Statistical Analysis Plan

A Real-world Study of the FARAPULSE Pulsed Field Ablation System in A Chinese Population with Paroxysmal Atrial Fibrillation (REPLACE Study)
PF109

CONFIDENTIAL

DO NOT COPY OR DISTRIBUTE WITHOUT WRITTEN PERMISSION

APPROVALS (Check/Complete one below):

☐ Approvals are captured electronically

☐ An electronic system for capturing approvals is not being used for this study; wet signatures are captured below:

Monica Nanduri	*Electronically signed by: Monica Nanduri Reason: I am the Approver Date: Aug 7, 2024 14:59 GMT+5.5*	07-Aug-2024
Lead Biostatistician – [Monica Nanduri, Assoc Stat Programmer]		Date (dd-mmm-yyyy)
Peng Lv	*Electronically signed by: Peng Lv Reason: I am the Approver Date: Aug 7, 2024 16:01 GMT+8*	07-Aug-2024
Clinical Project/Trial Manager – [Peng Lv, Senior Clinical Trial Manager]		Date (dd-mmm-yyyy)
xiuyue jia	*Electronically signed by: xiuyue jia Reason: I am the Approver Date: Aug 7, 2024 17:14 GMT+8*	07-Aug-2024
Medical Director – [Xiuyue Jia, Medical Affairs Manager]		Date (dd-mmm-yyyy)

Revision History

Document Revision Number	Template Number and Version	Section	Change	Reason for Change
27FEB2023 Version:AA	AA	NA	Initial Release	NA

TABLE OF CONTENTS

1 PROTOCOL SUMMARY

Study Objective: To observe the safety and effectiveness of the FARAPULSE Pulsed Field Ablation System for treatment of recurrent, symptomatic Paroxysmal Atrial Fibrillation (PAF) in a Chinese population in the real world.

Indication for Use: FARAPULSE Pulsed Field Ablation System is intended for the isolation of pulmonary veins for the treatment of PAF.

(Commercial) Device/System applied as Standard of Care and sizes

Component Name	Model
FARASTAR Pulsed Field Ablation Generator System	
FARASTAR Pulsed Field Ablation Generator	61M401
FARASTAR Recording System Module (RSM)	61M407
FARASTAR Stimulation Module Cable	61M404
FARASTAR EGM Cable	61M405
FARASTAR Stimulation Module Auxiliary Cable	61M408
FARASTAR Cable Set	61M406
FARASTAR Stimulation Module Male Cable	61M409
FARASTAR Stimulation Module Female Cable	61M410
FARASTAR Stimulation Module Y-Cable, Long	61M411
FARASTAR Stimulation Module Y-Cable, Short	61M412
FARASTAR Recording System Module Catheter Pin Cable	61M413
FARASTAR Recording System Module ECG Trunk Cable	61M415
FARASTAR Recording System Module ECG Output Module	61M416
FARASTAR Recording System Module EGM Input Module	61M417
FARAWAVE Pulsed Field Ablation Catheter	
FARAWAVE Pulsed Field Ablation Catheter, 35mm	41M402
FARAWAVE Pulsed Field Ablation Catheter, 31mm	41M401
FARASTAR Catheter Connection Cable	41M404
FARADRIVE Steerable Sheath	21M402

Study Design: This is a retrospective and/or prospective single-center single-arm observational study.

Planned Number of Subjects: At least 30 ATTEMPT and TREATMENT subjects

Planned Number of Sites / Countries: 1 site

Primary Endpoint:

Primary Effectiveness Endpoint:
Acute Procedural Success: Proportion of subjects that achieve electrical isolation* of all pulmonary veins (PVs) using FARAPULSE Pulsed Field Ablation system only.

