Statistical Analysis Plan Cover Page

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TactiSense IDE
Multi-Center Acute Safety Trial of TactiCath™ Contact Force Ablation Catheter, Sensor Enabled™ (TactiCath SE) for the Treatment of Drug Refractory Recurrent Symptomatic Paroxysmal Atrial Fibrillation
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TactiSense IDE

(SJM-CIP-10216 Ver E)

Statistical Analysis Plan (SAP)

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1 INTRODUCTION

This document is a statistical analysis plan for the TactiSense IDE trial (SJM-CIP-10216 Ver E).

2 TRIAL OBJECTIVES

The objective of this clinical trial is to demonstrate the acute safety and effectiveness of ablation with the TactiCath™ Contact Force Ablation Catheter, Sensor Enabled™ (TactiCath SE) for the treatment of drug refractory recurrent symptomatic PAF and is intended to support market approval of the TactiCath SE ablation catheter in the United States.

3 TRIAL DESIGN

This is a prospective, multi-center, single-arm clinical trial to evaluate the acute safety of the TactiCath SE catheter for the treatment of paroxysmal atrial fibrillation (PAF) against a performance goal. One hundred fifty six-(156) subjects will be enrolled at up to 35 investigational sites in the US, Europe, and Australia. Only sites that enroll at least one subject will be part of the analysis population. No center may contribute more than 20% of the total number of enrollments without sponsor pre-approval to exceed this proportion and at least 50% of subjects must be from the United States.
In addition to PVI, subjects with documented atrial flutter, AT or other SVT (spontaneous or induced) may undergo additional targeted ablation as clinically indicated.

[REDACTED] Subjects will be followed for 12 months after the index ablation procedure and then exit the clinical trial. **[REDACTED]** The pre-market approval (PMA) clinical report will be submitted when at least 140 subjects have been enrolled, had the investigational catheter inserted into their vasculature and either experienced an event as defined in CIP section 4.3.1, completed their 30 day follow up visit, or have been lost to follow up per CIP section 5.7.

A CEC will be responsible for providing an independent review and adjudication of adverse events. The primary function, responsibilities and membership of the CEC will be described in detail in a CEC charter.

4 TRIAL ENDPOINTS

There are two primary endpoints and ten descriptive endpoints for this trial. Since both primary endpoints must be met to declare a successful trial, no adjustments for multiplicity are required.

4.1 Primary Safety Endpoint

The primary safety endpoint is the rate of device- or procedure-related serious adverse events occurring within 7 days of the index procedure. SAEs related solely to arrhythmia recurrence (without coexisting conditions such as thromboembolism, worsening heart failure, etc.) will not be considered primary safety endpoint events. The SAEs that will be included in this endpoint are:

- Atrial esophageal fistula

- AV block
- Cardiac Perforation/Tamponade
- Death
- Diaphragmatic paralysis
- Gastroparesis
- Hospitalization
- Myocardial Infarction
- Pericarditis
- Pneumothorax
- Pulmonary edema
- Pulmonary vein stenosis
- Stroke
- Thromboembolism
- Transient ischemic attack
- Vascular access complication

These events must meet the criteria listed in Appendix C of the CIP to be included in the primary endpoint and will be adjudicated by an independent clinical events committee (CEC). Atrial-esophageal fistula, cardiac perforation/tamponade, and pulmonary vein stenosis that occur >7 days post procedure through 30 days will also contribute to the primary endpoint.

4.2 Primary Effectiveness Endpoint

The primary effectiveness endpoint is Acute Procedural Success, where acute procedural success is defined as confirmation of entrance block in all pulmonary veins.

4.3 Descriptive Endpoints

There are ten types of descriptive endpoints. Descriptive endpoints are reported using summary statistics and no hypothesis testing will be performed.

