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ADVANTAGE AF US IDE

Clinical Trial Results (Phase II)

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Reddy, V *et. al.*, 2025
A Prospective Single Arm Open Label Study of the FARAPULSE Pulsed Field Ablation System in subjects with Persistent Atrial Fibrillation (ADVANTAGE AF) NCT05443594

OBJECTIVE

The ADVANTAGE AF US IDE evaluated the safety and effectiveness of the FARAPULSE™ Pulsed Field Ablation (PFA) System for treatment of drug refractory, symptomatic persistent atrial fibrillation (PersAF). Ablation treatment with the FARAWAVE™ Pulsed Field Ablation Catheter included pulmonary vein isolation (PVI) and posterior wall ablation (PWA).

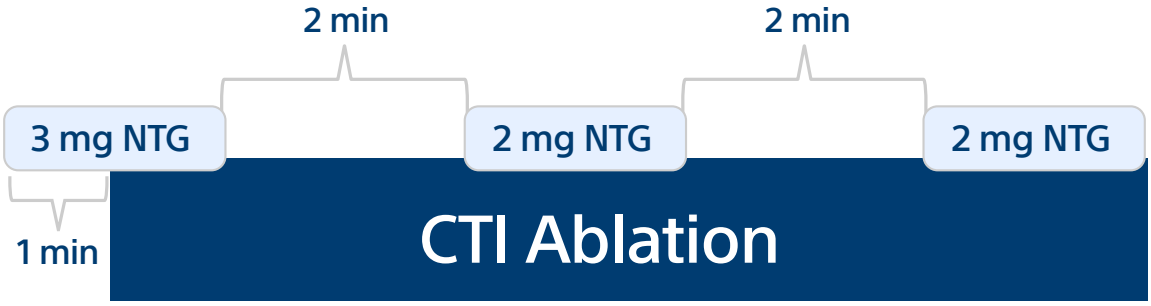
- **Phase II included two additions to the study:**
- The focal FARAPOINT™ Pulsed Field Ablation Catheter for cavotricuspid isthmus (CTI) ablation to treat typical atrial flutter (AFL).
- Use of the LUX-Dx™ Insertable Cardiac Monitor (ICM) System for continuous cardiac monitoring.

ADVANTAGE US IDE (PHASE II) CLINICAL TRIAL DESIGN

- **ADVANTAGE AF Phase II** included 29 US sites and 49 investigators.
- **255 PersAF patients** underwent PVI and PWA with the FARAWAVE PFA Catheter. CTI ablation with the FARAPOINT PFA Catheter was performed in 141 (55.3%) patients. Continuous monitoring was done with the LUX-Dx ICM and 12-lead ECG was done at 3 and 12 months.

CTI Ablation with FARAPOINT

- **Protocol Pre-Treatment:** 200 micrograms of phenylephrine was recommended prior to nitroglycerin (NTG) dosing. A 3 mg NTG IV bolus via FARADRIVE™ sheath (or other central access sheath) was required to be administered ~1 min prior to the first FARAPOINT application at the anterior position of the CTI line.
- **During Ablation:** Depending on the patient condition and procedure duration, an additional 2 mg IV bolus of NTG was administered via a central access sheath ~2 min apart until the ablation was complete or a max of 9 mg IV NTG was administered.
- If bi-directional block was not achieved and additional lesions were required, 2-3 mg of NTG was allowed per investigators discretion.



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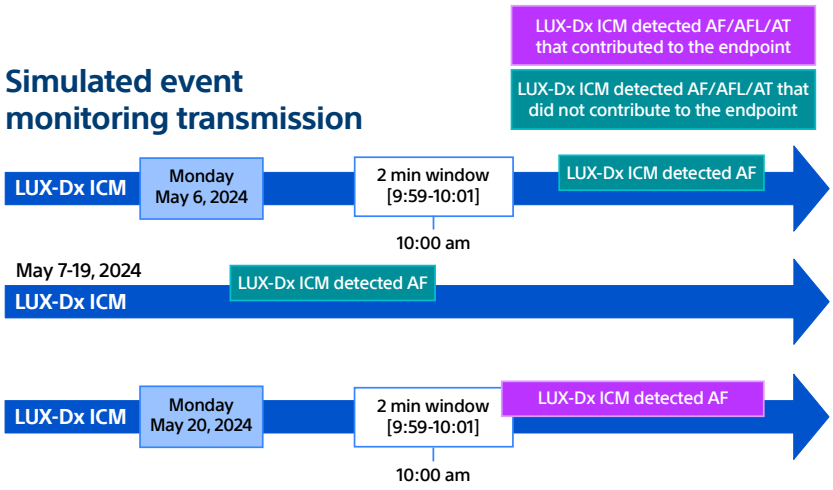
LUX-Dx™ ICM Monitoring System

- LUX-Dx ICM was used to simulate traditional cardiac event monitoring and Holter monitoring methodology.

