Pulsed Field Ablation Treatment in Paroxysmal and Persistent Atrial Fibrillation Patients:

Acute and Long-term Outcomes from the *PULSED AF* Pivotal Trial

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On behalf of the PULSED AF Investigators

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Disclosures

Company	Relationship
Medtronic	Consultant/ Honoraria/ Research grant
Biosense Webster	Consultant/ Honoraria/ Research grant
Biotronik	Research grant
Bayer	Research grant/ Honoraria
Kardium	Consultant
Medlumics	Consultant/ Honoraria

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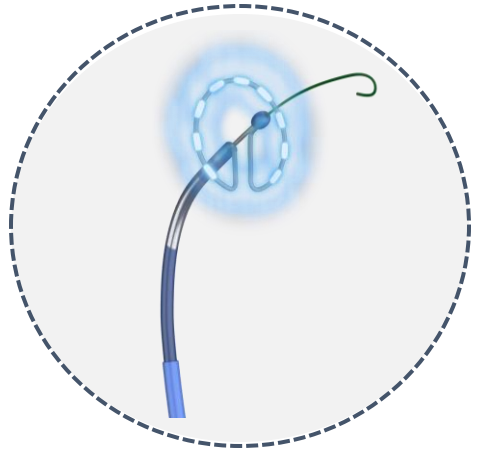
Reference materials were requested and obtained from Medtronic, Inc. for portions of this presentation.

The Medtronic PulseSelect™ PFA system is investigational, not approved in the US.

The following data and analyses have not been reviewed by any regulatory bodies, including FDA.

Introduction

- Catheter ablation is an effective treatment for patients with symptomatic, drug-refractory atrial fibrillation.[1,2]
- Thermal modes of ablation are limited by the potential for collateral tissue damage.[3]
- Pulsed field ablation creates lesions in cardiac tissue non-thermally and within milliseconds through the mechanism of irreversible electroporation (IRE).[4,5]
- IRE involves tissue exposure to high electric field gradients, inducing cell membrane hyper-permeabilization leading to cell death.[6]



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3. Cappato R et al. Circ Arrhythm and Electrophysiol. 2010;3:32-38
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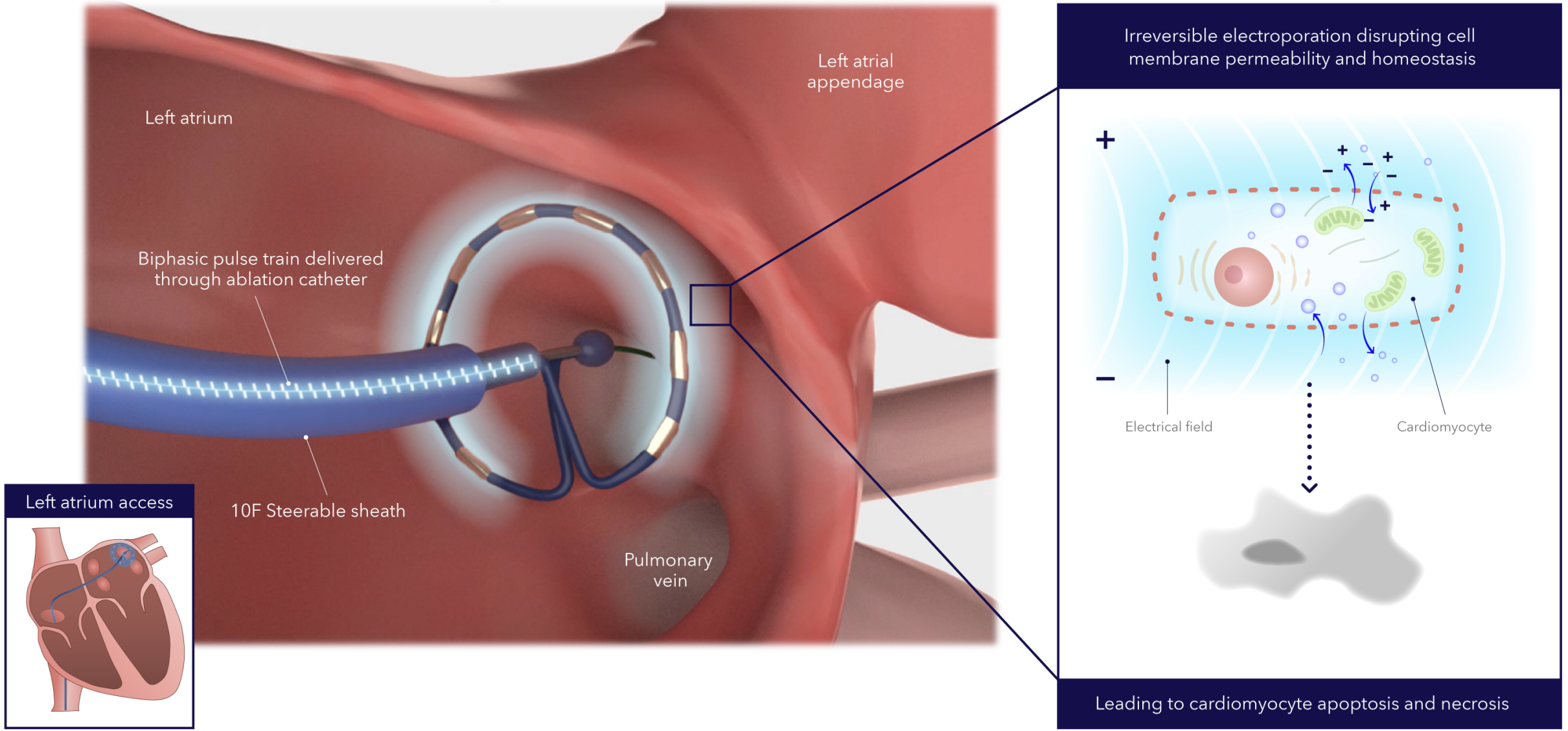


