

Cryterion Cardiac Cryoablation System CE Mark Study

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Statistical Analysis Plan

Cryterion Cardiac Cryoablation System CE Mark Study

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Revision History

Document Revision Number	Section	Change	Reason for Change
A	N/A	Initial Release	N/A
B	3.5, 3.6	Added description of subjects included in additional and secondary endpoint analysis	Missing in previous version
C	3.6	Updated eligible subjects for secondary endpoint of "Documentation of all targeted PVs that demonstrate isolation immediately post ablation and then show reconnection during entrance/exit block testing"	Worded incorrectly in previous version

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PURPOSE

The purpose of this statistical analysis plan is to provide endpoint analysis details to supplement the statistical methods provided in the Cryterion CE Mark Study protocol.

1 PROTOCOL SUMMARY

1.1 Study design

The study is a non-randomized, open label, prospective multi-center, clinical study designed to collect long-term (1 year), system-related, clinical and subject reported outcome data from subjects indicated for a de novo ablation of paroxysmal atrial fibrillation and treated with the Cryterion Cardiac Cryoablation System and components including the SmartFreeze Cryo-console, the Cryoablation Balloon Catheter, and the Circular Mapping catheter.

A protocol amendment of the original FIM protocol was initiated in May 2018 designed for the purpose of obtaining CE mark and intended to prolong the follow-up period from 30 days to 12 months and extend the number of enrolled subjects from 30 to 100.

Subjects will be followed for 12 months by each clinical center with specific scheduled visits to detect recurrent AF (Detectable AF) and adverse events (AEs).

1.2 Study devices

The Cryterion Cardiac Cryoablation System is designed to thermally ablate cardiac tissue in the management of atrial fibrillation. The components and accessories for the system are listed below:

- Cryoablation Balloon Catheter
- Cryo-Console
- Circular Mapping Catheter
- Steerable Sheath, 12 F
- Diaphragm Movement Sensor
- Esophageal Temperature Sensor Cable
- Inter Connection Box
- Cryo-Console Foot Switch

- Cryo-Cable
- Cryo-Catheter Extension Cable
- EP Electrical Cable

1.3 Follow-up

Visits include Screening & Baseline, Index Procedure, Discharge, 1 Month, 3 Months, 6 Months and 12 Months and additional follow-up visits (including potential repeat procedures).

1.4 Endpoints

1.4.1 Primary Safety Endpoint

Safety endpoint is assessed by freedom from device or procedure related serious adverse events (referred to as Major Adverse Events, MAE) at 12 months* post-procedure.

MAEs include the following:

- Death
- Myocardial infarction
- Cardiac perforation/ pericardial tamponade
- Cerebral infarct or systemic embolism
- Major bleeding requiring transfusion of blood products
- Mitral or tricuspid valvular damage
- Phrenic nerve damage causing persistent diaphragmatic paralysis**
- Symptomatic pulmonary vein stenosis
- Atrio-esophageal fistula
- Air embolism leading to a life-threatening event such as a ventricular arrhythmia, stroke or myocardial infarction
- Any other serious or non-serious adverse device effects (SADEs or ADEs)

*For 1 Month sub-analyses this endpoint will be presented as the rate at 1 Month. Any additional endpoint events reported for subjects with longer follow-up will be noted in the report

**According to the consensus document definition: Phrenic nerve paralysis is defined as absent phrenic nerve function as assessed by a sniff test. A phrenic nerve paralysis in this study is considered to be permanent when it is documented to be present at 12 months following ablation.

1.4.2 Primary Effectiveness Endpoint

The Primary Effectiveness Endpoint is the rate of successful pulmonary vein electrical isolation with confirmation of entrance and exit block achieved with the Cardiac Cryoablation System (Acute procedural success).

Acute procedural success is defined as the documentation of pulmonary vein isolation following the last cryo application for each of the targeted veins. Demonstration of electrical isolation in ≥ 3 PVs or their anomalous equivalents at the end of the first protocol-defined cryoablation procedure. Documentation will be completed with the Cryterion Circular Mapping Catheter to confirm PVI. The physician should confirm and document entrance and exit block by standard of-care pacing maneuvers during the index procedure.

