A prospective Single Arm Open Label Study of the FARAPULSE Pulsed Field Ablation System in Subjects with Persistent Atrial Fibrillation

Published: 11-05-2023
Last updated: 07-04-2024

The objective of the ADVANTAGE AF Study is to establish the safety and effectiveness of the FARAPULSE Pulsed Field Ablation System (FARAPULSE PFA System) for treatment of drug resistant, symptomatic persistent atrial fibrillation (PersAF).

Ethical review	Approved WMO
Status	Will not start
Health condition type	Cardiac arrhythmias
Study type	Interventional

Summary

ID

NL-OMON56113

Source
ToetsingOnline

Brief title
ADVANTAGE AF

Condition

- Cardiac arrhythmias
- Cardiac therapeutic procedures

Synonym
Persistent Atrial Fibrillation - Abnormal Heart Rythm

Research involving
Human

Sponsors and support

Primary sponsor: Boston Scientific
Source(s) of monetary or material Support: Boston Scientific Corporation

Intervention

Keyword: Persistent Atrial Fibrillation, Pulsed Field Ablation, PVI (Pulmonary Veins Isolation), PWI (Left Atrial Posterior Wall Isolation)

Outcome measures

Primary outcome

The primary safety endpoint (PSE) is the proportion of Treatment Subjects and

Attempt Subjects with one or more of the following device or procedure-related

Composite Serious Adverse Events (CSAEs) following the Index Procedure /

Rescheduled Index Procedure or the First Re-Ablation Procedure within the

Blanking Period, with an Onset Date following the procedure as specified below:

Composite Serious Adverse Events Onset Date - Day 0-7

• Death

• Myocardial infarction

• Stroke

• TIA

• Peripheral or organ thromboembolism

• Pulmonary edema

• Unresolved phrenic nerve palsy / paresis

• Vascular access complications

• Heart block

• Gastric motility / pyloric spasm disorders

Composite Serious Adverse Events Onset Date - Day 0 - Day 30

• Cardiac tamponade / perforation

• Pericarditis

Composite Serious Adverse Events Onset Date - Day 0 - Day 360

• PV stenosis

• Atrio-esophageal fistula

The primary effectiveness endpoint (PEE) is the proportion of Treatment

Subjects with Treatment Success through the Day 360 Assessment.

Treatment Success is defined as:

1. Persistent AF Acute Procedural Success AND

2. Persistent AF Chronic Success, defined as freedom from the following after

the Blanking Period (excluding documented CTI-dependent flutter):

i. Arrhythmia: Occurrence of any Detectable AF, AFL or AT

ii. Re-ablation: Any re-ablation for AF, AFL or AT

iii. Cardioversion: Any electrical cardioversion for AF, AFL or AT

iv. AAD Use: Use of a Non-Failed Class I / III AAD or amiodarone

Secondary outcome

Additional Safety Endpoints:

• Composite Non-Serious Adverse Event

• Related AEs

• Any SAE

• Post-Blanking Arrhythmia Hospitalizations

• Post-Blanking Cardioversions

Additional Efficacy Endpoints:

• Persistent AF Acute Procedural Success

• Persistent AF Chronic Success

• Single Procedure Treatment Success

• Off Drug Treatment Success

• Re-Ablation Rate

Study description

Background summary

Atrial Fibrillation
Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, affecting approximately 2.2 million people in the United States and 4.5 million in the European Union. The incidence increases with advancing age, affecting 6% of the population over age 60 and 10% of the population over age 80. Among Medicare beneficiaries, AF incidence is common and increases as individuals age, with incidence rates per 1,000 person-years reported at ages 70-74 of 18.8, increasing to 28.8 for persons 75-79 and 38.3 for persons 80-84. Similarly, the overall prevalence among Medicare beneficiaries age 70-74 is about 6% increasing to over 13% for individuals 80 years of age and older. Age-adjusted population trending projects 16 million people in the United States will have AF by 2050.

Atrial fibrillation remains a significant cause of morbidity and mortality in industrialized societies. The annual risk of AF related stroke is 5% per year and one of every six strokes diagnosed occurs in the presence of AF. 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 left atrium, tachycardia-induced cardiomyopathy, and reduced left ventricular function (heart failure). AF remains an extremely costly public health burden, with annual per patient cost of care approaching approximately USD 3200 or ¤3000.

