerre showed that premature discharges or rapid repeated firing from the pulmonary veins (PVs) could trigger AF episodes and that electrical isolation of the PVs could potentially cure the patient of AF. PV isolation currently is a painstaking process consisting of delivering radiofrequency energy in the left atrium to isolate these veins. Such procedures take 3-5 hr to complete depending on the complexity of the individual case, and a large percentage of patients require a 2nd or even 3rd procedure to achieve acceptable antiarrhythmic results. Despite considerable investigative effort, the exact pathophysiology of how PV triggers initiate and or maintain episodes of AF has been elusive.
Recently, Narayan et al have developed an algorithm that has been licensed for use with a novel mapping technology (RhythmView, Topera, Inc, Palo Alto, CA) for analyzing atrial recordings during human AF, finding that >95% of cases demonstrate either a rapidly spinning rotor (small circuit) or very rapid focal impulse formation. Furthermore, they have shown that catheter ablation at these relatively circumscribed areas can significantly affect AF, either by substantial slowing of the rate or termination (to an atrial tachycardia or sinus rhythm). In the CONFIRM (CONventional vs Focal Impulse and Rotor Modulation) trial, patients were treated with either conventional mapping and ablation (largely PV isolation or PVI) vs ablation of rotors or sites of focal impulse formation as designated by the mapping algorithm, followed by conventional ablation (PVI). The authors found much higher acute and long-term efficacy when focal impulse and rotor modulation (FIRM ablation) was used (82.4 vs 44% freedom from AF at 24 months post procedure). Although CONFIRM was a controlled registry, a randomized evaluation would be warranted.

E-FIRM is a registry to track Topera Inc.'s FIRM products in terms of clinical usage, handling, and the safety and effectiveness of FIRM procedures for the treatment of symptomatic atrial fibrillation. There will be at least 150 patients enrolled in this registry

Safety endpoint

Safety shall be evaluated both acute and long term.

Endpoint	Description
Acute success	Freedom from major adverse events related to the procedure within seven days of the procedure.
Long-term success	Freedom from cumulative major adverse events related to the procedure (including any repeat procedures required) within one year of the initial procedure.

Primary Efficacy endpoint

Efficacy endpoints are defined in the table below.

Endpoint	Definition
Acute success of FIRM ablation	The acute success of FIRM guided ablation is defined as elimination of the rotors defined by absence of rotors in the FIRMap.
Long term success	Two sequential endpoints will be used for long term efficacy after the initial AF ablation procedure (only): (1) Single Procedure Freedom from AF recurrence* at 3 months, and (2) Single Procedure Freedom from AF recurrence* from 3-12 months after the initial AF ablation procedure *Freedom from AF recurrence is defined as: No document episodes of AF >30 sec with conventional noninvasive monitoring or, in the case of an cardiac implanted electronic device (CIED), <1% AF noted overall and no episodes of AF>30 sec.

The design of the registry is summarized in the table below.

Registry design

Item	Description
Design	This is a prospective registry to assess the safety and effectiveness of FIRM procedures for the treatment of symptomatic any type of atrial fibrillation.

Sample Size	Each site will enroll all FIRM-guided patients undergoing AF ablation into this registry up to at least overall 150 subjects. FIRM-guided ablation is defined as ablating FIRM identified rotors independent of any additional ablation.
Randomization	The registry is non-randomized but consecutive.
Investigators	Up to 2 investigators per site
Investigative sites	Up to 10 investigative sites within Germany / Europe

Patient population

Subjects eligible for participation in the registry should be in accordance to the AF guidelines:

- Reported incidence of at least two (2) documented episodes of symptomatic AF (paroxysmal, persistent or long standing persistent) during the three months preceding trial entry (at least one episode should be documented by rhythm strip or ECG).
    - Attempt of at least one Class I or III anti-arrhythmia drug with failure defined as recurrence of symptomatic AF or adverse drug effect resulting in stopping the medication.

Registry schedule

The registry visits schedule will follow the standard routine procedure of each site. Proposed activities during the visits are described in the table below. Since this is a registry, these are data items that will be collected, if available, as consistent and applicable with routine and standard clinical care at each site.

Visit Timing	Description
Procedure and immediate post-procedure	Cardiac ablation procedure (see “Ablation Procedure” for details). During the procedure, the patient will be monitored for adverse events. Appropriate clinical measures will be taken to treat the adverse event, should one occur.
Seven-Ten Days Post Procedure	The following assessments/procedures will be performed: • Symptom and rhythm assessment per defined follow up monitoring • Follow up to assess for adverse events
Three Months Post Procedure	The following assessments/procedures will be performed: • Diagnostic 12-lead ECG • 48-hr or 72-hr ambulatory continuous ECG monitor (Holter) or CIED interrogation, if applicable • Symptom and rhythm assessment per defined follow up monitoring • Concomitant anti-arrhythmic medications • Adverse events
Six Months Post Procedure	The following assessments/procedures will be performed: • Diagnostic 12-lead ECG • 48-hr or 72-hr ambulatory continuous ECG monitor (Holter) or CIED interrogation, if applicable • Symptom and rhythm assessment per defined follow up monitoring • Concomitant anti-arrhythmic medications • Adverse events

Twelve Months Post Procedure	The following assessments/procedures will be performed: • Diagnostic 12-lead ECG • 48-hr or 72-hr ambulatory continuous ECG monitor (Holter) or CIED interrogation, if applicable • Symptom and rhythm assessment per defined follow up monitoring • Concomitant anti-arrhythmic medications • Adverse events

Ablation procedure description

Investigators should follow the standard procedure as defined by training from Topera Inc. and appropriate medical judgment for FIRM guided ablation with or without the conventional ablation procedure (mostly PVI) practiced at the individual site.