** Electrical isolation of a PV is recommended to be demonstrated by entrance block after a 20-minute waiting period at least if the subject is enrolled prospectively, otherwise the way to confirm electrical isolation should be recorded, including whether there is a waiting period and its duration. If exit block testing is performed, the PV will only be considered isolated if both entrance and exit block testing was successful.*

Primary Safety Endpoint: Occurrence of the acute serious procedure-related and/or device-related adverse events at 7 days post index procedure:

- Death
- Myocardial infarction
- Stroke/ Transient ischemic attack (TIA)
- Peripheral or organ thromboembolism
- Cardiac tamponade/perforation
- Pulmonary edema
- Vascular access complications
- Heart block*
- Gastric motility/pyloric spasm disorders
- Pericarditis
- Atrial esophageal fistula
- Severe PV stenosis
- Phrenic nerve palsy

*Heart block not attributable to medication effect or vasovagal reaction.

Secondary Endpoints:

Secondary Effectiveness Endpoints:

1. Chronic Success: Proportion of subjects that free from effectiveness events defined as failure as below at 12 months post-procedure.

   Effectiveness events determining a failure are defined as:
   a) Fail to achieve electrical isolation of all PVs using FARAPULSE Pulsed Field Ablation system only.
   b) After the Blanking Period (90 days post the procedure) to 12-month after the procedure:
      - Occurrence of any Detectable atrial fibrillation (AF), atrial flutter (AFL)* or atrial tachycardia (AT) captured by one of the following methods: ≥ 30 seconds in duration recording from 24-hour Holter

Monitor or ≥ 10 seconds recording from 12-lead Electrocardiography (ECG);
- Any cardioversion for AF, AFL* or AT;
- Use of any Class I or Class III antiarrhythmic drugs (AADs) for the treatment of AF, AFL* or AT.

c.) At any time through 12 months after the procedure:
- Re-ablation for AF, AFL* or AT;
- Use of amiodarone, except intra-procedurally to control an arrhythmia.

2. Proportion of PVs that achieve electrical isolation by using the FARAPULSE Pulsed Field Ablation System only.

3. Chronic success allowing AADs.

**excluding cavotricuspid isthmus (CTI)-dependent flutter confirmed by electrophysiology study*

Secondary Safety Endpoint:
Proportion of subjects that free from primary safety events defined as above through 7 days after the procedure and free from the following serious procedure-related and/or device-related adverse events at any time through the completion of 12-month follow-up visit.

- Atrial esophageal fistula
- Severe PV stenosis
- Persistent phrenic nerve palsy*

**The study will collect information on phrenic nerve palsy observed before the end of the index procedure and, in case of occurrence, will track information for potential recovery during data collection at the study visits.*

Method of Assigning Patients to Treatment: This is a real-world study, subjects who sign the consent form and meet all key eligibility criteria will be enrolled.

Follow-up Schedule: This is a retrospective and/or prospective observational study. For retrospectively enrolled subjects, data will be collected from each patient's scheduled and unscheduled follow-up visits for 12 months post-procedure per the standard of care follow-up schedule as defined by their center that performs the clinical follow-up visits.

For prospectively enrolled subjects, data collection at the following visits are recommended:

- Baseline Visit
- Procedure
- 7 days after the procedure (7-10 days) Telephone contact
- 1 month after the procedure (30 ±7 days) Telephone contact
- 3 months after the procedure (91-104 days) Clinic visit
- 6 months after the procedure (180 ± 30 days) Clinic visit
- 12 months after the procedure (365 ± 30 days) Clinic visit

Study Duration: This is a retrospective and/or prospective study. The 12-month follow-up data will be collected after the procedure. The study duration is estimated up to 18 months depending on the precent of subjects enrolled prospectively.

Participant Duration: The study duration for subjects enrolled prospectively is expected to be approximately 12 months, and up to 12months after the procedure for the subjects enrolled retrospectively.

Key Inclusion Criteria:

1. Subjects who are ≥ 18 and ≤ 75 years of age on the day of enrollment;
2. Subjects whose preoperative diagnosis is PAF confirmed by the clinician;
3. De novo ablation procedure for PAF with Class I or IIa recommendations* according to 2018 Chinese expert consensus on atrial fibrillation therapy;
4. Subjects who are able and willing to provide the defined observational data and/or participate in baseline and follow-up evaluations for the full study;
5. Subjects who are willing and capable of providing informed consent.

