Abbott	Statistical Analysis Plan Cover Page

NCT Number: NCT03650556
PERSIST-END Trial
Safety and Effectiveness of TactiCath™ Contact Force, Sensor Enabled™ (TactiCath SE) Catheter for Ablation of Drug Refractory, Symptomatic, Persistent Atrial Fibrillation Statistical Analysis Plan
Version F
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Sponsor

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CRD 901
PERSIST-END

Safety and Effectiveness of TactiCath Contact Force, Sensor Enabled (TactiCath SE) Catheter for Ablation of Drug Refractory, Symptomatic, Persistent Atrial Fibrillation

Statistical Analysis Plan (SAP)

[redacted]

[redacted]

[redacted]

[redacted]

Statistical Analysis Plan

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Statistical Analysis Plan

1.0 SYNOPSIS OF STUDY DESIGN

1.1 Purpose of the Statistical Analysis Plan

This statistical analysis plan (SAP) is intended to provide a detailed and comprehensive description of the planned methodology and analysis to be used for the CRD 901 PERSIST-END clinical investigation. [redacted]

1.2 Clinical Investigation Objectives

The objective of this clinical trial is to demonstrate that ablation with the TactiCath™ Contact Force Ablation Catheter, Sensor Enabled™ (TactiCath SE) is safe and effective for the treatment of drug refractory, symptomatic persistent atrial fibrillation (AF) when following standard electrophysiology mapping and radiofrequency (RF) ablation procedures.

1.3 Clinical Investigation Design

This is a prospective, single-arm, multi-center IDE clinical trial to evaluate the safety and effectiveness of ablation with the TactiCath SE catheter for the treatment of drug refractory, symptomatic persistent AF compared to a predetermined performance goal. A total of 224 subjects will be enrolled at up to 25 investigational sites worldwide.

[redacted] Subjects will be followed for 15 months after their initial ablation procedure. The 15-month follow-up includes a 90-day blanking period and 90-day therapy consolidation period followed by a 9-month follow-up period. The primary endpoints will be evaluated when all subjects have completed their 15-month follow-up visit. [redacted] The pre-market approval (PMA) clinical report will be prepared after the last subject has completed their final follow-up visit or has passed the end of their final follow-up visit window.

1.4 Endpoints

1.4.1 Primary Safety Endpoint(s)

The primary safety endpoint is the rate of device and/or procedure-related serious adverse events with onset within 7-days of any ablation procedure that uses the TactiCath SE catheter (initial or repeat procedure performed ≤180 days of initial procedure) that are defined below:

- Atrioesophageal fistula*
- Cardiac tamponade/perforation*
- Death
- Heart block
- Myocardial infarction (MI)
- Pericarditis^
- Phrenic nerve injury resulting in diaphragmatic paralysis
- Pneumothorax
- Pulmonary edema (respiratory insufficiency)
- Pulmonary vein stenosis*

- Stroke/cerebrovascular accident (CVA)
- Thromboembolism
- Transient ischemic attack
- Vascular access complications (including major bleeding events#)

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* Atrioesophageal fistula, cardiac tamponade/perforation and pulmonary vein stenosis will be evaluated through 15-months.
^ Pericarditis is a common occurrence for almost all procedures and will only be considered a primary safety endpoint event if the pericarditis pleuritic symptoms last longer than 7-days and/or requires hospitalization of greater than 24 hours for reasons other than for observational purposes only.
# Bleeding is a major complication of AF ablation if it requires and/or is treated with transfusion or results in a 20% or greater fall in hematocrit.

Serious AF/atrial flutter (AFL)/atrial tachycardia (AT) recurrences without coexisting conditions (e.g. thromboembolism, worsening heart failure, etc.) will be counted as effectiveness failures but will not count against the primary safety endpoint.

