AVANT GUARD Clinical Study

(A Prospecti**v**e R**an**domized Mul**t**icenter **G**lobal Study Comparing P**u**lsed Field **A**blation ve**r**sus Anti-Arrhythmic **D**rug Therapy as a First Line Treatment for Persistent Atrial Fibrillation)

Study Purpose: Establish safety and effectiveness of Pulsed Field Ablation (PFA) as a first-line treatment for **subjects with persistent atrial fibrillation** as compared to subjects who received an initial treatment with anti-arrhythmic drugs.

Important information on AVANT GUARD:

1. **To participate patients must have symptomatic persistent continuous AF for (> 7 days and ≤ 365 days) and:**
    - Anti-arrhythmic Drug (AAD) history:
        - ≤ 6 months preceding enrollment, < 7-day AAD history (Class I or III) or < 24 hours of amiodarone OR Treated with AAD > 6 months preceding enrollment, which did not fail (no adverse drug effects or frequent AF episodes).
        - Note: Pill-in-the-pocket AAD use is permitted

2. **When identifying a potential patient, contact the study physician prior to prescribing an AAD (class I or III) or referring for an ablation.** Subjects are not permitted to take AADs (class I or III) or amiodarone, following consent and confirmation of eligibility criteria, until initiation of randomized AAD treatment.

3. **Randomized and PFA Assigned (Non-Roll-In) subjects are strictly prohibited from taking amiodarone from the point of randomization until the Month 12 visit or until they are considered a primary endpoint failure.**

4. **All subjects are required to have a LUX-Dx ICM inserted (if not already inserted).**

5. **Patient participation is approximately 36 months after randomization.**

General Information

What is PFA and for whom is it currently indicated?

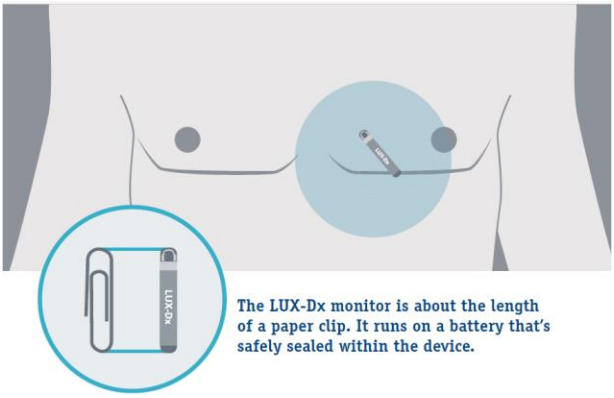
Pulsed Field Ablation (PFA) is a novel ablation modality for the treatment of atrial fibrillation (Afib) using electrical pulses that ablate the myocardium by electroporation of the cardiac cell membrane without tissue heating. The FARAPULSE PFA catheter has been approved in the US, Canada, EU, Asia-Pacific and Australia for treatment of paroxysmal Afib. Additional studies are required to obtain data on persistent Afib to expand the indication to a larger group of patients.

Why is it important to cover broader indications?

- Several randomized controlled trials with paroxysmal Afib patients have compared ablation to anti-arrhythmic drugs (AADs) as first line therapy showing that ablation is safe and effective before attempting AAD[1,2].
- The 2023 ACC/AHA/ACCP/HRS[3] AF ablation guidelines incorporated these recommendations for catheter ablation by upgrading ablation as first-line treatment to class 1 for selected patients with symptomatic paroxysmal AF and to class 2a for symptomatic paroxysmal and persistent Afib patients.
- AVANT GUARD is the first randomized, controlled trial comparing AAD therapy and first line PFA ablation for persistent AF patients aiming at demonstrating that first line treatment of these patients with PFA is safe and effective compared to AAD treatment.

Why is it important to follow these patients with an insertable cardiac monitor (ICM)?

- AVANT GUARD uses the LUX-Dx (ICM) for all patients (drug treated and ablation patients) to assess Afib recurrence and Afib burden through the 36-month follow-up. The insertion of the ICM, a small subcutaneous device, is low risk and will provide critical data on Afib in both groups of the study.



The LUX-Dx monitor is about the length of a paper clip. It runs on a battery that's safely sealed within the device.

- Technologies such as the ICM can ensure continuous rhythm monitoring and high patient compliance, as compared to traditional event monitors. The ICM collects AF burden and duration of asymptomatic episodes which are critical aspects linked to patient outcomes.

