iCLAS* for Persistent Atrial Fibrillation

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The objective of the clinical study is to evaluate the safety and efficacy of the Adagio Cryoablation System (iCLAS*) in the ablation treatment of persistent atrial fibrillation (PsAF). Data will be used to support a pre-market application (PMA).

Ethical review	Approved WMO
Status	Completed
Health condition type	Cardiac arrhythmias
Study type	Interventional

Summary

ID

NL-OMON56448

Source
ToetsingOnline

Brief title
iCLAS

Condition

- Cardiac arrhythmias

Synonym
Atrium fibrillation; irregular heartbeat

Research involving
Human

Sponsors and support

Primary sponsor: Manufacturer
Source(s) of monetary or material Support: industry

Intervention

Keyword: Atrial Fibrilation, Cryoablation

Outcome measures

Primary outcome

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 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). The primary effectiveness endpoint will be based on a centralized core lab interpretation.

Secondary outcome

Safety

• 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 postablation)

o Late onset (>30-days post ablation)

Procedural Endpoint (Acute Efficacy)

• Analysis of the proportion of subjects with acute procedural (ablation) success defined as:

o Documentation of pulmonary vein isolation (PVI) 20minutes 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

- BDB documentation using pacing maneuvers Clinical Endpoint (Chronic Efficacy)

• 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

Clinical Endpoint (Chronic Efficacy)

• 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

o Freedom from AF/AFL/AT with one repeat ablation following the blanking period

o Freedom from documented evidence of cavo-tricuspid atrial flutter

Descriptive Statistics for Procedural Outcomes

• 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 description

Background summary

Atrial fibrillation (AF) remains the most commonly treated sustained arrhythmia affecting approximately 1% to 2% of the general population worldwide. It is a major public health concern in the United States and in 2001, it was reported to be affecting an estimated 2.3 million Americans.

By the year 2050 this may reach 12-million. Age adjusted population trending projects 17.9 million people in the European Union will have AF by 2060. AF is associated with a five-fold risk of stroke, a three-fold incidence of congestive heart failure, and higher mortality.

Several factors have been associated with an increased risk of AF. The prevalence of AF increases with age and affects eight to ten percent of patients older than 80 years of age. AF is also more common in males. Data from the Framingham Heart Study suggest that men are 1.5 times more likely to develop AF than are women after controlling for age and comorbidities. Obesity increases the risk of developing AF. Data from community-based cohorts suggest that obese persons have a 1.5 to 2.3 greater risk of developing AF. Furthermore, obesity increases the likelihood that AF will progress from paroxysmal to permanent AF. Additional factors that have been associated with an increased risk of AF include smoking, hypertension, hyperthyroidism, obstructive sleep apnea, diabetes, myocardial infarction, heart failure, and cardiac surgery.

Atrial fibrillation is currently classified by the duration of the episode documented by ECGs, cardiac rhythm strips, loop recorders or intracardiac electrogram monitoring. The following definitions are used for AF classification:

Paroxysmal AF Defined as AF that terminates spontaneously or with intervention within 7 days of onset.

Persistent AF Defined as continuous AF that is sustained beyond 7 days.

Long-standing Persistent AF Defined as continuous AF of greater than 12 months* duration.

Permanent AF Permanent AF is defined as the presence of AF that is accepted by the patient and physician, and for which no further attempts to restore or maintain sinus rhythm will be undertaken. The term permanent AF represents a therapeutic attitude on the part of the patient and physician rather than an inherent pathophysiological attribute of AF. The term permanent AF should not be used within the context of a rhythm control strategy with antiarrhythmic drug therapy or AF ablation.

The heart*s normal conduction pathway (sinus rhythm) typically begins in the right atrium and proceeds in a single, orderly wave front at rates of 60 to 100 beats per minute. Atrial fibrillation disrupts normal rhythm by creating multiple wave fronts e from a rapid ventricular response leading to an irregular pulse as well as diminished cardiac output related to these uncoordinated contractions. Pooling of blood in areas of the atria (i.e. atrial appendage) may allow clots to form and lead to thromboembolic events such as stroke and transient ischemic attacks (TIAs).

Atrial fibrillation is characterized by a chaotic contraction of the atrium in which an electrocardiogram (ECG) recording is necessary to diagnose the arrhythmia. Any arrhythmia that has the ECG characteristics of AF and lasts sufficiently long for a 12-lead ECG to be recorded, or at least 30 seconds on a rhythm strip, should be considered an AF episode. The diagnosis requires an ECG or rhythm strip demonstrating: (1) Irregular RR

intervals (in the absence of complete AV block), (2) no distinct P waves on the surface ECG, and (3) an atrial cycle length (when visible) that is usually variable and less than 200 milliseconds. For many years, three major schools of thought competed to explain the mechanism(s) of AF: multiple random propagating wavelets, focal electrical discharges, and localized reentrant activity with fibrillatory conduction.
Significant progress has been made in defining the mechanisms of initiation and perpetuation of AF. One of the most important breakthroughs was the recognition that, in a subset of patients, AF was triggered by a rapidly firing focus and could be *cured* with a localized catheter ablation procedure. This landmark observation caused the EP community to refocus their attention on the pulmonary veins (PVs) and the posterior wall of the left atrium (LA), as well as the autonomic innervation in that region. It also reinforced the concept that the development of AF requires *trigger* and an anatomic or functional substrate capable of both initiation and perpetuation of AF.