** In 2018 Chinese expert consensus on atrial fibrillation therapy, subjects with recurrent, symptomatic PAF and refractory or intolerant to at least one class I or class III antiarrhythmic medication are recommended to accept ablation therapy under Class I recommendation; Subjects with recurrent, symptomatic PAF are recommended to accept ablation therapy as the first line therapy under Class IIa recommendation.*

Key Exclusion Criteria:

1. Subjects who, in the judgment of the investigator, have a life expectancy of less than one year before the procedure;
2. Women of childbearing potential who are, or plan to become, pregnant during the time of the study;
3. Subjects with any known contraindication to AF ablation with FARAPULSE Pulsed Field Ablation system, anticoagulation therapy, or contrast media in the judgment of the investigator or subjects unwillingness to use systemic anticoagulation
4. Subjects who are currently enrolled in another investigational study or registry that would directly interfere with the current study.

Additional Exclusion Criteria for modified Intent-to-Treat (mITT) set:

1. AF that is any of the following:
   - Persistent (both early and longstanding) by diagnosis or continuous duration > 7 days
   - Requires four or more direct-current cardioversions in the preceding 12 months before the procedure.
   - Secondary to electrolyte imbalance, thyroid disease, alcohol or other reversible/ non-cardiac causes

2. Any of the following atrial conditions:
   - Left atrial anteroposterior diameter ≥ 5.5 cm (by MRI, CT or transthoracic echocardiography [TTE]*)
   - Any prior atrial endocardial or epicardial ablation procedure, other than right sided CTI ablation or for right sided supraventricular tachycardia
   - Any prior atrial surgery
   - Intra-atrial septal patch or interatrial shunt
   - Atrial myxoma
   - Current left atrium (LA) thrombus#
   - LA appendage closure, device or occlusion, past or anticipated
   - Any PV abnormality, stenosis or stenting (common and middle PVs are admissible)[¥]
3. At any time, one or more of the following cardiovascular procedures, implants or conditions:
   - Sustained ventricular tachycardia or any ventricular fibrillation
   - Hemodynamically significant valvular disease:
     a) Valvular disease that is symptomatic

b) Valvular disease causing or exacerbating congestive heart failure
c) Aortic stenosis: if already characterized, valve area < 1.5 cm^2 or gradient > 20 mmHg
d) Mitral stenosis: if already characterized, valve area < 1.5 cm^2 or gradient > 5 mmHg
e) Aortic or mitral regurgitation associated with abnormal LV function or hemodynamic measurements

- Hypertrophic cardiomyopathy
- Any prosthetic heart valve, ring or repair including balloon aortic valvuloplasty
- Pacemaker, implantable cardioverter defibrillator or cardiac resynchronization therapy devices
- Any inferior vena cava (IVC) filter, known inability to obtain vascular access or other contraindication to femoral access
- History of rheumatic fever
- History of congenital heart disease with any residual anatomic or conduction abnormality.

4. Any of the following procedures, implants or conditions:

- At baseline or assessment before the procedure:
  i. New York Heart Association (NYHA) Class III/IV
  ii. Left ventricular ejection fraction (LVEF) < 40%
  iii. Symptomatic hypotension or Uncontrolled hypertension (Systolic blood pressure > 160 mmHg or Diastolic blood pressure > 95 mmHg on two blood pressure measurements at baseline assessment)
  iv. Symptomatic resting bradycardia
  v. Implantable loop recorder or insertable cardiac monitor
- Within the 3 months preceding the procedure:

  a) Myocardial infarction or Unstable angina or Percutaneous coronary intervention
  b) Heart failure hospitalization
  c) Treatment with amiodarone
  d) Pericarditis or symptomatic pericardial effusion
  e) Gastrointestinal bleeding

- Within the 6 months preceding the procedure:

a) Heart surgery
b) Stroke, TIA or intracranial bleeding
c) Any thromboembolic event
d) Carotid stenting or endarterectomy