One application = 4 bipolar, biphasic trains lasting 100-200 ms, 2800-3000 V peak to peak

PULSED AF Study Design

PULSED AF: prospective, global, multi-center, non-randomized paired single-arm trial

41	67	9	150	150
Centers	Operators	Countries	Paroxysmal AF	Persistent AF

Key Inclusion Criteria

- Prior antiarrhythmic drug failure
- Diagnosis of recurrent symptomatic paroxysmal or persistent AF
- 18-80 years old

Key Exclusion Criteria

- Long-standing persistent AF (continuous AF that is sustained >12 months)
- Left atrial diameter > 5.0 cm
- Prior left atrial ablation or surgery
- Patient not on oral anticoagulation therapy for at least 3 weeks prior to procedure

Patients underwent pulmonary vein isolation using the Pulsed Field Ablation System (PulseSelect™) and were followed for 12 months

Primary Efficacy Endpoint

Freedom from a composite endpoint of acute procedural failure, arrhythmia recurrence, repeat ablation, direct current cardioversion, left atrial surgery, or antiarrhythmic drug escalation through 12 months (excluding a 90-day blanking period)

Pre-Specified Performance Goal: >50% (paroxysmal) or >40% (persistent) at 12 months

All cardiac monitoring was adjudicated by an independent core laboratory

Cardiac Monitoring During Follow-up

	1-M	2-M	3-M	4-M	5-M	6-M	7-M	8-M	9-M	10-M	11-M	12-M
TTM				Weekly and symptomatic transmissions								
ECG			X			X						X
HM						X						X
	Blanking period			Post-blanking period								

