Statistical Analysis Plan (SAP)

Clinical study for workflow and acute performance evaluation of the THERMOCOOOL SMARTTOUCH® SF-5D system (the THERMOCOOL SMARTTOUCH® SF-5D catheter with temperature sensing capabilities and micro electrodes and CARTO 3 V 6.0 technology) in treatment of patients with Paroxysmal Atrial Fibrillation

(QDOT MICRO)

Protocol Version: 2.0

SAP Revision: # 1.0
SAP Revision Date: August 02, 2018

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(QDOT MICRO)
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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:

Elena Y. Lin

Digitally signed by Elena Y. Lin
DN: c=US, o=JNJ, ou=Subscribers, cn=Elena Y. Lin, 0.9.2342.19200300.100.1.1=702261162
Reason: I am certifying this document.
Date: 2018.08.02 23:16:32 -07'00'
Adobe Acrobat version: 11.0.20

(Print) (Sign) Date

Head of Biostatistics (or delegate):

Chithra Sangli

Digitally signed by Chithra Sangli
DN: c=US, o=JNJ, ou=Subscribers, cn=Chithra Sangli, 0.9.2342.19200300.100.1.1=1035766
Reason: I am approving this document.
Date: 2018.08.03 09:30:04 -07'00'
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(Print) (Sign) Date

Clinical Study Lead:

Carmen Rousseeuw

Digitally signed by Carmen Rousseeuw
DN: c=US, o=JNJ, ou=Subscribers, cn=Carmen Rousseeuw, 0.9.2342.19200300.100.1.1=702048369
Reason: I am approving this document.
Date: 2018.08.08 14:15:15 +02'00'
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(Print) (Sign) Date

Franchise Head of Clinical Research:

Anthony Hong

Digitally signed by Anthony Hong
DN: c=US, o=JNJ, ou=Subscribers, cn=Anthony Hong, 0.9.2342.19200300.100.1.1=1013587
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(Print) (Sign) Date

Franchise Head of Regulatory Affairs:

DIANA Bordley

Digitally signed by DIANA Bordley
DN: c=US, o=JNJ, ou=Subscribers, cn=DIANA Bordley, 0.9.2342.19200300.100.1.1=332810
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Revision History

Revision Number	Revision Date (DD/MM/YYYY)	Reasons for Revision
Version 1.0		Original Document

Table of Contents

1 Study Design

The QDOT MICRO study is a prospective, multi-center, non-randomized clinical study to evaluate the workflow and acute performance of the THERMOCOOL SMARTTOUCH® SF-5D system in patients diagnosed with Paroxysmal Atrial Fibrillation (PAF).

The changes in this document from the procotol are the definitions of safety and effectiveness populations. The study was stopped due to safety reasons after 8 subjects were enrolled and treated under protocol version 1.0 and then the study catheter was re-designed. Therefore, the subjects who were enrolled and treated under protocol version 2.0 were using a different design of the study catheters.

2 Treatment Assignment

All subjects will receive ablation using the THERMOCOOL SMARTTOUCH® SF-5D catheter with temperature sensing capabilities and micro electrodes and CARTO 3 V 6.0 technology. However, the catheter was redesigned after the first 8 subjected were treated.

3 Randomization and Blinding Procedures

The QDOT MICRO study is non-randomized and unblinded, all subjects will receive ablation via the THERMOCOOL SMARTTOUCH® SF-5D system.

4 Interval Windows

Refer to protocol Table 1 for summary of required schedule for subject treatments and evaluations.

5 Primary and Secondary Endpoint(s) and Associated Hypotheses

5.1 Primary Endpoint(s) and associated hypotheses

Acute Device Performance

Acute Device Performance is defined as confirmation of entrance block in all targeted PVs after adenosine and/or isoproterenol challenge.

5.2 Secondary Endpoints and associated hypotheses

- **Safety**
  - Incidence of early onset (within 7 days of ablation procedure) primary Adverse Events.

Serious Adverse Events occurring within the first week (7 days) following an ablation procedure with the THERMOCOOL SMARTTOUCH® SF-5D catheter and AE term is one of the adverse events listed, will be considered for Primary Event assessment

Table 1 Primary Adverse Events

• Death
• Atria-Esophageal Fistula*
• Cardiac Tamponade/Perforation*
• Myocardial Infarction
• Stroke/Cerebrovascular Accident
• Thromboembolism
• Transient Ischemic Attack
• Diaphragmatic Paralysis
• Pneumothorax
• Heart Block
• Pulmonary Vein Stenosis*
• Pulmonary Edema (Respiratory Insufficiency)
• Vagal Nerve Injury
• Pericarditis
• Major Vascular Access Complication/Bleeding

* Pulmonary vein (PV) stenosis, atrio-esophagael fistula and cardia tamponade/perforation that occurs greater than one week (7days) post-procedure shall be deemed Primary AEs.