5. Diagnosed disorder of blood clotting or bleeding diathesis
6. Subject who is not on anticoagulation therapy for at least 3 weeks prior to the ablation procedure
7. Medical conditions assessed before the procedure that would prevent participation in the study, interfere with assessment or therapy, significantly raise the risk of study participation, or modify outcome data or its interpretation, including but not limited to:
    - Body Mass Index (BMI) > 40.0 kg/m^2
    - Solid organ or hematologic transplant, or currently being evaluated for an organ transplant
    - Severe lung disease, pulmonary hypertension, or any lung disease involving abnormal blood gases or requiring supplemental oxygen
    - Renal insufficiency with an estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2, or any history of renal dialysis or renal transplant
    - Active malignancy or history of treated malignancy within 24 months of enrollment (other than cutaneous basal cell or squamous cell carcinoma)
    - Clinically significant gastrointestinal problems involving the esophagus or stomach including severe or erosive esophagitis, uncontrolled gastric reflux, gastroparesis, esophageal candidiasis or active gastroduodenal ulceration
    - Active systemic infection
    - COVID-19 disease
        a) Current confirmed, active COVID-19 disease
        b) Current positive test for SARS-CoV-2
        c) Confirmed COVID-19 disease not clinically resolved at least 3 months prior to the procedure
    - Other uncontrolled medical conditions that may modify device effect or increase risk, including uncontrolled diabetes mellitus (HgbA1c > 8.0% if test result already obtained), untreated obstructive sleep apnea or active alcohol abuse

8. Clinically significant psychological condition that in the Investigator's opinion would prohibit the subject's ability to meet the protocol requirements.

9. Employees/family members of:

- Boston Scientific or any of its affiliates or contractors
- The Investigator, sub-Investigators, or their medical office or practice, or healthcare organizations at which study procedures may be performed

10. Subjects known to require or have accepted ablation outside the PV region during the procedure except CTI region ablation.

**TTE obtained ≤ 6 months prior to procedure will be acceptable, unless a cardiac event has occurred (e.g. MI, acute heart failure or acute onset heart failure) between the date of the exam and the procedure. In this case, a new TTE is needed to confirm eligibility for mITT. The most recent report before the procedure will be used. LA anteroposterior diameter measured by M-mode from the parasternal long-axis view will be used.*
#The absence of thrombus must be confirmed by means of a trans-esophageal echocardiogram (TEE) within 48 hours prior to the procedure or Intracardiac Echography (ICE) during the procedure.

¥ Cardiac CT/MRI obtained ≤ 3 months prior to procedure will be acceptable.

Statistical Methods

Primary Statistical Hypothesis: There are no formal hypotheses testing in this small sample size observational study.

Statistical Test Method: Descriptive statistics will be conducted for the endpoint events. Explorative statistical analysis might be produced if appropriate, such as Bayesian estimation of the study results using ADVENT data as the prior.

Primary effectiveness endpoints will be summarized for TREATMENT subjects in modified Intent-to-Treat (mITT) set.

Secondary effectiveness endpoints will be summarized for TREATMENT subjects in Intent-to-Treat (ITT) set and mITT set respectively.

Primary and secondary safety endpoints will be summarized for ATTEMPT and TREATMENT subjects in ITT set.

The additional endpoints will be summarized for TREATMENT subjects in ITT set.

Sample Size Parameters: No formal sample size calculation is performed because there is no formal hypothesis testing in the study. The following table provides a 95% confidence interval (exact methods) for a sample size of 30 if there are 0 ~ 3 primary safety events.

Events	Rates (n=30)	Lower 95%CI	Upper 95%CI
0	0%	0%	11.6%
1	3.3%	0.1%	17.2%
2	6.7%	0.8%	22.1%
3	10%	2.1%	26.5%

2 INTRODUCTION

AF is the most common sustained cardiac arrhythmia, affecting approximately 33.5 million people worldwide estimated at 2010[1]. The currently estimated prevalence of AF in adults is between 2% and 4%, and a 2.3-fold rise is expected, owing to extended longevity in the general population and intensifying search for undiagnosed AF[2]. According to the atrial fibrillation prevalence survey of adults in China in 2021, it is estimated that there are about 7.9 million patients with atrial fibrillation in China[3] . The annual risk of AF-related stroke is 5% per year and 1 of every 6 strokes diagnosed occurs in the presence of AF[4]. Therefore, patients with AF require long-term anticoagulation to prevent embolic events. Failure to manage AF may also lead to anatomic and electrical remodeling of the LA, tachycardia-induced cardiomyopathy and reduced left ventricular function (heart failure). AF remains a significant cause of morbidity and mortality in industrialized societies.