ADVANTAGE Phase II Monitoring
Event Monitor Specific day/time (e.g. every other Monday at 10:00 am) A 2-min recording (the LUX-Dx ICM recording length) will be checked for confirmed AF/AFL/AT
Symptomatic Event Monitor Patient triggered symptomatic recorded on LUX-Dx ICM containing ≥ 30 seconds of AF/AFL/AT
Holter Monitor Asymptomatic or symptomatic (patient-triggered) AF/AFL/AT on LUX-Dx ICM during the 24-hour period on day 180 and day 360 visits
12-Lead ECG (not simulated) 3 and 12 months



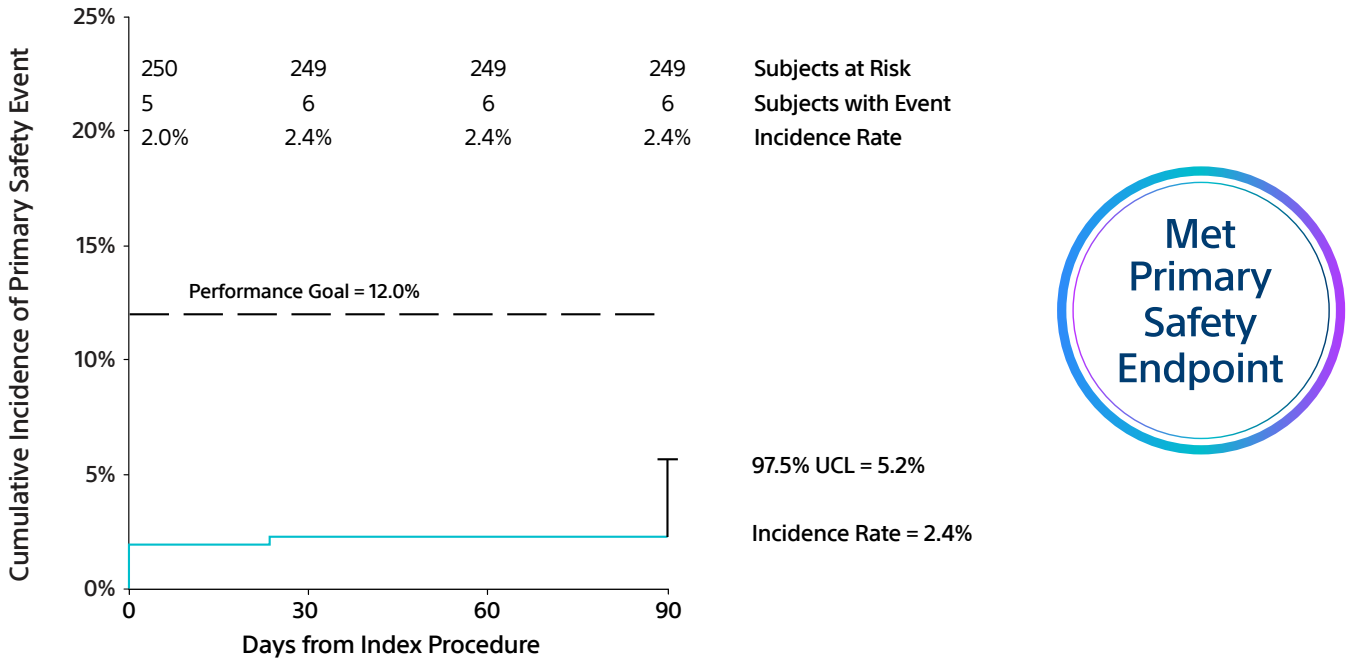
SAFETY

Primary Safety Endpoint (Phase II)

A composite endpoint defined as: 1) serious adverse event related to either the use of an ablation catheter or the ablation procedure with onset within 7 days of the primary procedure, 2) death, cardiac tamponade/perforation, pericarditis, cardiovascular or pulmonary adverse event related to either the use of the ablation system or procedure out to 30 days and 3) pulmonary vein stenosis or atrio-esophageal fistula out to 3 months.