1 Andrade J.G., Wells G.A., Deyell M.W., et al. Cryoablation or drug therapy for initial treatment of atrial fibrillation. N Engl J Med. 2021;384(4):305–315.
2 Knuiss, M, Pavlovic N., Velagic V. et al. Cryoballoon ablation vs. antiarrhythmic drugs: first-line therapy for patients with paroxysmal atrial fibrillation. Europace. 2021;23(7):1033-1041
3 Joglar et al J Am Coll Cardiol. 2024 Jan 2;83(1):109-279

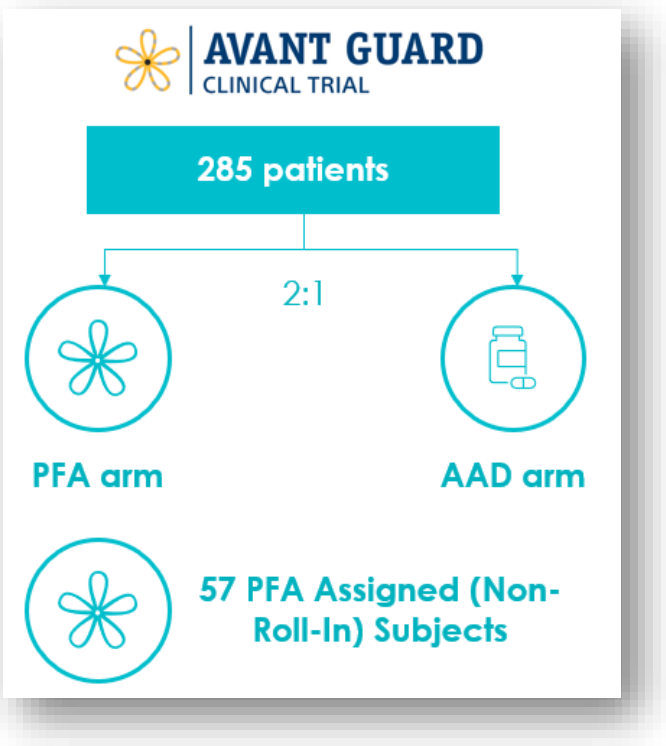
Can patients randomized to AAD treatment receive PFA ablation if AAD fails?

Yes. Although AVANT GUARD is a randomized controlled study, patients randomized to the AAD arm who fail AAD treatment can get an ablation, if clinically indicated, after the blanking period of 3 months. In AVANT GUARD, these patients may qualify for PFA ablation and will continue to be followed for up to 36 months.

AVANT GUARD aims to enroll diverse patients with respect to gender, race and ethnicity. Data show the need to enroll and treat underrepresented populations[4]. Given the increased AF risk factors and differences in management and treatment techniques among the underrepresented ethnic and racial groups, it is imperative to start improving the representation of these groups in catheter ablation trials. The study is looking to enroll more persons of color (12-15%) as well as women (43-45%) globally.

Study Design Overview

- Prospective, Multi-Center, Global, Pivotal IDE with up to 75 Global Sites in US, Europe, Canada, and Asia Pacific.
- Randomized (2 PFA : 1 AAD)
- After randomization is completed, approximately 57 additional subjects will be enrolled and automatically assigned to PFA treatment.



[4] Patel N, Deshmukh A, Thakkar B, et al. Gender, Race, and Health Insurance Status in Patients Undergoing Catheter Ablation for Atrial Fibrillation. Am J Cardiol. 2016;117(7):1117 1126. doi:10.1016/j.amjcard.2016.01.040

Eligibility Criteria

Patient's eligibility will be evaluated by the study enrolling physician. The tables below denote the main inclusion and exclusion criteria. Study patients need to meet all eligibility criteria. Please refer to the CT.gov website for a full list of criteria