The Heart Rhythm Society (HRS) 2017 Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation8 defines several different stages of AF based on its duration and include:
• Paroxysmal AF (PAF): AF that terminates spontaneously or with intervention within 7 days of onset

• Persistent AF (PersAF): continuous AF that is sustained beyond 7 days
• Long-standing PersAF: continuous AF of greater than 12 months* duration

Several studies have demonstrated that AF catheter ablation is a safe and superior alternative to anti-arrhythmic drugs (AADs) for maintenance of sinus rhythm and symptom improvement. In particular, the isolation of the pulmonary veins (PVI), where the majority of arrhythmogenic triggers is found, has been shown to be a safe and effective technique to reduce arrhythmia recurrence and related symptoms. Over the last 20 years PVI has remained the cornerstone catheter ablation technique for AF ablation in subjects with recurrent and symptomatic PAF refractory or intolerant to AADs. More recently, PVI for the treatment of PAF is increasingly being performed as first line therapy, and clinical evidence is accruing that this may well become an accepted first line treatment.

Persistent Atrial Fibrillation Ablation
Persistent AF (PersAF) represents approximately 25% of all AF cases. In comparison to patients with PAF, patients with PersAF are at a significantly greater risk for both cardiac mortality and all-cause mortality. The recent update of the 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation AF supports catheter ablation for maintaining sinus rhythm in patients with both PAF and PersAF, with the eligibility to treat PersAF patients with ablation being weighted by additional elements, including risk factors for recurrence (left atrial [LA] size, AF duration, patient age, renal dysfunction, and substrate visualization by means of MRI), heart failure with reduced ejection fraction, and patient choice. This recommendation is currently reflected in practice as approximately one third of all catheter ablation cases are performed on either persistent or long-standing persistent patients.

There are currently two catheters approved in the US to treat PersAF, supported by data obtained from the PRECEPT (Biosense Webster, Thermocool SmartTouch® SF catheter) and STOP Persistent AF trials (Medtronic, ArcticFront Advance® Cryoballoon), respectively. These trials showed that safety and effectiveness profile of catheter ablation for PersAF is well-established, with slight variations in rates depending upon the patient population and technology utilized. Although the PVs have been identified as the main triggers responsible for AF, PVI alone for the treatment of PersAF is less effective than for PAF, and PersAF ablation may require additional lesion sets beyond the PVs to achieve greater success.

PersAF ablation success is challenged by the heterogeneity of the underlying pathophysiologic mechanisms, and multiple ablation strategies have evolved in the attempt to improve long-term outcomes in this population. These include left atrial lines (roof, mitral isthmus), right atrial lines (superior vena cava, cavo-tricuspid isthmus) other techniques aimed at suppressing additional triggers outside the PV. To date, limited data from randomized trials exist on the effectiveness of these techniques compared to PVI alone. However, recent

studies have suggested a benefit associated with PVI and concomitant isolation of the portion the left atrial posterior wall (LAPW) lying between the PVs. The rationale for this ablation technique stands in the common embryological origin of this anatomical area in the PVs and the peculiar electrophysiological and structural characteristics of this region that give rise to its arrhythmogenic potential.

Specifically, spontaneous triggers located in the LAPW have been reported in previous studies, establishing ablation of this area in addition to PVI being a potential adjuvant strategy in ablation of PersAF. Several studies have been recently published adding a dedicated LAPW ablation strategy together with PVI, including different available energy sources for ablation. A recent systematic review and meta-analysis showed that LAPW isolation can be successfully achieved in a large proportion of patients and is associated with a low risk of major-procedure related complications.

Irreversible Electroporation
Al-Sakere 2007 described irreversible electroporation (IRE) as a non-thermal tissue ablation technique in which intense short duration electrical fields are used to permanently open pores in cell membranes, thus producing non-thermal tissue ablation. Their study, using a mouse model, showed complete regression in 92% of treated tumors. IRE ablation has a tissue-specific mechanism of ablation. The tissue injury from IRE ablation occurs at the cellular level with loss of homeostasis leading to necrosis or apoptosis. IRE ablation typically spares the extracellular matrix, which facilitates rapid wound healing.
With respect to cardiac tissue, multiple studies have been described reporting the effects of IRE in a porcine model. Across the studies, no stenosis was observed at 3-weeks and 3-months of follow-up, and the lesion depth was further characterized in the proximity of the phrenic nerve and coronary arteries, with no damage to the adjacent structures or tissues noted. These animal studies suggest that IRE can safely create deep lesions in heart tissue without harming adjacent tissues.

