A Phase 3, Randomized, Double-Blind, Placebo-Controlled Trial of Flecainide Acetate Inhalation Solution for Cardioversion of Recent-Onset, Symptomatic Atrial Fibrillation to Sinus Rhythm

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To compare the efficacy and safety of flecainide acetate inhalation solution to placebo for the conversion of atrial fibrillation (AF) to sinus rhythm (SR) in patients with recent-onset, symptomatic newly diagnosed or paroxysmal AF

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

Summary

ID

NL-OMON54054

Source
ToetsingOnline

Brief title
RESTORE-1

Condition

- Cardiac arrhythmias

Synonym
recent-onset, symptomatic newly diagnosed or paroxysmal AF / Atrial fibrillation

Research involving

Human

Sponsors and support

Primary sponsor: InCarda Therapeutics, Inc.
Source(s) of monetary or material Support: industry

Intervention

Keyword: Atrial fibrillation, FlecIH-103, Phase 3

Outcome measures

Primary outcome

Time to conversion of AF converts to SR <= 90 minutes after initiation of dosing:

- The time from the start of study drug dosing to the start of the first SR

event with a duration of >=1 minute, as adjudicated by a blinded CEC.

- Evaluated with a stratified log-rank statistic for p-value generation with a

2- sided significance level of 5% (primary analysis) and the Cox proportional

hazards model for calculation of an estimated hazard ratio and 95% confidence

interval. Both calculations will include adjustment for all randomization

stratification criteria.

- Patients whose AF does not convert to SR by the end of the Observation Period

will be censored at the 90-minute time point. Patients who require

intervention with standard of care for the treatment of AF prior to the 90-

minute time point will be censored at the time of the intervention.

- The Kaplan-Meier survival estimate of time to conversion of AF to SR within

90 minutes will be presented.

- A descriptive analysis of the median time to conversion of AF to SR will be

calculated for the subset of patients receiving FlecIH-103 whose AF converted

to SR.

Secondary outcome

- Presence of AF related symptoms at the 90--minute time point

- Additional AF-related interventions required prior to discharge

- Time to discharge-eligible status

- Non-voluntary hospitalizations prior to discharge

Study description

Background summary

Atrial fibrillation (AF) is the most common cardiac arrhythmia in clinical practice, with an estimated global prevalence of 33.5 million. It is estimated that approximately 2.3 million adults in the United States (US) have AF, and this number is projected to increase to 5.6 million by the year 2050. Once a person reaches the age of 40 years, the lifetime risk of AF is 1 in 4. In patients with AF, systemic thromboembolic events, hemodynamic instability, demand-induced ischemia, and ventricular arrhythmias contribute to a significant increase in morbidity, mortality, and frequent hospitalizations.

The management of AF depends on the type of AF, but the general objectives are to provide symptom relief, rate control (aimed at slowing the ventricular rate), and/or rhythm control (aimed at restoring sinus rhythm (SR)), antithrombotic therapy (aimed at reducing risk of thromboembolic events, and treatment of the comorbidities.

The aim of inhaled flecainide (in patients that have no contraindications for IV or oral flecainide) is the restoration of SR in symptomatic patients with recent-onset newly diagnosed or recurrent paroxysmal AF (of <48 hours duration) in a manner that is safe, rapid (in minutes) and convenient. These characteristics are ideal to address the unmet medical need for an acute treatment for AF to rapidly restore SR and alleviate AF-related symptoms, thereby reducing the time spent in the ED as well as the likelihood of hospital admission for AF.

Study objective

To compare the efficacy and safety of flecainide acetate inhalation solution to

placebo for the conversion of atrial fibrillation (AF) to sinus rhythm (SR) in patients with recent-onset, symptomatic newly diagnosed or paroxysmal AF

Study design

This is a Phase 3, multicenter, randomized, double-blind, placebo-controlled clinical study designed to evaluate the efficacy and safety of FlecIH-103 (flecainide acetate inhalation solution) compared with placebo in patients with recent-onset, symptomatic newly diagnosed or paroxysmal AF.