Post procedure rhythm monitoring

According to routine and standard procedure of the site preferred would be for all subjects without CIED (having AF diagnostic algorithms) to receive a 48 or 72 hour Holter monitor at 3, 6, and 12 months post-procedure.

AF symptoms should be documented as recurrent within the follow-up period, further treatment shall be at the discretion of the physician (e.g., drugs, re-ablation, etc.).

Description

This is a consecutive registry to assess the safety and effectiveness of FIRM procedures for the treatment of symptomatic atrial fibrillation.

Patient numbering

Subjects will be assigned consecutive numbers per participating site in combination to a site code

Expertise

In order to participate in this E-FIRM registry, investigators must have completed the following:

- Undergone the training provided by Topera, Inc. in the use of the FIRMap Catheter, RhythmView system and analysis of FIRMaps produced by the system

Synopsis

Registry data collection detail

Legend: ✪ = Data field ⛨ = if applicable

Event	Pre-proc	Intra-proc	Discharge	Day 7-10	1 month	3 month	6 month	12 month
Demographics, Medical Hx, Cardiac Dx	✪							
Lab work (Chemistry, UA, Cardiac enzymes, HCG, LFTs)	✪							
INR (as appropriate on post-ablation f/u)	✪			✪	✪	✪	✪	✪
TEE	✪				⛨	⛨	⛨	⛨
Diagnostic 12-lead ECG	✪		✪		✪	✪	✪	✪
Documentation of Symptomatic AF	✪							
Cardiac meds and any AF interventional procedures performed	✪				✪	✪	✪	✪
NYHA Class Assessment	✪							
AF Symptom and rhythm assessment per defined follow up monitoring	✪			✪	✪	✪	✪	✪
AE review		✪		✪	✪	✪	✪	✪
Interrogation of CIED for AF burden	⛨				⛨	⛨	⛨	⛨
48-hr or 72-hr ambulatory continuous ECG monitor					⛨	✪	✪	✪

Adverse Events

Overview

All adverse events (unanticipated and anticipated) must be classified as serious or minor.

Definitions

The table below describes the classifications of adverse events (AE). All major adverse events occurring during the registry will be included in the safety analysis.

Term	Definition
Serious	Any adverse event which occurs following use of the device and: • is life-threatening*; • results in permanent impairment of a body function or permanent damage to a body structure; or • necessitates significant intervention, such as major surgery, to prevent permanent impairment of a body function or permanent damage to a body structure; or • requires hospitalization or an extended hospital stay; or • results in moderate transient impairment of a body function or transient damage to a body structure; or • requires intervention such as medication or cardioversion* to prevent permanent impairment of a body function or damage to a body structure**.
Minor	Any adverse event that occurs following use of the procedure that results in minimal *transient* impairment of a body function or damage to a body structure, or which does not require any intervention other than monitoring.
Anticipated	Anticipated or known possible adverse events associated with cardiac electrophysiology procedures (see detail listing below in “Anticipated AE”)

Term	Definition
Unanticipated	EU guideline and requirements will be applicable

* In this context, the term refers to an event in which the subject was at immediate risk of death at the time of the event; it does NOT refer to an event that might have caused death if it were more severe.
** For example, if the occurrence of a “catheter insertion site hematoma” or an “AV fistula” requires a blood transfusion and/or surgical repair, it should be considered a major adverse event.

Anticipated AE

Anticipated adverse events include:

Description
Discomfort due to insertion/removal of vascular sheaths beyond what is normally observed
Hemorrhage and/or hematoma at sheath insertion requiring evacuation or transfusion
Extremity weakness, swelling, and/or pain
Discomfort and/or damage to the skin, muscles, or nerves due to remaining in a supine position for an extended period of time.
Complete AV block
Nausea /vomiting
Headache different from baseline
Hypertension >180 mm Hg systolic (repeated measures)
Hypotension <80 mm Hg systolic (repeated measures)
Brief “black out” periods
Shortness of breath/Dyspnea
Feeling of chest pain, skipped beats, and/or rapid heart rate different from baseline
Damage to skin from prolonged exposure to x-rays
New arrhythmias (not previously documented)
Arterial injury requiring intervention
Thromboembolism
Local/systemic infection
Pneumothorax
AV fistula
Thrombophlebitis
Pulmonary embolism
Myocardial infarction
Discomfort and/or damage to the skin, muscles, or nerves due to percutaneous access in excess of usual
Left heart access via trans-septal puncture has known potential adverse events of: cardiac perforation, cardiac tamponade, and embolic events.*

