SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Names:	Ablation Catheter, Generator, Irrigation Pump, Tubing Set, and Catheter Extension cable
Device Trade Names:	Sphere-9™ Catheter and Affera™ Ablation System Including: Sphere-9™ Catheter (Model AFR-00001); HexaGen™ RF Generator (Model AFR-00004); HexaPulse™ PF Generator (Model AFR-00008); HexaFlow™ Irrigation Pump (Model AFR-00005); Tubing Set (Model AFR-00002); Catheter Extension Cable (Model AFR-00006)
Device Procode:	Class III / QZI: Percutaneous Cardiac Ablation Catheter For Treatment Of Atrial Fibrillation With Irreversible Electroporation Class III/ OAE: Catheter, Percutaneous, Cardiac Ablation, For Treatment Of Atrial Fibrillation Class III/ OAD: Catheter, Percutaneous, Cardiac Ablation, For Treatment Of Atrial Flutter
Applicant's Name and Address:	Medtronic, Inc. 8200 Coral Sea Street NE Mounds View, MN 55112 USA
Date(s) of Panel Recommendation:	None
Premarket Approval Application (PMA) Number:	P240013
Date of FDA Notice of Approval:	October 24, 2024

II. INDICATIONS FOR USE

The Sphere-9 Catheter is indicated for use in cardiac electrophysiological mapping (stimulation and electrogram recording) and for treatment of drug refractory, recurrent, symptomatic persistent atrial fibrillation (episode duration less than 1 year) and radiofrequency ablation of cavotricuspid isthmus dependent atrial flutter when used with the Affera Mapping system.

III. CONTRAINDICATIONS

The Sphere-9 Catheter is contraindicated for use under the following circumstances:

- In patients with an active systemic infection.
- In patients who have had cardiac surgery in the preceding eight weeks, as the risk of perforation may increase.
- In patients with intracardiac thrombus or myxoma, as the catheter may precipitate an embolus.
- In coronary vessels with diameter smaller than the expandable ablation electrode, as the catheter may damage the coronary vessels.
- In patients with prosthetic valves, as the catheter may damage the prosthesis.
- Using the transaortic retrograde approach in patients who have had aortic valve replacement.
- Using the transseptal approach in patients with an interatrial baffle or patch, as the opening could persist and result in an iatrogenic atrial shunt.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the labeling (Instructions for Use) for the Sphere-9 Catheter, Tubing Set, Catheter Extension Cable, and Affera Ablation System (HexaGen RF Generator, HexaPulse PF Generator, HexaFlow Irrigation Pump).

V. DEVICE DESCRIPTION

The Sphere-9 Catheter and Affera Ablation System are used in conjunction with the Affera Mapping System for cardiac mapping, ablation, and pacing.

Sphere-9 Catheter

The Sphere-9 Catheter is a sterile, single-use 8F deflectable catheter that can be used for cardiac mapping and ablation. The Sphere-9 Catheter (shown in Figure 1) includes a handle to control bidirectional deflection of a steerable shaft. The ablation electrode on the tip of the catheter is compressed to pass through a standard 8Fr introducer sheath or an 8.5Fr steerable guiding sheath and expands to 9mm in diameter when advanced beyond the tip of the sheath. The electrodes in the catheter tip are radiopaque for visualization via standard x-ray fluoroscopy.

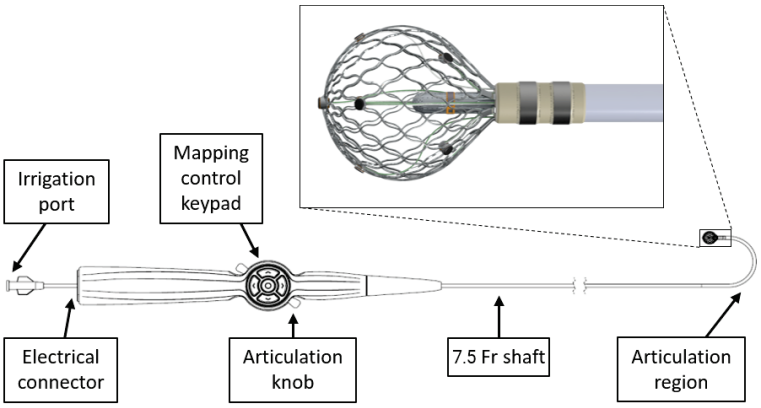


Figure 1. Sphere-9 Catheter

The Sphere-9 Catheter contains an irrigation nozzle at the center of the expandable electrode. The nozzle is flushed with heparinized saline at a low flow rate during mapping and can be irrigated at a higher flow rate during ablation. The irrigation nozzle is fed by a lumen that connects via a standard Luer connector to a custom tubing set and irrigation pump. The catheter contains passive electromagnetic sensors to allow display of the tip location and orientation by the Affera Mapping System.

Affera Ablation System

The Affera Ablation System is capable of delivering either radiofrequency (RF) energy or pulsed field (PF) energy to ablate cardiac tissue through the Sphere-9 Catheter.

The Affera Ablation System is composed of:

- HexaGen RF Generator: Acts as the user interface and control unit of the Ablation System and delivers RF energy to the ablation catheter.
- HexaPulse PF Generator: Delivers PF energy to the ablation catheter.
- HexaFlow Irrigation Pump: Provides controlled irrigation to cool the ablation electrode.

Electrical connection is made between the Affera Ablation System and the Sphere-9 Catheter via a disposable Catheter Extension Cable. To complete the electrical circuit for RF or PF energy delivery, the Ablation System requires the use of disposable return electrodes. The system is compatible with return electrodes that are commercially available on the market and used for this purpose. The disposable Tubing Set connects to the Sphere-9 Catheter to provide saline irrigation.

HexaGen RF Generator

The HexaGen RF Generator (Figure 2) delivers radiofrequency current for cardiac ablation. The device includes a touch screen and knobs that allow setting and display of ablation parameters, as well as real-time ablation information.

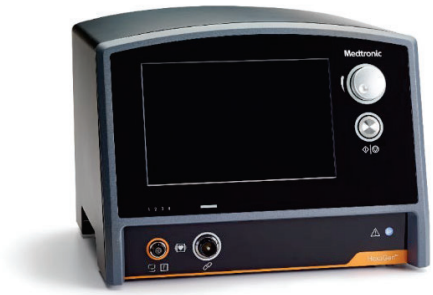
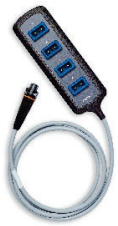


Figure 2. HexaGen RF Generator

The HexaGen RF Generator interfaces with the HexaFlow Irrigation Pump to provide the appropriate irrigation to the catheter. The following components are supplied as part of the device:

Foot Pedal



Return Electrode Adapter

Remote Control

- Remote Control Power Supply
- Fiber Optic Communication Cable
- Generator Link Cable
- Power Cord
- Equipotential Cable

HexaPulse PF Generator

The HexaPulse PF Generator (Figure 3) is connected to the Sphere-9 Catheter along with the HexaGen RF Generator and HexaMap CIU. The HexaPulse PF Generator delivers low-energy, high-voltage pulses.

Figure 3. HexaPulse PF Generator

The following components are supplied as part of the device:

- Generator Link Cable
- Ablation Return Link Cable
- Generator Communication Cable (qty 2)
- Power Cord
- Equipotential Cable

Catheter Extension Cable

The Catheter Extension Cable is a single-use, sterile cable which provides the electrical connection between the Sphere-9 Catheter and the HexaMap catheter interface unit (CIU).[1] The Catheter Extension Cable connectors are keyed, include a retention feature, and contain touch-proof contacts.

Figure 4. Catheter Extension Cable

Tubing Set

The Tubing Set (Figure 5) is a sterile, single-use disposable peristaltic tubing set used to

[1] Component of the Affera Mapping System, Class II device

provide saline irrigation from the HexaFlow Irrigation Pump to the Sphere-9 Catheter. The Tubing Set contains features for mounting into the HexaFlow Irrigation Pump and for interfacing with bubble detector on the Irrigation Pump. The Tubing Set employs a standard IV spike and drip chamber to interface with common irrigation bags, and it connects to the catheter via a standard Luer connector.

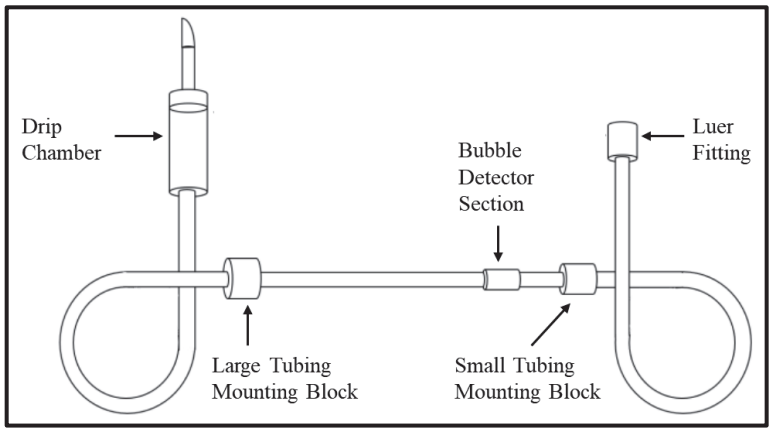


Figure 5. Tubing Set

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the treatment of drug refractory, recurrent, symptomatic persistent atrial fibrillation (episode duration less than 1 year) and cavotricuspid isthmus dependent atrial flutter, including the following:

- Anti-arrhythmic drugs
- Surgical ablation
- Catheter Ablation
    - PF ablation
    - RF ablation
    - Laser ablation
    - Cryoablation

Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

The Sphere-9 Catheter and Affera Ablation System is currently marketed in the European Economic Area, Switzerland, United Kingdom, Israel, and New Zealand. The device has not been withdrawn from marketing for any reason related to its safety or effectiveness.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Potential adverse events associated with catheter ablation and mapping procedures include, but are not limited to, the following conditions:

Access site complications (e.g. hematoma, laceration, arterio-venous fistula)
Allergic reaction (including anaphylaxis)
Anemia
Anesthesia complications
Arrhythmia (worsening, or outside of diagnosis, or life-threatening)
Atrioesophageal fistula
Asymptomatic cerebral ischemia
Bleeding
Bradycardia
Bronchial injury
Cardiac perforation / tamponade
Cardiac or respiratory arrest
Catheter entrapment
Cerebrovascular accident (CVA) / stroke
Chest pain
Conduction system injury
Coronary artery spasm/ occlusion/ stenosis
Damage/ dislodgement to ICD or implantable pacemaker
Death
Deep vein thrombosis
Embolism
Endocarditis
Esophageal ulceration / erythema
Fluid volume overload
Gastric hypomotility
Heart failure
Hemoptysis
Hematoma
Hemothorax
Hypotension
Hypoxia
Increased creatinine phosphokinase (CPK) level
Infection
Myocardial infarction
Muscle pain/ soreness
Perforation
Pericardial effusion
Pericarditis
Peripheral nerve injury
Phrenic nerve palsy / paralysis
Pleural effusion
Pneumonia
Pneumothorax
Pseudoaneurysm
Pulmonary edema
Pulmonary hypertension
Pulmonary vein stenosis
Radiation injury
Renal failure
Respiratory insufficiency
Skin burn, irritation or rash
Stiff left atrial syndrome
Transient ischemic attack
Vagal nerve injury
Valve damage
Vasovagal reactions
Vessel dissection

For the specific adverse events that occurred in the clinical study, please see Section X below.

IX. SUMMARY OF NONCLINICAL STUDIES

Nonclinical testing was performed to demonstrate the final design meets the defined design inputs. Testing was conducted following recognized standards and demonstrated acceptable results in accordance with the design inputs. Nonclinical testing included design verification (device level, system level, and software), design validation testing, biocompatibility of patient-contacting materials, sterilization, packaging, and shelf-life testing.

A. Laboratory Studies

Biocompatibility

Biocompatibility testing of the Sphere-9 Catheter and Tubing Set was conducted in accordance with ISO 10993-1 "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process".

The Sphere-9 Catheter is an external communicating device placed in direct contact with circulating blood for a limited duration (less than 24 hours). The Tubing Set is an external communicating device with indirect contact with the blood path for the same duration.

Table 1. Summary of Biological Endpoint Testing and Test Articles

Attribute	Test Method	Test Articles
Cytotoxicity per ISO-10993-5	L929 MEM Elution	Sphere-9 Catheter
	L929 Neutral Red Uptake	Tubing Set
Hemocompatibility per ISO-10993-4	Rabbit Blood Hemolysis: Direct Method	Sphere-9 Catheter
	Rabbit Blood Hemolysis: Indirect Method	Sphere-9 Catheter
		Tubing Set
	SC5B-9 Complement Activation: Direct Contact	Sphere-9 Catheter
	Thrombogenicity	Sphere-9 Catheter
Irritation and Sensitization per ISO-10993-10	Rabbit Intracutaneous Injection Reactivity	Tubing Set
	Guinea Pig Maximization Sensitization (Kligman)	Tubing Set
Irritation per ISO 10993-23	Rabbit Intracutaneous Injection Reactivity	Sphere-9 Catheter
Sensitization per ISO 10993-10	Guinea Pig Maximization Sensitization (Kligman)	Sphere-9 Catheter
Systemic Toxicity per ISO-10993-11	Acute Systemic Injection	Sphere-9 Catheter
		Tubing Set
Pyrogenicity per ISO-10993-11	Materials Mediated Pyrogenicity	Sphere-9 Catheter
		Tubing Set

Sphere-9 Catheter Design Verification

Non-clinical bench testing was performed and included the following areas:

- Exposure to 2X sterilization, environmental conditioning, simulated distribution, and accelerated aging
- Dimensional verifications and visual inspections
- Tip buckle force
- Cooling effectiveness
- Irrigation backpressure
- Shaft kink resistance
- Simulated use
- Mini electrode shear strength
- Tensile strength
- Temperature rise during use
- Corrosion resistance
- Dielectric strength
- Torsional and lateral stiffness
- Electrode retraction force
- Flex cycling
- RF and PF ablation after simulated use
- Catheter location verification
- Defibrillation resistance testing

Testing confirmed acceptable results to all performance requirements.

