CS1170 Rev D Clinical Study Synopsis

FARA-FREEDOM: A Prospective Open-Label Single Arm Post Market Clinical Follow-Up Trial of the FARAPULSE Pulsed Field Ablation System in Patients with Paroxysmal Atrial Fibrillation

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This study is to be performed in accordance with Good Clinical Practice (GCP), the ethical principles that have their origin in the Declaration of Helsinki, International Conference on Harmonisation E6 and ANSI / AAMI / ISO Standards 14155:2020.

Revision History

Rev	DCO	Description of Changes	Effective Date	Prepared By
B	21-289	To match the updated protocol	18Aug2021	A. Achyutha
B	21-302	Administrative changes: Deleted "in either the Pulsed Field or Thermal Groups" In section 5.2 Index Procedure, Pg #4 which was inadvertently missed during the review of the document. Formatted document throughout to have same font and size for consistency.	27 Aug 2021	J. Kothule
C	21-323	Aligning with the protocol change	19Sep2021	J. Kothule
D	22-126	Aligning with the protocol change Page #3: Update to reflect the increase in total sites from 15 to 25 Page #11: CT was added as approved procedure to exclude presence of LAA thrombus	18 May 2022	A. Vanderper

Executive Summary

SPONSOR NAME:	FARAPULSE, Inc.
TITLE OF STUDY:	A Prospective Open-Label Single Arm Post Market Clinical Follow-Up Trial of the FARAPULSE Pulsed Field Ablation System in Patients with Paroxysmal Atrial Fibrillation
REFERENCE CIP NUMBER / REVISION:	CS1169 Rev D
OBJECTIVE:	The purpose of the study is to provide ongoing post-market demonstration of the safety and performance of the FARAPULSE Pulsed Field Ablation System in the treatment of patients with paroxysmal atrial fibrillation (PAF).
NAME OF INVESTIGATIONAL DEVICE:	FARAPULSE Pulsed Field Ablation System • FARAWAVE™ Pulsed Field Ablation Catheter • FARASTAR™ Pulsed Field Ablation Generator • FARADRIVE™ Steerable Sheath
DESIGN:	Subjects will undergo percutaneous endocardial ablation for pulmonary vein isolation using the FARAPULSE Pulsed Field Ablation System. Subjects with typical right-sided (isthmus-dependent) atrial flutter (AFL) may undergo ablative interruption of the cavo-tricuspid isthmus (CTI). Class I / III antiarrhythmic drugs (AADs) will be discontinued at Day 60 ± 10, subject to Investigator discretion Subjects will then be followed at 7 days, 30 days, 90 days, 6 months, and 12 months for adverse events (AEs), **:** Subjects will be monitored with weekly scheduled plus symptom-driven event monitoring, as well as 6 and 12-month Holter monitoring, for freedom from recurrent arrhythmia (atrial fibrillation [AF], AFL or atrial tachycardia [AT]) after the Blanking Period (Days 0 - 90).
STUDY POPULATION:	Subjects with documented PAF who have had ≥ 2 episodes within 6 months of enrollment.
PLANNED ENROLLMENT:	180 subjects
CLINICAL SITES:	Up to 25 enrolling centers.

DURATION OF SUBJECT PARTICIPATION:	The enrollment period is estimated to take 12 months and subjects will be followed for up to 13 months. There will be a 3-month period of site close-out visits, for a planned study duration of approximately 34 months Coronavirus Disease 2019 (COVID 19)-related disruptions may alter this timeframe. Subject participation is anticipated to be 13 ± 1 months to allow for screening, pre-procedural diagnostic procedures, treatment and 12 ± 1 months of study follow-up.
PLANNED PROCEDURES:	**Index Procedure / Rescheduled Index Procedure:** All subjects will be screened for atrial thrombus just prior to or at the time of the Index Procedure and will be rescheduled if positive. **PVI:** Subjects will undergo an attempt to isolate all pulmonary veins or their anatomic equivalent with the FARAPULSE Pulsed Field Ablation System. **CTI:** Subjects with a past history of CTI-mediated (typical) AFL, who manifest typical AFL during a procedure or within the Blanking Period, or who have inducible typical flutter, may undergo ablation of the CTI at the discretion of the Investigator using any approved RF catheter during the Index / Rescheduled Index Procedure or any re-ablation procedure. **Other Ablation:** Other ablation is not permitted under this protocol except when the Investigator determines that subject welfare requires ablation for an accessory pathway, atrioventricular nodal reentrant tachycardia (AVNRT), treatment-emergent left-sided AFL or incessant AT.
RE-ABLATION PROCEDURE	Re-ablation under this protocol requires documentation of Detectable AF, AFL or AT. Any re-ablation procedure for AF, AFL or AT during study follow-up constitutes a Treatment Failure. However, CTI ablation or re-ablation for right-sided typical AFL may be performed at any time during study follow-up and does not constitute a Treatment Failure.

