[redacted]

TactiFlex PAF IDE

Safety and Effectiveness of TactiFlex™ Ablation Catheter, Sensor Enabled™ (TactiFlex SE) for the Treatment of Drug Refractory, Symptomatic, Paroxysmal Atrial Fibrillation

Statistical Analysis Plan (SAP)

[redacted]

April 15, 2020

[redacted]

[redacted]

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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 [redacted], the [redacted] TactiFlex PAF IDE clinical investigation. [redacted]

1.2 Clinical Investigation Objectives

1.2.1 Primary Objective

The primary objective of the TactiFlex PAF IDE clinical trial is to demonstrate that ablation with the TactiFlex Ablation Catheter, Sensor-Enabled™ (TactiFlex SE), in conjunction with a compatible RF generator and three-dimensional mapping system, is safe and effective for the treatment of drug refractory, symptomatic paroxysmal atrial fibrillation (PAF) when following standard electrophysiology mapping and radiofrequency (RF) ablation procedures.

1.2.2 Secondary Objectives

The TactiFlex PAF IDE clinical trial has two secondary objectives:

1. To provide supporting data for the safety and effectiveness of using TactiFlex SE at 40-50 Watts in the left atrium as part of an AF ablation procedure.
2. To provide supporting data for the safety and effectiveness of using TactiFlex SE to treat cavo-tricuspid isthmus (CTI)-dependent (or "typical") atrial flutter (AFL) through the ablation of the CTI in the right atrium. This data may be used to support an expanded indication for the treatment of CTI-dependent AFL.

1.3 Clinical Investigation Design

This is a prospective, non-randomized, multi-center pivotal clinical trial to evaluate the safety and effectiveness of ablation with the TactiFlex SE catheter for the treatment of PAF compared to pre-determined performance goals. The study design includes a substudy to assure that there will be at least 50 subjects ablated at the high-end of the ablation power setting recommendations in the investigational *Instructions for Use* document. Subjects in the HSP (High Standard Power) substudy are to undergo the same study procedures as subjects in the main study, except that ablation power settings of 40-50 Watts are to be used in the left atrium, unless there is a medical reason to use a lower power. Operators will be assigned to either the main study or the HSP substudy based on the ablation power settings they currently use in their standard practice. Subjects will be enrolled in either the main study or the substudy at the point of consent based on the operator that is expected to perform their ablation procedure. After the substudy has enrolled 50 subjects, or if the Sponsor has provided written permission, HSP operators may transition to the main study and treat main study subjects. No site may enroll more than 10 subjects (20%) in the HSP substudy without Sponsor pre-approval and at least 25 HSP substudy subjects (50%) must be from the United States.

Up to 40 sites worldwide will participate in the TactiFlex PAF IDE clinical study. The TactiFlex IDE Clinical Study will enroll a total of 355 subjects. Fifty (50) subjects will be enrolled in the HSP Substudy and 305 subjects will be enrolled in the Main Study. No center may contribute more than 20% (N=61) of

the total number of enrollments in the main study without Sponsor pre-approval. At least 50% (N=153) of the subjects will be from the US.

[redacted] Subjects will be followed for 12-months after their initial ablation procedure. The primary and secondary endpoints will be evaluated when all subjects have completed their 12-month follow-up visit. [redacted] All adverse events (AEs), with logical exceptions, from the point of enrollment through study exit will be documented and reported. A Clinical Event Committee (CEC) will be used to adjudicate all AEs that are determined by the Sponsor to potentially meet the criteria of 1) a serious AE and/or 2) an AE related to the investigational devices or ablation procedure.

The clinical investigation has been designed to involve as little pain, discomfort, fear, and any other foreseeable risk as possible for subjects. Refer to the Risks Analysis section of the clinical investigation plan for details.