1.4.2 Primary Effectiveness Endpoint(s)

The primary effectiveness endpoint for this clinical trial is freedom from AF/AFL/AT episodes of >30 seconds duration that is documented by an ECG (12-lead or TTM) or 24-hour Holter after the initial catheter ablation procedure through 15-months of follow-up (includes a 90-day blanking period followed by a 90-day therapy consolidation period). AF/AFL/AT recurrence during the blanking or therapy consolidation periods will not be considered a treatment failure. One repeat procedure is allowed for ablation of AF/AFL/AT recurrence during the blanking or therapy consolidation period (≤180 days post-initial procedure) without being considered a treatment failure.

AF/AFL/AT recurrence will only be assessed by 12-lead ECG, TTM, and 24-hour Holter monitoring devices for assessment of this primary endpoint so that all subjects are monitored equally with devices of the same sensitivity and specificity. Collected ECG, TTM, and 24-hour Holter data from sites will be evaluated by a physician at a core laboratory for independent and unbiased assessment of AF recurrence for endpoint analysis.

There are multiple situations in which subjects will be considered primary effectiveness endpoint failures:

- If AF/AFL/AT recurrence (>30 second episode) occurs at any time after the therapy consolidation period (>180 days after the initial procedure), or
- If the subject requires a repeat procedure for the treatment of AF after the therapy consolidation period, the subject will be considered an effectiveness endpoint failure regardless of documentation of a >30 second AF/AFL/AT episode, or
- If the subject requires a second repeat procedure at any time after the initial procedure, or
- If the subject requires a new AAD or a previously failed AAD at a dose greater than the highest ineffective historical dose for AF after the therapy consolidation period, or
- If the subject requires a cardioversion (electrical or pharmacological) for the treatment of AF after the therapy consolidation period, or
- If the subject has a continuous atrial arrhythmia throughout a 12-lead ECG recording after the therapy consolidation period to indicating arrhythmia recurrence, this will be considered sufficient documentation of recurrence unless there is evidence that the recorded arrhythmia is short-lived and less than 30 seconds.

As cavotricuspid isthmus-dependent atrial flutter is easily treated with cavotricuspid isthmus ablation and is not an iatrogenic arrhythmia following a left atrial ablation procedure for AF, occurrence of cavotricuspid isthmus-dependent atrial flutter confirmed by entrainment maneuvers that occurs at any time during the follow-up period

and is ablated, will not be considered a primary effectiveness endpoint failure.

1.4.3 Secondary Endpoint(s)

1.4.3.1 Achievement of acute procedural success

Proportion of subjects who achieve acute procedural success [redacted] for subjects who had the investigational catheter inserted into their vasculature, where acute procedural success is defined as confirmation of entrance block in all pulmonary veins.

1.4.3.2 Chronic success off antiarrhythmic drugs

Proportion of subjects off all AADs taken for the treatment of AF who achieve 15-month success [redacted], defined as freedom from documented AF/AFL/AT recurrence (episodes >30 seconds) during the 9-month period following the blanking and therapy consolidation periods.

1.4.3.3 15-month single procedure success – freedom from asymptomatic and symptomatic AF/AFL/AT recurrence

Proportion of subjects who achieve 15-month single procedure success [redacted], defined as freedom from documented AF/AFL/AT (episodes >30 seconds) during the 9-month period following the blanking and therapy consolidation periods after a single ablation procedure. Any repeat ablation procedure required by the subject at any time will be deemed an effectiveness failure in this analysis.

1.4.4 Additional Data

Additional data to be collected in this clinical investigation are described and will be reported using summary statistics, including but not limit to the following:

