A multi-center, Randomized, double-blind, placebo-controlled study to Evaluate the Safety and efficacy of a single oral dose of vanoxerine for The conversion Of subjects with REcent onset atrial fibrillation or flutter to normal Sinus Rhythm

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To evaluate the safety and efficacy of a single oral dose of vanoxerine for the conversion of subjects with recent atrial fibrillation (AF) or atrial flutter (AFL) to normal sinus rhythm.

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

Summary

ID

NL-OMON42537

Source
ToetsingOnline

Brief title
RESTORE SR

Condition

- Cardiac arrhythmias

Synonym
abnormal heart rhythm, atrial fibrillation

Research involving
Human

Sponsors and support

Primary sponsor: Laguna Pharmaceuticals, Inc
Source(s) of monetary or material Support: industry

Intervention

Keyword: atrial fibrillation, cardioversion, vanoxerine

Outcome measures

Primary outcome

Primary efficacy endpoint:

Conversion to sinus rhythm (or atrial paced rhythm in the case of subjects with a pacemaker and atrial leads) documented by ECG (Holter ECG, 12-lead ECG, monitor lead ECG, or other format ECG) of at least 1 continuous minute within the 24 hours defined by the time of study drug administration through 24 hours after the time of study drug administration.

The primary safety endpoint will comprise the occurrence of any of the following events:

a. Death through Day 8.

b. Ventricular fibrillation on ECG through 32 hours.

c. Ventricular tachycardia with heart rate >120 bpm requiring intervention through 32 hours.

d. Torsades de pointes >10 seconds on ECG through 32 hours. (All episodes of torsades de pointes will be reported [including duration] as a safety variable.

Only torsades de pointes >10 seconds will be included as a primary safety outcome endpoint.)

Primary pharmacokinetic endpoint:

• Plasma vanoxerine concentrations

Secondary outcome

Secondary efficacy endpoint:

• Length of Stay (from time of study drug administration)

Additional exploratory efficacy endpoints will include:

• Sinus rhythm present at 12 and 24 hours from study drug administration and at the Day 8 visit.

• Time to restoration of sinus rhythm through 24 hours.

• Change in subject symptom score from baseline to 4 and 24 hours from study drug administration and to Day 8.

Exploratory pharmacokinetic endpoints will include:

• Relationship between subject-specific covariates and pharmacokinetics

• Relationship between vanoxerine exposure and response (efficacy and safety)

Study description

Background summary

AF is the most common arrhythmia resulting in health care utilization, and by way of example, in the USA alone AF currently afflicts more than 2.3 million. It is estimated that there will be more than 12 million individuals with AF by 2050. Unfortunately, current antiarrhythmic drug options are limited due to poor efficacy, and associated toxicity. Antiarrhythmic drugs such as ibutilide and dofetilide are effective in terminating AF by blocking or inhibiting various ion currents, and causing QT prolongation which expose patients to the potential ventricular arrhythmia such as Torsades De Pointes (TdP) and the risk of sudden cardiac death. Alternatively, the blockade of multiple ion channels, such as is the case with amiodarone, is a more effective approach for maintaining sinus rhythm. However Amiodarone has been associated with variety of adverse events, of which is the most serious is amiodarone pulmonary toxicity. Vanoxerine is a compound uniquely suited for the proposed indication and may be of clinical benefit in several other important ways. Vanoxerine*s unique properties include the inhibition or blocking of well described ion channels that terminate AF. The principal antiarrhythmic effect of vanoxerine on AF and AFL is thought to be its inhibition of multiple cardiac ion channels. Nonclinical studies demonstrated a high degree of efficacy in terminating and preventing induction of AF/AFL, while also demonstrating no evidence of predisposition to ventricular proarrhythmia. Furthermore in the recently conducted phase 2 study in AF/AFL, Vanoxerine resulted in a dose dependent prolongation of QT but resulted in no cases of proarrhythmia. The unique set of ion channel properties suggest the potential for efficacy in termination of AF/AFL without proarrhythmia.