1.4 Endpoints

1.4.1 Primary Endpoints

1.4.1.1 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 that uses the TactiFlex SE catheter (initial or repeat procedure performed 31-80 days of initial procedure) that are defined below:

- Atrio-esophageal fistula[1]
- Cardiac tamponade/perforation[1]
- Death
- Heart block
- Myocardial infarction
- Pericarditis
- Phrenic nerve injury resulting in diaphragmatic paralysis
- Pulmonary edema
- Pulmonary vein stenosis[1]
- Stroke/cerebrovascular accident
- Thromboembolism
- Transient ischemic attack
- Vagal nerve injury/gastroparesis
- Vascular access complications (including major bleeding events[2])

1. Atrio-esophageal fistula, cardiac tamponade/perforation and pulmonary vein stenosis will be evaluated through 12-months.
2. 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.

These events must meet the criteria listed in **Appendix A** to be included in the primary endpoint as adjudicated by the clinical events committee (CEC).

The performance goal is set at [redacted] as determined by relevant studies for PAF that utilize radiofrequency ablation.

1.4.1.2 Primary Effectiveness Endpoint

The primary effectiveness endpoint for this clinical trial is freedom from documented (symptomatic or asymptomatic) AF/AFL/AT episodes of >30 seconds duration that are documented by 12-lead ECG, transtelephonic monitoring (TTM) or Holter monitor after the initial catheter ablation procedure through 12-months of follow-up (9 months after a 90-day blanking period).

AF/AFL/AT recurrence during the 90-day blanking period (≤90 days post-initial procedure) will not be considered a treatment failure. One repeat procedure will be allowed for ablation of AF/AFL/AT recurrence 31-80 days after the initial procedure and will not be considered a treatment failure. Failure to achieve acute procedural success (confirmation of entrance block after a 20-minute minimum waiting period) during the last ablation procedure[1] with the TactiFlex SE catheter will constitute failure to achieve this endpoint. After the 90-day blanking period, use of Class I or III AADs will not count as a therapy failure provided that only previously failed Class I or III AADs are taken at doses that do not exceed the previously failed dose.

AF/AFL/AT recurrence will only be assessed by 12-lead ECG, TTM, and Holter monitoring devices for assessment of this primary endpoint so that all subjects are monitored equally with devices of the same sensitivity and specificity (recurrence data collected from other devices such as pacemakers, ICDs, or ICMs will not be included in the assessment). ECG, TTM, and Holter data collected from sites will be evaluated by a core laboratory to ensure independent and unbiased assessment of AF/AFL/AT recurrence for endpoint analysis.

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

- If the subject fails to achieve acute procedural success, defined as confirmation of entrance block in all pulmonary veins after a minimum waiting period of 20-minutes, during last ablation procedure performed with the TactiFlex SE catheter, or
- If documented AF/AFL/AT recurrence (>30 second episode) occurs at any time after the blanking period (>90 days after the initial procedure), or
- If the subject requires a repeat procedure for the treatment of AF >80 days after the initial procedure, 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 AF ablation procedure ≤80 days after the initial procedure, or
- Any use of a new class I or III AAD for AF after the blanking period, or
- Any use of a class I or III ADD for AF at a dose higher than that previously failed by the patient, or
- If the subject requires a cardioversion (electrical or pharmacological) for the treatment of AF after the blanking period, or
- If the subject has a continuous atrial arrhythmia throughout a 12-lead ECG recording after the blanking period indicating AF/AFL/AT 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 determined by the investigator, or
- Any ablation in the left atrium using an ablation catheter other than TactiFlex SE.

[1] For subjects that have a repeat ablation procedure ≤80 days after the initial procedure, only failure to achieve acute procedural success during the repeat procedure will contribute to primary effectiveness endpoint.

Cavotricuspid isthmus (CTI)-dependent AFL that occurs alone either during or after the blanking period will be considered an exception to being considered a recurrence, as CTI-dependent AFL is easily treated with cavotricuspid isthmus ablation and is not an iatrogenic arrhythmia following a left atrial ablation procedure for AF. Occurrence of CTI-dependent AFL 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.

Counting the use of new or higher than previously failed doses of AADs after the blanking period as effectiveness failures is consistent with the primary effectiveness endpoint recommendations in the FDA Guidance on Clinical Study Designs for Percutaneous Catheter Ablation for the Treatment of Atrial Fibrillation [14].