FARAPULSE Pulsed Field Ablation System
Preclinical animal studies investigating the safety and efficacy of the FARAPULSE Pulsed Field Ablation (PFA) System have been performed to demonstrate that PFA using the FARAPULSE PFA Catheter reliably produces homogeneous, well-demarcated and transmural lesions in porcine atrial tissue. Seven- and 30-day studies show mild to moderate inflammatory and healing responses consistent with radiofrequency ablation lesions, and importantly demonstrated no tissue injury with respect to the esophagus or phrenic nerve as well as no degree of narrowing or flow impairment of the pulmonary veins.

Paroxysmal Atrial Fibrillation:
Initial safety and feasibility human clinical studies of the FARAWAVE PFA Catheter were conducted in Europe in a PAF population, including the IMPULSE, PEFCAT, and PEFCAT II trials. All studies supported the safety and feasibility

of the FARAPULSE PFA System using the FARAWAVE PFA Catheter in the treatment of patients with PAF, with a low rate of acute and long-term primary safety endpoint events and a high rate (100%) of acute procedural success resulting in CE Mark approval for the treatment of PAF in early 2021.

The randomized ADVENT Trial (A Prospective Randomized Pivotal Trial of the FARAPULSE PFA System Compared with Standard of Care Ablation in Patients with Paroxysmal Atrial Fibrillation) is being conducted in the United States to establish the safety and effectiveness of the FARAPULSE PFA System using the FARAWAVE PFA Catheter in a drug refractory symptomatic PAF patient population. Subjects in the study are either randomized to catheter ablation with the FARAPULSE PFA system or conventional thermal ablation (radiofrequency or cryoballoon ablation). The data will be used to gain initial market approval of the FARAPULSE PFA System using the FARAWAVE PFA Catheter in the US for the PAF population.

Persistent Atrial Fibrillation:
Initial data on treatment of PersAF with the FARAPULSE PFA System using the FARAWAVE PFA Catheter has been collected in the PersAFOne feasibility study (Feasibility Study of the FARAPULSE Endocardial Multi Ablation System in the Treatment of Persistent Atrial Fibrillation). The objective of the PersAFOne Study is to demonstrate that the endocardial creation of electrically isolating lesions in cardiac tissue via PFA using the FARAPULSE PFA System is a feasible and safe treatment for PersAF. Patients in the PersAFOne study, after the isolation of the PVs, received an additional set of lesions along the posterior wall region between the PVs, performed with the same FARAWAVE PFA Catheter used for PVI during the ablation procedure.

Reliable and safe electrical isolation of the left atrial posterior wall was confirmed via electro-anatomical mapping. Reddy et al reported 100% acute PV isolation, no primary safety events, and chronic isolation of the PVs (82 / 85) and LAPW (100% with the pentaspline catheter) after remapping at 82 days post-procedure in 25 subjects. The data collected in the study demonstrated that the approach proposed in the ADVANTAGE AF Study to ablate the left atrial posterior wall in addition to creating PVI using the FARAPULSE PFA System is feasible, leading to an acceptable safety and feasibility profile for the study device to date.

One of the acknowledged challenges to LAPW ablation is the risk of collateral damage to the esophagus, given the repeated and additional ablation applications in addition to the PVs that are delivered to an anatomical area close to the esophagus. Using PFA for LAPW ablation has the potential to substantially mitigate this risk, given the marked reduced risk of collateral damage to adjacent structures with the energy source noted above.

Although AF and CTI-dependent atrial flutter (AFL) are different arrhythmias with their own mechanisms and electrophysiologic presentation, their

interrelationship has long been recognized and they coexist in a significant percentage of patients. The relationship is reciprocal since patients diagnosed with AFL may develop AF after CTI ablation and patients with AF often go on to develop AFL. In particular, the presentation of AFL in the context of AF may be the sign of additional atria remodeling or the presence of non-PV triggers.