HexaGen RF Generator and HexaPulse PF Generator Hardware and System Design Verification

Non-clinical testing was performed for both the HexaGen RF Generator and HexaPulse PF Generator Module as part of design verification.

- Functional performance: electrical performance, operating limits, output characteristics, measurement ranges and accuracy
- Physical: generator dimensions, weight, user interface
- Safety: basic safety in accordance with IEC 60601-1

Testing confirmed acceptable results to all performance requirements.

HexaGen RF Generator and HexaPulse PF Generator Software Design Verification

The software for these devices consists of several modules that work together to control RF and PF energy delivery. Nonclinical testing was performed on all aspects of the software. This included:

- Unit/integration/system testing
- Firmware verification
- Operating system (OS) validation

- Cybersecurity feature testing and cybersecurity vulnerability scanning

Testing confirmed acceptable results to all software requirements and specifications.

HexaFlow Irrigation Pump HW Design Verification

Nonclinical testing was performed and included the following areas:

- Functional performance: bubble detection, audible indicators and volume, maximum pressure, and internal monitoring
- Physical: pump dimensions, weight, user interface, ingress protection and tamper resistance, and receptacles

Testing confirmed acceptable results to all performance requirements.

HexaFlow Irrigation Pump Software Design Verification

Nonclinical testing was performed on all aspects of the Irrigation Pump software. This included:

- Unit/integration/system testing
- Firmware verification
- Operating system (OS) validation
- Cybersecurity feature testing and cybersecurity vulnerability scanning

Testing confirmed acceptable results to all software requirements.

Tubing Set Design Verification

Non-clinical bench testing was performed and included the following areas:

- Exposure to 2X sterilization, environmental conditioning, simulated distribution, and accelerated aging
- Flow rate accuracy
- Simulated use
- Kink resistance
- Static pressure
- Tensile strength
- Alignment and retention

Testing confirmed acceptable results to all performance requirements.

Catheter Extension Cable Design Verification

Non-clinical bench testing was performed and included the following areas:

- Exposure to 2X sterilization, environmental conditioning, simulated distribution, and accelerated aging
- Mating/unmating cycles

- Electrical performance
- DC isolation
- Mechanical performance

Testing confirmed acceptable results to all performance requirements.

Basic Safety and EMC Design Verification

The Sphere-9 Catheter and the Affera Ablation System were tested in accordance with the following standards for basic safety and EMC:

- IEC 60601-1 Edition 3.2 2020-08: Medical Electrical Equipment - Part 1: General Requirements for Basic Safety and Essential Performance
- IEC 60601-1-2 Edition 4.1 2020-09: Medical Electrical Equipment – Part 1-2: General Requirements for Basic Safety and Essential Performance - Collateral Standard: Electromagnetic disturbances – Requirements and tests
- IEC 60601-2-2 Edition 6 2017-03: Medical electrical equipment - Part 2-2: Particular requirements for the basic safety and essential performance of high frequency surgical equipment and high frequency surgical accessories

System Human Factors/Usability Engineering and Design Validation

A risk-based usability engineering process was used to consider human factors as an integral part of the risk management and product development processes. The process was modeled after *ANSI/AAMI/IEC 62366-1:2015 Medical devices – Part 1: Application of usability engineering to medical devices*.

Design validation of the product requirements for each device was completed through a review of objective evidence contained in GLP animal studies, clinical studies, test reports, and other documentation.

B. Animal Studies

During the development of the Sphere-9 Catheter and the Affera Mapping and Ablation System, preclinical acute and chronic animal studies were conducted to support system development and provide an in-depth characterization of the safety profile of the system. Key animal studies conducted with the Sphere-9 Catheter and Affera Ablation System are summarized in Table 2.

Table 2. Summary of Animal Studies

Description	Objective	Number of Animals	Follow-up Duration	Results
GLP Thigh Preparation Study to Evaluate Lesion Formation and Safety	Characterize lesion formation using the RF-MI and RF-ANT ablation settings at two contact forces (10 g and 30 g) and two orientations (parallel and perpendicular); evaluate safety by assessing for incidence of steam pop, char and/or thrombus formation.	Four swine (eight thighs)	Acute	Lesion dimensions were reported across the range of ablation parameters, contact forces, and orientations. Safe performance was demonstrated as there was no evidence of thrombus, char, and steam pop across all applications of the studied parameters.
Chronic GLP Study to Evaluate Safety and Performance of Mapping and Ablation	Evaluate the safety and performance of the Sphere-9 Catheter and the Affera Mapping and Ablation System through mimicking clinical use of the device by three different electrophysiologists.	Six canines	Chronic (28 days)	Study demonstrated the safety and performance of the Sphere-9 Catheter and the Affera Mapping and Ablation System. Acceptance criteria for all study endpoints were met: • Overall animal health • Test device safety • Test device performance and effectiveness • Char and thrombus formation
Chronic Study to Evaluate the Safety of RF and PF Ablation	Evaluate the performance and safety of the Sphere-9 Catheter and the Affera Mapping and Ablation System using provocative measures to evaluate PF ablation adjacent to the phrenic nerve and esophagus and repeated ablations using both RF and PF.	Six swine	Chronic (26-28 days)	Study demonstrated the safety of radiofrequency (RF) and pulse field (PF) ablation with the Sphere-9 Catheter and the Affera Mapping and Ablation System. Acceptance criteria for all study endpoints were met: • Overall animal health • Test device safety
Acute Study to Evaluate Microbubbles and Embolic Debris	Evaluate and compare solid embolic debris and microbubble formation during ablation in the left atrium with the Sphere-9 Catheter (using both RF and PF ablation) and a commercially available irrigated RF ablation catheter.	Two swine	Acute	The results of the acute study support the safety of RF and PF ablation with the Sphere-9 Catheter and the Affera Mapping and Ablation System with respect to solid embolic debris and microbubble formation. The results of this study suggest that, compared to conventional irrigated RF catheter ablation, the risk of microbubbles, adherent char or thrombus, and embolic debris is similar or lower when ablating with the Sphere-9 Catheter using clinically relevant operating parameters.

C. Additional Studies

Sterilization, Packaging, and Shelf Life

The Sphere-9 Catheter, Tubing Set, and Catheter Extension Cable are all provided as sterile, single-use devices. These devices are sterilized using ethylene oxide (EO) cycles validated using the overkill approach per ISO 11135. The cycles were validated to achieve a minimum sterility assurance level of 10^{-6}. EO and ethylene chlorohydrin (ECH) residuals were under the limits of ISO 10993-7:2008/+A1:2022 after sterilization and aeration processing.

The packaged Sphere-9 Catheter, Tubing Set, and Catheter Extension Cable were evaluated to demonstrate product and packaging system performance after exposure to appropriate conditioning. The table below outlines the packaging performance tests.

Test	Test Performed
Sterilization	EO sterilization (two cycles)
Transport Simulation	Thermal conditioning per ISTA 3A
	Distribution simulation per ASTM D4169-16 DC 13 AL II
Accelerated Aging	13-month equivalent per ASTM F1980-16
Sterile Barrier Integrity	Pouch Seal Strength per ASTM F88/F88M-15
	Gross Leak Detection: Bubble test per ASTM F2096-11
Labeling Integrity	Legibility and adhesion

The Sphere-9 Catheter, Tubing Set, and Catheter Extension Cable are labeled for 13-month shelf life.

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study (SPHERE Per-AF) to establish a reasonable assurance of safety and effectiveness of mapping and ablation with the Sphere-9 Catheter with the Affera Mapping and Ablation System for persistent atrial fibrillation in the US, Czech Republic, and Israel under IDE G210170. Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

A. Study Design

The study was a prospective, multi-center, randomized, global pre-market clinical study with 360 days of post-ablation follow-up. Subjects were randomly assigned 1:1 to receive treatment with either the Sphere-9 Catheter with the Affera Mapping and Ablation System (investigational device) or the THERMOCOOL SMARTTOUCH® SF radiofrequency ablation catheter (control device). Subjects were blinded to their treatment arm until the completion of their 360-day follow-up visit. Adult subjects with a history of symptomatic persistent atrial fibrillation (PerAF) refractory or intolerant to drugs underwent pulsed field (PF) and radiofrequency (RF) ablation with either the investigational device or RF ablation with the control device. Following the index

ablation procedure and hospital discharge, study subjects were followed at 10 days, 30 days, 75 days, 90 days, 180 days, and 360 days. Arrhythmia recurrence was monitored with ECG at follow-up visits, 24-hour Holter monitoring at 6 and 12 months, and both scheduled and symptomatic transtelephonic monitor (event monitor) recordings.

Patients were enrolled and treated between December 14, 2021, and December 2, 2022. A total of 477 patients were enrolled, and 420 patients were treated. Subjects were enrolled at 22 investigational sites globally, including 18 sites in the United States, 3 sites in Czech Republic, and 1 site in Israel.

The study utilized an independent and blinded Clinical Events Committee (CEC) to adjudicate endpoint events, a rhythm monitoring core lab for distribution of equipment for rhythm monitoring and adjudication of arrhythmias, and an imaging core lab for review of chest and brain imaging. The study also utilized an independent Data and Safety Monitoring Board (DSMB) to oversee study progress and review clinical data and safety.

1. Inclusion and Exclusion Criteria

   Enrollment in the SPHERE Per-AF study was limited to patients who met the following inclusion criteria:

   1. Symptomatic PerAF documented by

      (1) a physician's note indicating symptoms consistent with AF sustained longer than 7 days but less than 12 months;
      AND either
      (2a) a 24-hour Holter documenting continuous AF within the past year
      OR
      (2b) two electrocardiograms (from any form of rhythm monitoring, including consumer devices) taken at least 7 days apart within the past year, each showing continuous AF.

   2. Failure or intolerance of at least one Class I or III anti-arrhythmic drug (AAD).
   3. Suitable candidate for catheter ablation.
   4. Adults aged 18 – 80 years.
   5. Willing and able to comply with all baseline and follow-up evaluations for the full length of the study.
   6. Willing and able to provide informed consent.

   Patients were <u>not</u> permitted to enroll in the SPHERE Per-AF study if they met any of the following exclusion criteria:

   1. Continuous AF lasting for 12 months or longer.
   2. AF secondary to electrolyte imbalance, thyroid disease, acute alcohol intoxication, or other reversible or non-cardiac cause.
   3. Previous left atrial ablation or surgical procedure (including septal closure or left atrial appendage closure).
   4. Valvular cardiac surgical/percutaneous procedure (e.g., ventriculotomy,

atriotomy, and valve repair or replacement and presence of a prosthetic valve).
5. Any carotid stenting or endarterectomy.
6. Any cardiac procedure (surgical or percutaneous) or percutaneous coronary intervention within the 90 days prior to the initial procedure.
7. Coronary artery bypass graft (CABG) procedure within the 6 months prior to the initial procedure.
8. Awaiting cardiac transplantation or other cardiac surgery within the 12 months following the initial ablation procedure.
9. Presence of a permanent pacemaker, biventricular pacemaker, or any type of implantable cardiac defibrillator (with or without biventricular pacing function).
10. Documented thromboembolic event (stroke or transient ischemic attack) within 6 months (180 days) prior to the initial ablation procedure.
11. Documented left atrial thrombus on imaging.
12. History of blood clotting or bleeding abnormalities.
13. Any condition contraindicating chronic anticoagulation.
14. Myocardial infarction (MI) within the 3 months (90 days) prior to the initial procedure.
15. Body mass index >40 kg/m2
16. Left atrial diameter >55 mm (anterioposterior).
17. Diagnosed atrial myxoma.
18. Left ventricular ejection fraction (EF) < 35%.
19. Uncontrolled heart failure or NYHA Class III or IV heart failure.
20. Rheumatic heart disease.
21. Hypertrophic cardiomyopathy.
22. Unstable angina.
23. Moderate to severe mitral valve stenosis.
24. Severe mitral regurgitation (regurgitant volume ≥ 60 mL/beat, regurgitant fraction ≥ 50%, and/or effective regurgitant orifice area ≥ 0.40cm2).
25. Primary pulmonary hypertension.
26. Significant restrictive or obstructive pulmonary disease or chronic respiratory condition.
27. Renal failure requiring dialysis.
28. History of severe Gastroesophageal Reflux Disease (GERD) requiring surgical and/or mechanical intervention.
29. Acute illness, active systemic infection, or sepsis.
30. Contraindication to both computed tomography and magnetic resonance angiography.
31. Significant congenital anomaly or medical problem that, in the opinion of the investigator, would preclude enrollment in this study or compliance with follow-up requirements or would impact the scientific soundness of the clinical study results.
32. Any woman known to be pregnant or breastfeeding, or any woman of childbearing potential who is not on a reliable form of birth regulation method or abstinence.
33. Current or anticipated participation in any other clinical study of a drug, device, or biologic during the duration of the study not pre-approved by the Sponsor.
34. Presence of intramural thrombus, tumor, or other abnormality that precludes vascular access, catheter introduction, or manipulation.