1.4.2 Powered Secondary Endpoints

1.4.2.1 AAD-Free Secondary Effectiveness Endpoint

The AAD-Free Secondary Effectiveness Endpoint has the same definition as the Primary Effectiveness endpoint, except that any use of Class I or III AADs after the 90-day blanking period will count as a therapy failure in this analysis.

1.4.2.2 Single-Procedure Secondary Effectiveness Endpoint

The Single-Procedure Secondary Effectiveness Endpoint has the same definition as the Primary Effectiveness endpoint, except that any repeat ablation in the left atrium will count as a failure.

1.4.2.3 Symptomatic Secondary Effectiveness Endpoint

The Symptomatic Secondary Effectiveness Endpoint has the same definition as the Primary Effectiveness Endpoint, except that episodes of documented recurrence without documented evidence of symptoms after the 90-day blanking period will not count as a therapy failure in this analysis.

1.4.3 Additional Data

The following additional data will be collected and reported using only summary statistics and no hypothesis tests with pre-specified criteria will be performed. These Additional Data will be reported separately for main study subjects and HSP substudy subjects. An as treated analysis will be conducted as specified in Section 1.4.4.

1. Proportion of subjects who achieve acute procedural success during the initial ablation procedure, where acute procedural success is defined as confirmation of entrance block in all pulmonary veins after a minimum waiting period of 20-minutes.
2. Proportion of subjects with successful first-pass PV isolation during the initial ablation procedure, defined as confirmation of entrance block in all pulmonary veins following the initial minimum waiting period of 20-minutes.
3. Proportion of subjects who experience any adverse event (AE)
4. Proportion of subjects who experience any serious adverse event (SAE)
5. Proportion of subjects that experience any procedure- and/or ablation catheter-related adverse event (AE) throughout the 12-month follow-up period.
6. Proportion of subjects requiring one or more repeat AF ablations at 12 months following the initial AF ablation procedure.

7. Changes in EQ-5D-5L and AFEQT scores from baseline to follow up at 3, 6, and 12-months after the initial procedure.
8. Procedure data, including but not limited to, ablation data, mapping data, usage of HD Grid, usage of AutoMark, target contact force, power setting data, procedure time, fluoroscopy time, total RF time, time to perform initial PVI, and ablation lesions performed in addition to PVI.
9. Proportion of subjects treated for concomitant typical AFL with the TactiFlex SE catheter
10. Proportion of subjects treated for typical AFL with no recurrent AFL at 3, 6 and 12 months.
11. Proportion of subjects that received CTI ablation with the TactiFlex SE catheter.
12. Proportion of subjects that received CTI ablation that achieved bi-directional block.
13. Evaluation of procedure data to determine target contact force as assessed by AF/AFL/AT recurrence.
14. Evaluation of the relationship between ablation power with time to perform initial PVI.

1.4.4 HSP Substudy Endpoints

The endpoints for the HSP substudy will be defined the same as the Primary and Secondary Endpoints for the main study. Results will be reported descriptively using summary statistics. No pre-specified hypothesis testing will be performed.

The following as-treated analyses will be performed analyzing the Primary and Secondary Endpoints and the Additional Data described above for main study and HSP substudy subjects (with the exception of Additional Data items 9-12).

1. Results will be summarized separately for subjects that have time-averaged power settings of ≥40 Watts vs. <40 Watts in the left atrium.
2. Results will be summarized separately for subjects that have ≥50% vs. <50% of lesions in the left atrium with power settings ≥40 Watts.
3. Results will be summarized separately for subjects that have ≥25% vs. <25% of lesions in the left atrium with power settings ≥40 Watts.

The rationale for the HSP Substudy is provided in **Appendix I**.

1.5 Randomization

Randomization is not applicable to the clinical investigation.

1.6 Blinding

Blinding is not applicable to the clinical investigation.