1. Ablation data collected during the procedure, including:
    - Power
    - Temperature
    - Irrigation flow rate
    - Contact force
    - Procedure time
    - Total ablation time
    - Total fluoroscopy time

- Total RF application time
- Usage of Automark

2. Proportion of index cases achieving achieving ≥ 90% lesions with ≥10g contact force
3. Serious adverse events and adverse events related to the procedure and/or ablation catheter through 30 days post index ablation
4. Serious adverse events and adverse events related to the procedure and/or ablation catheter through 1 year post index ablation
5. One-year success defined as freedom from symptomatic AF/AFL/AT lasting at least 30 seconds without a new Class I or III AAD or a higher dosage of pre-existing AAD as assessed from the end of the 3-month blanking period to 12 months following the ablation procedure.
6. One-year drug-free success defined as freedom from any AF/AFL/AT lasting at least 30 seconds or any Class I or III AAD after removal from antiarrhythmic drug therapy as assessed from the end of the 3-month blanking period to 12 months following the ablation procedure.
7. Changes in EQ-5D-5L scores from baseline to follow up at 3, 6, and 12 months
8. Changes in AFEQT scores from baseline to follow up at 3, 6, and 12 months
9. Cardiovascular-related health care utilization through 12 months post index ablation
10. Force time integral (FTI) and lesion index (LSI)

NOTE: For endpoints 5 and 6, a full 10-second 12-lead ECG recording of arrhythmia may be substituted for a 30-second recording unless there is evidence that the recorded arrhythmia is short-lived and less than 30 seconds.

5 STATISTICAL METHODS

There are two primary endpoints hypothesis for this study and 10 types of descriptive endpoints. Both primary endpoints must be met for trial success.

5.1 Primary Safety Endpoint

The primary safety endpoint is the rate of device- or procedure-related serious adverse events occurring within 7 days of the index procedure. The CEC will make the final determination whether or not an adverse event meets the criteria for the primary endpoint.

5.1.1 Hypothesis

The hypothesis is formally expressed as:

H_0: P ≥ 16.2%
H_a: P < 16.2%,

where P is the percentage of subjects with a primary safety endpoint event. The hypothesis will be tested based on a one-sided exact test of binomial proportions at the one-sided 0.05 alpha level. The performance

goal of 16.2% is based on relevant experience from prior clinical trials using the TactiCath family of ablation catheters.

5.1.2 Analysis Methodology

The primary safety endpoint event rate will be calculated based on the number of subjects experiencing a primary safety endpoint divided by the total number of subjects in the analysis population. The null hypothesis will be rejected if the upper bound of the one-sided 95% exact binomial confidence interval for the proportion of subjects with the primary safety endpoint is less than 0.162. Subjects who terminate the study prematurely without experiencing any primary safety endpoint events will be excluded.

5.1.3 Sample Size

[REDACTED]

5.1.4 Analysis Population

The analysis population for this endpoint will include all enrolled subjects who have also had the TactiCath SE inserted into their vasculature, and either had an event or completed a visit at or beyond their 30-day follow up visit window. Subjects without an event that are lost to follow up without a visit at or beyond their 30-day follow up visit window will be excluded from this analysis.

5.1.5 Poolability Analysis

5.1.5.1 Multiple Geography Effect

The trial will be conducted in 35 sites in the United States, Europe and Australia following the same investigational plan and inclusion and exclusion criteria. The trial will be conducted following the same procedures, monitoring plan and training plan in all regions. Poolability of the primary safety endpoint across region (i.e., US vs. OUS) will be evaluated for subjects included in the primary analysis population.

To evaluate the geography effect on the primary safety endpoint, Fisher's exact test will be tested for geography effect in the TactiSence trial against an alpha level of 0.15. If the p-value is less than 0.15, Abbott will examine subject demographics, baseline clinical characteristics for possible correlations and confounding factors.

5.1.5.2 Multiple Center Effect

Analysis will be performed by pooling data across study sites. The TactiSense trial will have 35 sites globally, with at least 50% of subjects in the United States. Subject enrollment is capped at 28 per site (20% of the total number of enrollments). This cap per site will prevent the scenario where the results from a few sites dominate the overall study result. For the analysis of center effect, data from smaller sites may be combined for the analysis. Smaller sites are defined as sites with fewer than 12 subjects per site. The pooling of the smaller sites will be based on the following rules:

- Sort all smaller sites based on the number of subjects per site in an ascending order. If there are ties, sort further by site number.
- Starting from the smallest site in this list, combine sites by going up the list until the combined group size first reaches 12 or larger. At this point, a super site is identified.
- Repeat the above grouping process from the next smallest site above the newly formed super site.
- The grouping process ends when all smaller sites have been accounted for.