35. Known drug or alcohol dependency.
36. Life expectancy less than 12 months.
37. Vulnerable subject (such as a prisoner or handicapped or mentally disabled person).

2. Follow-up Schedule

All patients were preoperatively screened at a baseline visit. Postoperatively, all patients were evaluated prior to hospital discharge and were scheduled for follow-up evaluations at 10 days, 30 days, 75 days, 90 days, 180 days, and 360 days post-ablation. Table 3 below provides the schedule of events for the study. Adverse events and complications were recorded at all visits.

Table 3. Schedule of evaluations and visits

	Enrollment / Baseline	Ablation	Pre-Discharge	Day 10 Call	Day 30 Visit	Day 75 Call[1]	Day 90 Visit	Day 180 Visit	Day 360 Visit	Repeat Ablation	Unscheduled
Window (days)		*0*		*7-13*	*14-42*	*60-90*	*76-104*	*150-210*	*330-390*		
Informed consent	X										
Adverse events	X	X	X	X	X	X	X	X	X	X	X
Eligibility criteria	X										
Demographics	X										
Medical history / hospitalization	X			X	X		X	X	X	X	X
Cardiac medications	X	X	X	X	X	X	X	X	X	X	X
Physical exam	X		X		X						X
12-Lead ECG	X		X		X[2]		X[3]	X[3]	X[3]		X
Transthoracic echocardiogram (TTE) / Transesophageal echocardiogram (TEE)	X[4]		X[5]								
Thrombus screening [6]	X[6]									X[6]	
Pregnancy test [7]	X[7]									X[7]	
Randomization	X										
Ablation		X								X	
Phrenic nerve		X	X[8]		X[8]				X[8]		
NIH Stroke Scale	X		X								
PV anatomy [9]					X[9]		X[9]	X[9]	X[9]		X[9]
Transtelephonic monitoring (TTM) transmission [10]							X	X	X		
Holter Monitor								X	X		
TTM/Holter review								X	X		
Quality of Life	X							X	X		

[1] Required if the Day 90 visit was not performed within the blanking period (on or before day 90)
[2] Allowed to be performed by the referring cardiologist as part of a "hybrid" visit including an office visit with the referring cardiologist and a telephone call with the investigator
[3] If the visit was a telehealth visit, transmission of TTM recordings was to be performed in lieu of 12-lead ECG
[4] Within 6 months prior to the ablation procedure (including prior to enrollment as part of routine clinical evaluations)
[5] TTE was required prior to discharge if the subject had symptoms suggestive of pericardial effusion and/or pericarditis
[6] Thrombus screening was required the day before or the day of the ablation procedure
[7] Pregnancy test was only required for women of childbearing potential
[8] Phrenic nerve evaluation was required if new phrenic nerve injury was observed/suspected in the ablation procedure and unresolved at previous assessment(s)
[9] Chest CT or MRI required if the subject experienced symptoms associated with PV stenosis
[10] Subjects were instructed to transmit TTM recordings at least monthly and when AF-related symptoms occurred after the 90-day blanking period

3. Clinical Endpoints

i. Primary Safety Endpoint

The primary safety endpoint is the incidence of the following device- or procedure-related serious adverse events (SAEs), as adjudicated by an independent and blinded Clinical Events Committee (CEC), following the index ablation procedure:

Within 7 days of ablation procedure:

- Death
- Myocardial infarction
- Phrenic nerve paralysis
- Transient ischemic attack (TIA)
- Stroke/cerebrovascular accident (CVA)
- Thromboembolism
- Major vascular access complications / bleeding
- Heart block
- Gastroparesis
- Severe pericarditis
- Hospitalization (initial and prolonged) due to cardiovascular or pulmonary AE[2]

Within 30 days of ablation procedure:

- Cardiac tamponade/perforation

Within 90 days of ablation procedure:

- Atrio-esophageal fistula

Within 180 days of ablation procedure:

- Pulmonary vein stenosis

The study aimed to demonstrate noninferiority of the investigational device compared to the control device with respect to the primary safety endpoint. Primary safety noninferiority was tested with a noninferiority margin of 8%.

ii. Primary Effectiveness Endpoint

The primary effectiveness endpoint is freedom from documented recurrence of atrial fibrillation (AF), atrial flutter (AFL), or atrial tachycardia (AT) based on electrocardiographic data through 12-month follow-up and excluding a 90-day

[2] Excludes hospitalization due to AF/AFL/AT recurrence.

blanking period. The following are considered primary effectiveness endpoint failures:

- Inability to isolate all targeted pulmonary veins during the index procedure.
- Ablation using devices other than the assigned study device for any left atrial ablation during the index procedure.
- Any repeat ablation, surgical ablation, or arrhythmia surgery for treatment of recurrent AF/AFL/AT after the index procedure.
- Documented AF/AFL/AT recurrence after the 90-day blanking period.
- Class I or III AAD dose increase from the historic maximum ineffective dose (prior to the index procedure) or initiation of a new Class I or III AAD for treatment of AF/AFL/AT after the 90-day blanking period.
- DC cardioversion for AF/AFL/AT after the 90-day blanking period.

A documented recurrence of AF/AFL/AT based on electrocardiographic data was (a) an episode ≥ 30 seconds in duration documented by ECG, TTM, or Holter monitor or (b) an episode covering an entire 12-lead ECG recording lasting at least 10 seconds.

Within the blanking period, recurrent arrhythmias could have been managed with antiarrhythmic drugs or cardioversions. Titration or initiation of Class I and III antiarrhythmic medications was allowed during the blanking period, but use of new or increased Class I or III antiarrhythmic medications after the blanking period was considered a primary effectiveness failure. Repeat ablation at any time after the index ablation procedure was considered a primary effectiveness failure.

The study aimed to demonstrate noninferiority of the investigational device compared to the control device with respect to the primary effectiveness endpoint. Primary effectiveness noninferiority was tested with a noninferiority margin of 15%.

iii. Secondary Endpoints

Secondary endpoints included:

- Incidence of early onset (within 7 days of the index ablation procedure), peri-procedural (>7 and ≤30 days), and late onset (>30 days) serious adverse events (SAEs)
- Changes in Quality of Life (QOL)
- Rate of acute ablation success
- Use of antiarrhythmic drugs (AADs)
- Ablation lesion sets delivered (ablation strategy)

B. Subject Accountability

477 subjects were enrolled in the study. Of those enrolled in the study, 37 were assigned to the roll-in cohort and had an ablation with the investigational device. Eight (8) subjects exited the study prior to randomization, and 432 were randomized. Of the randomized subjects, 12 exited the study prior to ablation, leaving 420 randomized subjects with an ablation. 444 subjects completed the study (see Figure 6).

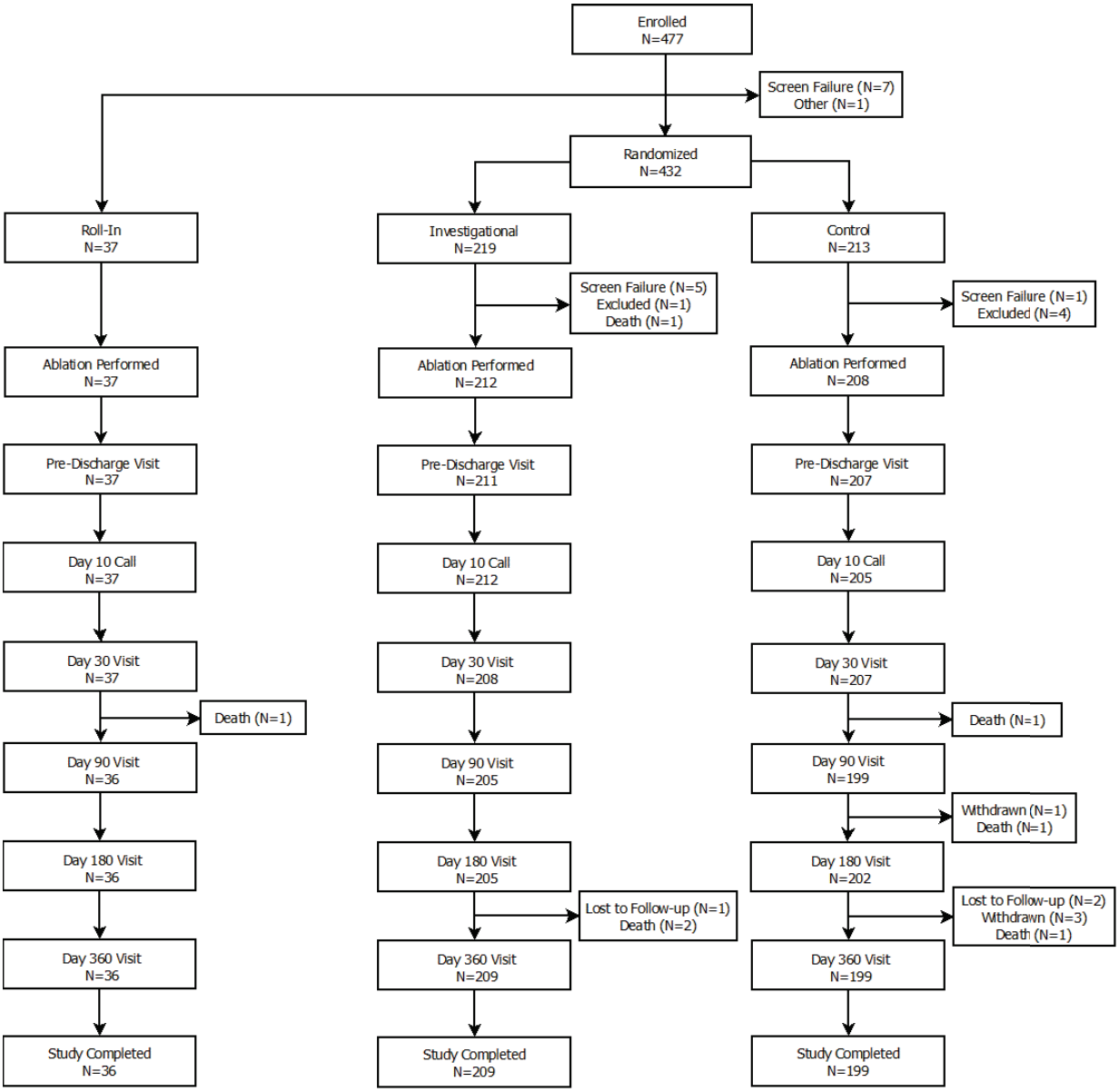


Figure 6: Subject Accountability [3]

[3] A total of five subjects were enrolled in the study and met all eligibility criteria but did not undergo a mapping and/or ablation procedure involving the assigned study device. These subjects were excluded from the primary analysis cohort. Subjects were excluded for investigational system unavailable (n=1), control system unavailable (n=3), or control device inadvertently not used (n=1).

The analysis populations included:

- Primary Analysis Cohort (PAC)[4] (N=420) includes subjects who were randomized and underwent insertion of the assigned study device.
- Atrial Flutter Cohort[5] (N=212) includes subjects who were randomized and received a cavotricuspid isthmus ablation line with the assigned study device.

C. Visit and Rhythm Monitoring Compliance

Summaries of the visit, Holter, TTM, and ECG compliance of the PAC subjects based on requirements outlined in the protocol are provided below. Holter, TTM, and ECG compliance represents those that have been received by the core lab and fully adjudicated.

Table 4: Compliance Summary – Follow-up Visits

	Investigational (N=212)			Control (N=208)		
Visit Name	Visits Expected	Visits Occurred (%)	In-Window Visits (%)	Visits Expected	Visits Occurred (%)	In-Window Visits (%)
Index Ablation	212	212 (100%)	NA	208	208 (100%)	NA
Pre-Discharge	212	211 (99.5%)	NA	208	207 (99.5%)	NA
Day 10 Call	212	212 (100%)	205 (96.7%)	208	205 (98.6%)	197 (94.7%)
Day 30 Visit	212	208 (98.1%)	200 (94.3%)	208	207 (99.5%)	185 (88.9%)
Day 75 Call [1]	153	131 (85.6%)	130 (85.0%)	145	121 (83.4%)	117 (80.7%)
Day 90 Visit	212	205 (96.7%)	190 (89.6%)	207	199 (96.1%)	181 (87.4%)
Day 180 Visit	212	205 (96.7%)	179 (84.4%)	205	202 (98.5%)	183 (89.3%)
Day 360 Visit	210	209 (99.5%)	188 (89.5%)	201	199 (99.0%)	179 (89.1%)

[1]Day 75 Call was only required if Day 90 Visit was not going to occur within 90 days of the index ablation procedure.