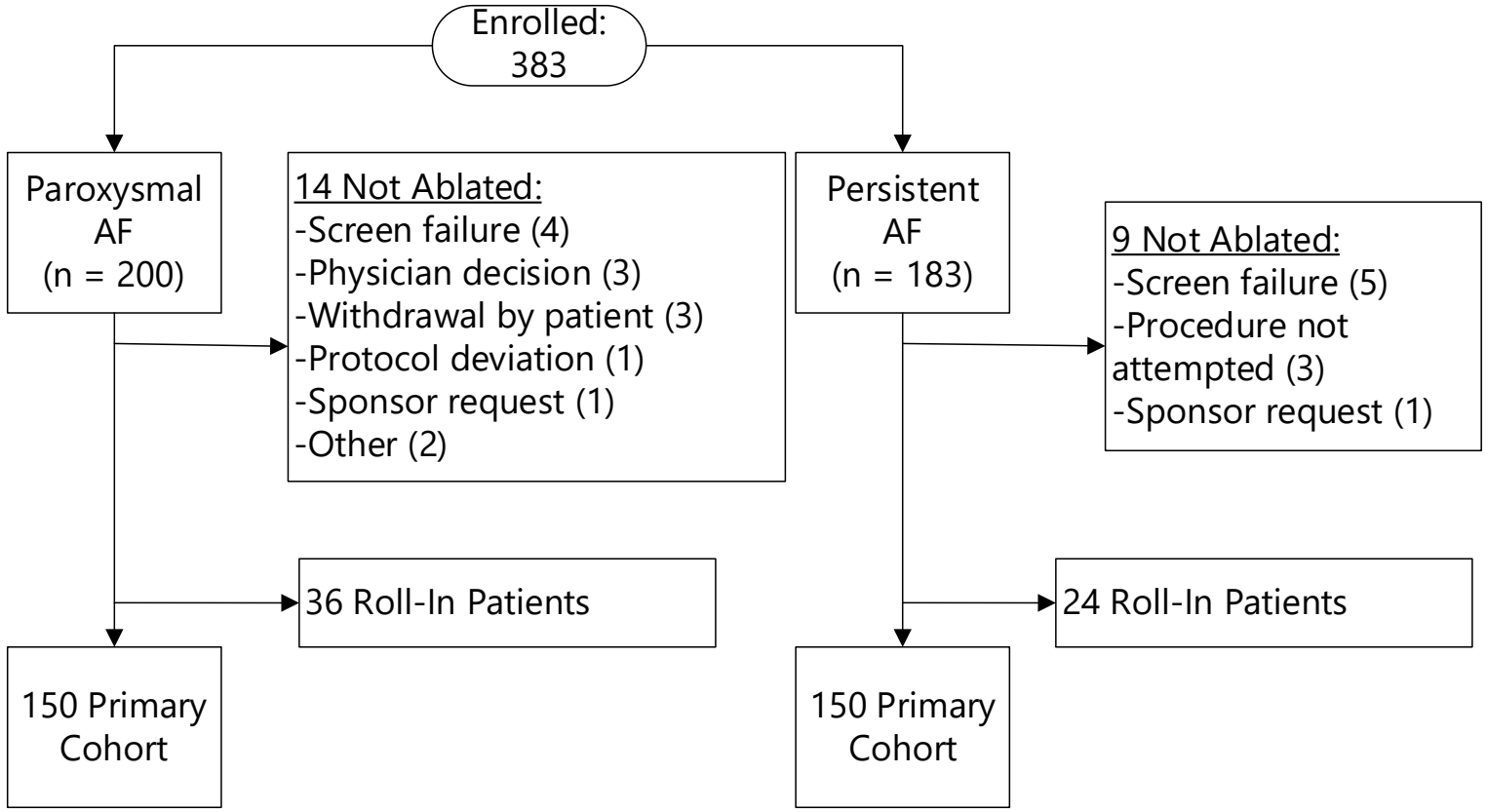
Primary Safety Endpoint

Freedom from a composite of serious procedure and device-related adverse events

Pre-Specified Performance Goal: <13%

All primary safety endpoint events were adjudicated by an independent clinical events committee

Patient Flow Diagram



96% of patients reached 12-month follow-up

Results: Patient Baseline Characteristics

Patient Characteristics		Paroxysmal (n = 150)	Persistent (n = 150)
Male Sex		64%	75%
Age (years)		63.4 ± 9.9	66.0 ± 9.0
Left Atrial Diameter (mm)		38.7 ± 5.8	42.0 ± 5.0
Left Ventricular Ejection Fraction (%)		60.3 ± 4.8†	57.6 ± 6.4
Years Since AF Onset		3.8 ± 6.2	2.7 ± 3.7
Number of Failed Antiarrhythmic Drugs		1.3 ± 0.6	1.3 ± 0.6
Cardioversions Prior to Enrollment	Electrical	22%	62%
	Pharmaceutical	10%	7%
Body Mass Index (kg/m^2)		28.6 ± 5.9	30.9 ± 6.8
Medical History			
Stroke		3%	2%
Transient ischemic attack		1%	2%
Myocardial infarction		5%	5%
Coronary artery disease		21%	21%
Hypertension		49%	65%
Obstructive sleep apnea		20%	31%
Valve dysfunction		15%	11%
Diabetes		16%	14%
CHA_2DS_2VASc		1.8 ± 1.4	2.1 ± 1.4