- At 3 months, the primary safety event rate was 2.4% [97.5% UCL = 5.2%] which met the 12.0% performance goal (Figure 1).
- Patients with events included cardiac tamponade or perforation (n=1), pulmonary edema (n=1), death (n=1), PFA system or procedure related cardiovascular or pulmonary event (n=2), stroke (n=3), and vascular access complication (n=1).
- There were no reports of PV stenosis or esophageal fistula.
- Hemolysis (not a composite primary safety endpoint event) was reported for 2 patients (1 lab confirmed, 1 suspected).

Figure 1. Primary Safety Event Rate



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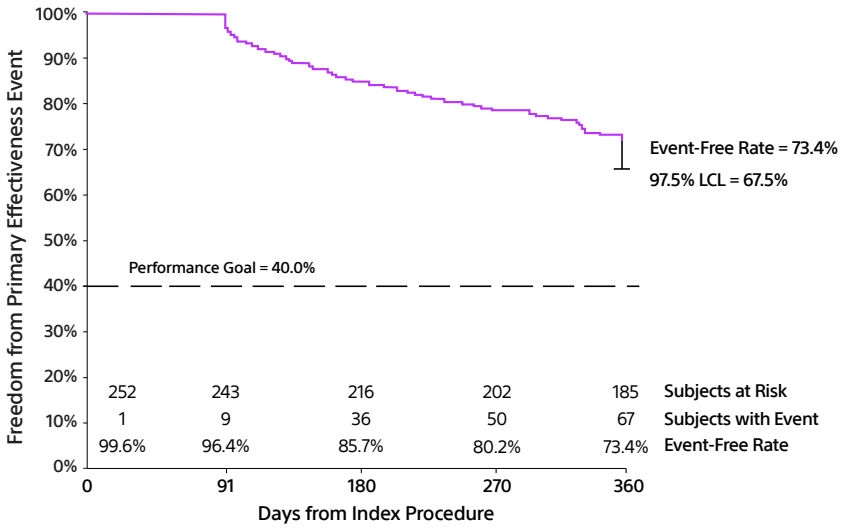
EFFICACY

Primary Effectiveness Endpoint (Phase II)

A composite endpoint defined as acute procedural success (isolation of PV and LAPW) and chronic ablation success through 12 months. After the 90-day blanking period, chronic success was defined as freedom from AF/AFL/AT recorded on the LUX-Dx ICM (≥30 seconds on simulated bimonthly cardiac event monitor periods ≥30 second or 24-hour Holter monitor periods at Day 180 and 360, and ≥10 seconds on ECG), re-ablation, cardioversion and use of a new or escalated dose of Class I/III AADs or Amiodarone.