- Incidence of Serious Adverse Device Effects (SADEs) during follow-up period (3 month)

- **Procedural data**
  - Rate for touch-up RF application post adenosine and/ or isoproterenol challenge
  - Target sites for RF lesion application
    - Target sites
    - Number of RF applications per target
    - Total RF duration per application (sec)
  - Ablation parameters, including but not limited to:
    - Total RF ablation time
    - Temperature (generator files)
    - Contact Force (CARTO® datafiles)
    - Power (generator files)
    - Impedance
  - Total Fluoroscopy time/dose
  - Total procedure time

- ECG data

- **Investigational device performance (rating with survey):**
  - Contact and stability of catheter
  - Signal Quality
  - Temperature visualization
  - Ease of use

6 Levels of Significance

All data will be summarized by descriptive statistics. No formal statistical inference will be performed.

7 Analysis Sets

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

Safety Population 1: The Safety population 1 will include all subjects enrolled under protocol version 1.0 who have the investigational device inserted, regardless if RF energy is delivered.

Safety Population 2: The Safety population 2 will include all subjects enrolled under protocol version 2.0 who have the investigational device inserted, regardless if RF energy is delivered.

Effectiveness Population 1: The effectiveness population will include all subjects enrolled under protocol version 1.0 who meet all eligibility criteria and have had the investigational device inserted and underwent ablation with the study catheter under guidance of the THERMOCOOL SMARTTOUCH® SF-5D Module.

Effectiveness Population 2: The effectiveness population will include all subjects enrolled under protocol version 2.0 who meet all eligibility criteria and have had the investigational device inserted and underwent ablation with the study catheter under guidance of the THERMOCOOL SMARTTOUCH® SF-5D Module.

8 Sample Size Justification

This is a clinical feasibility study for evaluation of workflow and acute performance of THERMOCOOL SMARTTOUCH® SF-5D system. This clinical investigation is intended to provide preliminary estimates of workflow and acute outcomes.

Because this study is a feasibility study, there is no statistical power calculation and no hypothesis to be generated. Fifty subjects are deemed sufficient to characterize the workflow and acute outcomes.

Enrollment in the clinical investigation will be approximately 50 evaluable subjects with approximately 10 subjects per investigational site, distributed over approximately 5 centers in Europe. The study catheter was redesigned in protocol v2.0. The total enrollment remains as approximately 50 evaluable subjects combining subjects enrolled under protocol v1.0 and v2.0.

9 Data Monitoring Committee (DMC)

The medical safety officer or designee will review, on regular or urgent basis, all applicable adverse events and deaths. This medical safety officer shall advise about the appropriateness of continuing or terminating the clinical investigation, based upon findings during his review of adverse events and deaths. The overall safety profile of the investigational device will be evaluated by the Sponsor at the end of the trial.

10 Analyses to be Conducted

10.1 General Conventions

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

10.2 Disposition of Study Subjects

The subject accountability and disposition will be summarized and listed for all enrolled subjects.

10.3 Demographic and Baseline Characteristics

Demographic and baseline charcteristics will be summarized and listed for all enrolled subjects and will also be summarized separately for subjects enrolled under protocol v2.0. Age at consent will be summarized with number of subjects, mean, standard deviation, median, quartiles, minimum, and maximum. Gender will be summarized with counts and percentages. Baseline Medical History information and baseline medical scores will be summized with number of subjects, mean, standard deviation, median, quartiles, minimum, and maximum for continuous variables and with counts and percentages for categorical variables.

10.4 Primary and Secondary Endpoint Analyses

10.4.1 Acute Device Performance

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. The analysis will be performed in the effectiveness populations.

10.4.2 Safety

Acute safety outcome will be reported as the number of primary adverse events and the number and percentage of subjects experiencing primary adverse events (within 7 days of catheter ablation, with exception for PV stenosis and AE fistula.

The number and percentage of subjects with early onset (within 7 days of ablation procedure with exception for PV stenosis and AE fistula) pre-defined primary Adverse Events will be summarized overall and by AE type, severity, causality, anticipated or not and outcome etc. The primary adverse events will also be listed.

The number and percentage of subjects with Serious Adverse Device Effects (SADEs) during follow-up period (3 months) will be summarized overall and by AE type, timing (< 7 days, 7-30 days, > 30 days), seriousness, severity, causality, anticipated or not and outcome etc. Listing of SADEs will also be provided. The safety analysis will be performed in the safety populations.

10.4.3 Procedural Data

Procedural data will be summarized in the safety and effectiveness populations and listed in the safety populations. For continuous variables, the 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.

10.4.4 Investigational Device Performance

Investigational device performance will be reported by means of survey questions. The scores of survey questions will be summarized by presenting the number of subjects with non-missing data, mean, standard deviation, median, minimum, and maximum for each sub-scale measurement. Listings of survey answers/scoring will also be provided. The analysis will be performed in the effectiveness populations.

10.5 Plans for Interim Analysis

No interim analyses are planned for this study.

10.5.1 Stopping Rules

The clinical investigation team will review and monitor the clinical safety data on a regular basis for any safety or catheter design issues. Should the team identify any safety issues, the impacted clinical sites, EC's and CA's will be immediately notified to ensure the safety of their patients and the study may be stopped.

The sponsor may either suspend or prematurely terminate the study for significant and documented reasons.

A principal investigator, EC, or regulatory authority may suspend or prematurely terminate participation in the study at the study sites for which they are responsible.

10.6 Handling of Missing Data

Missing questions will be queried for reasons and handled on an individual basis. Summary statistics will be reported based upon available data only.

Appendix: Tables, Listings and Graphs Shells

The tables, listings and graphs shells are provided separately.

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