TTM compliance is summarized in Table 5. TTM compliance is calculated for each subject in the PAC as the number of effectiveness evaluation months in which a TTM recording was transmitted divided by the total number of effectiveness evaluation months for that subject (typically 9). Expected transmissions are estimated based on a 31-day month. The protocol required TTM recordings at least monthly after the 90-day blanking period. If a subject's actual number of TTM recordings for a month is greater than 1, it is counted as 1 for the purpose of compliance calculation.

[4] PAC was prespecified in the protocol.
[5] Post-hoc cohort created for retrospective analyses on the Sphere-9 Catheter and Affera Ablation system safety and effectiveness profile when used to treat of cavotricuspid isthmus dependent atrial flutter.

Table 5: Compliance Summary – TTM

Month	#Occurred / #Expected (%)	
	Investigational (N=212)	Control (N=208)
Overall compliant patient-months	1592/1875 (84.9%)	1507/1831 (82.3%)
Month 4	187/212 (88.2%)	174/207 (84.1%)
Month 5	188/212 (88.7%)	174/207 (84.1%)
Month 6	181/212 (85.4%)	169/207 (81.6%)
Month 7	186/212 (87.7%)	173/206 (84.0%)
Month 8	181/212 (85.4%)	174/205 (84.9%)
Month 9	178/212 (84.0%)	175/205 (85.4%)
Month 10	183/211 (86.7%)	172/205 (83.9%)
Month 11	176/211 (83.4%)	170/205 (82.9%)
Month 12	132/181 (72.9%)	126/184 (68.5%)

Holter and 12-lead ECG compliance are summarized in Table 6. The protocol allowed subjects to transmit ECG recordings with the TTM in place of the 12-lead ECG if the visit was telehealth. Among the PAC, 12-lead ECG was collected for 840 of these visits, whereas subjects used the TTM in place of the 12-lead ECG 222 times. Only TTMs collected within the associated visit windows were used in place of ECGs.

Table 6: Compliance Summary – Holter and 12-Lead ECG

Visit	#Occurred / #Expected (%)	
	Investigational (N=212)	Control (N=208)
Day 180 Holter [1]	178/212 (84.0%)	170/205 (86.8%)
Day 360 Holter [1]	174/210 (82.9%)	174/201 (86.6%)
Day 90 12-Lead ECG + TTM [2]	(149 + 30)/212 (84.4%)	(141 + 26)/207 (80.7%)
Day 180 12-Lead ECG + TTM [2]	(132 + 48)/212 (84.9%)	(130 + 48)/205 (86.8%)
Day 360 12-Lead ECG + TTM [2]	(146 + 42)/210 (89.5%)	(142 + 28)/201 (84.6%)

[1] Holters less than 18 hours do not contribute to Holter compliance. Data from all Holters regardless of duration are used for endpoint analysis.
[2] If the visit is a telehealth visit, TTM is performed in lieu of 12-lead ECG and included in the count.

D. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for a persistent atrial fibrillation ablation treatment study performed in the US. The subject demographic and baseline health status characteristics of the treated primary analysis cohort subjects are shown in Table 7 below.

Table 7. Subject Demographics and Baseline Characteristics

Parameter	Investigational (N = 212)	Control (N = 208)
Age (years)		
Mean ± SD (N)	67.8 ± 8.3 (212)	66.7 ± 8.8 (208)
Median (Min, Max)	69.0 (28, 80)	68.0 (38, 80)
Sex		
Female	73 (34.4%)	61 (29.3%)
Male	139 (65.6%)	147 (70.7%)
Ethnicity		
Hispanic or Latino	2 (0.9%)	5 (2.4%)
Not Hispanic or Latino	206 (97.2%)	201 (96.6%)
Not Provided	4 (1.9%)	2 (1.0%)

Table 7. Subject Demographics and Baseline Characteristics

Parameter	Investigational (N = 212)	Control (N = 208)
Race		
American Indian or Alaska Native	1 (0.5%)	0 (0.0%)
Asian	4 (1.9%)	4 (1.9%)
Black or African American	4 (1.9%)	2 (1.0%)
Native Hawaiian/Other Pacific Is.	0 (0.0%)	1 (0.5%)
White	199 (93.9%)	199 (95.7%)
Not provided	4 (1.9%)	2 (1.0%)
Medical History		
Congestive heart failure	36 (17.0%)	26 (12.5%)
Coronary Artery Disease	37 (17.5%)	35 (16.8%)
Myocardial infarction	9 (4.2%)	7 (3.4%)
Hypertension (systemic)	160 (75.5%)	157 (75.5%)
Cardiomyopathy	22 (10.4%)	14 (6.7%)
Atrial Flutter	33 (15.6%)	36 (17.3%)
Atrial Tachycardia	5 (2.4%)	2 (1.0%)
Stroke/TIA	16 (7.5%)	11 (5.3%)
Chronic obstructive pulmonary disease (COPD)	16 (7.5%)	13 (6.3%)
Diabetes	38 (17.9%)	34 (16.3%)
Obstructive sleep apnea (OSA)	47 (22.2%)	57 (27.4%)
Renal disease	22 (10.4%)	15 (7.2%)
Other structural heart disease	9 (4.2%)	11 (5.3%)
PerAF History		
Time from first diagnosis of PerAF (years)		
Mean ± SD (N)	1.3 ± 2.6 (212)	1.3 ± 2.2 (208)
Median (Min, Max)	0.5 (0, 28)	0.5 (0, 18)
Duration of longest PerAF episode (weeks)		
Mean ± SD (N)	8.1 ± 9.9 (171)	7.3 ± 9.0 (172)
Median (Min, Max)	4.0 (1, 44)	3.0 (1, 45)
Atrial Arrhythmia Cardioversion History		
Previous electrical cardioversion for atrial arrhythmias	146 (68.9%)	140 (67.3%)
Previous pharmacological cardioversion for atrial arrhythmias	13 (6.1%)	15 (7.2%)
Height (cm)		
Mean ± SD (N)	175.1 ± 10.0 (211)	176.7 ± 11.2 (207)
Median (Min, Max)	175.0 (140, 200)	178.0 (137, 208)
Weight (kg)		
Mean ± SD (N)	92.5 ± 18.4 (211)	95.3 ± 20.1 (207)
Median (Min, Max)	90.0 (53, 149)	93.0 (53, 144)
BMI (kg/m^2)		
Mean ± SD (N)	30.0 ± 4.8 (211)	30.3 ± 4.9 (207)
Median (Min, Max)	29.7 (17, 40)	30.3 (19, 40)
LA Diameter (mm)		
Mean ± SD (N)	43.0 ± 6.1 (210)	44.0 ± 5.4 (208)
Median (Min, Max)	43.0 (22, 55)	44.0 (24, 55)
LVEF (%)		
Mean ± SD (N)	57.7 ± 7.2 (212)	55.5 ± 8.0 (208)
Median (Min, Max)	60.0 (35, 75)	55.0 (35, 75)
CHA2DS2-VASC Score		
Mean ± SD (N)	2.4 ± 1.4 (212)	2.3 ± 1.4 (207)
Median (Min, Max)	2.0 (0, 6)	2.0 (0, 5)
CHA2DS2-VASC Score		
0	17 (8.0%)	22 (10.6%)
1	36 (17.0%)	39 (18.8%)

Table 7. Subject Demographics and Baseline Characteristics

Parameter	Investigational (N = 212)	Control (N = 208)
≥ 2	159 (75.0%)	146 (70.2%)
Heart Failure		
NYHA Class I	27 (12.7%)	28 (13.5%)
NYHA Class II	47 (22.2%)	36 (17.3%)
Not Available	1 (0.5%)	0 (0.0%)
No signs of heart failure	137 (64.6%)	144 (69.2%)
Failed AAD Type[1]		
Class I	65 (30.7%)	66 (31.7%)
Class II	98 (46.2%)	91 (43.8%)
Class III	147 (69.3%)	133 (63.9%)
Class IV	18 (8.5%)	17 (8.2%)

[1] Percent of total subjects having one or more failed medications within each AAD Class

E. Safety and Effectiveness Results

1. Primary Analyses

i. Primary Safety Endpoint

Among the 420 primary analysis cohort subjects, the primary safety endpoint occurred in 3 (1.4%) subjects in the investigational arm and 2 (1.0%) subjects in the control arm. The three primary safety events in the investigational arm were hospitalizations due to cardiovascular or pulmonary adverse events including chronic obstructive pulmonary disease exacerbation, pulmonary edema, and hemoptysis. In the control arm, the two primary safety endpoints were hospitalizations due to cardiovascular or pulmonary adverse events including one for hypervolemia and one for hypoxia. The difference in the incidence of primary safety events between the investigational and control arms was 0.5% (90% CI: [-2.8%, 3.7%]). Based on the prespecified safety non-inferiority margin of 8%, the investigational device was non-inferior to the control device, $p<0.0001$. A summary of the primary safety endpoint events and non-inferiority testing are summarized in Table 8 and Table 9, respectively.

Table 8. Primary Safety Endpoint Components

Primary Safety Endpoint Event	# Events (# Subjects, % Subjects)	
	Investigational (N=212)	Control (N=208)
Primary Safety Endpoint Failure	**3 (3, 1.4%)**	**2 (2, 1.0%)**
Within 7 days of procedure		
Death	0 (0, 0.0%)	0 (0, 0.0%)
Myocardial infarction	0 (0, 0.0%)	0 (0, 0.0%)
Phenic nerve paralysis	0 (0, 0.0%)	0 (0, 0.0%)
Transient ischemic attack (TIA)	0 (0, 0.0%)	0 (0, 0.0%)
Stroke/cerebrovascular accident (CVA)	0 (0, 0.0%)	0 (0, 0.0%)
Thromboembolism	0 (0, 0.0%)	0 (0, 0.0%)
Major vascular access complications / bleeding	0 (0, 0.0%)	0 (0, 0.0%)
Heart block	0 (0, 0.0%)	0 (0, 0.0%)
Gastroparesis	0 (0, 0.0%)	0 (0, 0.0%)
Severe pericarditis	0 (0, 0.0%)	0 (0, 0.0%)

Table 8. Primary Safety Endpoint Components

Primary Safety Endpoint Event	# Events (# Subjects, % Subjects)	
	Investigational (N=212)	Control (N=208)
Hospitalization (initial or prolonged) due to cardiovascular or pulmonary AE	3 (3, 1.4%)	2 (2, 1.0%)
Within 30 days of procedure		
Cardiac tamponade/perforation	0 (0, 0.0%)	0 (0, 0.0%)
Within 90 days of procedure		
Atrio-esophageal fistula	0 (0, 0.0%)	0 (0, 0.0%)
Within 180 days of procedure		
Pulmonary vein stenosis	0 (0, 0.0%)	0 (0, 0.0%)

Table 9. Primary Safety Endpoint – Farrington Manning Non-Inferiority Test

Parameter	Number, Percent of Failures (90% CI)		Difference (90% CI)	One-sided *p*-value (Non-Inferiority Margin = 8%)
	Investigational (N=212)	Control (N=208)	Investigational – Control	
Primary Safety Endpoint Failure	3, 1.4% (0.4%, 3.6%)	2, 1.0% (0.2%, 3.0%)	0.5% (-2.8%, 3.7%)	<0.0001

ii. Primary Effectiveness Endpoint

Of the 420 subjects in the primary analysis cohort, 412 completed the study or had a primary effectiveness failure and were included in the final analysis of the primary endpoint (210 subjects in the investigational arm, 202 subjects in the control arm). Freedom from primary effectiveness endpoint failure for the investigational arm was 73.8% compared to 65.5% in the control arm. The difference in primary effectiveness endpoint success for the investigational device and the control device was 8.0% (95% CI: [-0.9%, 16.8%]). Based on the prespecified effectiveness non-inferiority margin of 15%, the investigational device was non-inferior to the control device, $p<0.0001$.

A summary of the primary effectiveness endpoint and non-inferiority testing are summarized in Table 10 and Table 11, respectively.

Table 10. Primary Effectiveness Endpoint and Failure Modes

Parameter	Investigational (N=210)	Control (N=202)
Primary Effectiveness Endpoint Success	**155 (73.8%)**	**133 (65.8%)**
Primary Effectiveness Endpoint Failure[1]	**55 (26.2%)**	**69 (34.2%)**
Inability to isolate all targeted pulmonary veins during the index procedure	0 (0.0%)	0 (0.0%)
Any left atrial ablation done with non-assigned study device during the index procedure	0 (0.0%)	2 (1.0%)
Any repeat ablation or surgery for AF/AFL/AT recurrence after the index procedure	10 (4.8%)	17 (8.4%)
DC cardioversion for AF/AFL/AT recurrence during the effectiveness evaluation period	13 (6.2%)	13 (6.4%)
Documented AF/AFL/AT recurrence during the effectiveness evaluation period	49 (23.3%)	55 (27.2%)
Class I/III AAD dose increase from the historic maximum ineffective dose or initiation of new class I/III AAD during the effectiveness evaluation period	8 (3.8%)	15 (7.4%)

[1] Failure modes are not mutually exclusive since the same subject can experience multiple failure modes.