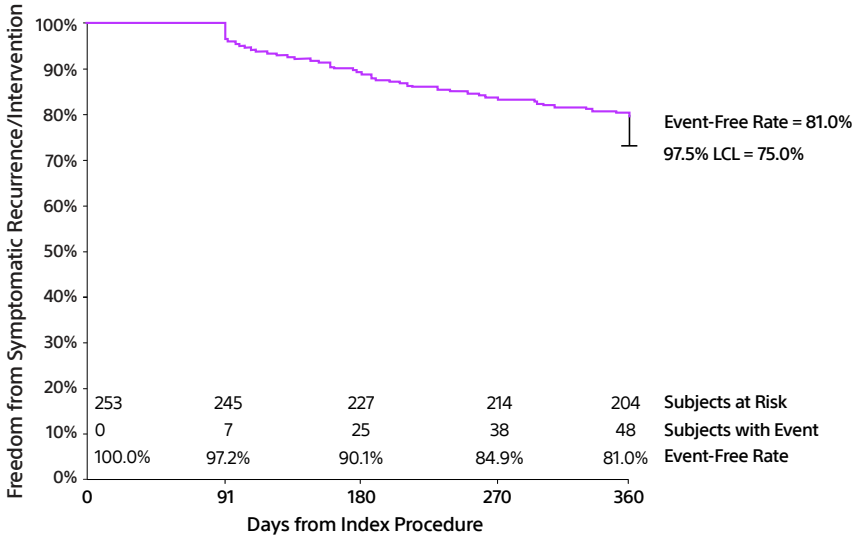
Met Primary Effectiveness Endpoint

Figure 2. Primary Effectiveness Recurrence-Free Rate



- At 12 months, the primary effectiveness event-free rate was 73.4% [97.5% LCL = 67.5%] which met the 40.0% performance goal (Figure 2). The most common chronic treatment failure event was documented recurrence of a sustained atrial arrhythmia (AF/AFL/AT).
- The post-blanking period redo ablation rate was 5.5% (n=14), (7 AF, 8 AFL [3 CTI-dependent]).
- Durability data was based on 16 redo patients that had gap assessment. The PV durability was 87.5% (62.5% per patient) for PVI, and 62.5% for PWA.

Figure 3. Freedom from Symptomatic Recurrence and Intervention to Treat AF, AFL, or AT



Symptomatic Effectiveness Endpoint

Freedom from Symptomatic Recurrence defined as symptomatic documented arrhythmia, clinical intervention (cardioversion or re-ablation), or use of escalated or new Class I/III AAD.

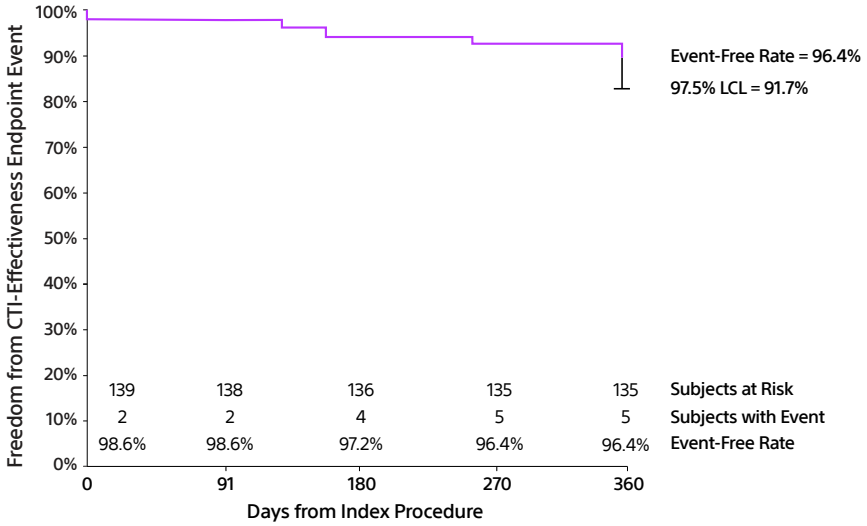
- At 12 months, the freedom from symptomatic documented recurrence and intervention to treat atrial arrythmias was 81.0% [97.5% LCL = 75.0%] (Figure 3).

CTI Effectiveness Endpoint

Composite endpoint of CTI dependent AFL acute (bidirectional conduction block at index procedure) and chronic (freedom from documented CTI dependent AFL (≥ 10 sec on ECG) without a repeat CTI ablation) procedural success.

- CTI ablation using the focal FARAPOINT PFA Catheter was conducted on 141 patients (55.3%). Bidirectional block was achieved in 139/141 (98.6%; 1 cable issue, 1 failure to confirm block due to patient being in AF) of patients with no reported adverse event such as ST changes or ventricular fibrillation.

Figure 4. CTI Effectiveness Event-Free Rate



(continued)

CTI Effectiveness Endpoint

- There were no reports of coronary spasm and CTI ablation took an average of 8 ± 13 minutes and required 18 ± 6 PFA applications, 4 ± 2 mg IV NTG was administered, on average.
- At 12 months, the CTI effectiveness event-free rate was 96.4% [97.5% LCL = 91.7%] (Figure 4).

ATRIAL ARRHYTHMIA (AA) BURDEN

LUX-Dx ICM detected AA episodes were adjudicated by BeatLogic™. The BeatLogic algorithm is a cloud-based ECG analysis platform that leverages artificial intelligence (AI) algorithms and deep learning to automate ECG interpretation. The below formula was used to calculate AA burden.

$$\text{AA Burden} = \frac{\text{Total duration of LUX-Dx detected AA episode } \textbf{adjudicated as the true AA ≥ 30s by BeatLogic}}{\text{Total follow up duration} - \text{Total duration of LUX AA episodes with no stored ECG to adjudicate}} \times 100$$

- **At 12 months, after the blanking period:**
  - 71.6% of patients had virtually no AA burden (≤0.1%) (Figure 5).
  - 52.0% of patients had no AA recurrence (Figure 6) and 70.0% did not have atrial arrhythmia episodes longer than 1 hour.