At present, radiofrequency ablation and cryoablation are the main energy forms for atrial fibrillation ablation, but both ablation mechanisms rely on heat conduction and have no tissue selectivity. If the ablation is insufficient, the prevalence of electrical reconnection of pulmonary vein is high; if the ablation is excessive, there is a risk of adjacent injury. According to 2018 Chinese expert consensus statement on atrial fibrillation therapy, the incidence of complications after radiofrequency ablation of atrial fibrillation is about 6.29%, and the late recurrence rate of atrial arrhythmia is about 25%-40%[1]. Thus, it has become a mission for cardiac electrophysiologists to find a strategy to improve the safety and efficacy of atrial fibrillation ablation.

The objective of the study is to observe the safety and effectiveness of the FARAPULSE Pulsed Field Ablation system for treatment of recurrent, symptomatic PAF in a Chinese population in the real world. The REPLACE study will be conducted to generate local clinical evidence to support FAREAPULSE Pulsed Field system regulatory approval in China.

The study duration is estimated up to 18 months. Primary endpoints analysis is planned to be conducted after all enrolled subjects have completed data collection at 1-month follow-up visit. All the subjects underwent study device treatment will be followed up to 12 months after the procedure, and the secondary and other endpoints will be analyzed.

3 ENDPOINT ANALYSIS

3.1 Primary Effectiveness Endpoint:

The primary effectiveness endpoint is acute Procedural Success, defined as proportion of subjects that achieve electrical isolation of all PVs using FARAPULSE Pulsed Field Ablation system only.

3.1.1 Hypotheses

This is an observational real-world study with small sample size, no formal hypothesis is performed in this study.

3.1.2 Sample Size

There is no formal hypothesis for this study, thus no sample size calculation is performed in this study. The study device has achieved CE mark and accumulated a large amount of clinical data. This trial with 30 PAF subjects will be used to produce data in Chinese population.

3.1.3 Statistical Methods

Descriptive statistics will be conducted for the effectiveness endpoint events. The number, incidence (amount of events/number of subjects) and its 95% confidence interval (exact methods) will be calculated. The primary effectiveness endpoints will be analyzed for TREAMENT subjecs in the mITT set. Explorative statistical analysis might be produced if appropriate, e.g., Bayesian estimation of the study results using FARAPULSE IDE data as the prior.

3.2 Primary Safety Endpoint:

The primary safety endpoint is defined as occurrence of the acute serious procedure-related and/or device-related adverse events at 7 days post index procedure.
Primary safety events will consist of a composite of serious procedure and/or device-related adverse events like,

- Death
- Myocardial infarction
- Stroke/ TIA
- Peripheral or organ thromboembolism
- Cardiac tamponade / perforation
- Pulmonary edema
- Vascular access complications
- Heart block*
- Gastric motility/pyloric spasm disorders
- Pericarditis
- Atrial esophageal fistula
- Severe PV stenosis
- Phrenic nerve palsy

3.2.1 Hypotheses

This is an observational real-world study with small sample size, no formal hypothesis is performed in this study.

3.2.2 Sample Size

There is no formal hypothesis for this study, thus no sample size calculation is performed in this study. The study device has achieved CE mark and accumulated a large amount of clinical data. This trial with 30 PAF subjects will be used to produce data in Chinese population.

The following table provides a 95% confidence interval (exact methods) for a sample size of 30 if there are 0 ~ 3 primary safety events.

Events	Rates (n=30)	Lower 95%CI	Upper 95%CI
0	0%	0%	11.6%
1	3.3%	0.1%	17.2%
2	6.7%	0.8%	22.1%
3	10%	2.1%	26.5%

3.2.3 Statistical Methods

Descriptive statistics will be conducted for the safety endpoint events. The number, incidence (amount of events/number of subjects) and its 95% confidence interval (exact methods) will be calculated. The primary safety endpoints will be analyzed for ATTEMPT and TREATMENT subjects in the ITT set. Explorative statistical analysis might be produced if appropriate, e.g., Bayesian estimation of the study results using FARAPULSE IDE data as the prior.