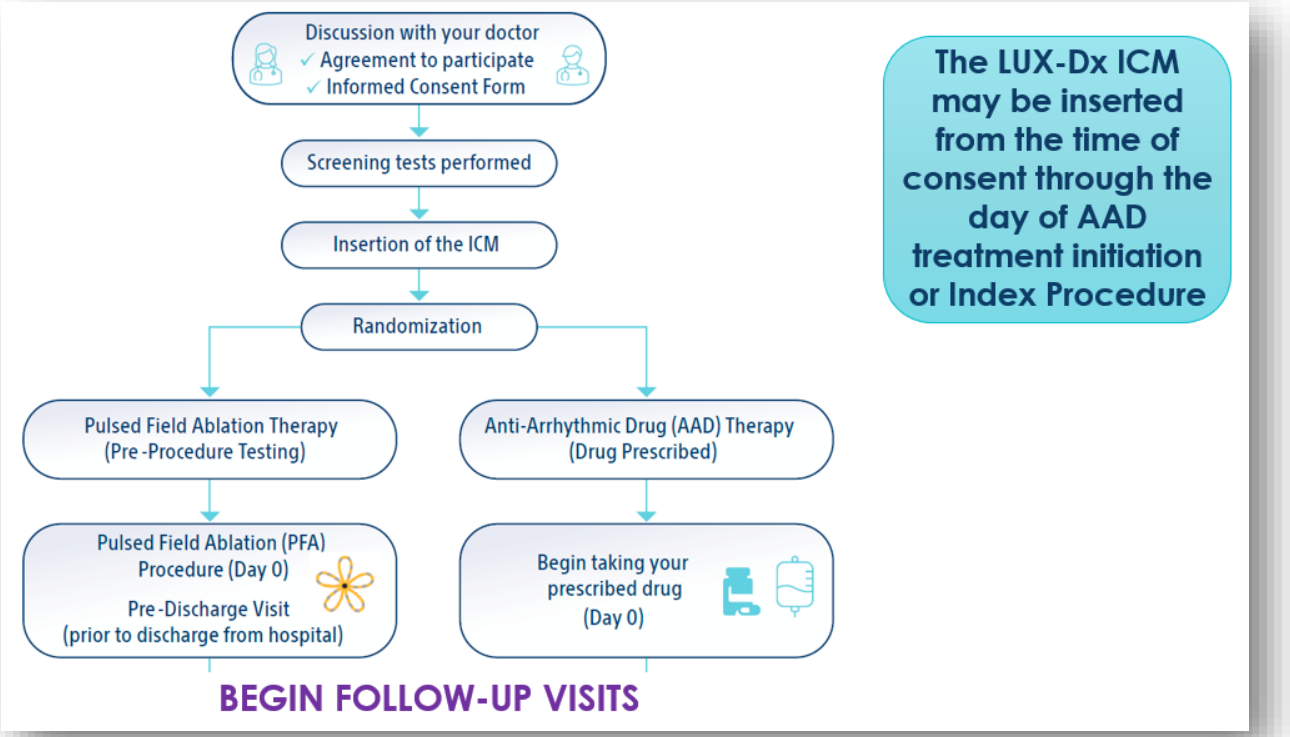
CT.gov website: https://clinicaltrials.gov/study/NCT06096337.

Main Inclusion Criteria
Age ≥ 18 years of age, or older if specified by local law
Have symptomatic persistent AF, confirmed by both A & B: A. Documentation, within 180 days of randomization, or treatment assignment for roll-in subjects, of either: ○ A 24-hour continuous ECG recording (from any regulatory cleared rhythm monitoring device) confirming continuous AF, OR ○ Two ECGs (from regulatory cleared rhythm monitoring device) with continuous AF taken at least 7 days apart B. Documentation, such as physician note, of persistent continuous AF for > 7 days and ≤ 365 days
Willing to receive LUX-Dx™ insertable cardiac monitor (ICM) during the study or already has a LUX-Dx™ ICM that was inserted ≤ 6 months of consent

Main Exclusion Criteria
Treated with AAD (Class I or III) ≤ 6 months (i.e., within 180 days) before enrollment, A. More than 7-day history of therapeutic AAD use (Class I or III), or B. ≥ 24 hours amiodarone, except for pill-in-the-pocket AAD use, which is permitted.
Treated with AAD > 6 months before enrollment and experienced AAD failure (adverse drug effects or frequent AF episodes)
Contraindication to, or unwillingness to use, systemic anticoagulation, AADs (Class I and III, excluding amiodarone), and PFA treatment

May require an ablation, besides the PV and PW, in the left atrium including, but not limited to, those with Left-Sided Atrioventricular Reentrant Tachycardia (AVRT), Left-Sided Atrial Tachycardia (AT), or Atypical Left-Sided Atrial Flutter

AVANT GUARD Patient Schedule



Please contact the Principal Investigator (PI) of the study site for more information.

Study Site: _____

PI Name: _____ **PI contact information:** _____

RC Name: _____ **RC contact information:** _____

For more information on Pulsed Field Ablation go to www.bostonscientific.com