iCLAS™
for Persistent Atrial Fibrillation

IDE Revision G

Protocol Number CS-200

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1. Protocol Summary

TITLE	iCLAS™ for Persistent Atrial Fibrillation
OBJECTIVE	Clinical study to evaluate the safety and efficacy of the Adagio AF Cryoablation System (iCLAS™) in the ablation treatment of symptomatic, persistent atrial fibrillation (PsAF). Data will be used to support a pre-market application (PMA)
INVESTIGATIONAL DEVICE	The Adagio Medical AF Cryoablation System (Adagio System) that includes the following: ▪ The Cryoablation Console ▪ The AF3 and AF4 Cryoablation Catheters ▪ The Esophageal Warming Balloon Catheter ▪ Pre-shaped Catheter Stylets
PROPOSED INDICATION FOR USE	The Adagio AF Cryoablation System is indicated for the treatment of drug refractory, recurrent, symptomatic, persistent atrial fibrillation (PsAF). The Cryoablation Catheters are used for the following: ▪ Create transmural linear and focal lesions for the isolation of pulmonary veins. ▪ Create transmural linear and focal lesions for the isolation of the left atrial posterior wall ▪ Create transmural linear and focal lesions at the cavo-tricuspid isthmus (CTI) to result in bi-directional block.
STUDY DESIGN	A prospective, single-arm, multi-center, open-label, pre-market, clinical study designed to provide safety and efficacy data regarding the use of the Adagio System in the treatment of PsAF. For the purposes of this study, PsAF is defined as: • Continuous AF that is sustained beyond 7 days and ≤ 12-months. Enrolled subjects will be treated (ablation) with the Adagio System. Treatment will include the isolation of all assessable pulmonary veins (PVI), isolation of the left atrial posterior wall (PWI), and a right atrial cavo-tricuspid line for bi-directional block may be performed at discretion and clinical judgment of the investigator, for example, if the patient has a history of typical AFL or typical AFL is induced at the time of the ablation[8]. Data will be collected at procedure, discharge, 1-, 3-, 6-, and 12-months to assess safety and efficacy of the device. Testing for recurrence of atrial arrhythmias will include 12-lead ECGs and a 24-h continuous ECG recording at 3-, 6-, and 12-months post ablation. Symptom triggered rhythm monitoring will be used throughout the post-ablation period. A subset of forty (40) subjects will be randomly selected and consented to a sub-study evaluating the evidence of discrete lesions in the PV. Qualifying subjects will be entered into the randomization module once the roll-in subjects are completed for an Investigator and until 40 have been selected in the study.

	Qualifying subjects in the PV sub-study will be required to complete a CTA or MRA at baseline (pre-ablation) and again during the 3-month follow-up (post ablation). The same imaging modality should be used at baseline and 3-month follow-up. A centralized core lab will interpret the presence and degree of PV stenosis. Upon completion of enrollment of the PMA cohort using the AF4 catheter, a smaller sub-study using the AF3 catheter will be initiated. The same procedure will be followed as with the AF4 catheter and the sub-study will have the same primary endpoints as the main study, with a statistical equivalency and poolability analysis added to the statistical analysis plan. The purpose of the sub-study is to obtain sequential approval for the AF3 catheter after approval of the AF4 catheter. Both, the AF3 and AF4 catheters have the same therapeutic treatment section and equivalency is expected for both effectiveness and safety to be demonstrated by the study data.
STUDY SIZE	Up to 200 subjects (including "roll-in" subjects) for the main study using the AF4 Catheter Up to 60 subjects for the AF3 sub-study.
INVESTIGATIONAL SITES	Up to 30 Clinical Sites including up to ten (10) Clinical Sites from Europe and Canada for the main study using the AF4 Catheter and AF3 sub-study. At least 50% of subjects will be from US sites.
STUDY DURATION	The AF4 primary cohort study is anticipated to take approximately 12-months to enroll and will include a 12-month follow-up period. Total study duration is anticipated to be less than 30 months. The AF3 sub-study is anticipated to take approximately 6-months to enroll and will include a 12-month follow-up period. Total study duration is anticipated to be less than 18 months.
STUDY PRIMARY ENDPOINTS	The **Primary Endpoint for Safety** is an analysis of the proportion of subjects who are free from device/procedure related Major Adverse Events (MAEs) that occur during or following the cryoablation procedure. MAEs include any of the following: • Death • Myocardial infarction • Cardiac perforation/pericardial tamponade • Cerebral infarct or systemic embolism • Major bleeding requiring transfusion of blood products • Mitral or tricuspid valve damage • Symptomatic pulmonary vein stenosis • Severe (≥ 70%) pulmonary vein stenosis • Permanent phrenic nerve injury