2.0 ANALYSIS CONSIDERATIONS

2.1 Analysis Populations

[redacted]

[redacted]

2.1.1 Full Analysis Set (FAS)

[redacted]

2.1.2 Per Treatment Evaluable (PTE) Analysis Population

[redacted]

2.1.3 Primary Safety Analysis Population

[redacted]

2.1.4 Primary Effectiveness Analysis Population

[redacted]

2.1.5 Per Protocol (PP) Analysis Population

[redacted]

2.1.6 As-Treated (AT) Analysis Population

[redacted]

2.2 Statistical Methods

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, medians, 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 B).

2.2.2 Descriptive Statistics for Categorical Variables

For binary variables (e.g. sex, diabetic status, etc.), results will be summarized with patient counts, percentages/rates, and if specified in the table mockups, 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 C).

2.2.3 Survival Analyses

Survival analysis will be conducted to analyze time-to-event variables. Subjects without events will be censored at their last known event-free time point. Survival curves will be constructed using Kaplan-Meier estimates.

[redacted]

2.3 Endpoint Analysis

2.3.1 Primary Endpoints

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 that uses the TactiFlex SE catheter (initial or repeat procedure performed 31-80 days of initial procedure).

The primary safety endpoint hypothesis is stated as follows:

H_0: $P_S \geq$ [redacted]
H_a: $P_S <$ [redacted]

where P_S is the percentage of subjects with a primary safety endpoint event and [redacted] is the performance goal. [redacted]

Events will be adjudicated by the Clinical Events Committee (CEC).

[redacted]

[redacted] The null hypothesis will be rejected if the upper bound of the one-sided 97.5% exact binomial confidence limit for the proportion of subjects with a primary safety endpoint is less than [redacted].

2.3.1.2 Primary Effectiveness Endpoint

The primary effectiveness endpoint for this clinical trial is freedom from documented (symptomatic or asymptomatic) AF/AFL/AT episodes of >30 seconds duration that are documented by 12-lead ECG, transtelephonic monitoring (TTM) or Holter monitor after the initial catheter ablation procedure through 12-months of follow-up (9 months after a 90-day blanking period).

The primary effectiveness endpoint hypothesis is stated as follows:

H_0: $P_E \leq$ [redacted]
H_a: $P_E >$ [redacted]

where P_E is the percentage of subjects free from any primary effectiveness endpoint event and the performance goal (PG) is set at [redacted].

[redacted]

[redacted]

The primary effectiveness endpoint rate will be calculated using the Kaplan-Meier method based on the primary effectiveness analysis population. [redacted]

2.3.2 Secondary Endpoints

2.3.2.1 AAD-Free Secondary Effectiveness Endpoint

The AAD-Free Secondary Effectiveness Endpoint has the same definition as the Primary Effectiveness endpoint, except that any use of Class I or III AADs after the 90-day blanking period will count as a therapy failure in this analysis.

The hypothesis is stated as follows:

H_0: P ≤ [redacted]

H_a: P > [redacted]

where P is the percentage of subjects free from any primary effectiveness endpoint event and/or any use of Class I or III AADs after the 90-day blanking period, and [redacted] is the performance goal (PG). [redacted]

The AAD-Free secondary effectiveness endpoint rate will be calculated using the Kaplan-Meier method based on the primary effectiveness analysis population. [redacted]

2.3.2.2 Single-Procedure Secondary Effectiveness Endpoint

The Single-Procedure Secondary Effectiveness Endpoint has the same definition as the Primary Effectiveness endpoint, except that any repeat ablation in the left atrium will count as a failure.

The hypothesis is stated as follows:

H_0: P ≤ [redacted]

H_a: P > [redacted]

where P is the percentage of subjects free from any primary effectiveness endpoint event and/or any repeat ablation in the left atrium, and [redacted] is the performance goal (PG). [redacted]

The analysis population for this secondary endpoint is the primary effectiveness analysis population. The single-procedure secondary effectiveness endpoint rate will be calculated using the Kaplan-Meier method based on the primary effectiveness analysis population. [redacted]

2.3.2.3 Symptomatic Secondary Effectiveness Endpoint

The Symptomatic Secondary Effectiveness Endpoint has the same definition as the Primary Effectiveness endpoint, except that documented recurrence without documented evidence of symptoms after the 90-day blanking period will not count as a therapy failure in this analysis.