Table 11. Primary Effectiveness Endpoint Result

Parameter	Number, Percent of Successes (95% CI)		Difference (95% CI)	One-sided *p*-value (Non-Inferiority Margin = 15%)
	Investigational (N=210)	Control (N=202)	Investigational – Control	
Primary Effectiveness Endpoint Success	155, 73.8% (67.5%, 79.3%)	133, 65.8% (59.1%, 72.0%)	8.0% (-0.9%, 16.8%)	<0.0001

Kaplan-Meier estimates of freedom from primary effectiveness endpoint failure are presented in Figure 7 for the investigational arm (blue) and the control arm (red). The log-rank test *p*-value was 0.064. Note that the window for the Day 360 visit extended from study day 330 to study day 390, so data censoring during the last 30 days is expected, accounting for the low number at risk at day 360. In case of failure at the Day 360 visit, within the visit window but beyond study day 360, the date of failure was set to study day 360 so that the failure was included in the Kaplan-Meier analysis.

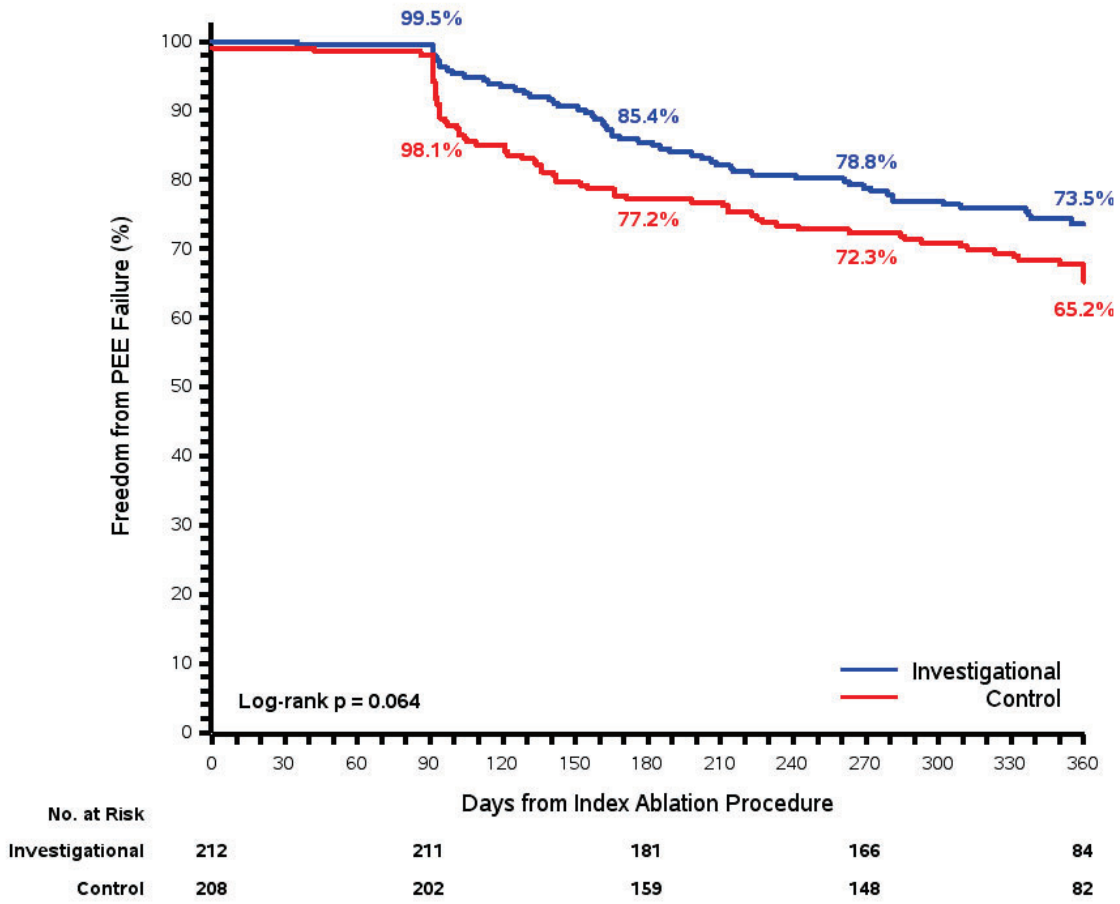


Figure 7: Primary Effectiveness Endpoint: Kaplan-Meier Plot
Population: PAC

2. Secondary Analyses (Sequential Superiority Testing)

Prespecified superiority testing was performed for four endpoints including three procedural times and the primary effectiveness endpoint. Energy application time was 29.2 minutes less (95% CI: [-31.7, -26.8]), treatment time was 26.8 minutes less (95% CI: [-32.2, -21.4]), and total procedure time was 25.1 minutes less (95% CI: [-33.0, -17.3]) in the investigational arm compared to the control arm. The investigational device was superior for each of these three endpoints compared to the control device, with one-sided $p<0.0001$ for each of the three hypothesis tests.

The null hypothesis of no difference between the underlying rate of the primary effectiveness endpoint in the two arms was not rejected, with one-sided $p=0.039$ ($\alpha=0.025$). While the observed rate of primary effectiveness endpoint success was numerically higher with the investigational device, primary effectiveness with the investigational device was not shown to be superior to the control device.

Table 12. Sequential Superiority Testing

Parameter	Mean ± SD (N) or Proportion of subjects (95% CI) (N)		Difference (95% CI)	One-sided *p*-value	α-level	Success (Yes/No)
	Investigational	Control	Investigational - Control			
Energy application time (min)	7.1 ± 2.0 (212)	36.4 ± 17.7 (206)	-29.2 (-31.7, -26.8)	<0.0001	0.005	Yes
Treatment time (min)[1]	46.7 ± 20.0 (212)	73.5 ± 34.4 (208)	-26.8 (-32.2, -21.4)	<0.0001	0.005	Yes
Procedure time (min)[2]	100.9 ± 30.8 (212)	126.1 ± 49.2 (208)	-25.1 (-33.0, -17.3)	<0.0001	0.005	Yes
Primary Effectiveness Endpoint Success	73.8% (67.5%, 79.3%) (210)	65.8% (59.1%, 72.0%) (202)	8.0% (-0.9%, 16.8%)	0.039	0.025	No

[1] Treatment time is defined as the time from first ablation to last ablation.
[2] Procedure time is defined as the time from venous access to sheath removal.

3. Additional Analyses

i. Secondary Safety Endpoint

A total of 123 serious adverse events (57 in the investigational arm, 66 in the control arm) occurred during or post index ablation procedure in subjects in the PAC. Table 13 summarizes the incidence of early onset (within 7 days of the index ablation procedure) SAEs, incidence of peri-procedural (>7 and ≤30 days) SAEs, and incidence of late onset (>30 days) SAEs stratified by treatment group.

Table 13. Secondary Safety Endpoint: SAEs by Timepoint

Parameter	# Events (#, % of Subjects)	
	Investigational (N=212)	Control (N=208)
SAEs during procedure or ≤ 7 days after procedure	9 (7, 3.3%)	8 (8, 3.8%)
SAEs 8 – 30 days after procedure	5 (4, 1.9%)	4 (4, 1.9%)
SAEs > 30 days after procedure	43 (28, 13.2%)	54 (33, 15.9%)

ii. Adverse events

Adverse events were collected starting at the time of signing the informed consent form through the duration of the subject's participation in the study. There were no unanticipated adverse device effects reported in the study. All adverse events related to the primary safety endpoint were reviewed and adjudicated by an independent and blinded Clinical Events Committee (CEC).

A total of 271 adverse events were reported in the study. 126 were serious adverse events, and 87 were classified as being related or possibly related to the study device and/or procedure. Table 14 summarizes the 16 serious adverse events related or possibly related to the study device and/or procedure. Adverse events are reported per the Medical Dictionary for Regulatory Activities (MedDRA) preferred term.

Table 14. Primary Analysis Cohort: Procedure or Device Related Serious Adverse Events During or After the Index Ablation Procedure Summary by MedDRA Category

		# Events (# Subjects, % Subjects)	
MedDRA System Organ Class	**MedDRA Preferred Term**	**Investigational (N=212)**	**Control (N=208)**
Total	**Total**	**9 (8, 3.8%)**	**7 (7, 3.4%)**
Cardiac disorders	Bradycardia	2 (2, 0.9%)	0 (0, 0.0%)
	Myocardial infarction	0 (0, 0.0%)	1 (1, 0.5%)
	Pericardial effusion	1 (1, 0.5%)[1]	0 (0, 0.0%)
	Pericarditis	0 (0, 0.0%)	1 (1, 0.5%)
Gastrointestinal disorders	Oesophageal mucosa erythema	0 (0, 0.0%)	1 (1, 0.5%)
Infections and infestations	Sepsis	1 (1, 0.5%)	1 (1, 0.5%)
Injury, poisoning and procedural complications	Vascular access site haemorrhage	1 (1, 0.5%)	0 (0, 0.0%)
Investigations	Troponin increased	1 (1, 0.5%)	0 (0, 0.0%)
Metabolism and nutrition disorders	Hypervolaemia	0 (0, 0.0%)	1 (1, 0.5%)
Respiratory, thoracic and mediastinal disorders	Chronic obstructive pulmonary disease	1 (1, 0.5%)	0 (0, 0.0%)
	Haemoptysis	1 (1, 0.5%)	0 (0, 0.0%)
	Hypoxia	0 (0, 0.0%)	1 (1, 0.5%)
	Pleuritic pain	0 (0, 0.0%)	1 (1, 0.5%)
	Pulmonary oedema	1 (1, 0.5%)	0 (0, 0.0%)

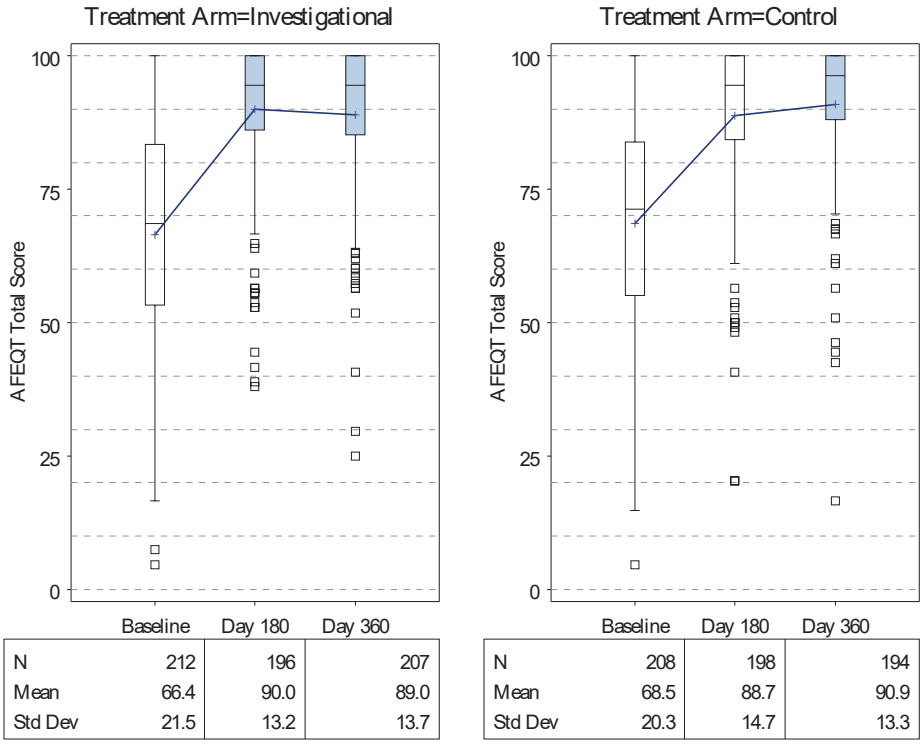
[1] Subject had a history of pericardial effusion (diagnosed in 2021). In May 2023, 284 days post index ablation procedure, pericardial effusion was noted after subject underwent a TEE after presenting with dyspnea and lower extremity edema.

Seven (7) deaths occurred in the study, of which one was prior to the index ablation procedure, one was in a Roll-In subject, and five were in the primary analysis cohort. None of the deaths were reported to be device- or procedure-related.

iii. Secondary Effectiveness Endpoint – Quality of Life (QOL)

The Atrial Fibrillation Effect on Quality-of-Life (AFEQT) score is a QOL measure specific to atrial fibrillation, with a range of 0 (complete disability) to 100 (no disability). The SF-12v2 Health Survey is a validated general QOL survey that can be summarized using two overall scores, the Mental Component Summary and the Physical Component Summary. Each score ranges from 0 to 100, with higher scores indicating improved QOL.

