Statistical Analysis Plan (SAP)

Clinical Study for Safety and Acute Performance Evaluation of the THERMOCOOL SMARTTOUCH® SF-5D System used with Fast Ablation Mode in Treatment of Patients with Paroxysmal Atrial Fibrillation (QDOT-FAST)

Protocol Version: 2.0

SAP Revision: #2.0
SAP Revision Date: 11/13/2018

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The following individuals have reviewed this version of the Statistical Analysis Plan and are in agreement with the content:

Signature Page

Study Biostatistician:

(Print) (Sign) Date

Head of Biostatistics (or delegate):

(Print) (Sign) Date

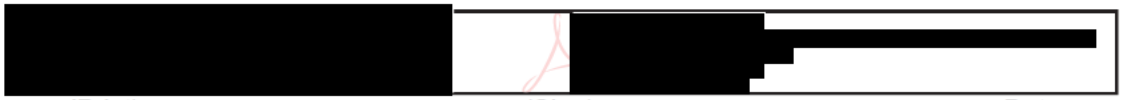
Clinical Study Lead:

(Print) (Sign) Date

Franchise Head of Clinical Research:

(Print) (Sign) Date

Franchise Head of Regulatory Affairs:



(Print) (Sign) Date

Revision History

Revision Number	Revision Date (DD/MM/YYYY)	Reasons for Revision
V2.0	11/12/2018	The definition of NAE population is updated to be consistent with the protocol Section 14.6. Changed the requirement of 'having post-ablation MRI' to 'having any post-ablation neurological assessments'.

Table of Contents

1 Study Design

The QDOT FAST study is a prospective, multi-center, non-randomized clinical study to evaluate the safety and acute performance of the THERMOCOOL SMARTTOUCH® SF-5D system with the nMARQ™ Multi-Channel RF Generator with TGA mode in patients diagnosed with Paroxysmal Atrial Fibrillation (PAF) during standard electrophysiology mapping and RF ablation procedures.

The study population will consist of approximate 50 subjects with PAF as an indication for radiofrequency(RF) ablation. The study will be conducted up to 10 sites in Europe. Follow-up will be conducted at 7 days, 1-month and 3-month post-ablation procedure.

2 Treatment Assignment

All subjects will receive ablation via the THERMOCOOL SMARTTOUCH® SF-5D system and will attempt a very short ablation using the TGA mode (Temperature Guided Ablation).

3 Randomization and Blinding Procedures

Randomizaiton and blinding procedures do not apply for this study.

4 Interval Windows

Refer to protocol Table 3 Summary of Subject Assessment for subject treatments and evaluations.

5 Primary and Secondary Endpoint(s) and Associated Hypotheses

This is a fesibility study and no statistical hypotheses are tested for either primary endpoints or secondary endpoints.

5.1 Primary Endpoint(s) and Associated Hypotheses

Acute Safety

The primary safety endpoint is the incidence of Primary Adverse Events (PAEs) (within seven (7) days of the initial mapping and ablation procedure). PAEs include the following AEs:

Atrio-Esophageal Fistula*	Phrenic Nerve Paralysis

Cardiac Tamponade/perforation	Pulmonary Vein Stenosis*
Death*	Stroke/CVA
Major Vascular Access Complication/Bleeding	Thromboembolism
Myocardial Infarction	TIA

**Device or procedure related death, pulmonary vein stenosis and atrio-esophageal fistula that occur greater than one week (7 days) post-procedure are considered and analyzed as primary AEs.*

Acute Effectiveness

Acute Procedural Success defined as confirmation of entrance block in all targeted PVs after adenosine and/or isoproterenol challenge. The use of a non-study catheter for PVI will be considered an effectiveness failure.