Study objective

To evaluate the safety and efficacy of a single oral dose of vanoxerine for the conversion of subjects with recent atrial fibrillation (AF) or atrial flutter (AFL) to normal sinus rhythm.

Study design

Up to 625 subjects will be randomized in a 2:1 fashion so that at least 400 vanoxerine and 200 placebo subjects receive study drug. Vanoxerine HCl, 400 mg (2 capsules of 200 mg vanoxerine HCl per capsule) or identical appearing placebo capsules will be assigned randomly and administered orally in a single dose in a double-blind fashion.
After informed consent is obtained, the screening process will be undertaken, followed by randomization. Atrial fibrillation (AF) or atrial flutter (AFL) must be reconfirmed electrocardiographically, e.g., bedside monitor, telemetry, paper ECG, etc., immediately (within 5 minutes) prior to the time of study drug administration. Subjects who spontaneously convert to sinus rhythm after randomization but before study drug administration will not receive study drug. The subject*s ECG will be continuously displayed for safety monitoring. In addition, a Holter ECG will be recorded continuously to document safety

beginning 45 to 30 minutes prior to study drug administration and through a minimum of 32 hours after study drug administration and until QTc criteria have been met. Extractions by a central Holter ECG laboratory at specified time points will be used to document rhythm and measure ECG intervals. All episodes of termination of AF or AFL as well as predefined brady- and tachy- arrhythmias will be adjudicated by a blinded clinical events committee (CEC). In addition, 12-lead ECGs (paper) will be performed at specified time points. During the interval from administration of study drug through 24 hours, if and when the investigator observes that AF/AFL has terminated, two 12-lead ECGs separated by at least 1 minute will be recorded to document persistence of sinus rhythm. Subjects will be hospitalized in a monitored bed for a minimum of 32 hours after study drug administration.
Subjects may be discharged from observation at 32 hours after study drug initiation; however, discharge is allowed only when the QTc is no greater than 460 msec for men or 480 msec for women. Also, any clinically important rhythm disturbance identified during the observation period could, at the discretion of the investigator, result in continued in-hospital observation.
If the subject requires continued monitoring because of a prolonged QTc (not due to use of another antiarrhythmic known to prolong QT), the Holter monitor as well as bedside monitoring should be continued until such time that the QTc falls below the pre-specified threshold. Once QTc falls below the threshold, a final 12-lead ECG should be recorded.
Subjects will return for a clinic visit on Day 8 (+1 day). The subjects* vital status as of Day 30 will also be assessed.

Intervention

Patients will be randomised in a 2:1 ratio to receive vanoxerine or placebo 400mg (2 capsules of 200mg to be taken orally) via a pre-determined randomization scheme.

Study burden and risks

participation involves screening/baseline visit. Patient will be randomised and stay hospitalised for a minimum of 32 hours. In addition to routine practise patient will have additional blooddraws, 5 or 6 in total during the stay.
Patient will get a holter ECG for minimum of 32 hours. At 3 times during the stay patient will be asked several questions regarding his symptoms.

At day 8 post randomisation the patient will visit the hospital. A blood draw, physical exam, questions about sympoms will be asked and whether the patient experienced any adverse events.

Patient will receive phonecall at day 30 to check vital status.

Patient may benefit from participation in having sinus rhythm restored.

Patient may suffer from side effects previously reported in studies with vanoxerine. However, patient may also suffer adverse event not previously reported.

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

Onset of Atrial fibrillation/Atrial Flutter within the 7 calendar days preceding randomisation, based on symptoms. AF/AFL documented by ECG during the screening period and immediately prior to study drug administration. (see protocol page 30)

Exclusion criteria

See protocol page 30 and 31

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:	Recruitment stopped
Start date (anticipated):	03-11-2015
Enrollment:	16
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Vanoxerine HCl
Generic name:	Vanoxerine HCl

Ethics review

Approved WMO

Date:	25-06-2015
Application type:	First submission

Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	03-11-2015
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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	EUCTR2015-001529-18-NL
ClinicalTrials.gov	NCT02454283
CCMO	NL53704.042.15