	• Access site complications requiring pharmacological or surgical intervention • Atrio-esophageal fistula • Pericarditis • Heart block requiring a permanent pacemaker • Vagal nerve injury with GI dysmotility • Other serious adverse device effects (SADEs), including TIAs, adjudicated by an independent Clinical Events Committee (CEC) as "probably or definitely related" to the Adagio System The **Primary Endpoint for Efficacy** is an analysis of the proportion of subjects receiving a single cryoablation who are free from any documented left atrial arrhythmia (AF/AFL/AT) lasting longer than 30 seconds following the Blanking Period (3-months plus 14-days post index ablation) using a continuous 24-hour ECG recording (Holter monitor), 12-lead ECG at each visit, and symptom- driven event monitoring (Event recording). The primary effectiveness endpoint will be based on a centralized core lab interpretation. The primary effectiveness endpoint failure modes include: 1. Documented > 30 seconds AF/AFL/AT on Holter monitor, event monitoring, or 12-lead ECG (continuous AF/AFL/AT on a 10-sec 12-lead ECG) after the blanking period. 2. Any treatment, during the index or subsequent retreatment, with a non-study device (catheter). 3. Any re-ablation procedure following the index ablation. 4. Taking a new AAD (Class I or III) or a previously failed AAD (Class I or III) at a greater than the highest ineffective historical dose for AF after the blanking period. 5. Any surgical AF ablation of AF surgery. 6. Any cardioversion for atrial arrhythmia after the blanking period (plus 14-days).
STUDY SECONDARY ENDPOINTS	<u>Safety</u> • Recording and analysis of all identified serious adverse events (SAEs) and serious adverse device effects (SADEs) through 12 months post-procedure. Events will be adjudicated by an independent Clinical Events Committee (CEC) for severity and relationship to the Adagio System. Events will be sub-stratified based on time to event as follows: o Early onset (procedure through 7-days post-ablation) o Peri-procedure (> 7-days through 30-days post-ablation) o Late onset (>30-days post ablation) <u>Procedural Endpoint (Acute Efficacy)</u>

	• Analysis of the proportion of subjects with acute procedural (ablation) success defined as:
	  o Documentation of pulmonary vein isolation (PVI) 20-minutes following the last ablation for each vein
	  - PVI documentation using entrance block (exit block optional) with pacing maneuvers as appropriate; or
	  - Documentation using 3D EAM voltage mapping.
	  - Utilization of adenosine or isoproterenol is at the discretion of the investigator and not required per protocol.
	  o Documentation of posterior wall isolation (PWI)
	  - PWI documentation using pacing maneuvers as appropriate; or
	  - Documentation using 3D EAM voltage mapping
	  o Documentation of BDB of the CTI when the CTI ablation is performed
	  - BDB documentation using pacing maneuvers
	
	<u>Clinical Endpoint (Chronic Efficacy)</u>
	• A sub-analysis that will include:
	  o Freedom from AF without anti-arrhythmic drugs (AADs)
	  o Freedom from AF with previously failed AADs
	  o Freedom from AF/AFL/AT without AADs
	  o Freedom from AF/AFL/AT with previously failed AADs
	  o Freedom from AF with one repeat ablation following the blanking period
	  o Freedom from AF/AFL/AT with one repeat ablation following the blanking period
	  o Freedom from documented evidence of cavo-tricuspid atrial flutter
	
	<u>Descriptive Statistics for Procedural Outcomes</u>
	• Procedure fluoroscopy time
	• Ablation time to complete PVI
	• Ablation time for any PWI ablation
	• Ablation time for right atrial ablation
	• Total procedure time
	• Reconnection of PVs following the 20-minute waiting period for confirmation of PVI
	• Number of subjects where adenosine and/or isoproterenol was used in the PVI confirmation
	• Number of DCCV during the Blanking Period
	• Recording of the use of AADs in the follow up period beyond a 90-day blanking period

	• Comparative analysis of baseline and follow-up Patient Reported Outcomes (AFEQT)
STUDY POPULATION	The patient population will consist of men and women between 18 – 80 years of age scheduled for a de novo endocardial ablation of symptomatic, drug-refractory PsAF. A potential study patient will be eligible for study enrollment only if all the following inclusion criteria apply: <u>Inclusion Criteria</u> IC 1 Male or female between the ages of 18 - 80 years IC 2 Currently scheduled for an ablation of symptomatic PsAF defined as continuous AF that is sustained > 7-days and ≤ 12-months and documented by the following: a. Physician's note indicating continuous AF > 7 days and ≤ 12 months, and b. One of the following: i. 24-hour Holter within 180 days of enrollment showing continuous AF, or ii. Two electrocardiograms from any forms of rhythm monitoring (e.g., 12-lead ECGs or single lead ECGs) completed ≥ 7 days apart within 180 days of enrollment. IC 3 Refractory to at least one class I or III AAD. (Refractory defined as not effective, not tolerated or not desired) IC 4 Willingness, ability and commitment to participate in baseline and follow-up evaluations for the full length of the study IC 5 Willingness and ability to give an informed consent
	A potential study patient will be eligible for study enrollment only if none of the following exclusion criteria apply: <u>Exclusion Criteria</u> EC 1 In the opinion of the Investigator, any known contraindication to an atrial ablation, TEE, or anticoagulation. Including but not limited to the identification of any atrial thrombus or evidence of sepsis EC 2 Any duration of continuous AF lasting longer than 12-months EC 3 History of previous left atrial ablation or surgical treatment for AF/AFL/AT EC 4 Atrial fibrillation secondary to electrolyte imbalance, active thyroid disease, or any other reversible or non-cardiac cause EC 5 Structural heart disease as described below: a. Left ventricular ejection fraction (LVEF) < 40% based on most recent TTE b. Left atrial size > 55 mm (parasternal long axis view) documented within 6-months of screening c. NYHA Class III or IV heart failure documented within the previous