5.2 Secondary Endpoints

- **Safety**
  - Incidence of Serious Adverse Device Effects (SADEs)
  - Incidence of Serious Adverse Events (SAEs) within 7 days (early-onset), >7-30 days (peri-procedural) and >30 days (late onset) of initial ablation procedure
  - Incidence of non-serious adverse events
  - Incidence of pre-and post-ablation asymptomatic and symptomatic cerebral emboli as determined by MRI evaluations
  - Incidence of new or worsening neurological deficits compared to baseline
  - Summary of NIHSS, mRS and MoCA scores at baseline and follow-up timepoints

- **Effectiveness**
  - PVI achieved with TGA mode only among all targeted veins and by subject
  - PVI achieved with combined use of TGA and Q-mode among all targeted veins and by subject
  - Ablation of acute reconnection (touch-up) among all targeted veins and by subject
  - Ablation by a non-study catheter among all targeted veins and by subject
  - Touch-up applications with TGA, Q-mode and non-study catheter applications

- **Additional analyses on procedural data, including but not limited to:**
  - Use of QDOT Micro™ catheter ablation outside the PV area
  - Use of a non-study catheter for ablation outside the PV area

- Total procedure time, mapping time, PV ablation time, total ablation time, RF application time, LA dwell time
- Total number of RF applications, % TGA applications and % Q-mode applications
- Anatomical location of touch-up applications
- Temperature, power, contact force, impedance
- Total Fluoroscopy time/dose

6 Levels of Significance

All data will be summarized by descriptive analyses. No formal statistical inference will be made. Sub-analyses will be done for subjects where TGA was the only application mode used and for subjects where applications were done through a combination of TGA and Q-mode. Where confidence intervals are used they will be two-sided 95% confidence intervals, unless stated otherwise.

7 Analysis Sets

The following analysis populations will be used to complete the analyses of data:

- **Safety Population (SP)**: The safety population will include all enrolled subjects who have the investigational device inserted, regardless if RF energy is delivered. All safety analyses will be performed on the Safety Population.
- **Effectiveness Population (EP)**: The effectiveness population will include all enrolled subjects, have had the investigational device inserted and underwent ablation with the study catheter used in conjunction with TGA mode for PVI. The subjects without any TGA mode application for PVI will be excluded from the effectiveness population. All effectiveness analysis will be performed on the Effectiveness Population.
- **Neurological Assessment Evaluable (NAE) Population:** The NAE Population will include all enrolled subjects have been treated with the study catheter and have any post-ablation neurological assessment. Assessment of incidence of new lesions requires availability of pre-and post MRI. The subjects without pre-MRI but no lesion on post-MRI will be included in the NAE population. Assessment of incidence of new deficits requires availability of pre-and post-neurological evaluation. Analysis of neurological data will be performed on the NAE Population.

8 Sample Size Justification

This is a clinical feasibility study for evaluation of safety and acute performance of THERMOCOOL SMARTTOUCH® SF-5D system with TGA mode application for PVI. This clinical investigation is intended to provide preliminary estimates of safety and acute performance. Enrollment in the clinical investigation will be approximate 50 subjects,

distributed over up to 10 centers in Europe. Minimum attrition is expected for safety assessment. No more than 10% attrition is expected to assess effectiveness outcomes.

Because this study is a feasibility study, there is no statistical power calculation and no hypothesis to be tested. 50 subjects are deemed sufficient to clinically characterize safety and acute outcomes.

9 Data Monitoring Committee (DMC)

Safety review will be performed by the medical safety officer as described by Safety Management Plan.

10 Analyses to be Conducted

10.1 General Conventions

All data will be summarized by descriptive analyses. No formal statistical inference will be made.

Standard descriptive summaries for continuous data include the number of observations with data, mean, standard deviation, median, minimum, and maximum values. For categorical data, the count and percent will be provided. Percentages will be based on the number of subjects without missing data.

10.2 Disposition of Study Subjects

The subject accountability and disposition will be summarized in tables for all enrolled subjects and listings will be provided.

10.3 Demographic and Baseline Characteristics

Age at consent will be summarized with sample size, mean, standard deviation, median, quartiles, and min and max. Gender will be summarized with counts and percentages. Baseline Medical History information and baseline medical scores will be summarized with sample size, mean, standard deviation, median, quartiles, minimum, and maximum for continuous variables and with counts and percentages for categorical variables.