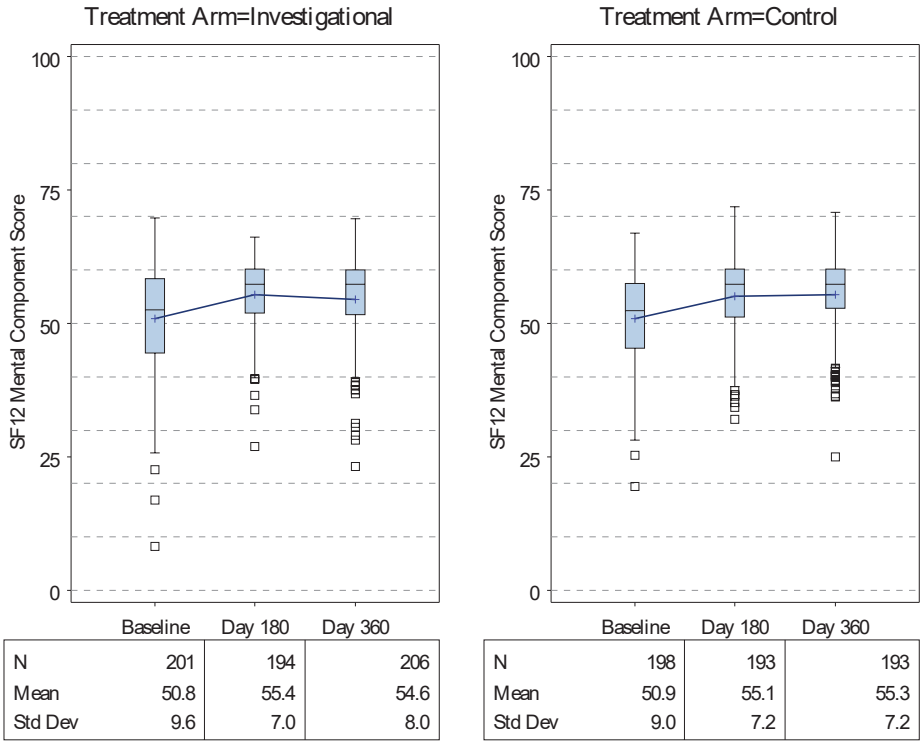
The AFEQT Questionnaire and the SF-12v2 Health Survey were performed at baseline, Day 180 and Day 360 follow-up timepoints. In both the investigational and control arms, there was a trend of increased scores (improved quality of life) on both the AFEQT and SF-12v2 Health Survey at Day 180 and Day 360 follow-up when compared to baseline assessments.



	Baseline	Day 180	Day 360
N	212	196	207
Mean	66.4	90.0	89.0
Std Dev	21.5	13.2	13.7

	Baseline	Day 180	Day 360
N	208	198	194
Mean	68.5	88.7	90.9
Std Dev	20.3	14.7	13.3

Figure 8: AFEQT Total Score Trend



	Baseline	Day 180	Day 360
N	201	194	206
Mean	50.8	55.4	54.6
Std Dev	9.6	7.0	8.0

	Baseline	Day 180	Day 360
N	198	193	193
Mean	50.9	55.1	55.3
Std Dev	9.0	7.2	7.2

Figure 9 : SF-12v2 Mental Component Score Trend

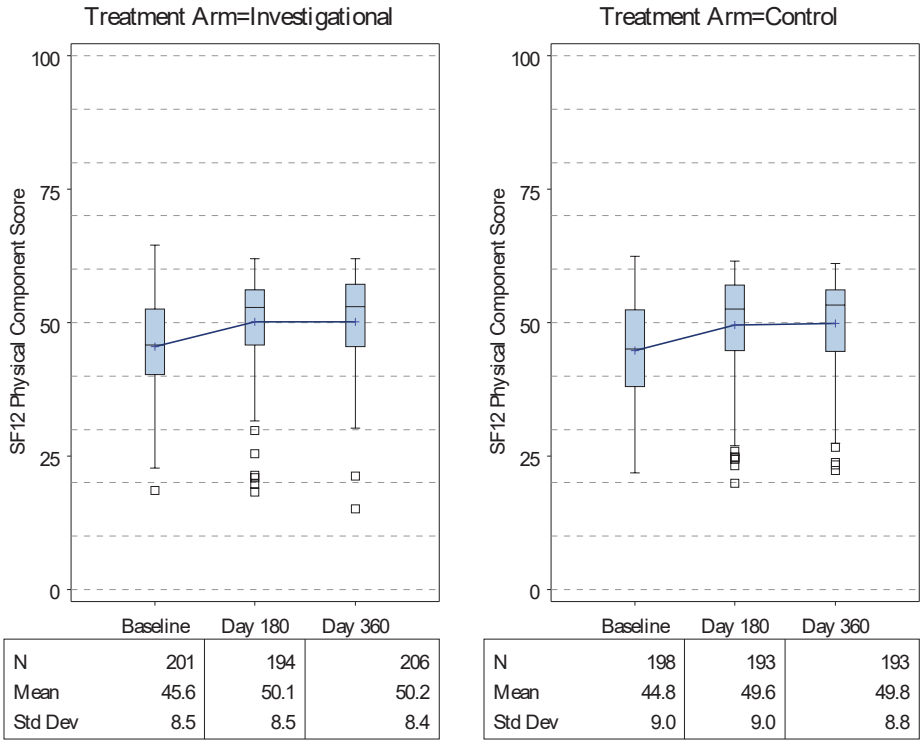


Figure 10: SF-12v2 Physical Component Score Trend

iv. Secondary Effectiveness Endpoint – Acute Procedural Success

Table 15 shows the rate of acute procedural success with the assigned study device, defined as confirmation of entrance block in all targeted pulmonary veins, rate of pulmonary vein isolation on a per-vein basis, and rate of acute block across linear ablations.

Rate of acute procedural success, defined as isolation of all targeted pulmonary veins using only the assigned study catheter, was 100% in the investigational arm and 99.5% in the control arm, with one control subject requiring use of a non-study catheter to achieve isolation of the left superior pulmonary vein. On a per-vein basis, pulmonary vein isolation was achieved with the assigned study catheter in 100% and 99.9% of the investigational and control arm subjects, respectively.

Additional linear ablation was only required for treatment of documented macro-reentrant tachycardias, and empiric linear lesions were discouraged. Acute procedural success for linear ablations is defined as confirmed block across the lesion using ablation with only the assigned study catheter. There were 115 cavotricuspid isthmus (CTI) lines treated in the investigational arm and 97 in the control arm. Rate of acute block across CTI lines was 100% in the investigational and control arms. Rate of acute block across mitral isthmus lines was 100% in the investigational arm and 95% in the control arm, with one control subject requiring the additional use of alcohol ablation to achieve block in the Vein of Marshall. There were 198 subjects with treated LA roof, posterior or inferior lines in the

investigational arm and 137 in the control arm. Rate of acute block across these lines were 100% in both arms.

Table 15. Secondary Effectiveness: Acute Ablation Result (Isolation/Block with Assigned Study Device)

Parameter	Numerator / Denominator (%)		Difference
	Investigational	Control	Investigational - Control
Acute pulmonary vein isolation with the assigned study device (per subject)[1]	212/212 (100%)	207/208 (99.5%)	0.5%
Pulmonary veins isolated with the assigned study device (per vein)[2]	844/844 (100%)	828/829 (99.9%)	0.1%
Cavotricuspid isthmus line with the assigned study device (per subject)[3]	115/115 (100%)	97/97 (100%)[4]	0.0%
Mitral isthmus line with the assigned study device (per subject)[5]	72/72 (100%)	21/22 (95.5%)	4.5%
LA roof, posterior, or inferior line with the assigned study device (per subject)[6]	198/198 (100%)	137/137 (100%)	0.0%

[1] Percent of subjects with confirmed entrance block in all targeted PVs out of all subjects with PVI attempted.
[2] Percent of pulmonary veins isolated (i.e. with confirmed entrance block) out of all pulmonary veins targeted.
[3] Percent of subjects with confirmed bidirectional block out of all subjects with cavotricuspid isthmus line targeted.
[4] In one control patient the cavotricuspid isthmus line was blocked with an RF catheter that was not the assigned study device. No attempt was made to use the control device for this lesion. Lesion excluded from this table.
[5] Percent of subjects with confirmed block (bidirectional, or unidirectional if bidirectional block was not tested) out of all subjects with mitral isthmus line targeted.
[6] Percent of subjects in whom LA roof, posterior or inferior line was targeted with confirmed block across all such lines (bidirectional, or unidirectional if bidirectional block was not tested).
Program Name: SEE-AcuteAbl Res.sas

v. Secondary Effectiveness Endpoint – Use of Antiarrhythmic Drugs

Table 16 summarizes the use of Class I or III antiarrhythmic drugs at baseline and at the Day 360 visit or study exit. A trend of decreased antiarrhythmic drug use was observed in both study arms.

Table 16. Secondary Effectiveness: Class I or III Antiarrhythmic Drug Usage Summary during Effectiveness Evaluation Period

Parameter	At Baseline # Subjects (%)		At Day 360 or Study Exit # Subjects (%)	
	Investigational (N=212)	Control (N=208)	Investigational (N=212)	Control (N=208)
Any Class I or III	143 (67.5%)	135 (64.9%)	37 (17.5%)	33 (15.9%)
Any Class I	41 (19.3%)	39 (18.8%)	12 (5.7%)	9 (4.3%)
Any Class III	103 (48.6%)	96 (46.2%)	25 (11.8%)	24 (11.5%)

4. Subgroup Analyses

The subgroup analysis results (as shown in Table 17 and Table 18) do not suggest heterogeneity of treatment effect by sex, age, or left atrial diameter.

Table 17. Primary Safety Endpoint Subgroup Analysis

Parameter	Category	#Failures / #Subjects (%)		Difference (95% CI)	Heterogeneity Test *p*-value
		Investigational	Control	Investigational - Control	
Sex	Female	2/73 (2.7%)	0/61 (0.0%)	2.7% (-3.3%, 9.5%)	0.31
	Male	1/139 (0.7%)	2/147 (1.4%)	-0.6% (-4.2%, 2.7%)	
Age	<65	1/61 (1.6%)	2/73 (2.7%)	-1.1% (-8.1%, 6.3%)	0.32
	≥65	2/151 (1.3%)	0/135 (0.0%)	1.3% (-1.5%, 4.7%)	
LA Diameter (mm)	<45	2/125 (1.6%)	0/106 (0.0%)	1.6% (-1.9%, 5.7%)	0.34
	≥45	1/85 (1.2%)	2/102 (2.0%)	-0.8% (-5.9%, 4.6%)	

Table 18. Primary Effectiveness Endpoint Subgroup Analysis

Parameter	Category	#Successes / #Subjects (%)		Difference (95% CI)	Heterogeneity Test *p*-value
		Investigational	Control	Investigational - Control	
Sex	Female	50/72 (69.4%)	31/59 (52.5%)	16.9% (0.1%, 33.0%)	0.30
	Male	105/138 (76.1%)	102/143 (71.3%)	4.8% (-5.6%, 15.0%)	
Age	<65	50/61 (82.0%)	53/71 (74.6%)	7.3% (-7.1%, 21.2%)	0.98
	≥65	105/149 (70.5%)	80/131 (61.1%)	9.4% (-1.7%, 20.4%)	
LA Diameter (mm)	<45	100/124 (80.6%)	72/105 (68.6%)	12.1% (0.8%, 23.4%)	0.22
	≥45	55/84 (65.5%)	61/97 (62.9%)	2.6% (-11.5%, 16.4%)	

5. Atrial Flutter Post Hoc Analyses

The study protocol required CTI linear ablation in cases with documented typical right AFL either prior to or during the index ablation procedure. The protocol also required confirmation of bidirectional conduction block across each line created during the index procedure.

Post-hoc analyses of treatment of CTI-dependent AFL were conducted using the atrial flutter cohort. The atrial flutter cohort consists of a total of 212 randomized subjects (115 investigational arm, 97 control arm) who received a CTI ablation line with the assigned study device, of whom 8 subjects exited the study early. Table 20 summarizes the arrhythmia history and site reported justification for CTI line.

i. Demographics and Baseline Parameters

The subject demographic, baseline health status characteristics, and rationale for CTI line for of the treated atrial flutter cohort subjects are shown in Table 19 and Table 20.

Table 19. Subject Demographics and Baseline Characteristics
Population: Atrial Flutter Cohort

Parameter	Investigational (N = 115)	Control (N = 97)
Age (years)		
Mean ± SD (N)	67.9 ± 8.0 (115)	66.9 ± 8.5 (97)
Median (Min, Max)	69.0 (28, 80)	68.0 (44, 80)
Sex		
Female	42 (36.5%)	29 (29.9%)