The sizes of the super sites (which are a result of grouping smaller sites) will range between 12 and up to 22 (11+11). This represents a reasonable range of sample sizes which will provide meaningful estimates of within-sites variations and will not alter between-sites variation.

To evaluate the multiple center effect on the primary safety endpoint, Fisher's exact test will be tested for center effect in the TactiSence trial against an alpha level of 0.15.

5.1.6 Sensitivity Analysis

To demonstrate robustness with respect to missing data, a tipping point analysis will be performed for the primary safety endpoint. This will involve imputing all possible combinations of outcomes for the primary endpoint among subjects who terminate the study prematurely without experiencing any primary safety endpoint events.

5.1.7 Subgroup Analysis

Subgroup analyses will be performed to examine the consistency of the primary safety endpoint event rate across subgroups. Subgroups to be examined include, but are not limited to, those defined by achieving >90% of lesions with ≥10g contact force, age (both <65 vs ≥65 and age ≥ median vs < median), sex, and race/ethnicity. Since the number of subjects not achieving >90% lesions with ≥10g contact force in this study is likely to be small, the results from similar subjects from the Toccastar IDE study will be pooled with results from this trial. The results for this endpoint will be presented separately for those achieving/not achieving >90% of lesions with ≥10g contact force. As needed and appropriate (i.e., for comparison of subgroups), categorical variables will be tested using Fisher's exact test and continuous variables will be tested using two sample t-test. No subgroup specific labeling claims are desired for the primary safety endpoint and no adjustments for multiplicity will be made.

5.1.8 Interim Analysis

There are no plans for interim analyses for potential early stopping for benefit or for trial or sample size adjustments.

5.2 Primary Effectiveness Endpoint

The performance goal is set at 90% based on experience from previous IDE trials of approved devices relying on pulmonary vein isolation for effectiveness. The hypothesis is formally expressed as:

H_0: P < 90%

H_a: P ≥ 90%,

where P is the percentage of subjects with acute success. The hypothesis will be tested based on a one-sided exact test of binomial proportions at the one-sided 0.05 alpha level. Rejection of the null hypothesis will indicate study success.

5.2.1 Analysis Methodology

The primary effectiveness endpoint event rate will be calculated based on the number of subjects experiencing a primary effectiveness endpoint divided by the total number of subjects in the analysis population. The null hypothesis will be rejected if the lower bound of the one-sided 95% confidence interval for the proportion of subjects in this trial with the primary effectiveness endpoint is greater than 90%.

5.2.2 Sample Size

[REDACTED]

5.2.3 Analysis Population

The analysis population for this endpoint will include enrolled subjects who have also had the TactiCath SE inserted into their vasculature.

5.2.4 Subgroup Analysis

Subgroup analyses will be performed to examine the consistency of results for the primary effectiveness endpoint. Analysis will be based on Fisher's exact test. No subgroup specific labeling claims are desired for this endpoint and no adjustments for multiplicity will be made. Subgroups to be examined include, but are not limited to, those defined by age (both <65 vs ≥65 and age ≥ median vs < median), sex, and race/ethnicity.

5.3 Justification of Clinical Investigation Design

This is a prospective, multi-center, single-arm clinical trial to demonstrate the acute safety and effectiveness of the TactiCath SE catheter for the treatment of PAF against two performance goals. This clinical investigation will be conducted under an investigational device exemption (IDE) and is intended to support market approval of the TactiCath SE ablation catheter in the United States. **[REDACTED]**

5.4 Adjustment for Multiple Testing

Both primary endpoints must pass hypothesis testing for the trial to be a success. Descriptive endpoints and subgroup analyses are not intended to support labeling claims. Therefore, multiplicity adjustment is not applicable.

5.5 Overall Sample Size

[REDACTED]

5.6 Timing of Analysis

The primary endpoint analysis will be performed and the pre-market approval (PMA) clinical report will be submitted when 140 subjects have data available to assess the primary safety and effectiveness endpoints.

5.7 Trial Success

The trial will be considered successful if the null hypotheses for both the primary safety and effectiveness endpoints are rejected.