52% **NO AA Recurrence** at 12 months

70% **<1 Hour AA Episode Duration** at 12 months

Figure 5. Atrial Arrhythmia Burden

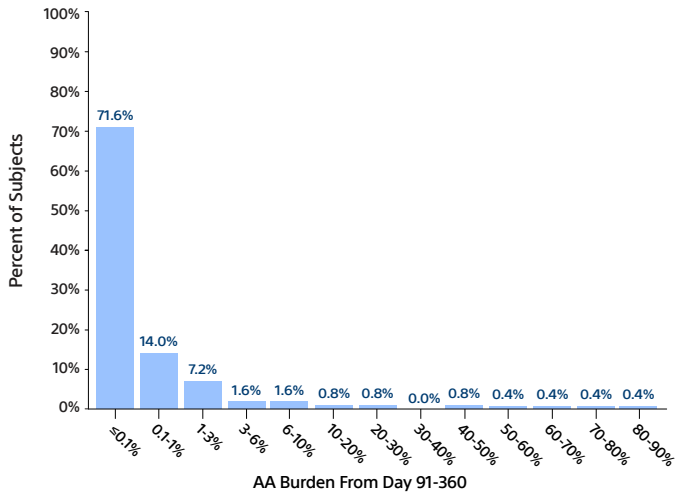
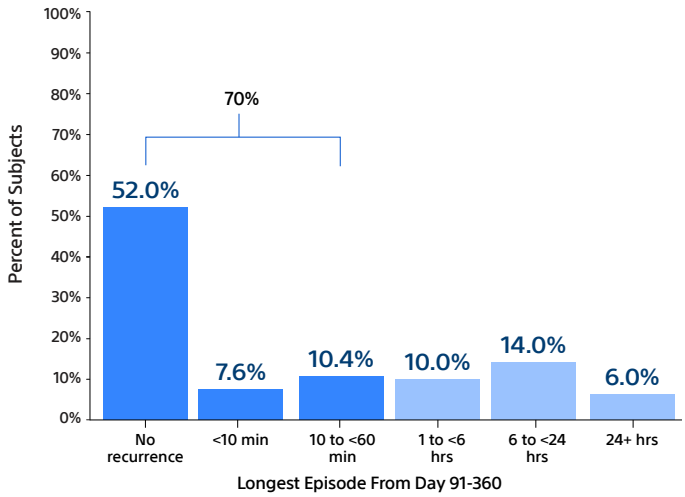


Figure 6. Longest AA Episode



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HEALTH CARE UTILISATION

Health care utilisation (HCU) (all-cause hospitalisation, re-ablation, DCCV, new or escalated dose of AAD, or unscheduled cardiovascular clinical visits) was correlated to AA burden and AA episode duration to validate if previously established ranges of AA burden and episode durations are clinically meaningful.

- At 12 months, patients with AA burden ≥0.01% had significantly higher HCU than patients with no AA burden (p<0.0125) (Figure 7).
- Patients with AA episode durations of 1 hour or longer had significantly higher HCU than patients with no recurrence (p<0.01) (Figure 8).