Data represented as mean ± SD or percentage; †n=149

Procedural Characteristics

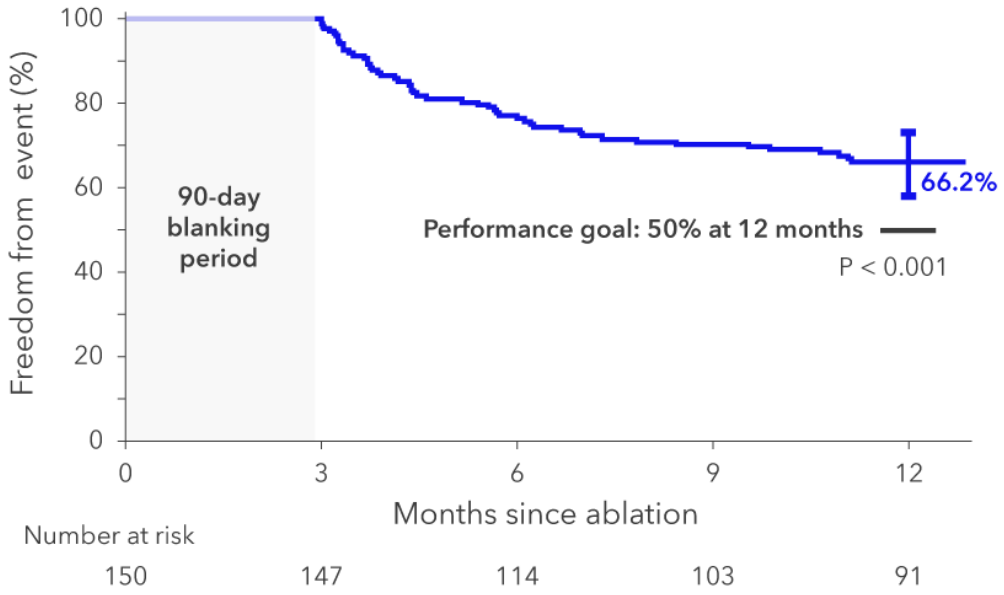
Parameter	Paroxysmal (n = 150)	Persistent (n = 150)
Acute Pulmonary Vein Isolation	100%	100%
Skin-to-skin Procedure Time (min)*	125 (102-157)	133.5 (107-173)
Device Left Atrial Dwell Time (min)†	58.5 (46-76)	62.5 (51-84)
Time Between First and Last Application	53 (40-68)	60 (45-77)
Fluoroscopy Time (min)	21 (15-31)	23 (14-38)
Total pulsed field ablation energy delivered (sec)	23 (19-28)	27 (23-34)
Number of applications per procedure	43.5 (37-54)	52.5 (44-67)
Type of anesthesia used – no. (%)		
General anesthesia	89%	84%
Deep sedation	5%	7%
Conscious sedation	5%	9%
Neuromuscular Blockade Use	5%	7%
Intra-procedural Cardioversions	17%	65%
Max esophageal temperature change from baseline (°c)	0.3 (0.1-0.5) §	0.2 (0.0-0.5) ‖
Mapping / Navigation system used – no. (%)		
CARTO	26%	23%
EnSite	57%	59%
Rhythmia	11%	10%
None	5%	8%

Data represented as median (IQR) or percentage; *First sheath in, to last sheath out; †Includes protocol-mandated 20-minute wait period and post-ablation mapping §Data were available for 67 patients; ‖Data were available for 73 patients.

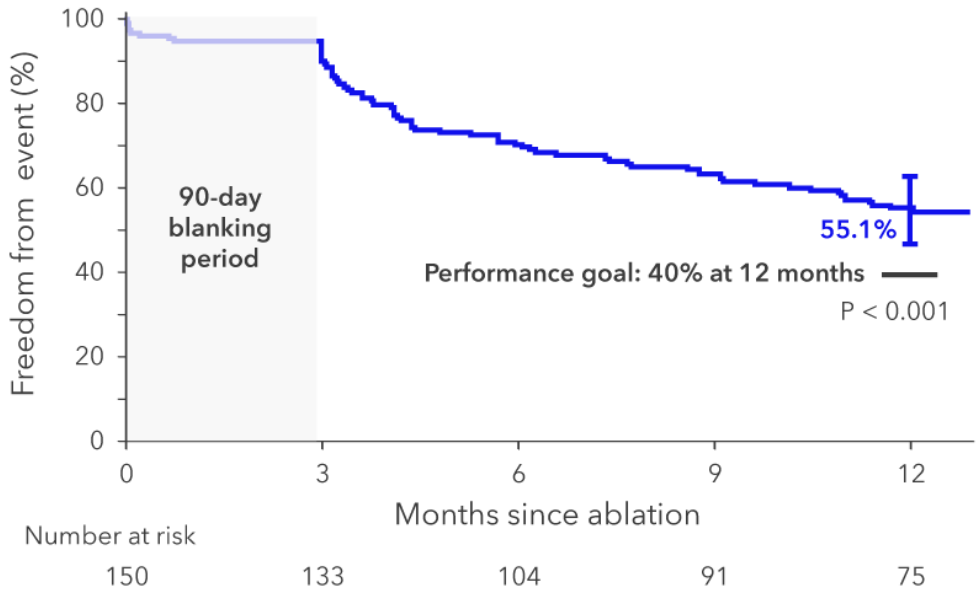
Primary Efficacy Results

Freedom from a composite endpoint of acute procedural failure, arrhythmia recurrence, repeat ablation, direct current cardioversion, left atrial surgery, or antiarrhythmic drug escalation through 12 months (excluding a 90-day blanking period)