1.4.3 Additional Effectiveness Endpoint: 12 Month Treatment Success

Treatment success is defined as the proportion of subjects free from symptomatic atrial arrhythmias at 12 months. A treatment failure is defined as a subject being an acute procedural failure, having more than one repeat procedure during the 90-day blanking period or having a documented, symptomatic episode(s) of atrial fibrillation or atrial tachycardia, between 91 and 365 days post index procedure (windows allowed per protocol as shown in Table 2 included). Occurrence or recurrence of a right atrial arrhythmia is not considered a treatment failure post the 90-day blanking period.

1.4.4 Secondary Endpoints

Secondary Endpoint Measurements will include:

- All Procedure and device related adverse events*
- Documentation of all targeted PVs that demonstrate isolation immediately post ablation and then show reconnection during entrance/exit block testing
- Recording of time to demonstration of PVI using the Circular Mapping catheter following the initiation of a freeze cycle
- Operator's assessment of handling characteristics with a System Performance Questionnaire**

* be accessed directly from the clinical database (eCRFs hosted on IBM Clinical platform)

** The System Performance Questionnaire is included in the study clinical database and includes questions to the operator to assess quality characteristics of the products, alone and compared to commercially available cryoballoon ablation technologies and circular mapping catheters. The system performance questionnaire will be used with all new clinical users for the first five (5) cases performed with the Cryterion System. After the first 5 cases, users can use the questionnaire to provide specific product feedback related to user experience(s) on an as needed basis (for example: the ability of the cryoablation system to deal with tortuous anatomy of the LA/PVs). In case the investigator reports quality issues in the questionnaire, he should consider if needed, to enter a device deficiency

2 SUBJECT CLASSIFICATION DEFINITIONS

For the purposes of this clinical study, the following definitions regarding the status of a subject will apply:

Enrolled Subject - Any subject who has signed an informed consent form (ICF)

Consent Ineligible Subject – Any subject who has signed the informed consent but is found not to meet all the inclusion/exclusion criteria. This includes a subject who has signed an informed consent form but may be excluded based on the results of the pre-procedure TEE or intracardiac echocardiogram (ICE) evaluation of the left atrial appendage (LAA) and/or PV anatomy. In the event these subjects completed a trans-septal puncture, they will be followed through discharge for the recording of any procedure related adverse events. These subjects will not count towards the enrollment ceiling and will not be considered for the primary endpoints analysis.

Intent Subject – Any subject who has signed an informed consent form (ICF) and is deemed study eligible by meeting all the inclusion and none of the exclusion criteria but does not undergo the ablation procedure. This subject will be withdrawn from the study. Data will be collected up to the point of withdrawal, will not count towards the enrollment ceiling and will not be considered for primary endpoints analysis.

Attempt Subject - Any subject who has signed an informed consent form (ICF) and is deemed study eligible by meeting all the inclusion and none of the exclusion/criteria and undergoes the ablation procedure with any of the investigational device entered in the subjects' body but no energy is delivered to the PVs. This subject will be followed through the 30 days follow up then withdrawn from the study. Data will be collected up to the point of withdrawal, will not count towards the enrollment ceiling and will not be considered for primary endpoints analysis.

Treated Subject – Any screened subject who completes the ablation procedure to the point that any of the investigational products are introduced into the body and Cryo-energy is delivered. Enrolled subjects will be followed for all study outcome measures for the full duration of the clinical study.

3 ENDPOINT ANALYSES

3.1 Analysis Details

3.1.1 Analysis Populations

The overall analysis of the endpoints of the study will be based on the Enrolled Subject Population. All Enrolled subjects will be included in this analysis and the analysis will be

performed when all subjects have exited the study (either reaching End of Study or having been withdrawn) and all data cleaning activities have occurred.

A sub-analysis will be performed on the first 30 enrolled subjects when they have reached 1 Month of follow up for the purpose of CE Mark. This analysis will include all data on the first 30 subjects enrolled, as determined based on their enrollment date, and will occur when all data cleaning activities on the submission data have occurred.