ANTIARRHYTHMIC DRUGS	Antiarrhythmic drugs (AADs), except for amiodarone, may be utilized during the Blanking Period at the Investigator's discretion. On Day 60 ± 10 each subject will be contacted by telephone to stop all AADs. Class I / III AADs should be stopped at the Day 60 Assessment. However, at the Investigator's discretion, Class I / III AADs may be continued up to Day 90 without creating a primary performance endpoint failure. The use of amiodarone at any time during the study, except intra-procedurally to control an arrhythmia, or the use of Class I / III AADs after Day 90, constitute a Treatment Failure.
PRIMARY SAFETY ENDPOINT:	The primary safety endpoint is the Composite Safety Endpoint (CSE) defined as the proportion of Safety Subjects with one or more of the following device- or procedure-related SAEs as adjudicated by the CEC based on protocol definitions. Early onset (within 7 days of an index or Rescheduled Index procedure: • Death • Myocardial infarction • Persistent phrenic nerve palsy • Stroke • Transient ischemic attack (TIA) • Peripheral or organ thromboembolism • Cardiac tamponade / perforation • Pericarditis • Pulmonary edema • Vascular access complications • Heart block • Gastric motility/pyloric spasm disorders Late onset (any time through the completion of 12 month follow-up visit) • Pulmonary vein stenosis • Atrio-esophageal fistula
ADDITIONAL SAFETY ANALYSES:	1. Severe Ablation Complications 2. Nonserious / Serious CSEs 3. Post-Blanking Direct Current Cardioversions 4. Post-Blanking Arrhythmia Hospitalizations 5. Any Related SAE 6. Any Related Stroke or TIA

PRIMARY EFFECTIVENESS ENDPOINT:	The primary performance endpoint is Treatment Success in Modified Intent-to-Treat (mITT) subjects, defined as: Acute Procedural Success, AND 1. Chronic Success, defined as freedom from: a. At the Index / Rescheduled Index Procedure: Use of a non-PFA treatment modality for PVI b. After the Blanking Period: i. Occurrence of any Detectable AF, AFL or AT (excluding CTI-dependent AFL confirmed by EP study) ii. Cardioversion for AF, AFL or AT (excluding for CTI-dependent AFL) iii. Use of any Type I or Type III antiarrhythmic medication for the treatment of AF, AFL or AT c. At any time: i. Re-ablation for AF, AFL or AT (other than for CTI-dependent AFL) Use of amiodarone, except intra-procedurally to control an arrhythmia
ADDITIONAL EFFECTIVENESS ANALYSES:	1. Acute Procedural Success 2. Acute Vein Success 3. Chronic Success 4. Chronic Success Allowing Re-ablation 5. Chronic Success Allowing AADs 6. Treatment Success Allowing Re-ablation 7. Treatment Success Allowing AADs 8. Treatment Success with PVI/CTI Only 9. Early Recurrence of AF 10. Rate of Re-ablation 11. AF Symptom Assessment
PROCEDURAL ASSESSMENTS:	1. Assessments of duration for procedure components a. Procedure time (initiation of venous access to venous access closure). b. Left atrial dwell time (total time an ablation catheter is in the left atrium [LA]) c. Total ablation time (first ablation to last ablation) d. Fluoroscopy time (total duration of exposure). 2. Characterization of lesion sets: a. PVI ablations b. CTI ablations c. For subjects undergoing required LA ablations for an accessory pathway, AVNRT, left-sided AFL or incessant AT, a description of lesion sets utilized
QUALITY OF LIFE MEASURES	Subjects will undergo assessment with the EQ-5D-3 L instrument and Atrial Fibrillation Effect on Quality of Life (AFEQT) questionnaire at baseline and 12 months.