5.8 Interim Analysis

No interim analysis is planned for this clinical investigation.

5.9 Statistical Critieria for Termination

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

6 DESCRIPTIVE ENDPOINTS AND ADDITIONAL DATA

Ten descriptive endpoints will be summarized for completeness and supportive information.

6.1 Descriptive Endpoint #1:

Descriptive endpoint #1 is ablation data collected during the procedure, including:

- Power
- Temperature
- Irrigation flow rate
- Contact force
- Procedure time
- Total ablation time
- Total fluoroscopy time
- Total RF application time
- Usage of Automark

6.1.1 Analysis Methodology

Descriptive statistics will be generated for all variables.

6.1.2 Analysis Population

The analysis population for this endpoint will include all enrolled subjects who have also had the TactiCath SE inserted into their vasculature and radiofrequency energy was delivered.

6.2 Descriptive Endpoint #2:

Descriptive endpoint #2 is the proportion of index cases achieving ≥ 90% lesions with ≥10g contact force. Corresponding exact two-sided 95% binomial confidence intervals will also be calculated.

6.2.1 Analysis Methodology

Subjects with at least 90% of lesions with ≥10g achieved will be divided by the analysis population. Corresponding exact two-sided 95% binomial confidence intervals will also be calculated.

6.2.2 Analysis Population

The analysis population for this endpoint will include all enrolled subjects who have also had the TactiCath SE inserted into their vasculature and radiofrequency energy was delivered.

6.3 Descriptive Endpoint #3:

Descriptive endpoint 3 is defined as serious adverse events and adverse events related the device and/or ablation catheter through 30 days post ablation.

6.3.1 Analysis Methodology

The number and percentage of subjects experiencing adverse events will be summarized, by seriousness and relatedness. Corresponding exact two-sided 95% binomial confidence intervals will also be calculated. Subjects who terminate the study prematurely without experiencing any adverse events through 30 days post ablation will not be considered as having any events for this analysis.

6.3.2 Analysis Population

The analysis population for this endpoint will include all enrolled subjects who have also had the TactiCath SE inserted into their vasculature.

6.4 Descriptive Endpoint #4:

Descriptive endpoint 4 is defined as serious adverse events and adverse events related the device and/or ablation catheter through 1 year post ablation.

6.4.1 Analysis Methodology

The number and percentage of subjects experiencing adverse events will be summarized, by seriousness and relatedness. Corresponding exact two-sided 95% binomial confidence intervals will also be calculated. Subjects who terminate the study prematurely without experiencing any adverse events through 1 year post ablation will not be considered as having any events for this analysis.

6.4.2 Analysis Population

The analysis population for this endpoint will include all enrolled subjects who have also had the TactiCath SE inserted into their vasculature.

6.5 Descriptive Endpoint #5

Descriptive endpoint #5 is one-year success, defined as freedom from symptomatic AF/AFL/AT lasting at least 30 seconds without a new Class I or III AAD or a higher dosage of pre-existing AAD as assessed from the end of the 3-month blanking period to 12 months following the ablation procedure.

A full 10-second 12-lead ECG recording may also count as a failure unless there is evidence that the recorded arrhythmia is short-lived and less than 30 seconds.

6.5.1 Analysis Methodology

Freedom from AF will be calculated as the number of subjects without a failure as defined in section 6.5 divided by the total number of subjects in the analysis population. Corresponding exact two-sided 95% binomial confidence intervals will also be calculated.

6.5.2 Analysis population

The analysis population for this endpoint will include all enrolled subjects who have also had the TactiCath SE inserted into their vasculature and who have completed their 1-year visit or crossed the 1-year visit window without the visit but with an event as defined above for the descriptive endpoint #5.

6.5.3 Subgroup Analysis

The following subgroups will be evaluated for the analysis population as defined in section 6.5.2.

- Subjects who also meet descriptive endpoint #2 (achieving ≥ 10g contact force)
- Achieving ≥ 90% lesions with ≥10g contact force (Yes vs No)
- Agilis (Yes vs No)

For the comparison between two subgroups, the analysis might be performed if there are at least 30 subjects in each group. Analysis will be based on Fisher's exact test.