	12-months d. An implanted pacemaker or ICD e. Previous cardiac surgery, ventriculotomy, or atriotomy (excluding atriotomy for CABG), f. Previous cardiac valvular surgical or percutaneous procedure, or prosthetic valve g. Interatrial baffle, closure device, patch, or PFO occluder h. Presence of a left atrial appendage occlusion device i. Presence of any pulmonary vein stenting devices j. Coronary artery bypass graft (CABG) or PTCA procedure within six (6) months prior to procedure k. Unstable angina or ongoing myocardial ischemia l. Myocardial infarction within the previous six (6) months prior to procedure m. Moderate or severe mitral insufficiency or stenosis based on most recent TTE n. Atrial myxoma o. Significant congenital anomaly EC 6 BMI > 40 • BMI>35 and no prior sponsor approval into the study EC 7 Any previous history of cryoglobulinemia EC 8 History of blood clotting or bleeding disease EC 9 History of severe COPD requiring steroid use in the previous 12-months EC 10 History of severe sleep apnea (AHI > 30) not currently treated with a CPAP machine or other mechanical device EC 11 Any prior history of documented cerebral infarct including recent TIA (within one year) or systemic embolism (excluding a post-operative DVT) EC 12 Any prior history or current evidence of hemidiaphragmatic paralysis EC 13 Pregnant or lactating (current or anticipated during study follow-up EC 14 Current enrollment in any other study protocol where testing or results from that study may interfere with the procedure or outcome measurements for this study EC 15 Any other condition that, in the judgment of the investigator, makes the patient a poor candidate for this procedure, the study or compliance with the protocol (includes vulnerable patient population, mental illness, addictive disease, terminal illness with a life expectancy of less than two years, extensive travel away from the research center, COVID-19 related concerns).
STATISTICAL ANALYSIS	The objectives of the statistical analyses are to make a comparative assessment of the safety and effectiveness of the Adagio device to findings reported in the literature for a similar patient population.

	The AF4 main study will use co-primary endpoints for safety and efficacy. • For the primary safety endpoint, the goal is to verify that the proportion of subjects with at least one device/procedure related MAE, as adjudicated by the Clinical Events Committee (CEC) is no worse than historical rates. • For the primary efficacy endpoint, the goal is to verify that the proportion of subjects receiving a single ablation, who are free from any of the primary efficacy failure modes at one year is significantly greater than historical rates (Reference section 6.3 for details of all the failure modes). • The primary analysis will be performed for a complete dataset of patients treated with the AF4 catheter. This analysis will be used to support the Original PMA application for the AF4. After completion of the AF4 main study analysis and Original PMA, a secondary analysis for the same safety and efficacy endpoints will be performed for the subset of patients treated with the AF3 catheter to demonstrate equivalency and poolabilitly with the AF4 data. This analysis will be used to support a PMA supplement for the AF3.
DATA COLLECTION	See Table Below

	Screening & Baseline	Procedure	Discharge	7 Days (±3 days) Phone Contact	1-Month (±7 days)	3-Month (±14 days)	6-Month (±30 days)	12-Month (±30 days)
CIP Informed Consent	X							
Medical History	X							
History & Physical Exam	X		X		X	X	X	X
Neurologic Assessment (NIHSS and mRS by certified personnel)	X		X		X	X	X	X
Medications	X		X	X	X	X	X	X
Transthoracic Echo (TTE)	X							
LA Thrombus Assessment		X						
Labs	X							
Pregnancy Test (female patients)	X							
CTA or MRA (required for subjects randomized for PV sub-study)	X					X		
Adverse Events		X	X	X	X	X	X	X
12-lead ECG	X	X	X		X	X	X	X
24-hour Continuous ECG Recording, using the Sentinel/Sirona Event Recorder						X	X	X
Symptom Triggered Rhythm Monitoring, using the Sentinel/Sirona Event Recorder			X					
AFEQT Questionnaire	X				X	X	X	X