Accordingly, a strategy that includes both PVI and CTI ablation has become an established practice in the percutaneous ablative treatment of patients with AF. The current guidelines for the management of AF indicate that CTI ablation may be beneficial during procedures of AF ablation, in particular for those patients with history of typical AFL and where AFL is induced at the time of AF ablation. The present IDE study incorporates the treatment strategy for PersAF ablation utilized in PersAFOne using the FARAWAVE PFA Catheter for electrical isolation of the PV and isolation of the LAPW region between the PVs. In the PersAFOne II study, LAPW ablation was performed using the FARAWAVE Catheter in the fully deployed configuration. Consistent with the proposed treatment, two applications at 2000V at each catheter location was performed, with approximately 50% overlap between adjacent catheter positions. These catheter positions along the posterior wall linked the PVI lesion to create a continuous lesion set encompassing the PVs and LAPW, between the superior and inferior insertions of the left and right PV pairs. As of the date of the PersAFOne II interim clinical study report, 17 subjects have returned for the invasive remapping procedure. Sixty-four of sixty-eight (94.2%) of PVs and sixteen of seventeen (94%) of LAPWs remained durably isolated. Again, two SAEs in two patients, both pericardial effusions, were reported, related to the required remapping procedure.

Expanding the indication of the FARAPULSE PFA System for approval to treat PersAF patients would fulfill a clinical need in a growing population of subjects indicated to receive a catheter ablation. The present single arm, prospective cohort IDE study has been designed to demonstrate safety and effectiveness of the FARAPULSE PFA System in treating symptomatic drug-refractory PersAF patients.

Study objective

The objective of the ADVANTAGE AF Study is to establish the safety and effectiveness of the FARAPULSE Pulsed Field Ablation System (FARAPULSE PFA System) for treatment of drug resistant, symptomatic persistent atrial fibrillation (PersAF).

Study design

The FARAPULSE ADVANTAGE AF Study is a prospective, single arm, open label, multi-center IDE pivotal study utilizing the FARAPULSE PFA System in the treatment of patients with PersAF.

After ablative isolation of the pulmonary veins (PVs), the left atrial posterior wall (PW) and if warranted the cavotricuspid isthmus (CTI), subjects will be followed at Pre-Discharge, Day 7, Day 30, Day 90, Day 180, and Day 360. The Blanking Period will include Days 0 through 90, after which subjects will be monitored twice per month plus symptom-driven event monitoring, as well as Day 180 and Day 360 24-hour Holter monitoring.

Intervention

Pulmonary Vein Isolation (PVI): PVI will be achieved in target veins using the FARAWAVE PFA Catheter.
Posterior Wall Isolation (PWI): PWI will be achieved in the left atrial posterior wall between the PVs using the FARAWAVE PFA Catheter.
CTI: Ablation of the CTI will be performed using a commercially available BSC RF catheter in the following situations:
• Required: For subjects with a history of CTI-mediated (typical) AFL and
o Who have not had a CTI ablation procedure, or
o Who have had a CTI ablation procedure but have recurrent CTI conduction.
• Required: subjects who manifest CTI-mediated AFL (spontaneous or induced) during the Index Procedure, or
• At Investigator discretion: subject welfare indicates that CTI ablation should be performed.
Other Ablation: When the Investigator determines that subject welfare requires intervention for either an accessory pathway, AVNRT or spontaneously occurring treatment-emergent AFL or AT, ablation for these arrhythmias may be performed using any commercially available RF ablation catheter. These permitted ablations and the associated data will be documented in the CRF and do not constitute Persistent AF Acute Procedural Failure.
Ablation for an arrhythmia that is provoked only by catheter manipulation or is only inducible by pacing or pharmacologic stimulation is not permitted.

Study burden and risks

Patients who take part in this study are subject to similar risks shared by all patients who have an ablation procedure but are not in this study.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Study subjects are required to meet all the following inclusion criteria:
1. Age >= 18 years of age, or older if specified by local law
2. Subjects have symptomatic, documented, drug-resistant, Persistent AF, defined as:
a. Documented: at a minimum a physician*s note confirming the arrhythmia symptoms and durations AND, within 180 days of Enrollment Date, either:
i. A 24-hour continuous ECG recording confirming continuous AF OR
ii. Two ECGs from any regulatory cleared rhythm monitoring device showing continuous AF taken at least 7 days apart
b. Drug-resistant: effectiveness failure of, intolerance to, or specific contraindication to at least one (1) AAD (Class I or III).
c. Persistent: continuous AF for > 7 days and <= 365 days
3. Subjects who are willing and capable of providing informed consent
4. Subjects who are willing and capable of participating in all testing associated with this clinical investigation at an approved clinical investigational center