An additional sub-analysis will be performed on the first 50 enrolled subjects, determined by enrollment date, for the purpose of PMDA submission. The analysis will occur when the first 50 enrolled subjects have reached a minimum of 1 month of follow up and all data cleaning activities on the submission data have occurred. Submission data will include all available data on the 50 subject cohort, including up to 12 months of follow up. Enrollment date will be considered the date informed consent was signed. When determining the 50 subject cutoff, in the event more than one subject are consented on the same day if subjects are consented at the same site, the first consented subject based on subject ID number will be included. If subjects are consented at different sites both will be included.

3.1.2 Sample Size

[REDACTED]

3.1.3 Control of Bias

Selection of subjects for the overall study will be made from the Investigator's standard of care population. All subjects meeting the eligibility criteria and having signed the ICF will be eligible for enrollment in the study and all enrolled subjects will be included in the overall analysis.

Sample sizes for the sub-analyses were determined in conjunction with the corresponding regulatory body prior to performing the data analysis. Subject eligibility for each analysis was determined based on the order of subject enrollment.

3.2 Statistical Analysis

Analysis of study endpoints will be performed on an intent-to-treat basis. All partial data that is available on subjects who drop out during the course of the study will be included.

Descriptive analysis will be used to present the study. Continuous variables will be reported as median and range, mean \pm standard deviation; categorical variables will be reported as n/N (%).

3.3 Primary Safety Endpoint

The primary safety endpoint outcome is freedom from a composite MAE list, outlined in Section 2.4.1 above, and all other serious or non-serious adverse device effects (SADEs or ADEs).

The rate of MAEs and rate of SADEs and ADEs will each be presented separately as well as an overall combined rate of all events. Rates will be presented as the binomial rate (N events/ N subjects) with corresponding exact binomial 95% confidence interval. These rates will be compared to the safety outcome rates derived from available literature data.

Additionally, all adverse events will be summarized by type of event, severity, relationship to the device and/or procedure, and timing of event relative to the procedure date. Listings of all adverse events and separate listings of events meeting the safety endpoint will be provided.

The primary safety endpoint will be assessed in all enrolled subjects who undertake the ablation procedure to the point that the Cryoablation Balloon is inserted into the subject (Attempt and Treated subjects).

3.4 Primary Effectiveness Endpoint

The primary effectiveness endpoint is acute success defined as rate of successful pulmonary vein electrical isolation with confirmation of entrance/exit block.

The rate of acute success will be presented as a binomial rate (N events/ N subjects) with corresponding exact binomial 95% confidence interval. The rates will be compared to the acute success rates derived from available literature data.

The primary effectiveness endpoint will be assessed in all enrolled subjects who undertake the ablation procedure to the point that the Cryoablation Balloon is used to deliver at least one cryo application (Treated subjects).

3.5 Additional Effectiveness Endpoint

The additional effectiveness endpoint is 12 month treatment success, defined as the proportion of subjects free from symptomatic atrial arrhythmias at 12 months.

The rate of 12 month success will be presented as a binomial rate (N events/ N subjects) with corresponding exact binomial 95% confidence interval. The rates will be compared to the 12 month success rates derived from available literature data.

The additional effectiveness endpoint will be assessed in all enrolled subjects who undertake the ablation procedure to the point that the Cryoablation Balloon is used to deliver at least one cryo application (Treated subjects). Subjects who withdraw from the study prior to their 12 month visit without experiencing an event will be considered ineligible for this analysis.

3.6 Secondary Endpoints

Secondary Endpoints, listed in Section 2.4.4, will be assessed in all available subjects.

Due to protocol changes impact on data collection, the secondary endpoint “Documentation of all targeted PVs that demonstrate isolation immediately post ablation and then show reconnection during entrance/exit block testing” will only be able to be evaluated in subjects who were enrolled and had their index procedure performed under protocol version CEM01 or earlier.

Summary statistics will be presented for each analysis. E.g. event rates and confidence intervals will be provided for binary endpoints, and mean \pm SD and/or min, max, and median and quartiles will be presented for continuous endpoints. No p-values will be presented.

4 PROGRAMMING CONSIDERATIONS

All statistical analyses will be conducted in SAS version 9.3 or higher (SAS Institute, Cary, N.C.).

5 VALIDATION

Validation of all study analyses will be performed prior to report submission, as outlined in Global Clinical WI: Clinical Data Reporting Validation (90702587).