1) Procedure- and/or ablation catheter-related adverse events throughout the 15-month follow-up period
2) Success (defined as freedom from >30 second documented episodes of AF/AFL/AT recurrence) without Class I or III AAD dose increase from the historic maximum ineffective dose (prior to the ablation procedure) or initiation of a new Class I or III AAD for arrhythmia recurrence after the blanking and therapy consolidation periods.
3) Proportion of subjects who achieve 15-month symptomatic single procedure success (defined as freedom from >30 second documented symptomatic episodes of AF/AFL/AT recurrence) after the blanking and therapy consolidation periods.
4) Cardiovascular-related health care utilization through 15-months after the initial procedure.
5) Procedure data, including but not limited to, ablation data, mapping data, and usage of Automark.
6) Proportion of cases achieving ≥ 90% lesions with ≥10g of contact force.
7) Evaluation of procedure data to determine target lesion index (LSI) value(s) as assessed by AF/AFL/AT recurrence.
8) Changes in EQ-5D-5L and AFEQT scores from baseline to follow up at 3, 6, 12, and 15-months after the initial procedure.
9)

1.5 Randomization

[redacted].

1.6 Blinding

[redacted]

2.0 ANALYSIS CONSIDERATIONS

2.1 Analysis Populations

[redacted]

2.1.1 [redacted]

[redacted]

2.1.2 [redacted]

[redacted]

[redacted]

[redacted]

2.2 Statistical Methods

Descriptive analysis will be performed to summarize baseline, procedural, and safety event data. Depending on the type of data (e.g., continuous or categorical), appropriate statistical methods described in the section below will be used.

2.2.1 Descriptive Statistics for Continuous Variables

For continuous variables, such as age, results will be summarized with the numbers of observations, means, and standard deviations, and if specified in the table mockups, with quartiles, minimums, maximums, and 95% confidence intervals for the means. When performing subgroup analyses, differences between the two groups, where specified, will be summarized with the differences of the two means, and 95% confidence intervals for the difference between the means. These calculations will be done under the assumption that data for the two groups are independent and approximately normally distributed. The confidence interval for the difference of two means will be calculated under the assumption of unequal variances. If the asymptotic assumptions fail, then nonparametric summary statistics (medians, 25th and 75th percentile) may be displayed as an alternative (Appendix F).

2.2.2 Descriptive Statistics for Categorical Variables

For binary variables (e.g. gender, diabetic status, etc.), results will be summarized with patient counts and percentages/rates with exact 95% Clopper-Pearson confidence intervals. When performing subgroup analyses, differences between the two groups, when specified, will be summarized with the difference in percent and the Newcombe[3] score 95% confidence interval for the difference of two percentages (Appendix G).

2.2.3 Categorical variable effect analysis

The effect of categorical variable on binary outcome (i.e. primary safety endpoint, primary effectiveness endpoint) will be analyzed using a logistic regression model.

Summary tables for each category in the categorical variable will include odds ratios and confidence intervals.

2.3 Endpoint Analysis

2.3.1 Primary Endpoint(s)

2.3.1.1 Primary Safety Endpoint

The primary safety endpoint is the rate of device and/or procedure-related serious adverse events with onset within 7 days of any ablation procedure (initial or repeat procedure)

The primary safety endpoint hypothesis is stated as follows:

[redacted]

- [redacted]

[redacted]

[redacted]

[redacted].

2.3.1.2 Primary Effectiveness Endpoint

The primary effectiveness endpoint for this clinical trial is freedom from AF/AFL/AT episodes of >30 seconds duration that is documented by an ECG (12-lead or TTM) or 24-hour Holter after the initial catheter ablation procedure through 15 months of follow-up.

The hypothesis is formally expressed as:

[redacted]

[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

[redacted]

[redacted]

2.3.2 Secondary Endpoints

2.3.2.1 Achievement of Acute Procedural Success

The secondary endpoint is the proportion of subjects who achieve acute procedural success at the end of the initial procedure; where acute procedural success is defined as confirmation of entrance block in all pulmonary veins.

The hypothesis is stated as follows:

[redacted]

[redacted]

[redacted]

2.3.2.2 Chronic Success Off Antiarrhythmic Drugs

This secondary endpoint is chronic success off antiarrhythmic drug; where chronic success is defined as freedom from documented AF/AFL/AT recurrence (episodes >30 seconds) during the 9-month period following the blanking and therapy consolidation periods.