3.3 Secondary Effectiveness Endpoint:

1. Chronic Success: Proportion of subjects that free from effectiveness events defined as failure as below at 12 months post-procedure.

Effectiveness events determining a failure are defined as:

- Fail to achieve electrical isolation of all PVs using FARAPULSE Pulsed Field Ablation system only.
- After the Blanking Period (90 days post the procedure) to 12-month after the procedure

  a) Occurrence of any Detectable AF, AFL* or AT captured by one of the following methods: ≥ 30 seconds in duration recording from 24-hour Holter Monitor or ≥ 10 seconds recording from 12-lead ECG, or
  b) Any cardioversion for AF, AFL* or AT, or
  c) Use of any Class I or Class III AADs[#] for the treatment of AF, AFL* or AT.

- At any time through 12 months after the procedure:

  a) Re-ablation for AF, AFL* or AT, or
  b) Use of amiodarone, except intra-procedurally to control an arrhythmia.

2. Proportion of PVs that achieve electrical isolation by using the FARAPULSE Pulsed Field Ablation system only.
3. Chronic success allowing AADs.

#It won't be considered as a failure if the subject has three-month visit happened after 90 days post the procedure, but still in the window (<=104 day) with AADs on, and physicians decide to take AADs off after this visit.
**excluding CTI-dependent flutter confirmed by EP study.*

3.4 Secondary Safety Endpoint:

Proportion of subjects that free from primary safety events defined as above through 7 days after the procedure and free from the following serious procedure-related and/or device-related adverse events at any time through the completion of 12-month follow-up visit.

- Atrial oesophageal fistula
- Severe PV stenosis
- Persistent phrenic nerve palsy*

**The study will collect information on phrenic nerve palsy observed before the end of the index procedure and, in case of occurrence, will track information for potential recovery during the study visits.*

3.5 Additional Endpoints:

1. AF symptoms assessment: Descriptive analysis of atrial fibrillation symptoms at baseline versus 12 months after the procedure.
2. Procedural parameters:
   - Total procedure time (initiation of interventional venous access puncture to all devices remove from the body)
   - Left atrial dwell time (total time an ablation catheter is in the left atrium)
   - Total ablation time (first ablation to last ablation for PVI)
   - Fluoroscopy time (total duration of exposure)

4. GENERAL STATISTICAL METHODS

Descriptive statistics will be conducted for the primary, secondary and other endpoint events. When descriptive statistics are used, continuous variables will be summarized using standard quantitative statistics: number of available observations, mean, standard deviation, median, quartiles and range (minimum and maximum observed values) and its 95% confidence interval. Categorical variables will be summarized using the number, incidence (amount of events/number of subjects) and its 95% confidence interval (exact methods).

Explorative statistical analysis might be produced if appropriate, e.g., Bayesian estimation of the study results using FARAPULSE IDE data as the prior.

4.1 Analysis Sets

ITT set will involve subjects who have signed informed consent and satisfied with all key criteria.Primary effectiveness endpoints will be summarized for TREATMENT subjects in mITT set.

Secondary effectiveness endpoints will be summarized for TREATMENT subjects in ITT set and mITT set respectively.

Primary and secondary safety endpoints will be summarized for ATTEMPT and TREATMENT subjects in ITT set.
The additional endpoints will be summarized for TREATMENT subjects in ITT set.

4.2 Control of Systematic Error/Bias

This is a real-world study. Selection of patients will be made from the Investigational site's routine patients. All patients meeting the key eligibility criteria and having signed the ICF will be eligible for enrollment in the study. Control and reduction of potential bias associated with a single-arm study design have been taken into account by defining key inclusion and exclusion criteria to represent a population similar to the patients with AF ablation in the real world and defining a mITT group with population similar to the subjects enrolled in ongoing ADVENT trial and other trials about AF ablation.

4.3 Number of Subjects per Investigative Site

Thirty ATTEMPT or TREATMENT subjects will be enrolled from one site.