The hypothesis is stated as follows:

H_0: P ≤ [redacted]

H_a: P > [redacted]

where P is the percentage of subjects free from any primary effectiveness endpoint event other than asymptomatic recurrence after the 90-day blanking period, and [redacted] is the performance goal. [redacted]

The analysis population for this secondary endpoint is the primary effectiveness analysis population. The symptomatic secondary effectiveness endpoint rate will be calculated using the Kaplan-Meier method based on the primary effectiveness analysis population. [redacted]

2.4 Sample Size Calculations

[redacted]

2.4.1 Sample Size for Primary Safety Endpoint

[redacted]

2.4.2 Sample Size for Primary Effectiveness Endpoint

[redacted]

2.4.3 Sample Size for AAD-Free Secondary Effectiveness Endpoint

[redacted]

2.4.4 Sample Size for Single-Procedure Secondary Effectiveness Endpoint

[redacted]

2.4.5 Sample Size for Symptomatic Secondary Effectiveness Endpoint

[redacted]

2.5 Interim Analysis

No formal interim analyses are planned for this study. [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 all subjects have exited the clinical investigation.

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

All analyses will be based on available data with missing data excluded unless otherwise specified in the analysis population for each endpoint.

2.10 Poolability Issue

The poolability analysis for the primary safety endpoint and primary effectiveness endpoint will be performed by pooling data across regions (US and OUS) and study sites and will be performed on the Primary Safety Analysis Population for the primary safety endpoint (Section 2.3.1.1) and the Primary Effectiveness Analysis Population for the primary effectiveness endpoint (Section 2.3.1.2) respectively. [redacted]

For the analysis of site effect, sites with enrollment fewer than 10 subjects will be excluded from the poolability analysis. [redacted]

[redacted]

[redacted]

2.11 Multiplicity Issues

Since the trial will be considered successful if the null hypotheses for both the primary safety and effectiveness endpoints are rejected, no adjustment for multiplicity will be made for analysis for the primary endpoints.

[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 Analyses

In order to assess the impact of missing data on the primary endpoint analysis results, the following sensitivity analyses are planned:

2.13.1 Multiple Imputation

[redacted]

2.13.2 Best Case Analysis

[redacted]

2.13.3 Worst Case Analysis

[redacted]

2.14 Per-Protocol Analyses

[redacted]

3.0 ADDITIONAL DATA

3.1 Baseline and Demographic Characteristics

[redacted]

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 enrollment (after consent) and throughout the 12-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.

All adverse events regardless of severity and relationship to the study device(s) or the study procedure should be submitted; exceptions listed below.

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 should be reported on an appropriate Follow-Up Visit CRF.

Unchanged, chronic, non-worsening or pre-existing conditions are not AEs and should not be reported. A planned hospitalization for pre-existing condition, or a procedure required by the CIP, without a serious deterioration in health, is not considered and SAE.

All adverse events (AEs), adverse device effects (ADEs), serious adverse events (SAEs), serious adverse device effects (SADEs), unanticipated adverse device effects (UADEs), and unanticipated serious adverse device effects (USADEs), with logical exceptions, will be summarized for all subjects

enrolled in this trial in terms of the number of events and the percentage of subjects with events. All device deficiencies/malfunctions will also be reported.

CEC adjudicated results will be used for analysis, when available. All AEs including those not sent to the CEC for adjudication will be reported with logical exceptions.

AEs will be reported using the FAS population and will be summarized separately for subjects who are in the PTE vs. those who are not 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 signs consent until they exit the study.