Table 19. Subject Demographics and Baseline Characteristics

Population: Atrial Flutter Cohort

Parameter	Investigational (N = 115)	Control (N = 97)
Male	73 (63.5%)	68 (70.1%)
Ethnicity		
Hispanic or Latino	0 (0.0%)	2 (2.1%)
Not Hispanic or Latino	111 (96.5%)	94 (96.9%)
Not Provided	4 (3.5%)	1 (1.0%)
Race		
American Indian or Alaska Native	1 (0.9%)	0 (0.0%)
Asian	3 (2.6%)	1 (1.0%)
Black or African American	2 (1.7%)	2 (2.1%)
Native Hawaiian/Other Pacific Is.	0 (0.0%)	0 (0.0%)
White	109 (94.8%)	93 (95.9%)
Not provided	0 (0.0%)	1 (1.0%)
Medical History		
Congestive heart failure	13 (11.3%)	14 (14.4%)
Coronary Artery Disease	18 (15.7%)	15 (15.5%)
Myocardial infarction	5 (4.3%)	3 (3.1%)
Hypertension (systemic)	84 (73.0%)	73 (75.3%)
Cardiomyopathy	6 (5.2%)	5 (5.2%)
Atrial Flutter	23 (20.0%)	26 (26.8%)
Atrial Tachycardia	3 (2.6%)	0 (0.0%)
Stroke/TIA	9 (7.8%)	9 (9.3%)
Chronic obstructive pulmonary disease (COPD)	8 (7.0%)	8 (8.2%)
Diabetes	17 (14.8%)	17 (17.5%)
Obstructive sleep apnea (OSA)	18 (15.7%)	26 (26.8%)
Renal disease	8 (7.0%)	6 (6.2%)
Other structural heart disease	2 (1.7%)	0 (0.0%)
PerAF History		
Time from first diagnosis of PerAF (years)		
Mean ± SD (N)	1.1 ± 1.9 (115)	1.2 ± 2.1 (97)
Median (Min, Max)	0.4 (0, 12)	0.5 (0, 11)
Typical AFL History		
Time from first diagnosis of typical AFL (years)		
Mean ± SD (N)	1.3 ± 2.1 (23)	1.9 ± 3.4 (26)
Median (Min, Max)	0.5 (0, 8)	0.2 (0, 11)
BMI (kg/m^2)		
Mean ± SD (N)	29.5 ± 4.9 (114)	30.4 ± 5.1 (96)
Median (Min, Max)	29.0 (17, 40)	30.4 (19, 40)
LA Diameter (mm)		
Mean ± SD (N)	42.8 ± 6.3 (115)	43.4 ± 5.6 (97)
Median (Min, Max)	43.0 (22, 55)	43.5 (24, 54)
LVEF (%)		
Mean ± SD (N)	58.2 ± 6.8 (115)	55.0 ± 8.6 (97)
Median (Min, Max)	60.0 (35, 74)	55.0 (35, 75)
CHA2DS2-VASC Score		
Mean ± SD (N)	2.5 ± 1.4 (115)	2.4 ± 1.3 (96)
Median (Min, Max)	3.0 (0, 6)	3.0 (0, 5)
CHA2DS2-VASC Score		
0	9 (7.8%)	8 (8.2%)
1	19 (16.5%)	17 (17.5%)
≥ 2	87 (75.7%)	71 (73.2%)
Heart Failure		
NYHA Class I	17 (14.8%)	14 (14.4%)

Table 19. Subject Demographics and Baseline Characteristics

Population: Atrial Flutter Cohort

Parameter	Investigational (N = 115)	Control (N = 97)
NYHA Class II	25 (21.7%)	22 (22.7%)
Not Available	0 (0.0%)	0 (0.0%)
No signs of heart failure	6 (5.2%)	4 (4.1%)
No history of heart failure	67 (58.3%)	57 (58.8%)
Failed AAD Type[1] for treatment of PerAF		
Class I	29 (25.2%)	21 (21.6%)
Class II	42 (36.5%)	34 (35.1%)
Class III	89 (77.4%)	70 (72.2%)
Class IV	12 (10.4%)	6 (6.2%)

[1] Percent of total subjects having one or more failed medications within each AAD Class

Table 20: Subject Rationale for CTI Line: Arrhythmia History, Procedural AFL, Site Reported Justification

Population: Atrial Flutter Cohort

Parameter	Investigational (N=115)	Control (N=97)
History of typical atrial flutter - or - Atrial flutter observed prior to index ablation procedure - or - Site reported atrial flutter as justification for CTI line	**84 (73.0%)**	**72 (74.2%)**
History of Typical Atrial Flutter	**23 (20.0%)**	**26 (26.8%)**
Atrial Flutter observed during index ablation procedure prior to first ablation	**7 (6.1%)**	**10 (10.3%)**
Typical Atrial Flutter	5 (4.3%)	10 (10.3%)
Atypical Atrial Flutter	1 (0.9%)	0 (0.0%)
Atrial Flutter - Unspecified	1 (0.9%)	0 (0.0%)
Justification for CTI Line during index ablation procedure		
Typical Atrial Flutter	7 (6.1%)	11 (11.3%)
Atypical Atrial Flutter	1 (0.9%)	1 (1.0%)
Atrial Flutter - Unspecified	71 (61.7%)	59 (60.8%)
Empirical justification for CTI Line	36 (31.3%)	26 (26.8%)
N/A justification for CTI Line	0 (0.0%)	0 (0.0%)

ii. Atrial Flutter Ablation Safety Endpoint

The post hoc atrial flutter ablation safety endpoint was a composite endpoint based on the incidence of the device- or procedure-related serious adverse events listed in Table 21 following the index ablation procedure.

Of the subjects in the atrial flutter cohort, one subject from each treatment arm met the atrial flutter ablation safety endpoint. One subject from the investigational arm was hospitalized for chronic obstructive pulmonary disease exacerbation, and one subject from the control arm was hospitalized for hypoxia.

The incidence of these atrial flutter safety events was similar between the study arms, occurring in 0.9% vs. 1.0% of subjects in the investigational and control arm, respectively.

Table 21. Atrial Flutter Safety Events

Population: Atrial Flutter Cohort

	# Events (# Subjects, % Subjects)	
Primary Safety Endpoint Event	**Investigational (N=115)**	**Control (N=97)**
Primary Safety Endpoint Failure	**1 (1, 0.9%)**	**1 (1, 1.0%)**
Within 7 days of procedure		
Death	0 (0, 0.0%)	0 (0, 0.0%)
Myocardial infarction	0 (0, 0.0%)	0 (0, 0.0%)
Phrenic nerve paralysis	0 (0, 0.0%)	0 (0, 0.0%)
Transient ischemic attack	0 (0, 0.0%)	0 (0, 0.0%)
Stroke / cerebrovascular accident	0 (0, 0.0%)	0 (0, 0.0%)
Thromboembolism	0 (0, 0.0%)	0 (0, 0.0%)
Major vascular access complications / bleeding	0 (0, 0.0%)	0 (0, 0.0%)
Heart block	0 (0, 0.0%)	0 (0, 0.0%)
Gastroparesis	0 (0, 0.0%)	0 (0, 0.0%)
Severe pericarditis	0 (0, 0.0%)	0 (0, 0.0%)
Hospitalization (initial or prolonged) due to cardiovascular or pulmonary AE[1]	1 (1, 0.9%)	1 (1, 1.0%)
Within 30 days of procedure		
Cardiac tamponade/perforation	0 (0, 0.0%)	0 (0, 0.0%)

[1] Excludes hospitalization due to AF/AFL/AT recurrence

Table 22. Atrial Flutter Safety Event Rate

Population: Atrial Flutter Cohort

	Number, Percent of Failures		Difference
Parameter	**Investigational (N=115)**	**Control (N=97)**	**Investigational - Control**
CTI Safety Endpoint Failure	1, 0.9%	1, 1.0%	-0.2%

iii. Acute Effectiveness of Atrial Flutter Ablation

The post hoc analysis of atrial flutter acute ablation effectiveness was based on acute procedural success, defined as completion of the cavotricuspid isthmus ablation line with only the assigned study device followed by confirmation of bidirectional conduction block.

Acute procedural success was demonstrated in all subjects in the atrial flutter cohort. In investigational cohort subjects whom a cavotricuspid isthmus line was delivered, RF alone was used in 67.0% of these lines, while a combination of RF and PF energy was used in 30.4%, and PF alone was used for the remaining 2.6%.

Table 23. Atrial Flutter Acute Ablation Outcomes Effectiveness

Population: Atrial Flutter Cohort

	# Subjects/# Subjects Ablated (% Subjects)	
Parameter	**Investigational (N=115)**	**Control (N=97)**
Atrial flutter acute ablation effectiveness success	115/115 (100%)	97/97 (100%)

Table 24. Atrial Flutter Acute Ablation Effectiveness Success Rate

Population: Atrial Flutter Cohort

Parameter	Number, Percent of Successes		Difference
	Investigational (N=115)	Control (N=97)	Investigational - Control
CTI Acute Effectiveness Success	115, 100%	97, 100%	0.0%

iv. Chronic Effectiveness of Atrial Flutter Ablation

The atrial flutter cohort post hoc chronic effectiveness analysis presented in Table 25 evaluates freedom from documented recurrence of AFL based on electrocardiographic data. The following are considered atrial flutter ablation chronic effectiveness failures:

- Documented AFL recurrence after the index procedure.
- Any repeat ablation for AF/AFL/AT recurrence with documented CTI reconnection after the index procedure
- DC cardioversion for AFL recurrence after the index procedure

There was one subject in the investigational arm, and six subjects in the control arm who did not complete the Day 360 follow-up and did not experience a chronic effectiveness failure event. These subjects were considered to be missing the chronic effectiveness outcome and therefore were not included in the analysis presented in Table 26.

The observed rate of chronic effectiveness was higher in the investigational arm than in the control arm. Freedom from chronic effectiveness endpoint failure for the investigational arm was 86.8% compared to 76.9% in the control arm. The difference in chronic effectiveness endpoint success for the investigational and control device was 9.9%.

Table 25. Chronic Effectiveness Outcomes and Failure Modes

Population: Atrial Flutter Cohort

Parameter	Investigational (N=114)	Control (N=91)
Chronic Effectiveness Success	**99 (86.8%)**	**70 (76.9%)**
Chronic Effectiveness Failure [1]	**15 (13.2%)**	**21 (23.1%)**
Documented AFL after the index procedure	13 (11.4%)	16 (17.6%)
Within 90 days	0 (0.0%)	4 (4.4%)
Within 180 days	5 (4.4%)	5 (5.5%)
Within 360 days	8 (7.0%)	7 (7.7%)
Any repeat ablation for AF/AFL/AT recurrence with documented CTI reconnection after the index procedure	1 (0.9%)	3 (3.3%)
Within 90 days	0 (0.0%)	0 (0.0%)
Within 180 days	1 (0.9%)	0 (0.0%)
Within 360 days	0 (0.0%)	3 (3.3%)
DC cardioversion for AFL recurrence after the index procedure	2 (1.8%)	5 (5.5%)
Within 90 days	1 (0.9%)	4 (4.4%)
Within 180 days	1 (0.9%)	0 (0.0%)
Within 360 days	0 (0.0%)	1 (1.1%)

[1] Failure modes are not mutually exclusive since the same subject can experience multiple failure modes.

Table 26. Chronic Effectiveness Success Rate

Population: Atrial Flutter Cohort

	Number, Percent of Successes		Difference
Parameter	**Investigational (N=114)**	**Control (N=91)**	**Investigational - Control**
CTI Chronic Effectiveness Success	99, 86.8%	70, 76.9%	9.9%

Kaplan-Meier estimates of freedom from atrial flutter ablation chronic effectiveness failure are presented in Figure 11 for the investigational arm (blue) and the control arm (red). The log-rank test *p*-value was 0.077. Note that the window for the Day 360 visit extended from study day 330 to study day 390, so data censoring during the last 30 days is expected, accounting for the low number at risk at day 360. In case of failure at the Day 360 visit, within the visit window but beyond study day 360, the date of failure was set to study day 360 so that the failure was included in the Kaplan-Meier analysis.

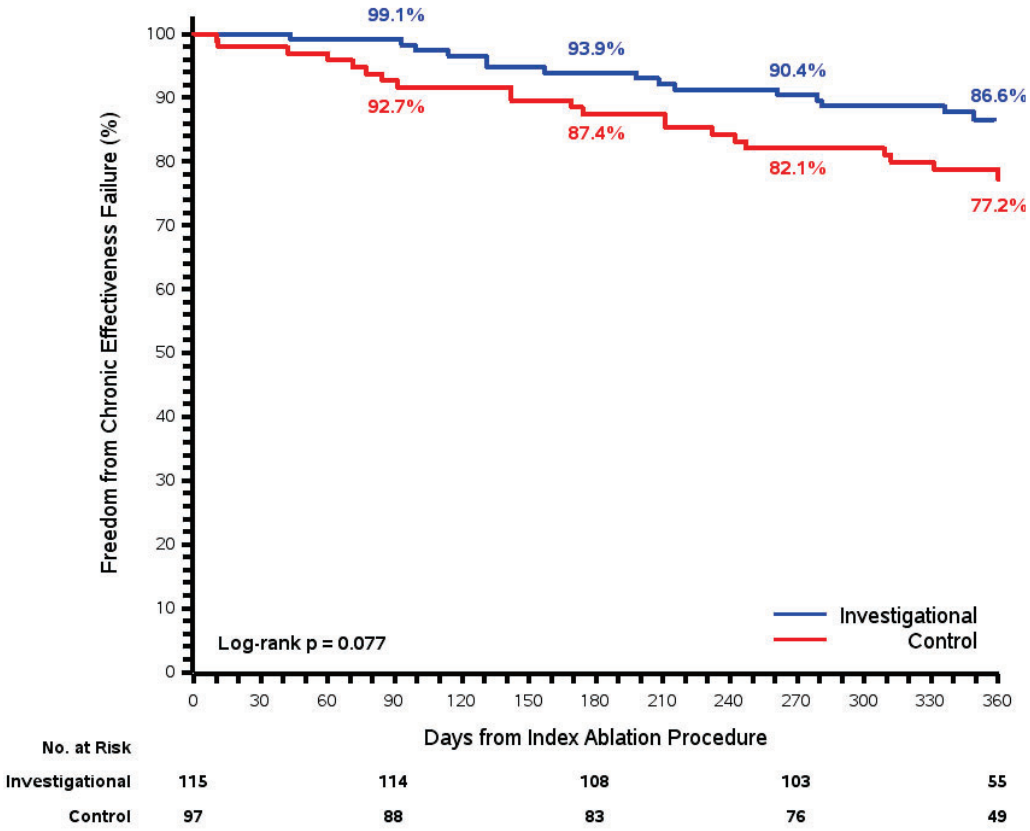


Figure 11: Atrial Flutter: Chronic Effectiveness Kaplan-Meier Plot

Population: Atrial Flutter Cohort

v. Serious Adverse Events

A total of 62 serious adverse events (27 in investigational arm, 35 in control arm) occurred during or post index ablation procedure in the atrial flutter cohort. Table 27 summarizes the incidence of early onset (within 7 days of the index ablation procedure) SAEs, incidence of peri-procedural (>7 and ≤30 days) SAEs, and incidence of late onset (>30 days) SAEs.