Paroxysmal Atrial Fibrillation



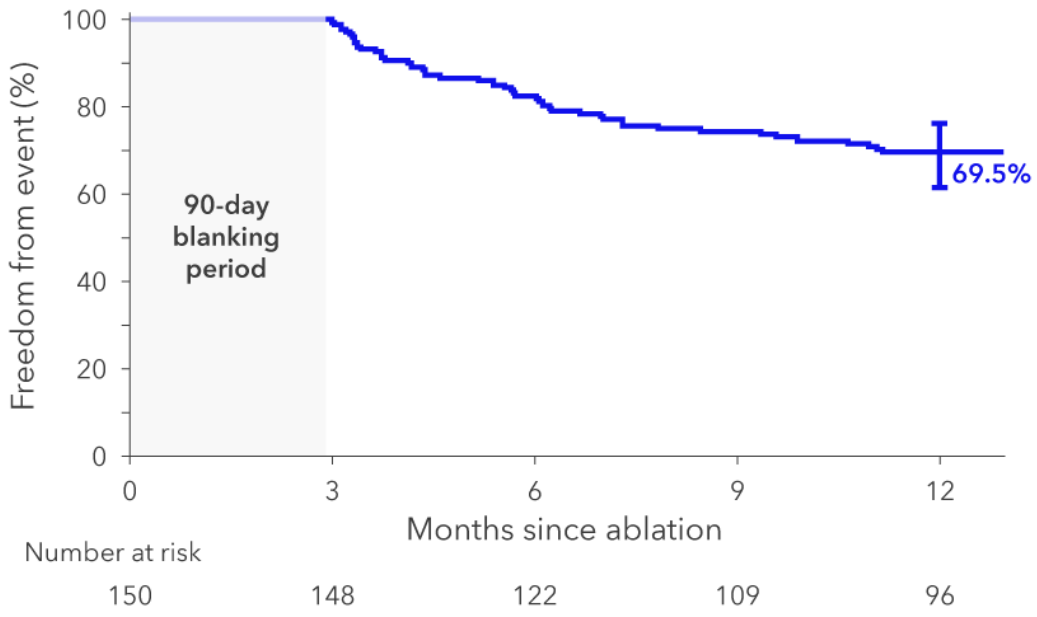
Persistent Atrial Fibrillation



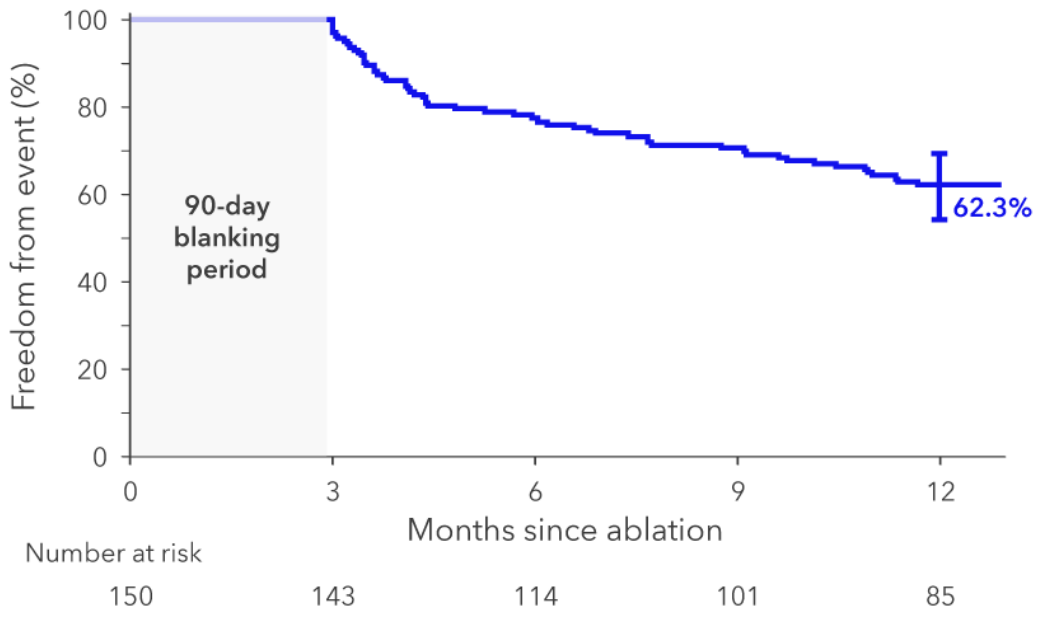
Both paroxysmal and persistent atrial fibrillation cohorts met predetermined effectiveness performance goals.