5 ADDITIONAL DATA ANALYSES

The additional endpoints will be analyzed after all TREATMENT subjects finishing Twelve-month Visit data collection. The additional endpoints will be analyzed for TREATMENT subjects in ITT set. Descriptive statistics will be conducted for the effectiveness endpoint events. The number, incidence (amount of events/number of subjects) and its 95% confidence interval will be calculated (exact methods).

5.1 Other Endpoints/Measurements

1. AF symptoms assessment: Descriptive analysis of atrial fibrillation symptoms at baseline versus 12 months after the procedure
2. Procedural parameters:

- Total procedure time (initiation of interventional venous access puncture to all devices remove from the body)
- Left atrial dwell time (total time an ablation catheter is in the left atrium)
- Total ablation time (first ablation to last ablation for PVI)
- Fluoroscopy time (total duration of exposure)

5.2 Interim Analyses

There is no formal statistical hypothesis test in this study, thus interim analysis can be made according to actual needs.

5.3 Subgroup Analyses

The primary and secondary endpoints will be sub analyzed based on the following variables, including but not limited to:

- Gender
- Whether ablation is performed as first-line therapy.
- Whether the subject is enrolled prospectively.

5.4 Univariable Analyses

Univariable analysis will be performed to assess the impact of potential baseline data and clinical characteristics on the primary endpoints.

5.5 Changes to Planned Analyses

Any changes to the planned statistical analyses made prior to performing the analyses will be documented in an amended Statistical Analysis Plan approved prior to performing the analyses. Changes from the planned statistical methods after performing the analyses will be documented in the clinical study report along with a reason for the deviation

6 VALIDATION

All clinical data reports generated per this plan will be validated per 90702587, Global WI: Clinical Data Reporting Validation. The validation level R1 chosen for all primary, secondary, safety and other additional endpoints. The validation program includes checking logs and generating compare reports in comparing with main programming datasets. Statistical analyses and validation will be performed by IQVIA team.

7 PROGRAMMING CONSIDERATIONS

All statistical programming tasks will be performed by IQVIA™ independently.

7.1. Statistical Software

All statistical analyses will be done using The SAS System Version 9.2 software or above (Copyright © 2000 SAS Institute Inc., SAS Campus Drive, Cary, North Carolina 27513, USA. All rights reserved.).

7.2. Format of Output

Statistical analysis will be performed using SAS. All output for the final statistical report will be in the form of a Word document, which may include tables, figures, graphs, and listings, as appropriate.

7.3. Rules and Definitions

For baseline categorical variables, subjects with missing values will not be counted in the corresponding denominators for proportions. Number of patients completing the visit will be considered in denominators.

7.4. The Method of Handling Missing Value and Outliers

The distribution of missing and/or incorrect data will be analyzed separately based on whether the data is collected prospectively or not.

For the missing data, only the missing primary endpoint indicators will be carried forward during analysis, Sensitivity analyses will be performed on the primary safety and effectiveness endpoints to assess the impact of missing data on study results. In addition to worst-case missing data filling, Tipping Point Analysis will be performed as a post-hoc Analysis to assess the impact of different missing data filling methods on the results.

Sensitivity analyses will be performed to assess the impact of unreasonable data on the stability of the results if appropriate.

When calculating rates of all adverse events, both device and/or procedure related with missing event date (i.e. mm/dd/yyyy), the ideal is to work with safety and/or data

management representatives to query sites for missing data. However missing and partial missing dates may be handled as using the worst-case scenario as follows:

Partial Date	Action Taken
Entire adverse event onset date is missing	The procedure date will be used for the onset date.
The month and the day of the month are missing but the year is available	January 1st will be used for the month and day of the onset date. However, if the imputed date falls before the procedure date, then the procedure date will be used for the onset date.
Day is missing, but the month and year are available	The 1st will be used as the day of the onset date. However, if the imputed date falls before the procedure date, then the procedure date will be used for the onset date.