SAMPLE SIZE CONSIDERATIONS	**Sample size requirements for safety:** Sample size is estimated assuming an underlying CSE rate of 9% compared to a performance goal (PG) of 17% using a binomial exact test. Assuming 80% power and one-sided Type I error of 2.5%, a minimum sample size of 150 is required. **Sample size requirements for performance:** Sample size is estimated assuming an expected percent success of 65% compared to a PG of 50% using a binomial exact test. Assuming 80% power and one-sided Type I error of 2.5%, a minimum sample size of 85 is required. **Number of subjects:** The sample requires 150 analyzable subjects to meet both safety and performance calculations. To allow for up to 15% subject losses, the study size has been set at approximately 180 subjects.
CLINICAL EVENTS COMMITTEE	An independent panel of 3 electrophysiologists will review AEs, adjudicate seriousness and relatedness of potential SAEs and adjudicate primary safety and performance outcomes.
ARRHYTHMIA CORE LABORATORY	A qualified Arrhythmia Core Lab (ACL) will be established to receive, review and assess all protocol-stipulated ECGs, EMs and Holter monitors.
INCLUSION CRITERIA:	Study subjects are required to meet all the following inclusion criteria to participate in this study: 1. Patients with PAF that meets all the following criteria: a. Paroxysmal: AF that terminates spontaneously or with intervention within 7 days of onset. b. Frequency: i. Physician documentation of recurrent PAF (two or more episodes) within 6 months, AND ii. At least one (1) documented episode by an approved recording device within 12 months of enrollment c. Drug Failed atrial fibrillation drug (AAD) treatment, meaning therapeutic failure of at least one AAD (class I – IV) for efficacy and / or intolerance. 2.Patients who are ≥ 18 and ≤ 80 years of age on the day of enrollment. 3. Patient participation requirements: a. Is willing and capable of providing Informed Consent to undergo study procedures. b. Is willing to participate in all examinations and follow-up visits and tests associated with this clinical study.

EXCLUSION CRITERIA:	Subjects will be excluded from participating in this study if they meet any one of the following exclusion criteria: 1. Atrial fibrillation that is any of the following: a. Persistent (both early and longstanding) by diagnosis or continuous duration > 7 days b. Secondary to electrolyte imbalance, thyroid disease, alcohol or other reversible / non-cardiac causes c. Requires four (4) or more direct-current cardioversions in the preceding 12 months 2. Any of the following atrial conditions: a. Left atrial anteroposterior diameter ≥ 5.5 cm b. Any prior atrial endocardial or epicardial ablation procedure, other than right sided cavotricuspid isthmus ablation or for right sided SVT c. Any prior atrial surgery d. Interatrial septal patch or interatrial shunt e. Atrial myxoma f. Current LA thrombus g. LA appendage closure, device or occlusion h. Any PV abnormality, stenosis or stenting (common and middle PVs are admissible) 3. At any time, one or more of the following cardiovascular procedures, implants or conditions: a. Sustained ventricular tachycardia or any ventricular fibrillation b. Hemodynamically significant valvular disease c. Clinically significant hypertrophic cardiomyopathy d. Any prosthetic heart valve, ring or repair including balloon aortic valvuloplasty e. Contraindication to femoral venous access 4. Any of the following procedures, implants or conditions: a. At baseline: i. Congestive heart failure with New York Heart Association (NYHA) Class III or IV ii. Left ventricular ejection fraction (LVEF) < 35% iii. Uncontrolled hypertension (SBP > 160 mmHg or DBP > 95 mmHg on two BP measurements at baseline assessment) iv. Implantable loop recorder or insertable cardiac monitor b. Within the 3 months preceding the Consent Date: i. Myocardial infarction ii. Unstable angina iii. Percutaneous coronary intervention iv. Implantation of a pacemaker, cardioverter defibrillator or cardiac resynchronization therapy device v. Heart failure hospitalization vi. Treatment with amiodarone vii. Pericarditis or symptomatic pericardial effusion

viii. Gastrointestinal bleeding

c. Within the 6 months preceding the Consent Date:
   i. Heart surgery
   ii. Stroke, TIA or intracranial bleeding
   iii. Any thromboembolic event
   iv. Carotid stenting or endarterectomy