Freedom from AT/AF/AFL

Paroxysmal Atrial Fibrillation



Persistent Atrial Fibrillation

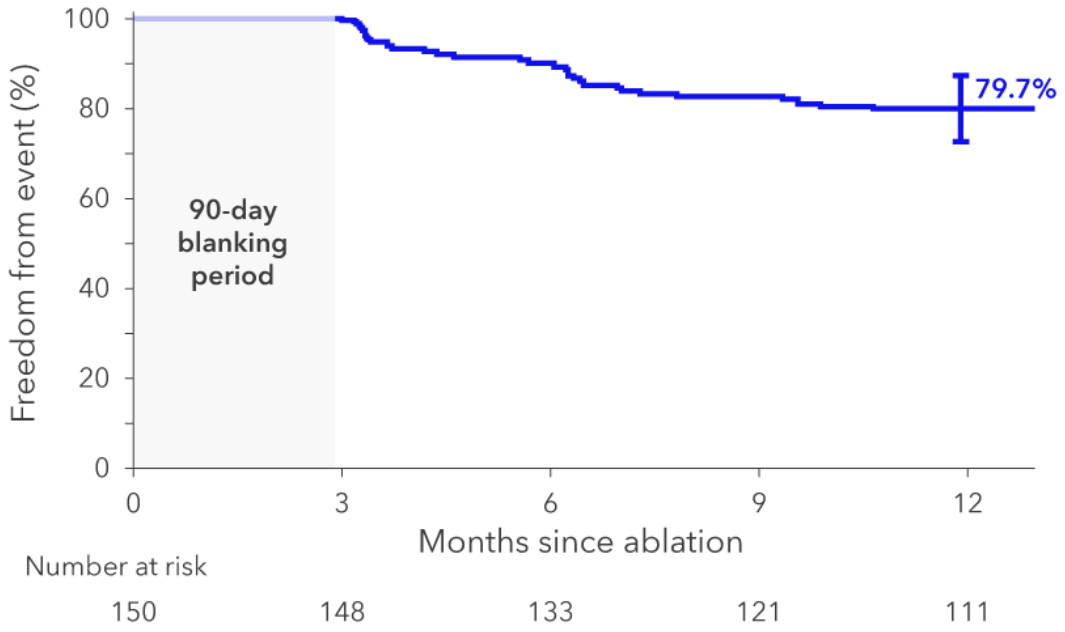


Freedom from atrial arrhythmia recurrence at 12 months was 69.5% in the paroxysmal and 62.3% in the persistent atrial fibrillation cohort