Exclusion criteria

1. Any of the following atrial conditions:

a. Left atrial anteroposterior diameter >= 5.5 cm, or if LA diameter not available, non-indexed volume >100 ml (by MRI, CT or TTE report or physician note)
b. Any prior atrial endocardial, epicardial or surgical ablation procedure for arrhythmia, other than right sided cavotricuspid isthmus ablation or for right sided SVT
c. Current atrial myxoma
d. Any PV abnormality, stenosis, or stenting (common and middle PVs are admissible)
e. Current left atrial thrombus
2. Cardiovascular exclusions - Any of the following CV conditions:
a. History of sustained ventricular tachycardia or any ventricular fibrillation
b. AF that is secondary to electrolyte imbalance, thyroid disease, alcohol, or other reversible / non-cardiac causes
c. Current or anticipated pacemaker, implantable cardioverter defibrillator or cardiac resynchronization therapy devices, interatrial baffle, closure device, patch, or patent foramen ovale occluder, LA appendage closure, device or occlusion, active implantable loop recorder or insertable cardiac monitor at the time of ablation
d. Valvular disease that is any of the following:
i. Symptomatic
ii. Causing or exacerbating congestive heart failure
iii. Associated with abnormal LV function or hemodynamic measurements
e. Hypertrophic cardiomyopathy
f. Any prosthetic heart valve, ring or repair including balloon aortic valvuloplasty
g. Any IVC filter, known inability to obtain vascular access or other contraindication to femoral access
h. Rheumatic heart disease
i. Congenital heart disease with any clinically significant residual anatomic or conduction abnormality
j. Awaiting cardiac transplantation or other cardiac surgery within the next 12 months
3. Any of the following conditions at baseline:
a. Heart failure associated with NYHA Class III or IV
b. LVEF < 40%
c. Uncontrolled hypertension (SBP > 160 mmHg or DBP > 95 mmHg on two (2) BP measurements at baseline assessment
4. Any of the following events within 90 days of the Consent Date:
a. Myocardial infarction (MI), unstable angina or coronary intervention
b. Any cardiac surgery
c. Heart failure hospitalization
d. Pericarditis or symptomatic pericardial effusion
e. Gastrointestinal bleeding
f. Stroke, TIA, or intracranial bleeding
g. Any non-neurologic thromboembolic event
h. Carotid stenting or endarterectomy

5. Thrombocytosis, thrombocytopenia, disorder of blood clotting or bleeding diathesis
6. Contraindication to, or unwillingness to use, systemic anticoagulation
7. Patients who have not been on anticoagulation therapy for at least 4 weeks prior to the ablation procedure
8. Women of childbearing potential who are pregnant, lactating, not using medical birth control or who are planning to become pregnant during the anticipated study period
9. Health conditions that in the investigator*s medical opinion 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:
a. Body Mass Index (BMI) > 42.0
b. Solid organ or hematologic transplant, or currently being evaluated for a transplant
c. Any prior history or current evidence of hemi-diaphragmatic paralysis or paresis.
d. Severe lung disease, pulmonary hypertension, or any lung disease involving abnormal blood gases or requiring supplemental oxygen
e. Renal insufficiency if an estimated glomerular filtration rate (eGFR) is < 30 mL / min / 1.73 m2, or with any history of renal dialysis or renal transplant
f. Active malignancy or history of treated malignancy within 24 months of enrollment (other than cutaneous basal cell or squamous cell carcinoma)
g. Clinically significant gastrointestinal problems involving the esophagus or stomach including severe or erosive esophagitis, uncontrolled gastric reflux, gastroparesis, esophageal candidiasis or active gastroduodenal ulceration
h. Active systemic infection
i. COVID-19 disease
i. Current confirmed, active COVID-19 disease
ii. Current positive test for SARS-CoV-2
iii. Confirmed COVID-19 disease not clinically resolved at least 3 months prior to the Consent Date
j. Uncontrolled diabetes mellitus or a recorded HgbA1c > 8.0% in the 90 days prior to the Consent Date
k. Untreated diagnosed obstructive sleep apnea with apnea hypopnea index classification of severe (>30 pauses per hour)
10. Predicted life expectancy less than one (1) year
11. Subjects who are currently enrolled in another investigational study or registry that would directly interfere with the current study, except when the subject is participating in a mandatory governmental registry, or a purely observational registry with no associated treatments; each instance must be brought to the attention of the Sponsor to determine eligibility

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	33
Type:	Anticipated

Medical products/devices used

Generic name:	FARAPULSE Pulsed Field Ablation System
Registration:	Yes - CE outside intended use

Ethics review

Approved WMO Date:	11-05-2023
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
ClinicalTrials.gov	NCT05443594
CCMO	NL81771.000.22