The hypothesis is stated as follows:

[redacted]

[redacted]

[redacted]

2.3.2.3 Asymptomatic and Symptomatic Single Procedure Success

This secondary endpoint is asymptomatic or symptomatic single procedure success; where single procedure success is defined as freedom from all documented AF/AFL/AT recurrence of >30 seconds.

The hypothesis is stated as follows:

[redacted]

2.4 Sample Size Calculations

[redacted]

2.4.1 [redacted]

[redacted]

2.4.2 [redacted]

[redacted]

[redacted]

2.5 Interim Analysis

[redacted]

2.6 Timing of Analysis

The primary endpoint analysis will be performed and the pre-market approval (PMA) clinical report will be submitted after the last subject has completed the 15-month follow-up or passed the end of their 15-month visit window.

2.7 Study/Trial Success

[redacted]

2.8 Subgroups for Analysis

Subgroup analyses will be performed to examine the consistency of results for the primary safety and effectiveness endpoints. [redacted]

2.9 Handling of Missing Data

[redacted]

2.10 Poolability Analysis

[redacted]

2.11 Multiplicity Issues

[redacted]

2.12 Adjustments for Covariates

Unless otherwise specified, no adjustments for covariates will be made for any of the variables in the analyses.

2.13 Sensitivity Analysis

2.13.1 Missing Data

[redacted]

[redacted]

2.13.2 Protocol Compliance

[redacted]

2.13.3 Covid-19

To assess the impact of Covid-19 on primary safety endpoint and primary effectiveness endpoint, the following sensitivity analyses will be performed on the PTE population:

- Primary safety endpoint

[redacted]

- Primary effectiveness endpoint

[redacted]

3.0 ADDITIONAL INFORMATION

3.1 Baseline and Demographic Characteristics

The following baseline and demographic variables, including but not limited to: gender, age, ethnicity, race, cardiac disease history, arrhythmia history, etc. will be summarized for subjects in PTE analysis population.

3.2 Adverse Events

Safety surveillance and reporting starts as soon as the patient is enrolled in the clinical investigation. Adverse event data, including deaths, will be collected starting at the time of consent and throughout the 15-month follow-up period and will be reported to the Sponsor on the Adverse Event CRF. Safety surveillance and reporting will continue until the last follow-up visit has been performed, the subject is deceased, the subject concludes participation in the clinical investigation or the subject withdraws from the clinical investigation.

For the purposes of this clinical investigation, the following adverse events will be reported:

- Adverse events that are adjudicated by the investigator as being related to either the ablation catheter or the ablation procedure
- Serious adverse events, regardless of relatedness to the procedure and/or the ablation catheter

Recurrence of AF, AFL, or AT are not considered reportable adverse events unless they occur in severity, frequency, or other manner that is significantly worse than the subject's baseline condition. Recurrence of AF, AFL, or AT will affect the primary effectiveness endpoint and should be reported on the Follow-Up Visit CRF.

Additionally, urinary tract infections (UTIs) that occur after a procedure and do not require a Foley catheter will not be considered adverse events. UTIs that require a Foley catheter will be reported as AEs if related to the procedure or meet serious criteria.

Unchanged, chronic, non-worsening or pre-existing conditions are not AEs and should not be reported.

All adverse events (AEs), adverse device effects (ADEs), serious adverse events (SAEs), serious adverse device effects (SADEs), and unanticipated adverse device effect (UADEs) will be summarized for all subjects enrolled in this trial in terms of the number of events and the percentage of subjects with events.

CEC adjudicated results will be used for analysis. The investigator adjudicated results will be summarized in the final report.

AEs from the FAS population will be summarized separately for subjects who were consented but did not have an investigational catheter inserted into their vasculature from those subjects who are in the PTE population.

3.3 Subject Early Termination

Subject early termination reasons including deaths, withdrawals, and lost-to-follow-up and will be summarized from the time the subject meets eligibility criteria (after consent) throughout the 15-month trial follow-up period.