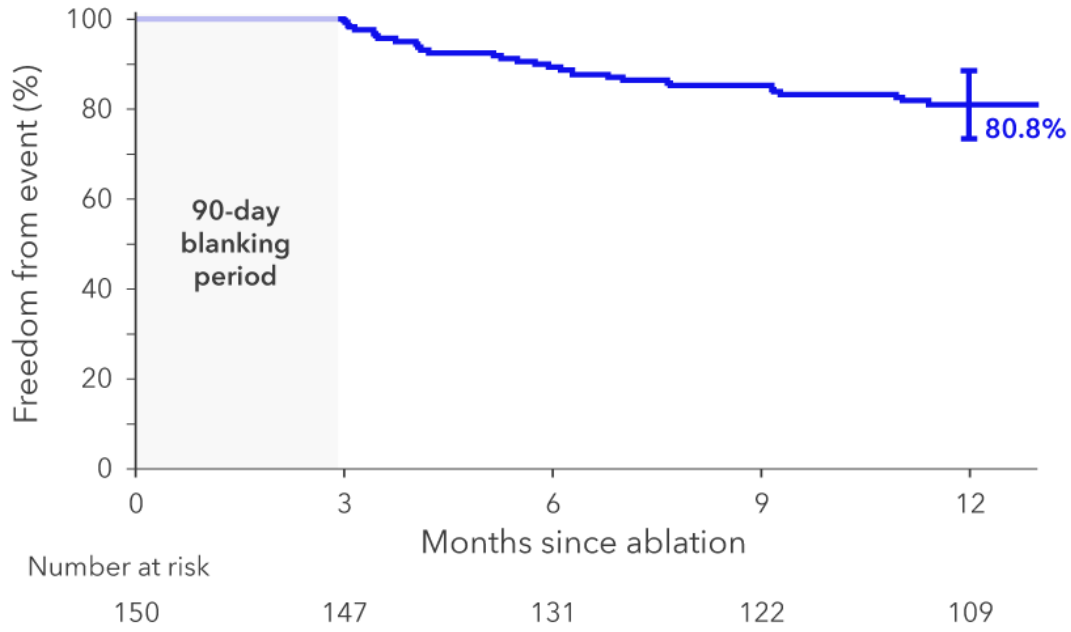
Clinical Success

Clinical success was defined as freedom from symptomatic atrial arrhythmia recurrence at 12 months

Paroxysmal Atrial Fibrillation



Persistent Atrial Fibrillation



Freedom from symptomatic recurrence is based on trans-telephonic monitoring only

Primary Safety Results

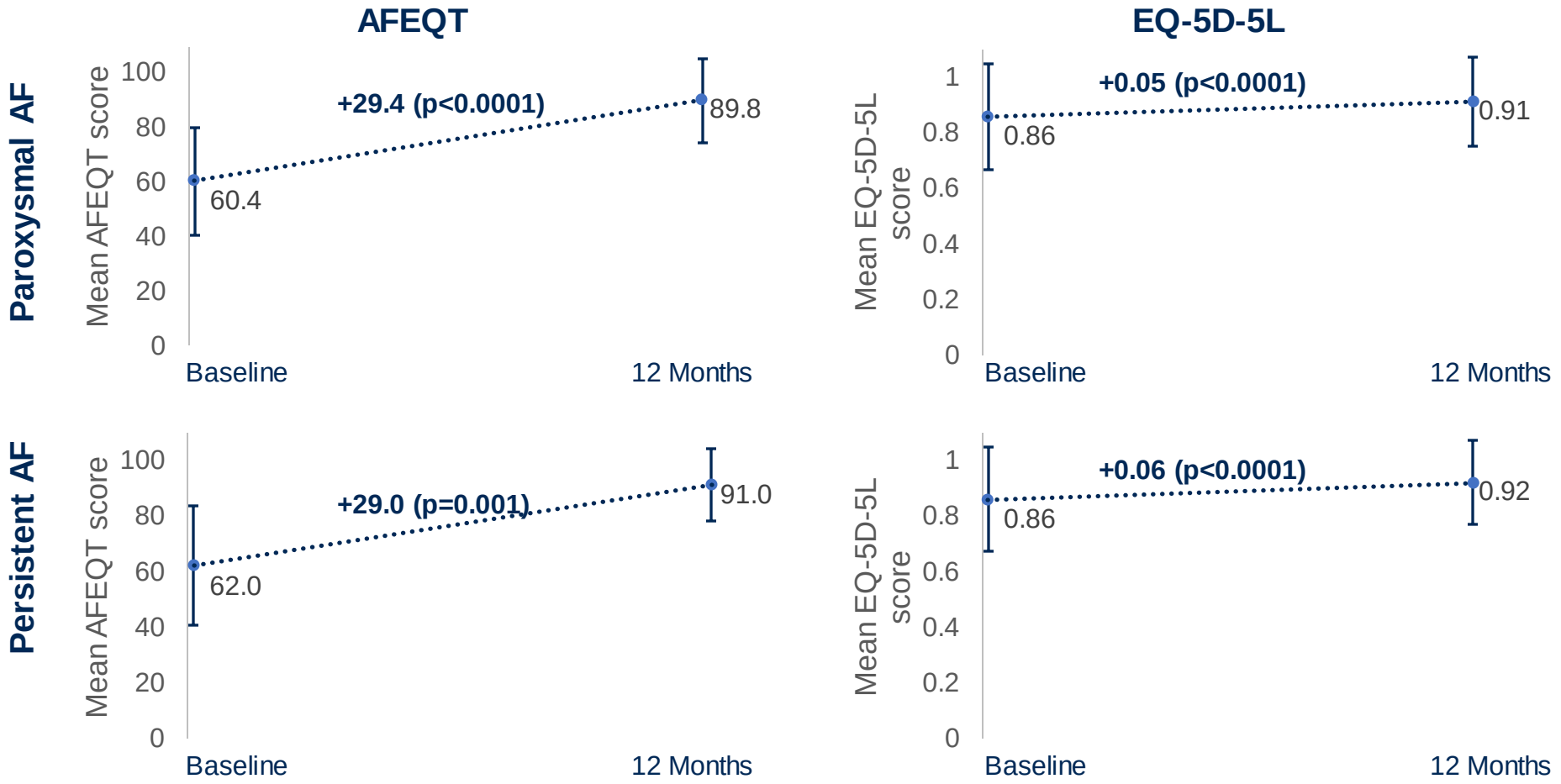
0.7% safety event rate in each cohort

Both paroxysmal and persistent atrial fibrillation cohorts met predetermined safety performance goals (<13%, p=0.002)