The management of AF involves rate control, rhythm control with antiarrhythmic drugs (AADs), and more recently catheter ablation. The 2017 HRS/EHRA/ECAS/APHRS/SOLACE expert consensus has stated: *The role of catheter ablation as first-line therapy, prior to a trial of a Class I or III antiarrhythmic agent, is an appropriate indication*. The most commonly used catheter ablation approaches to treat AF are pulmonary vein isolation (PVI) and pulmonary vein antrum isolation (PVAI). Isolation of the pulmonary veins may also be achieved through wide area circumferential ablation (WACA). If the pulmonary veins are targeted, complete electrical isolation should be the desired endpoint.

As AF progresses into a more persistent state, additional non-PV targets may be included in the ablation strategy. In a recent land-mark clinical study, Verma, et al randomized the persistent AF population into three treatment groups.
• PVI
• PVI plus a roof line and a mitral isthmus line
• PVI plus ablation of complex fractionated electrograms
Single treatment efficacy results demonstrated the PVI only group had improved longer-term outcomes although the sample size was much smaller than the other groups (67 versus 259 versus 263). There was no statistical difference in outcomes between the latter two groups.
In 2008, Hummel, et al investigated a persistent and long-standing persistent AF population with a treatment strategy that included PVI plus elimination of fractionated electrograms on the left atrial septum and posterior wall.
A two- treatment efficacy was reported to be 55.8% as measured by a 48-hour Holter at 6-months. Cryoablation of AF Two major multi-center studies have been published where cryoenergy was used for the isolation of PVs. The Fire and Ice study prospectively randomized to two comparative arms including the Artic Front Cryoballoon (Medtronic, Minneapolis,MN) and RF ablation while the STOP-AF was the initial IDE study leading to the cryoballoon approval.
Both treated the PAF population and the study was limited to PVI as the only

ablation strategy.

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Study objective

The objective of the clinical study is to evaluate the safety and efficacy of the Adagio Cryoablation System (iCLAS*) in the ablation treatment of persistent atrial fibrillation (PsAF). Data will be used to support a pre-market application (PMA).

Study design

A prospective, single-arm, multi-center, open-label, controlled, premarket, 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 <= 12months.
Enrolled subjects will be treated (ablation) with the Adagio System. Treatment will include the isolation of all assessible pulmonary veins (PVI), isolation of the left atrial posterior wall (PWI), and a right atrial cavo-tricuspid line for bi-directional block.
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. Subjects in the PV sub-study will be required to complete a CTA or MRA at baseline (pre-ablation) and again during the 3month
follow-up (post ablation). A centralized core lab will interpret the presence and degree of PV stenosis.

Intervention

A de novo endocardial ablation of symptomatic, drug-refractory PsAF, followed by clinical follow up visits at discharge, 7 days, 1 month, 3 months, 6 months and 12Months.

For patients participating in the substudy the baseline visit and the clinical follow up visits at 3 months will also include a CTA or MRA.

Study burden and risks

Patient burden includes additional hospital contacts beyond the standard of care for ablations. Those visits are at 7 days (by phone), 1 month and 6 months (at the hospital). There is additional burden for wearing a rhythm monitor to record individual events and for 24-hour recordings at the follow up time points. There is another burden for those selected to participate in the PV sub-study because they will need a baseline and 3-month CTA or MRA. The risks associated with the iCLAS ablation procedure are the same as for any ablation procedure. There is minimal risk of radiation exposure and contrast allergy for those who are selected for the PV sub-study and receive CTA scans. The benefits include the potential to reduce or eliminate, either temporarily or permanently, the symptoms of atrial fibrillation.

Contacts

Public
Selecteer

Rudolf-Diesel-Ring 27
Holzkirchen 83607
DE
Scientific
Selecteer

Rudolf-Diesel-Ring 27
Holzkirchen 83607
DE

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

Male or female between the ages of 18 and 80 years
Currently scheduled for an ablation of symptomatic, PsAF defined as continuous AF that is sustained > 7-days and <= 12months. Continuous AF should be documented in the patient*s medical record and validated with a 24-h Holter recording within180-days of enrollment or two 12-lead ECGs completed >= 7days apart within 90-days of enrollment.
Refractory to at least one class I or III AAD. (Refractory defined as not effective, not tolerated or not desired)
Willingness, ability and commitment to participate in baseline and follow-up evaluations for the full length of the study
Willingness and ability to give an informed consent

Exclusion criteria

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
Any duration of continuous AF lasting longer than 12-months
History of previous left atrial ablation or surgical treatment for AF/AFL/AT
Atrial fibrillation secondary to electrolyte imbalance, active thyroid disease, or any other reversible or non-cardiac cause
Structural heart disease
BMI > 40, BMI>35 and no prior sponsor approval into the study
Any previous history of cryoglobulinemia
History of blood clotting or bleeding disease
History of severe COPD requiring steroid use in the previous 12-months
History of obstructive sleep apnea not currently treated with a CPAP machine or other mechanical device
ANY prior history of documented cerebral infarct or systemic embolism (excluding a post-operative DVT)
Any prior history or current evidence of hemidiaphragmatic paralysis
Pregnant or lactating (current or anticipated during study follow-up
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
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)

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	05-02-2021
Enrollment:	30
Type:	Actual

Medical products/devices used

Generic name:	iCLAS
Registration:	Yes - CE intended use

Ethics review

Approved WMO Date:	05-06-2020
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	10-09-2020
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	21-01-2021
Application type:	Amendment

Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	24-08-2021
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	07-11-2023
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
ClinicalTrials.gov	NCT04061603
CCMO	NL71852.100.20