Figure 7. HCU through 12 months by AA Burden

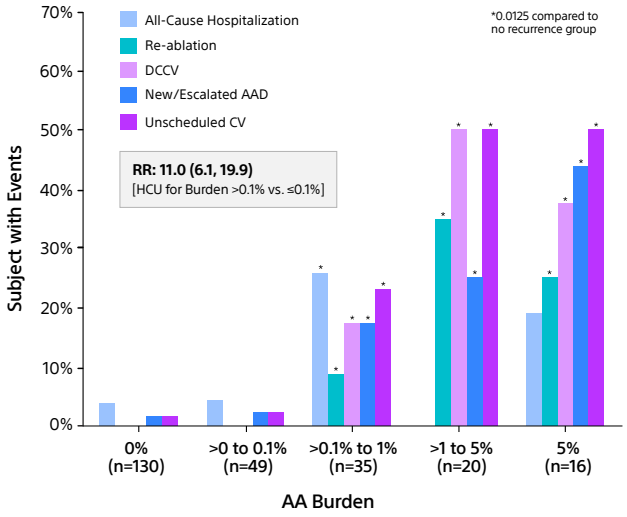
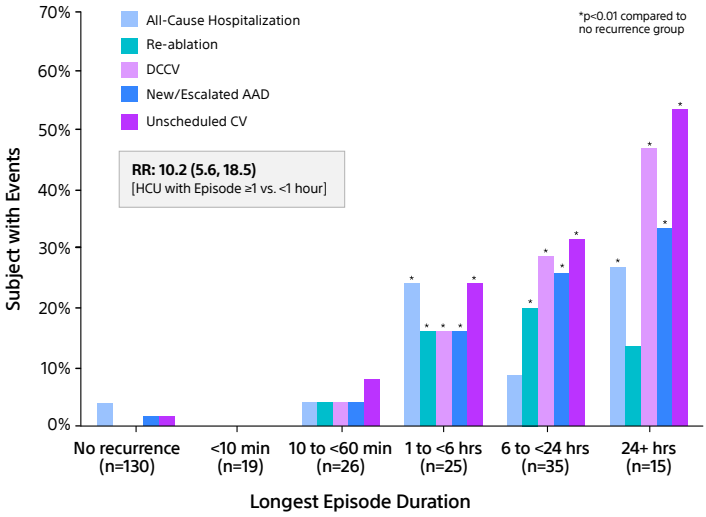


Figure 8. HCU through 12 months by Longest Episode



Health care utilisation was over tenfold higher in patients with AA burden ≥0.1% or episodes lasting 1 hour or more

10x

PROCEDURAL DETAILS

- Mapping was utilised in 88.6% of the procedures with many of the ablations being performed with the smaller 31 mm catheter (90.6%).
- PVI took an average of 22 ± 11 minutes with 46 ± 11 PFA applications, while PWA averaged 16 ± 13 minutes with 36 ± 16 PFA applications.
- The CTI ablation time was 8 ± 13 min and 18 ± 6 PFA applications were delivered on average.

Procedural Characteristics	
Procedure Time (min)*	105 ± 36
LA Dwell Time (min)*	59 ± 24
Fluoroscopy Time (min)	18 ± 12
Pulmonary Vein Isolation Time (min)	22 ± 11
Posterior Wall Ablation Time (min)	16 ± 13
CTI Time (min)	8 ± 13
PFA Applications	
Pulmonary Vein Isolation	46 ± 10
Posterior Wall Ablation	36 ± 16
CTI Ablation (FARAPOINT PFA)	18 ± 6

*Includes a mandatory 20-minute post-PVI waiting period

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CONCLUSIONS

- Phase II of the ADVANTAGE AF USE IDE examined PVI and PWA using FARAWAVE™ on 255 PersAF patients. If patients were indicated for CTI, ablation was performed with the focal FARAPOINT™ PFA Catheter (n=141) and continuous monitoring was done with the LUX-Dx™ ICM.
- At 3 months, the primary safety endpoint was met with a low incidence of major safety events (2.4%), [97.5% UCL = 5.2%] which met the 12.0% performance goal with no reported PV stenosis, or esophageal fistula.
- The primary effectiveness event-free rate was 73.4% [97.5% LCL = 67.5%] at 12 months which met the 40.0% performance goal.
- CTI with focal FARAPOINT was performed in 141 (55.3%) patients with no reports of coronary spasm. CTI ablations with FARAPOINT were efficient (8 min) and at 12 months the CTI effectiveness event-free rate was 96.4% [97.5% LCL = 91.7%].
- At 12 months, after the blanking period; 71.6% of patients had virtually no AA burden (≤0.1%), 52.0% of patients had no AA recurrence and 70.0% had less than 1 hour of AA burden.
- Patients with AA burden ≥0.01% or AA episode durations of 1 hour or more had significantly higher HCU than patients with no AA burden ($p<0.0125$ and $p<0.01$, respectively).
- The average LA dwell times were under an hour with the pulmonary vein and posterior wall ablation times averaging 22 and 16 minutes, respectively.

Reference:
1. Reddy, Vivek, *et al.* (in press). "Pulsed Field of Persistent Atrial Fibrillation with Continuous ECG Monitoring Follow-Up." *Circulation*.

Phase II included the addition of studying the focal FARAPOINT™ Pulsed Field Ablation Catheter for cavotricuspid isthmus (CTI) ablation to treat typical atrial flutter which is not available for sale.

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