Primary Safety Event	Number with a Primary Safety Event	
	Paroxysmal AF (n = 150)	Persistent AF (n = 150)
Within 6 months		
Pulmonary vein stenosis (>70% diameter reduction)	0	0
Phrenic nerve injury/diaphragmatic paralysis ongoing at 6 months	0	0
Atrioesophageal fistula	0	0
Within 30 days		
Cardiac tamponade/perforation	0	1
Cerebrovascular accident	1	0
Transient ischemic attack	0	0
Major bleeding requiring transfusion	0	0
Myocardial infarction	0	0
Pericarditis requiring intervention	0	0
Vagal nerve injury resulting in esophageal dysmotility or gastroparesis	0	0
Vascular access complications requiring intervention	0	0
Death	0	0
PFA system- or procedure-related cardiovascular and pulmonary adverse event prolonging/requiring hospitalization >48 hours (excluding recurrent AF/AFL/AT)	0	0

Quality of Life

Quality of life measures indicate a clinically meaningful improvement[1-3]



22% more patients were **not anxious or depressed** at 12 mo vs. baseline

11% more patients had **no problems doing their usual activities** at 12 mo vs. baseline

19% more patients were **not anxious or depressed** at 12 mo vs. baseline

21% more patients had **no problems doing their usual activities** at 12 mo vs. baseline

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2, Holmes DN et al. Circ Cardiovasc Qual Outcomes. 2019;12:e005358.
3, Coretti S et al. Expert Rev Pharmacoecon Outcomes Res. 2014;14:221-233.

MCID: 5 points AFEQT, 0.3 EQ5D (Holmes et al, 2019; Coretti et al, 2014)

PV Stenosis Sub-Study

No moderate or severe stenosis was observed in 275 pulmonary veins on cardiac computed tomography or MRI imaging at 3 months

Pulmonary Vein Stenosis Sub-Study

		Pulmonary Vein Diameter Change	
Vein	N*	Moderate Change no. (%)[1]	Severe Change no. (%)[2]
All	**275**	**0 (0)**	**0 (0)**
RIPV	63	0 (0)	0 (0)
RSPV	62	0 (0)	0 (0)
RMPV	9	0 (0)	0 (0)
LIPV	63	0 (0)	0 (0)
LSPV	63	0 (0)	0 (0)
LCPV	15	0 (0)	0 (0)

[1]50-70% reduction, [1]≥70% reduction.

Cerebral MRI Sub-Study

New silent cerebral lesions were observed in 4 of 45 patients (9%) undergoing cerebral MRI at baseline and within 72 hours post-ablation

Cerebral MRI Sub-Study

Cohort	Number of Patients	Silent Cerebral Lesions -- no. (%)
Paroxysmal AF	26	2 (8)
Persistent AF	19	2 (11)
Total	**45***	**4 (9)**

Conclusion

- **Primary safety endpoint rate of 0.7% observed for both cohorts**
  - No occurrence of phrenic, esophageal, pulmonary vein injury, or coronary artery spasm
  - Both paroxysmal and persistent atrial fibrillation cohorts met predetermined safety performance goals (<13%)
- **Acute isolation was demonstrated in 100% of all pulmonary veins**
- **Both paroxysmal and persistent atrial fibrillation cohorts met predetermined effectiveness performance goals**
  - 66.2% freedom from a primary efficacy endpoint event in paroxysmal AF patients
  - 55.1% freedom from a primary efficacy endpoint event in persistent AF patients
- **Pulsed field ablation resulted in a clinically meaningful improvements in quality of life**
- **Pulsed field ablation resulted in 79.7% (paroxysmal) and 80.8% (persistent) clinical success**

PULSED AF Committees

Steering Committee

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Thank you to all PULSED AF investigators and all patients

On behalf of Dr. Atul Verma and the PULSED AF steering committee

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Circulation

ORIGINAL RESEARCH ARTICLE

Pulsed Field Ablation for the Treatment of Atrial Fibrillation: PULSED AF Pivotal Trial

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