Table 27. SAEs by Timepoint

Population: Atrial Flutter Cohort

	# Events (# Subjects, % Subjects)	
SAE by Timepoint	**Investigational (N=115)**	**Control (N=97)**
SAEs during procedure or ≤ 7 days after procedure	4 (3, 2.6%)	5 (5, 5.2%)
SAEs 8-30 days after procedure	3 (2, 1.7%)	2 (2, 2.1%)
SAEs > 30 days after procedure	20 (13, 11.3%)	28 (21, 21.6%)

6. Pediatric Extrapolation

In this premarket application, existing clinical data was not leveraged to support approval of a pediatric patient population.

F. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The SPHERE Per-AF clinical study included 79 investigators of whom six had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) and described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0
- Significant payment of other sorts: 6
- Proprietary interest in the product tested held by the investigator: 0
- Significant equity interest held by investigator in sponsor of covered study: 3

The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. Statistical analyses were conducted by FDA to determine whether the financial interests/arrangements had any impact on the clinical study outcome. The information provided does not raise any questions about the reliability of the data.

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

None.

XII. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Circulatory System Devices Advisory Panel, an FDA advisory committee, for review and recommendation because the information in the PMA demonstrates that the pertinent issues for safety and effectiveness of a pulsed field ablation system have been vetted through comprehensive bench and clinical evaluations.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The effectiveness results of the SPHERE Per-AF study demonstrate that the Sphere-9 Catheter and the Affera Ablation System are effective for treatment of both persistent atrial fibrillation and cavotricuspid isthmus dependent atrial flutter.

In the SPHERE Per-AF clinical study, primary effectiveness with the Sphere-9 Catheter and the Affera Mapping and Ablation System was noninferior to the control device. The primary effectiveness endpoint included freedom from atrial tachyarrhythmia recurrence after the blanking period, acute procedural failure, new or increased antiarrhythmic drugs or cardioversion after the blanking period, and any repeat ablation at any time after the index ablation. Freedom from primary effectiveness endpoint failure for the investigational arm was 73.8% compared to 65.8% in the control arm.

In SPHERE Per-AF, a trend of increased quality of life measured with the AFEQT Questionnaire and the SF-12v2 Health Survey was observed at Day 180 and Day 360 in both groups as compared to baseline. The observed changes were consistent with a clinically meaningful improvement in quality of life[6,7,8].

Atrial Flutter Cohort

Acute effectiveness of atrial flutter ablation was evaluated based on acute procedural success, defined as completion of the cavotricuspid isthmus ablation line with only the assigned study device followed by confirmation of bidirectional conduction block. Acute procedural success was achieved in all 212 (100%) subjects (115 investigational arm, 97 control arm).

Chronic effectiveness was evaluated based on freedom from documented recurrence of

[6] P. Dorian et al., "Interpreting changes in quality of life in atrial fibrillation: How much change is meaningful?," *American Heart Journal*, vol. 166, no. 2, pp. 381-387.e8, 2013.
[7] D. N. Holmes et al., "Defining Clinically Important Difference in the Atrial Fibrillation Effect on Quality-of-Life Score: Results From the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation," *Circ: Cardiovascular Quality and Outcomes*, vol. 12, no. 5, p. e005358, 2019.
[8] T. Pezawas, R. Ristl, C. Schukro, and H. Schmidinger, "Health-related quality of life changes in patients undergoing repeated catheter ablation for atrial fibrillation," *Clin Res Cardiol*, vol. 105, no. 1, pp. 1–9, 2016.

AFL through 12-month follow-up. Additional chronic effectiveness failure modes included any repeat ablation for AF/AFL/AT recurrence with documented CTI reconnection after the index procedure or cardioversion for AFL recurrence after the index procedure. Of the 212 subjects in the atrial flutter cohort, 205 completed the study and were included in the analysis of chronic effectiveness. Chronic effectiveness appeared to be more prevalent with the investigational device compared to the control device. The observed rate of chronic effectiveness was higher in the investigational arm compared to the control arm. Freedom from chronic effectiveness failure for the investigational arm was 86.8% compared to 76.9% in the control arm. The difference in chronic effectiveness at 12 months between the investigational arm and the control arm was 9.9%, in favor of the investigational arm.

B. Safety Conclusions

The risks of the device are based on data collected in the SPHERE Per-AF clinical study conducted to support PMA approval as described above.

In the SPHERE Per-AF clinical study, primary safety with the Sphere-9 Catheter and the Affera Mapping and Ablation System was noninferior to the control device. The primary safety endpoint was a composite of serious device- or procedure-related adverse events following the index ablation procedure. In the investigational arm, the three (1.4%) primary serious adverse events were due to hospitalization for cardiovascular or pulmonary adverse events, specifically chronic obstructive pulmonary disease exacerbation, pulmonary edema, and hemoptysis.

No new risks or unanticipated adverse device effects were encountered during the SPHERE Per-AF study.

Atrial Flutter Cohort

Safety of atrial flutter ablation was evaluated based on a composite of serious device- or procedure-related adverse events following the index ablation procedure. Analysis of these atrial flutter ablation safety events using the 212 subjects in the atrial flutter cohort demonstrated similar results between the study arms. In the investigational arm, one subject (0.9%) was hospitalized for chronic obstructive pulmonary disease exacerbation. In the control arm, one subject (1.0%) was hospitalized for hypoxia.

The difference in the composite safety endpoint between the investigational arm and the control arm was -0.2%, in favor of the investigational arm.

C. Benefit-Risk Determination

The probable benefits of the device are based on data collected in a clinical study conducted to support PMA approval as described above. The benefits of treatment using the device include a high probability in freedom from atrial arrhythmia recurrence and trend toward clinically significant improvement of quality of life. Based on the SPHERE Per-AF clinical study, 74% of the investigational arm patients were free from all primary effectiveness failure events (including atrial arrhythmia recurrence) through 360 days after treatment with the Sphere-9 Catheter and Affera Ablation System. Further, mean change in quality of life from baseline to 360 days post ablation was consistent with a clinically significant improvement.

The probable risks of the device are also based on data collected in a clinical study conducted to support PMA approval as described above. In the SPHERE Per-AF randomized clinical study, the incidence of primary adverse events was 1.4%, and all of these events were due to hospitalization. No new or unanticipated adverse device effects or patient risks were identified in the SPHERE Per-AF clinical study.

Cavotricuspid Isthmus Dependent Atrial Flutter

The probable benefits of the device are based on data collected in a clinical study conducted to support PMA approval as described above. The benefits of treatment using the device include a high probability in achieving acute procedural success and freedom from atrial flutter recurrence. Based on the SPHERE Per-AF clinical study, 100% of all investigational arm subjects achieved acute procedural success and 86.1% of the investigational arm patients were free from all chronic effectiveness failure events (including atrial flutter recurrence) through 360 days after treatment with the Sphere-9 Catheter and Affera Ablation System.

The probable risks of the device are also based on data collected in a clinical study conducted to support PMA approval as described above. Among 115 investigational arm subjects treated, 1 of 115 subjects (0.9%) had a CEC-adjudicated adverse event that contributed to the atrial flutter safety endpoint. The event was a hospitalization due to cardiovascular or pulmonary adverse events for chronic obstructive pulmonary disease exacerbation. No new or unanticipated adverse device effects or patient risks were identified in the SPHERE Per-AF clinical study.

Patient Perspective

The submission did not include specific information on patient perspectives for this device.

In conclusion, given the available information above, the data support that the probable benefits outweigh the probable risks for the catheter ablation treatment of persistent atrial fibrillation and radiofrequency ablation of cavotricupsid isthmus dependent atrial flutter with the Sphere-9 Catheter and Affera Ablation System.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use. The SPHERE Per-AF clinical study met its primary safety and effectiveness objectives. The Sphere-9 Catheter and Affera Ablation System demonstrated a reasonable assurance of effectiveness and safety for the treatment of drug refractory and/or intolerant, recurrent, symptomatic persistent atrial fibrillation (episode duration less than 1 year) and radiofrequency ablation of cavotricuspid isthmus dependent atrial flutter.

XIV. CDRH DECISION

CDRH issued an approval order on October 24, 2024. The final clinical conditions of approval cited in the approval order are described below.

The SPHERE Per-AF Post Approval Study (PAS) is a prospective, multi-center, non-randomized, observational study to evaluate the long-term effectiveness and safety of the Sphere-9 Catheter and Affera Ablation System in a post-approval setting for the treatment of drug-refractory, recurrent, symptomatic, persistent atrial fibrillation (AF). Adult subjects in the United States who intend to undergo their de novo catheter ablation procedure using the Sphere-9 Catheter and Affera Ablation System to treat symptomatic persistent atrial fibrillation (episode duration less than one year) refractory or intolerant to at least one Class I or III antiarrhythmic medication will be enrolled and ablated using the Sphere-9 Catheter and Affera Ablation System. The study will enroll approximately 200 subjects to ensure 175 subjects are treated, with at least 50% of patients treated in the United States and from at minimum 15 sites. The study will include a diverse (i.e., race, ethnicity, gender) patient population. Following consent, all subjects will complete an enrollment/baseline visit, ablation procedure, and be followed through 3 years post-ablation. Enrolled subjects will have scheduled follow-up visits at 6, 12, 24 and 36 months post-ablation. 24-hour Holter monitoring will be performed at the 6, 12, 24, and 36 month follow-up visits. A 12-lead ECG and transthoracic echocardiogram will be performed at baseline and 12 months post-ablation in all subjects.

The primary objectives of the PAS will be the following:

1) Estimate the primary safety adverse event rate for ablation using the Sphere-9 Catheter and Affera Ablation System.

2) Estimate the 36-month freedom from AF/AFL/AT recurrence following ablation procedure using the Sphere-9 Catheter and Affera Ablation System.

The secondary objectives and additional analyses will include, but not be limited to, the following:

1) Characterize the Sphere-9 Catheter and Affera Ablation System ablation procedure, including but not limited to:

    a. Rate of acute procedural success, defined as confirmation of entrance block in all targeted pulmonary veins.
    b. Rate of pulmonary vein isolation on a per-vein basis.
    c. Rate of acute block across linear ablations.

2) Characterize procedural parameters, including but not limited to:

    a. Fluoroscopy Time.
    b. Procedure Time.
    c. Treatment Time.
    d. Mapping Time.
    e. Ablation lesion sets delivered and their associated ablation parameters and energy type (RF or PF).

3) Estimate change in quality of life (QoL) through 36 months.

4) Estimate the freedom from symptomatic AF/AFL/AT recurrence through 36 months.

5) Estimate the freedom from AF/AFL/AT recurrence post-90-day blanking period through 12 months post-ablation using the Sphere-9 Catheter.

6) Estimate the freedom from AF/AFL/AT recurrence post-90-day blanking period through 36 months post-ablation using the Sphere-9 Catheter for subjects off all Class I/III antiarrhythmic medications.

7) Characterize all reported adverse events through 36 months.

8) Estimate the rate of device- or procedure-related serious adverse events through 12 months post-procedure.

9) Estimate the rate of procedure-related acute renal failure through 30 days post-procedure.

10) Estimate the rate of procedure-related mortality of the ablation procedure.

11) Estimate the rate of early mortality after ablation through 3 months post-procedure

From the date of study protocol approval, you must meet the following timelines for the SPHERE Per-AF PAS:

- First subject enrolled within 6 months
- 20% of subjects enrolled within 12 months

- 50% of subjects enrolled within 18 months
- 100% of subjects enrolled within 24 months

In addition, you must submit separate periodic reports on the progress of the SPHERE Per-AF PAS as follows:

- PAS Progress Reports every six (6) months until subject enrollment has been completed, and annually thereafter, from the date of the PMA approval letter, unless otherwise specified by FDA.

- If any enrollment milestones are not met, you must begin submitting quarterly enrollment status reports every 3 months in addition to your periodic (6-month) PAS Progress Reports, until FDA notifies you otherwise.

- Submit the Final PAS Report three (3) months from study completion (i.e., last subject's last follow-up date).

Each PAS report should be submitted to the address below identified as a "PMA Post-Approval Study Report" in accordance with how the study is identified above and bearing the applicable PMA reference number.

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.

XVI. REFERENCES

P. Dorian et al., "Interpreting changes in quality of life in atrial fibrillation: How much change is meaningful?," *American Heart Journal*, vol. 166, no. 2, pp. 381-387.e8, 2013.

D. N. Holmes et al., "Defining Clinically Important Difference in the Atrial Fibrillation Effect on Quality-of-Life Score: Results From the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation," *Circ: Cardiovascular Quality and Outcomes*, vol. 12, no. 5, p. e005358, 2019.

T. Pezawas, R. Ristl, C. Schukro, and H. Schmidinger, "Health-related quality of life changes in patients undergoing repeated catheter ablation for atrial fibrillation," *Clin Res Cardiol*, vol. 105, no. 1, pp. 1–9, 2016.