Description
Ventricular arrhythmia requiring defibrillation
Cardiac tamponade due to perforation
Nerve injury (diaphragmatic paralysis, pyloric spasm, gastric hypomotility)
Air embolism
Allergic reaction
Endocarditis
Esophageal-atria fistula
Hemothorax
Pericarditis
Pseudo aneurysm
Pulmonary vein stenosis
Radiation injury
Renal failure form IV contrast
Respiratory failure
Stroke/TIA
Valvular damage
Pleural effusion
Pulmonary edema
Anemia requiring transfusion
Vasovagal reaction
New pericardial effusion >1 cm
Death **(must be reported within the regulation of serious adverse events)**

* Literature reviews have demonstrated that the risk of such events are <1%. Mullins, Charles E. “Trans-septal left heart catheterization: Experience with a new technique in 520 pediatric and adult subjects.” Pediatric Cardiology, v. 4, pgs. 239-246 (1983)

Occurrence

The table below describes actions taken for adverse events that occur during and after the procedure.

Timing	Action
Intra-procedure	If the investigator determines that an adverse event occurs while the patient is in the electrophysiology lab (before or during the procedure), the investigator shall manage the patient as he/she would if a similar event occurred during a standard EP procedure.
Post-procedure	Once the patient has left the electrophysiology lab, all medical/surgical management will be carried out in the standard manner for that institution

Reporting SAEs, & deaths

Reporting requirements for deaths or other adverse events considered to be serious or unanticipated are described in the table below.

Report to	Reporting Requirements
Principal Investigative Site	Must be reported according to the rules of the respective Ethics Committee
EC	Report of the adverse event to the site’s Institutional Review Board is the responsibility of the Principal Investigator. The investigator is responsible for reporting such events to their EC within 10 working days of knowledge of the event. Adverse events clearly unrelated to the device (e.g., broken limb, malignancy) may be reported in accordance with institutional requirements and recorded on CRFs as appropriate

Details are found in Medical Event Report Form “MERF” below.

MERF The table below describes the information required on the initial and final MERF reports.

Information	Initial	Final
Patient registry number	√	√
Gender	√	√
Date of birth	√	√
Date of procedure	√	√
Adverse experience/complication and classification (major/minor)	√	√
Period of hospitalization (if required)	√	√
Investigator's opinion as to the relationship of event/complication to the device	√	√
The disposition of the device (if returned, provide date)	√	√
Description of the event or problem	√	√
Classification of event (anticipated/unanticipated and minor/major)		√
Date of onset		√
Date of resolution		√
Date of discovery		√
Reporter name, title, and contact information		√
Patient outcome		√
Treatment or therapy used to treat		√
Relevant laboratory tests		√
Relevant history, including pre-existing medical conditions		√
Suspect device name, part number, and lot number		√

Data Collection

Data will be entered according to the source documents into an electronic database (online).

Statistical Analysis Plan

[redacted]

Special Requirements and Procedures

A ring binder with one Source Document Form (SDF) could be provided to each participating site. Below are the guidelines for SDF completion and conclusion.

Source document forms

Item	Instruction
1	Data entry via a secure data line to a centralized independent database
2	Maintain each SDF and all relevant source documentation in the appropriate individual notebook.
3	Complete SDF or type.
4	Cross out erroneous entries with a single line, initial and date, and record the correct entry.

Source documents

Copies of pertinent records (i.e., source documents, patient charts, laboratory data, etc.) in connection with the registry not included in the notebook will be made available on request with due diligence toward protecting the privacy of the subject.

Disclosure of data

All information obtained during the conduct of this registry will be regarded as confidential. Manuscripts prepared for publication will be submitted to a steering committee/principal investigator, mutually agreed upon by participating sites, for review and comments prior to submission to the publisher. This condition should not be construed as a means of restricting publication but is intended solely to assure mutual concurrence regarding data, evaluations, and conclusion, to provide an opportunity to share with the investigator any new and/or unpublished information of which he/she may be unaware, and to assure regulatory compliance of the results presented.

EC

This protocol and the patient consent form will be reviewed and approved by the Ethics Committee (EC).

Informed consent

It is the responsibility of the institution to ensure compliance with relevant regulation regarding sharing personal health information during the course of this research. Written informed consent is required prior to enrollment in the registry. It is the responsibility of the investigator to obtain that consent.

Acknowledgement

The Principal Investigator understands and acknowledges that any industry personnel such as those from Topera without appropriate medical training and/or licensure shall not directly participate in the procedure. Such individuals may be present, at the discretion of the physician, solely as advisors and/or observers. Advice shall be contained to the operation, function, and/or maintenance of the equipment and/or software. Any and all medical decisions regarding patient care and treatment shall solely be the responsibility of the Principal Investigator.

Document retention	The investigator must retain the registry data for a time period required by the current guidelines unless other rules require a longer retention period.
Additional consideration	The registry procedure will be carried out in a manner consistent with local procedure standard and with current contractual agreements between each individual site Principal Investigator and their associated educational and medical institutions. The site Principal Investigator shall strictly adhere to clinical standards defined by the guidelines of the European and German societies.