Replace_SAP_Final

Final Audit Report 2024-08-07

Created:	2024-08-07
By:	Monica Nanduri (monicalakshmibharathi.nanduri@iqvia.com)
Status:	Signed
Transaction ID:	CBJCHBCAABAATij6lqRz03GBd5EZH4AZhYsBh7_0UPZW
Number of Documents:	1
Document page count:	19
Number of supporting files:	0
Supporting files page count:	0

"Replace_SAP_Final" History

Document created by Monica Nanduri (monicalakshmibharathi.nanduri@iqvia.com)
2024-08-07 - 7:38:56 AM GMT

Document emailed to Peng Lv (Peng.Lv@bsci.com) for signature
2024-08-07 - 7:41:18 AM GMT

Document emailed to xiuyue.jia@bsci.com for signature
2024-08-07 - 7:41:18 AM GMT

Document emailed to Monica Nanduri (monicalakshmibharathi.nanduri@iqvia.com) for signature
2024-08-07 - 7:41:18 AM GMT

Email viewed by xiuyue.jia@bsci.com
2024-08-07 - 7:45:46 AM GMT

Email viewed by Peng Lv (Peng.Lv@bsci.com)
2024-08-07 - 7:58:42 AM GMT

xiuyue.jia@bsci.com authenticated with Adobe Acrobat Sign.
Challenge: The user opened the agreement.
2024-08-07 - 7:59:04 AM GMT

Peng Lv (Peng.Lv@bsci.com) authenticated with Adobe Acrobat Sign.
Challenge: The user opened the agreement.
2024-08-07 - 7:59:46 AM GMT

Peng Lv (Peng.Lv@bsci.com) authenticated with Adobe Acrobat Sign.

Challenge: The user completed the signing ceremony.

2024-08-07 - 8:01:20 AM GMT

Peng Lv (Peng.Lv@bsci.com) has agreed to the terms of use and to do business electronically with Boston Scientific

2024-08-07 - 8:01:22 AM GMT

Document e-signed by Peng Lv (Peng.Lv@bsci.com)

Signing reason: I am the Approver

Signature Date: 2024-08-07 - 8:01:22 AM GMT - Time Source: server

xiuyue.jia@bsci.com authenticated with Adobe Acrobat Sign.

Challenge: The user completed the signing ceremony.

2024-08-07 - 8:02:37 AM GMT

xiuyue.jia@bsci.com authenticated with Adobe Acrobat Sign.

Challenge: The user completed the signing ceremony.

2024-08-07 - 8:03:48 AM GMT

xiuyue.jia@bsci.com authenticated with Adobe Acrobat Sign.

Challenge: The user opened the agreement.

2024-08-07 - 8:16:09 AM GMT

xiuyue.jia@bsci.com authenticated with Adobe Acrobat Sign.

Challenge: The user opened the agreement.

2024-08-07 - 9:03:58 AM GMT

xiuyue.jia@bsci.com authenticated with Adobe Acrobat Sign.

Challenge: The user completed the signing ceremony.

2024-08-07 - 9:14:52 AM GMT

Signer xiuyue.jia@bsci.com entered name at signing as xiuyue jia

2024-08-07 - 9:14:52 AM GMT

xiuyue jia (xiuyue.jia@bsci.com) has agreed to the terms of use and to do business electronically with Boston Scientific

2024-08-07 - 9:14:54 AM GMT

Document e-signed by xiuyue jia (xiuyue.jia@bsci.com)

Signing reason: I am the Approver

Signature Date: 2024-08-07 - 9:14:54 AM GMT - Time Source: server

Monica Nanduri (monicalakshmibharathi.nanduri@iqvia.com) authenticated with Adobe Acrobat Sign.

Challenge: The user completed the signing ceremony.

2024-08-07 - 9:29:47 AM GMT

Monica Nanduri (monicalakshmibharathi.nanduri@iqvia.com) has agreed to the terms of use and to do business electronically with Boston Scientific

2024-08-07 - 9:29:48 AM GMT

Document e-signed by Monica Nanduri (monicalakshmibharathi.nanduri@iqvia.com)

Signing reason: I am the Approver

Signature Date: 2024-08-07 - 9:29:48 AM GMT - Time Source: server

Agreement completed.

2024-08-07 - 9:29:48 AM GMT