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 OHER CONSIDERATIONS

[redacted]

5.0 ACRONYMS AND ABBREVIATIONS

Acronym or Abbreviation	Complete Phrase or Definition
AAD	Anti-Arrhythmic Drug
ADE	Adverse Device Effect
AE	Adverse Event
AF	Atrial Fibrillation
AFL	Atrial Flutter
AT	Atrial Tachycardia
CEC	Clinical Events Committee
CIP	Clinical Investigation Plan
CRF	Case Report Form
CTI	Cavotricuspid Isthmus
ECG	Electrocardiogram
HSP	High Standard Power
ICD	Implantable Cardioverter-Defibrillator
ICM	Implantable Cardiac Monitor

[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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7.0 [redacted]

[redacted]

Primary Safety Event	Description
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

APPENDIX B: STATISTICAL METHODS FOR CONTINUOUS VARIABLES

[redacted]

[redacted]

[redacted]

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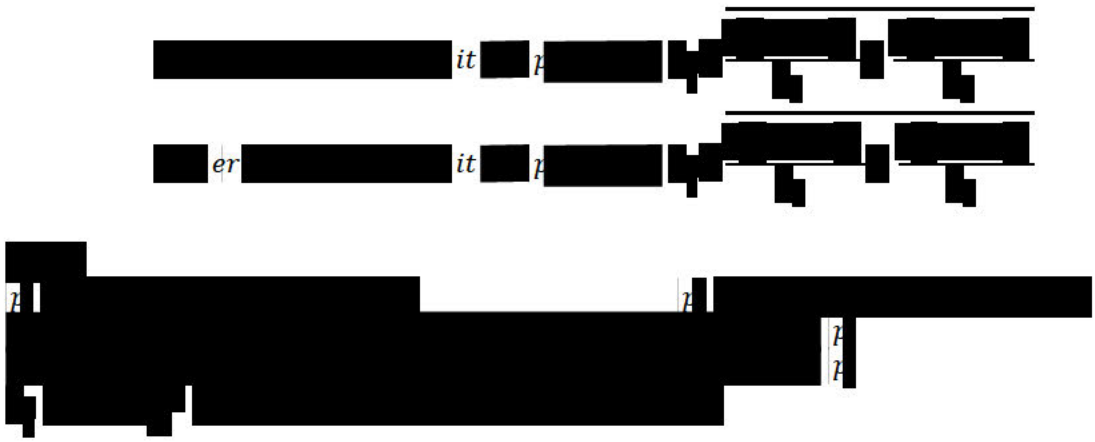

APPENDIX D: CLINICIAL RATIONALE FOR PRIMARY SAFETY ENDPOINT

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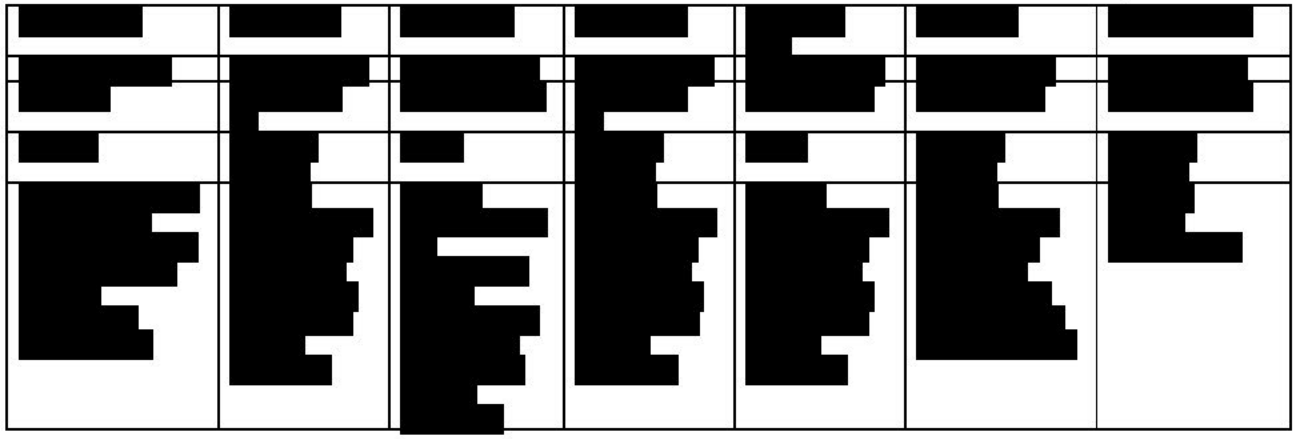