5. Diagnosed disorder of blood clotting or bleeding diathesis
6. Contraindication to, or unwillingness to use, systemic anticoagulation
7. Patient who is not on anticoagulation therapy for at least 3 weeks prior to the ablation procedure
8. Women of childbearing potential who are pregnant, lactating, not using birth control or planning to become pregnant during the anticipated study period
9. Medical conditions that would prevent participation in the study, interfere with assessment or therapy, significantly raise the risk of study participation, or confound data or its interpretation, including but not limited to:
   a. Body mass index (BMI) > 45.0
   b. Solid organ or hematologic transplant, or currently being evaluated for an organ transplant
   c. Severe lung disease, pulmonary hypertension, or any lung disease associated with chronic abnormal blood gases or requiring supplemental oxygen
   d. Renal insufficiency with an estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2, or any history of renal dialysis or renal transplant
   e. Active malignancy or history of treated malignancy within 24 months of enrollment (other than cutaneous basal cell or squamous cell carcinoma)
   f. Active systemic infection
   g. 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
   h. Other uncontrolled medical conditions that may modify device effect or increase risk, including uncontrolled diabetes mellitus, untreated sleep apnea or active alcohol abuse
   i. Predicted life expectancy less than one (1) year

EXCLUSION CRITERIA (CONTINUED):	10. Clinically significant psychological condition that in the investigator's opinion would prohibit the subject's ability to meet the protocol requirements. 11. Current or anticipated enrollment in any other clinical study. (data collection for registries or retrospective studies is permitted)

Schedule of Event

Assessment	Baseline[1]	Index Procedure	Pre-Discharge	Day 7 (7-11 days)	Day 30 (± 7 days)	Day 60 (± 10 days)	Re-Ablation Procedures	Day 90 (90 ± 14 days)	Month 6 (180 ± 30 days)	Month 12 (360 ± 30 days)	Unscheduled
Informed consent, baseline assessments	X[2]										
Anti-arrhythmic drugs (AADs)	X		X	X	X	D/C AADs	X	X	X	X	X
Recurrent arrhythmia, cardioversions, ablations, hospital admissions			X	X	X		X	X	X	X	X
Pregnancy test	X[3]	X[3]					X[3]				
12-lead ECG	X		X					X	X	X	X
Event monitors	Training		Training					Weekly + symptomatic transmissions			X
72-Hour continuous ECG (Holter)	Training		Training						X	X	
TEE/CT/ICE to exclude LA thrombus		X[4]					X[4]				
NIHSS	X		X								
Radiologic examination of diaphragm		X					X	X[5]	X[5]	X[5]	
Post-procedure assessments of PVI and CTI ablation		X					X				
AF Symptom, EQ-5D-3 L and AFEQT assessments	X									X	
Neuro assessment			X[6]								
Adverse events		X	X	X	X		X	X	X	X	X

[1] All Baseline Assessments must be generated in the window beginning 30 days prior to the Consent Date and ending on the date of the Index Procedure.
[2] Baseline assessments include the inclusion/exclusion criteria and the data stipulated in **Section 4.6.1**
[3] Females of childbearing potential only. The pre-procedural pregnancy test is not required if the Index Procedure / Rescheduled Index Procedure is within 30 days of the baseline pregnancy test.
[4] Performed at the beginning of the procedure prior to ablation. See **Section 5.3** for managing subjects whose procedure is delayed by intracardiac thrombus.
[5] Only if resolution of phrenic nerve palsy has not yet been demonstrated. May be performed either by fluoroscopic sniff test or inspiration/expiration CXR.
[6] If the post-procedure NIHSS score has increased by 1 or more points or if there is a clinical suspicion of stroke/TIA, then a consulting neurologist will perform a stroke assessment and include the results of a concurrent brain MRI. If stroke is diagnosed, a Modified Rankin Scale assessment will be performed prior to discharge and again at 3 months.