Approximately 400 patients are expected to be enrolled in this study. Patients will be randomized 3:1 to receive
FlecIH-103 at a total dose of up to 120 mg estimated total lung dose (eTLD) (n=300) or placebo inhalation solution (n=100). Randomization will be stratified by geographic region (US and ex-US) and duration of symptoms of the current AF episode (>=1 hour to <=24 hours and >24 hours to <=48 hours). The study will consist of the following periods: Screening, Observation, and Follow-up.

Intervention

Up to 120 mg estimated total lung dose of FlecIH-103 (flecainide acetate inhalation solution) or placebo inhalation solution

Study burden and risks

For full details see schedule of assessments in the protocol page 53-54
The patient participation in this study will last approximately 5 days. During this time the patient will visit the hospital
approximately 1 time, there will be a 24- and 96-hour telephone follow-up contact. The visit will take about 2.5 hours.
During the visit the following tests and procedures will take place:
-physical examinations will be done and questions will be asked about medical history.
- ECGs will be done
-weight, height, blood pressure, temperature, heart rate will be measured
- blood sampling will be taken.
- The research physician will also test female participants of childbearing potential for pregnancy.
- Patients will be asked about their AF-related symptoms

Possible side effects that are already known are described in the IB and patient information sheet.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. >=18 and <=87 years of age
2. Ongoing event of newly diagnosed or paroxysmal AF
a. Newly diagnosed AF is AF that has not been diagnosed previously.
b. Paroxysmal AF is defined as recurrent AF in a patient whose previous AF episode(s) self-terminated (ie, without treatment) or terminated with intervention <=7 days of onset.
c. AF must be monitored on cardiac telemetry/monitoring for >=45 minutes prior to randomization (may include monitoring time prior to informed consent)
3. Presence of AF-related symptom(s) with a time of onset >=1 and <=48 hours (ie, recent-onset) at the time of randomization. AF-related symptoms are defined as any of the following:
a. pitations (pounding, racing or irregular heartbeat)

b. Chest pain/pressure
c. Dizziness/lightheadedness
d. Shortness of breath

Exclusion criteria

Atrial Fibrillation (AF)/Atrial Flutter (AFL) history
1. Most recent pharmacological cardioversion failed to restore SR or >=2 previous failed attempts to restore SR with pharmacological cardioversion
2. Has had >=4 electrical cardioversion procedures <=1 years prior to screening
3. Current diagnosis or prior history of persistent AF
a. Persistent AF defined as AF that is continuously sustained >7 days, including episodes terminated by cardioversion (drugs or electrical cardioversion) after >7 days.
b. Patients who have undergone an ablation procedure for persistent AF are not eligible.
4. Cardiac ablation <=28 days prior to screening
Vital signs
5. Hemodynamic or cardiac instability during the screening period, defined as any of the following:
a. Systolic blood pressure (SBP) <100 or >=160 mmHg
b. Diastolic blood pressure (DBP) <60 or >=95 mmHg
c. Ventricular heart rate (HR) <80 or >160 bpm
If any of the above criteria are observed, they must be confirmed by >=3 consecutive measurements (ie, assessed >=2 more times) over >=5 minutes to be exclusionary. Failure to perform confirmatory assessments is also exclusionary.
6. Uncontrolled hyperventilation (ie, inability to maintain a respiratory rate <=22 breaths per minute prior to randomization)
Relevant structural heart disease
7. Evidence of significant HF defined as any of the following:
a. Hospitalization in the last 12 months for HF or suspected HF event (eg, acute decompensated HF)
b. Most recent assessment of left ventricular ejection fraction (LVEF) <45%, if available
i. For patients in the United States, a standard diagnostic echocardiogram assessed <=180 days prior to screening is required to ascertain eligibility. If none is available, the patient must undergo a standard diagnostic echocardiogram or a diagnostic echocardiogram using a portable ultrasound device (handheld echocardiogram [HHE]) during screening to confirm eligibility.
c. New York Heart Association (NYHA) Class III-IV symptoms
d. Previous or current evidence of significant left ventricular (LV) hypertrophy in the opinion of the Investigator
e. Medication history suggestive of HF per the Investigator's discretion
8. Signs or symptoms of ongoing myocardial ischemia, including any of the following observed during screening:

a. Significant ST segment elevation or depression (ie, >=2 mm) on a standard 12-lead ECG
b. Echocardiogram findings (eg, wall motion abnormalities) suggestive of acute myocardial infarction (MI), if an echocardiogram is obtained
c. Angina pectoris, atypical angina pectoris, or receiving antianginal medication for ischemia
9. History of MI <=3 months of screening
10. Current or previous history of uncorrected moderate or severe aortic or mitral valvular stenosis, in the opinion of the Investigator
Other CV conditions
11. Stroke (including transient ischemic attack) <=3 months prior to randomization
12. Known history of any of the following cardiac abnormalities:
a. Long QT syndrome
b. Conduction system disease (eg, PR interval >200 ms, second- or thirddegree heart block, bundle branch block)
c. Brugada syndrome
d. Torsades de pointes
e. Diagnosed with sinus node dysfunction (eg, sick sinus syndrome) or any of the following:
i. History of unexplained or cardiovascular syncope
ii. Bradycardia suggestive of sinus node dysfunction
iii. Prior electrical or pharmacological cardioversion associated with sinus or ventricular pause >3 seconds or ventricular HR <45 bpm at time of conversion
13. Any of the following ECG-related features at screening:
a. QT interval corrected for HR using the Fridericia formula (QTcF) >480msec
b. Wide QRS complex (ie, duration >=110 msec) observed during screening or documented history of ventricular tachycardia (ie, ventricular rate >100 bpm) with wide QRS complex
c. VT >=4 beats observed during the screening period
14. Presence of a pacemaker
15. Cardiac surgery for any of the exclusionary conditions (eg, valvular disease, hypertrophy, coronary artery disease) <=6 months prior to randomization

Refer to Protocol for:
- Prior and concomitant non-CV conditions
- Prior and concomitant medications and procedures
- Other

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	16-09-2022
Enrollment:	40
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	flecainide acetate
Generic name:	flecainide acetate

Ethics review

Approved WMO Date:	05-10-2021
Application type:	First submission
Review commission:	RTPO, Regionale Toetsingscie Patientgebonden Onderzoek (Leeuwarden)
Approved WMO Date:	08-05-2022
Application type:	Amendment
Review commission:	RTPO, Regionale Toetsingscie Patientgebonden Onderzoek (Leeuwarden)
Approved WMO Date:	07-06-2022

Application type:	First submission
Review commission:	RTPO, Regionale Toetsingscie Patientgebonden Onderzoek (Leeuwarden)
Approved WMO Date:	06-08-2022
Application type:	Amendment
Review commission:	RTPO, Regionale Toetsingscie Patientgebonden Onderzoek (Leeuwarden)
Approved WMO Date:	08-08-2022
Application type:	Amendment
Review commission:	RTPO, Regionale Toetsingscie Patientgebonden Onderzoek (Leeuwarden)
Approved WMO Date:	01-10-2022
Application type:	Amendment
Review commission:	RTPO, Regionale Toetsingscie Patientgebonden Onderzoek (Leeuwarden)
Approved WMO Date:	02-01-2023
Application type:	Amendment
Review commission:	RTPO, Regionale Toetsingscie Patientgebonden Onderzoek (Leeuwarden)
Approved WMO Date:	06-01-2023
Application type:	Amendment
Review commission:	RTPO, Regionale Toetsingscie Patientgebonden Onderzoek (Leeuwarden)
Approved WMO Date:	25-03-2023
Application type:	Amendment
Review commission:	RTPO, Regionale Toetsingscie Patientgebonden Onderzoek (Leeuwarden)
Approved WMO Date:	15-05-2023
Application type:	Amendment
Review commission:	RTPO, Regionale Toetsingscie Patientgebonden Onderzoek (Leeuwarden)

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
EudraCT	EUCTR2021-001627-40-NL
ClinicalTrials.gov	NCT05039359
CCMO	NL77621.099.21

Study results

Date completed: 17-05-2023

Results posted: 12-06-2024

First publication
11-06-2024