

Acknowledgements

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Supplementary Table 1: *Inclusion and Exclusion Criteria*

INCLUSION CRITERIA
<ul style="list-style-type: none"> • Non-permanent atrial fibrillation documented on a 12 lead ECG, Trans Telephonic Monitoring (TTM) or Holter monitor within the last 24 months (Episodes of AF must be >30 seconds in duration to qualify as an inclusion criterion) • Age of 18 years or older on the date of consent • Candidate for ablation based on AF that is symptomatic and refractory (ineffective or intolerant) to at least one class 1 or 3 antiarrhythmic. • Continuous anticoagulation with warfarin (INR 2-3), low molecular weight heparin, or a direct oral antithrombotic (dabigatran, apixaban, rivaroxaban) for ≥4 weeks prior to the ablation; or a TEE that excludes LA thrombus ≤48 hours before ablation
EXCLUSION CRITERIA
<ul style="list-style-type: none"> • Previous left atrial (LA) ablation or LA surgery • AF due to reversible cause (e.g. hyperthyroidism, cardiothoracic surgery) • Intracardiac Thrombus • Pre-existing pulmonary vein stenosis or PV stent • Pre-existing hemidiaphragmatic paralysis • Contraindication to anticoagulation or radiocontrast materials • Anteroposterior LA diameter greater than 5.5 cm by TTE • Cardiac valve prosthesis • Clinically significant (moderately-severe, or severe) mitral valve regurgitation or stenosis • Myocardial infarction, PCI / PTCA, or coronary artery stenting during the 3-month period preceding the consent date • Cardiac surgery during the three-month interval preceding the consent date • Significant congenital heart defect (including atrial septal defects or PV abnormalities but not including PFO) • NYHA class III or IV congestive heart failure • Left ventricular ejection fraction (LVEF) less than 35% • Hypertrophic cardiomyopathy (Wall thickness >1.5 cm) • Significant Chronic Kidney Disease (CKD - eGFR <30 µMol/L) • Uncontrolled hyperthyroidism • Cerebral ischemic event (strokes or TIAs) during the six-month interval preceding the consent date • Pregnancy • Life expectancy less than one (1) year • Currently participating or anticipated to participate in any other clinical trial of a drug, device or biologic during the duration of this study • Unwilling or unable to comply fully with study procedures and follow-up

Supplementary Table 2: Implantable cardiac monitor programming

AF detection threshold	Balanced Sensitivity
Ectopy rejection	Nominal
Episode storage threshold	All (Record ECG of 2 minutes)

These parameters were chosen to optimise detection of AF (reported sensitivity of 96.1% with a positive predictive value [PPV] of 73%), however all arrhythmia episodes will be independently adjudicated.^{18, 19}

Supplementary Table 3: Gradation of pulmonary venous occlusion during cryoballoon ablation

Grade 1 – negligible occlusion with immediate rapid outflow from the PV

Grade 2 – mild backflow into the atrium

Grade 3 – minimal backflow into the atrium

Grade 4 – total contrast retention with no backflow into the atrium.

Supplementary Table 4: Secondary Endpoints

<p>1) Time to first recurrence of symptomatic documented AF/AFL/AT between days 91 and 365 after ablation or a repeat ablation procedure between days 0 and 365 post ablation</p> <p>2) Arrhythmia burden (daily AF burden - hours/day; overall AF burden - % time in AF)</p> <p>3) Proportion of patients experiencing an acute or adenosine provoked PV reconnection during the index ablation procedure</p> <p>4) Proportion of patients requiring a repeat ablation procedure because of documented recurrence of symptomatic AF/AFL/AT</p> <p>5) Proportion of patients prescribed AADs because of documented recurrence of symptomatic AF/AFL/AT; 6) Proportion of patients with AF/AFL/AT during the first 90 days post ablation</p> <p>7) Emergency visit or hospitalization >24h in a health-care facility</p> <p>8) Major complications including death, stroke, TIA, Myocardial Infarction or systemic thromboembolism, PV stenosis, phrenic nerve palsy, pericarditis, pericardial effusion, cardiac perforation or tamponade, hematoma, AV fistula, pseudoaneurysm, esophageal injury and atrio-esophageal fistulae (both individually and as a composite endpoint)*</p> <p>9) Overall and disease specific quality of life</p> <p>10) Single and multiple procedure success (freedom from symptomatic or asymptomatic electrocardiographically documented AF/AFL/AT) after the first and last ablation procedure respectively</p> <p>11) Single and multiple procedure success (freedom from symptomatic electrocardiographically documented AF/AFL/AT) after the first and last ablation procedure respectively.</p>
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CIRCA-DOSE: Methods and Rationale

*Complication definition as per 2012 HRS/EHRA/ECAS recommendations. Acute peri-procedural complications will be defined as occurring within 30 days of ablation, with delayed complications occurring 31-365 days after ablation

A major complication is a complication that results in permanent injury or death, requires intervention for treatment, or prolongs or requires hospitalization for more than 48 hours. Because early recurrences of AF/AFL/AT are to be expected following AF ablation, recurrent AF/AFL/AT within 3 months that requires or prolongs a patient's hospitalization should not be considered to be a major complication of AF ablation.