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APPENDIX E: CLINICIAL RATIONALE FOR PRIMARY EFFECTIVENESS ENDPOINT

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APPENDIX F: AAD-FREE SECONDARY EFFECTIVENESS ENDPOINT

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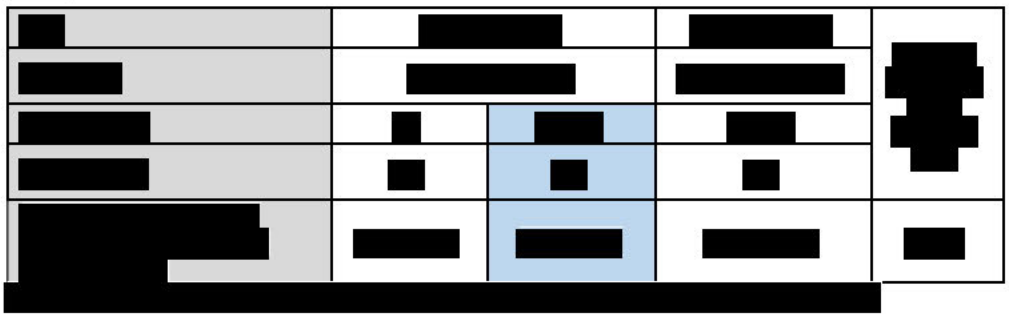

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APPENDIX G: SINGLE-PROCEDURE SECONDARY EFFECTIVENESS ENDPOINT

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APPENDIX H: SYMPTOMATIC SECONDARY EFFECTIVENESS ENDPOINT

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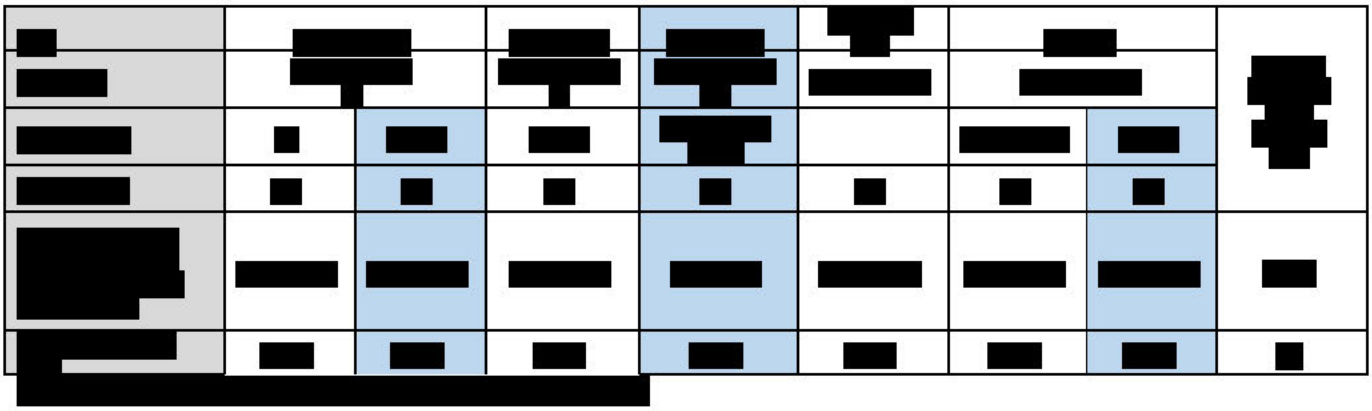

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Statistical Analysis Plan

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APPENDIX I: RATIONALE FOR THE HSP SUBSTUDY

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APPENDIX J: POWER AND SAMPLE SIZE CALCULATIONS

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