3.4 Protocol Deviation

Protocol deviations will be summarized by deviation categories for subjects in whom a protocol deviation was reported.

4.0 DOCUMENTATION AND OTHER CONSIDERATIONS

All analyses will be performed using SAS® for Windows, version 9.2 or higher.

5.0 ACRONYMS AND ABBREVIATIONS

Acronym or Abbreviation	Complete Phrase or Definition
AF	Atrial fibrillation
AFL	Atrial flutter
AT	Atrial tachycardia
AE	Adverse Event
ADE	Adverse device effect
AAD	Antiarrhythmic drug
APHRS	Asian Pacific Heart Rhythm Society
AFEQT	Atrial fibrillation effect on Quality-of-life
CEC	Clinical Events Committee
CIP	Clinical Investigation Plan
CRF	case report form
CVA	Cerebrovascular accident
ECG	Electrocardiography
EHRA	European Heart Rhythm Association

Acronym or Abbreviation	Complete Phrase or Definition
ECAS	European Cardiac Arrhythmia Society
HRS	Heart Rhythm Society
LSI	Lesion size index
MI	Myocardial Infarction
OPC	Optimal Performance
PG	Performance goal
PMA	Pre-market approval
PP	Per Protocol
PTE	Per-treatment evaluable
RF	Radiofrequency
TTM	Transtelephonic monitoring
SADE	Serious adverse device effect
SAE	serious adverse event
SAP	Statistical analysis plan
SOLAECE	Sociedad Latinoamericana de Estimulación Cardíaca y Electrofisiología
UTI	Urinary tract infection
UADE	Unanticipated adverse device effect

6.0 REFERENCES

[redacted]

7.0 APPENDICES

APPENDIX A: CLINICIAL RATIONALE FOR PRIMARY SAFETY ENDPOINT

[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]

[redacted]

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	
[redacted]			[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

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[redacted]

APPENDIX B: CLINICIAL RATIONALE FOR PRIMARY EFFECTIVENESS ENDPOINT

[redacted]

[redacted]

APPENDIX C: CLINICIAL RATIONALE FOR SECONDARY ENDPOINT – ACUTE PROCEDURAL SUCCESS

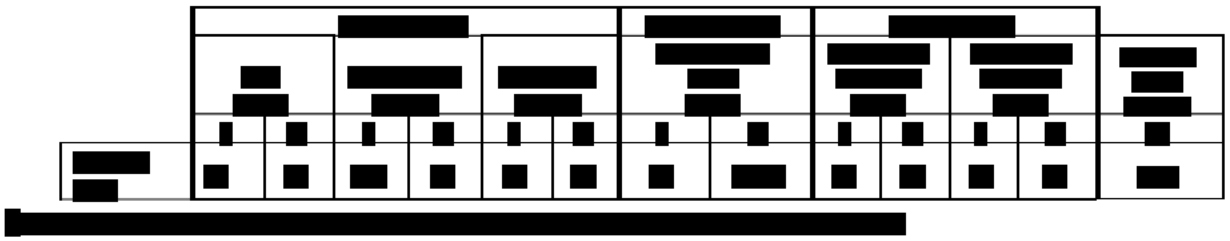
[redacted]

[redacted]

APPENDIX D: CLINICIAL RATIONALE FOR SECONDARY ENDPOINT – ASYMPTOMATIC AND SYMPTOMATIC SINGLE PROCEDURE SUCCESS

It is known that asymptomatic AF represents a greater proportion of all AF post-ablation than prior to ablation. Therefore, catching potential AF recurrence prior to the patient experiencing symptoms would be important for determining the effectiveness of ablation, which is the reason for assessing this as a secondary endpoint.

[redacted]



[redacted]

APPENDIX E: CLINICIAL RATIONALE FOR SECONDARY ENDPOINT – CHRONIC SUCCESS OFF ANTIARRHYTHMIC DRUGS

[redacted]