Baseline assessments includes:

- Demographics (age, gender).
- Medical history: arrhythmia, heart disease, thromboembolic events
- AF history
- Medication history
- AAD medication
- CHA2DS2 VASc Score

- Transthoracic Echo (TTE)
- Electrocardiogram (12-Lead ECG)
- Adverse Events
- Cerebral MRI, Neurological Exam and Neurological Evaluation using the Montreal Cognitive Assessment (MoCA), NIH Stroke Scale (NIHSS) and Modified Rankin Scale (mRS)

10.4 Primary and Secondary Endpoint Analyses

Primary Safety

Primary safety outcome will be reported as primary adverse events (PAEs) (within 7 days of the intial mapping and ablation procedure, with exception for PV stenosis, death, tamponade and AEF). The number of events and the number and percentage of subjects experiencing primary adverse events will be reported. The primary safety endpoint will be summarized overall and by AE type, seriousness, severity, causality, anticipated or not. The Primary Safety analysis will be performed on the Safety Population.

Primary Effectiveness

Acute Procedural Success: Acute success is defined as achieving confirmation of entrance block in all targeted PVs after adenosine and/ or isoproterenol challenge. The number and percentage of subjects who have reached acute success will be summarized. Primary Effectiveness analysis will be performed on the Effectiveness Population.

Secondary Safety

The number of events and the number and percentage of subjects with SADEs, SAEs and non-SAEs during follow-up period (3 months) will be summarized overall and by AE type, seriousness, severity, causality, timing (< 7 days, 7-30 days, > 30 days), and outcome etc. The subjects with SADEs and SAEs will also be listed.

The number of events and the number and percentage of subjects with pre- and post-ablation asymptomatic and symptomatic cerebral emboli as determined by MRI evalutaions will be summarized. The incidence of new or worsening neurological deficits compared to baseline will be summarized and listed. NIHSS, mRS and MoCA scores at baseline and follow-up timepoints will be summarized and listed as well. The NAE endpoints will be analyzed in the NAE population.

Secondary Effectiveness

The number of PV isolation achieved among all targeted veins and the number and percentage of subjects with PVI achieved with TGA mode only will be summarized and listed. The number of PV isolation achieved among all targeted veins and the number and percentage of subjects with PVI achieved with combined use of TGA and Q-mode will be summarized and listed. The number of PV with acute reconnection (touch-up) among all targeted veins and the number and percentage of subjects with touch-up ablations will be summarized and listed. Touch-up applications with TGA, Q-mode and non-study catheter will be summarized by PVs and subjects. PV ablations by a non-study catheter among all targeted veins and by subject will be summarized and listed. These analyses will be performed in the effectiveness population.

Additional Analyses on Procedural Data

Procedural data will be summarized and listed. For continuous variables, number of subjects with non-missing data, mean, standard deviation, median, 25% percentile, 75% percentile, minimum, and maximum will be reported. For categorical variables, the frequency and percentage will be presented for each category. Procedural data will be summarized in the effectiveness population.

10.5 Plans for Interim Analysis

No interim analyses are planned for this study.

10.6 Handling of Missing Data

Missing questions will be queried for reasons and handled on an individual basis. No missing data imputation will be performed.

10.7 Subgroup Analyses

For the primary and secondary endpoints, subgroup analysis will be performed for the following subgroups. Effectiveness population will be used to primary and secondary effectiveness endpoints and safety population will be used for primary and secondary safety endpoint.

- TGA application mode used only for PVI vs. the application with combination TGA and Q-mode for PVI in the Effectiveness Population

- TGA application mode used only for the overall procedure vs. the application with combination TGA and Q-mode for the overall procedure in the Safety Population

Appendix: Tables, Listings and Graphs Shells

The tables, listings and graphs shells will be approved and provided separately.

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