6.6 Descriptive Endpoint #6

Descriptive endpoint #6 is one-year drug-free success, defined as freedom from any AF/AFL/AT lasting at least 30 seconds or any Class I or III AAD after removal from antiarrhythmic drug therapy as assessed from the end of the 3-month blanking period to 12 months following the ablation procedure.

A full 10-second 12-lead ECG recording of arrhythmia may be substituted for a 30-second recording unless there is evidence that the recorded arrhythmia is short-lived and less than 30 seconds.

6.6.1 Analysis Methodology

Freedom from AF will be calculated as the number of subjects without a failure as defined in section 6.6 divided by the total number of subjects in the analysis population. Corresponding exact two-sided 95% binomial confidence intervals will also be calculated.

6.6.2 Analysis Population

The analysis population for this study will be based on all subjects in whom a study device was introduced and who have completed their 1-year visit or crossed the 1-year visit window without the visit but with an event as defined above for the descriptive endpoint #6.

6.6.3 Subgroup Analysis

The following subgroups will be evaludated for the analysis population as defined in section 6.6.2.

- Subjects who are also off of antiarrhythmic medication at the end of the blanking period.
- Subjects who also meet descriptive endpoint #2 (achieving ≥ 10g contact force).
- Achieving ≥ 90% lesions with ≥10g contact force (Yes vs No)
- Agilis (Yes vs No)

For the comparison between two subgroups, the analysis might be performed if there are at least 30 subjects in each group. Analysis will be based on Fisher's exact test.

6.7 Descriptive Endpoint #7

Descriptive endpoint #7 is change in EQ-5D-5L scores from baseline to follow up at 3, 6, and 12 months.

6.7.1 Analysis Methodology

Changes in EQ-5D-5L score between baseline and follow up visits will be summarized with descriptive statistics. Scores will be used to calculate utility values and QALYs.

6.7.2 Analysis Population

The analysis population for this endpoint will include all enrolled subjects who have also had the TactiCath SE inserted into their vasculature, have a baseline EQ-5D-5L, and who have completed their applicable follow up visit.

6.8 Descriptive Endpoint #8

Descriptive endpoint #8 is change in AFEQT scores from baseline to follow up at 3, 6, and 12 months.

6.8.1 Analysis Methodology

Changes in AFEQT between baseline and follow up visits will be summarized with descriptive statistics to assess change in functional improvement.

6.8.2 Analysis Population

The analysis population for this endpoint will include all enrolled subjects who have also had the TactiCath SE inserted into their vasculature, have a baseline AFEQT, and who have completed their applicable follow up visit.

6.9 Descriptive Endpoint #9

Descriptive endpoint #9 is cardiovascular-related health care utilization through 12 months post index ablation.

6.9.1 Analysis Methodology

Descriptive statistics will be generated for all variables.

6.9.2 Analysis Population

The analysis population for this endpoint will include all enrolled subjects who have also had the TactiCath SE inserted into their vasculature and who have health care utilization data available.

6.10 Descriptive Endpoint #10

Descriptive endpoint #10 is force time integral (FTI) and lesion index (LSI).

6.10.1 Analysis Methodology

FTI and LSI will be derived from the from the available Ensite Precision data. Descriptive statistics will be generated for both variables.

6.10.2 Analysis Population

The analysis population for this endpoint will include all enrolled subjects who have also had the TactiCath SE inserted into their vasculature.

6.11 Baseline and Demographic Characteristics

Descriptive statistics of continuous variables will be presented and will include number of subjects, mean, median, standard deviation, minimum and maximum. For categorical variables, the number and percentage of subjects in each category will be presented as appropriate. Baseline characteristics will be tabulated. As needed and appropriate, categorical variables will be tested using Fisher's exact test and continuous variables will be tested using two sample t-test.

6.12 Mortality

The number and causes of deaths will be summarized.

6.13 Withdrawal

Withdrawal from the study and reasons for withdrawal will be summarized.

6.14 Protocol Deviation

Protocol deviations will be summarized for subjects in whom protocol deviations are reported.

There is no plan to deviate from this Statistical Analysis Plan. If any deviations from the original statistical plan occur, such deviations will be documented in the clinical study report or statistical report containing the analysis results.

7 REVISION DESCRIPTION

[REDACTED]