A Phase 3 Multi-Center, Randomized, Double-Blind, Placebo-Controlled Study of the Effects of Once-Daily Oral Doses of 75 mg Azimilide Dihydrochloride on the Incidence of Cardiovascular Hospitalizations/Emergency Department Visits or Cardiovascular Death in Patients with an Implantable Cardioverter Defibrillator

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

Summary

ID

NL-OMON39164

Source
ToetsingOnline

Brief title
SHIELD-2

Condition

- Cardiac arrhythmias

Synonym
abnormal heartbeats, Ventricular arrhythmia

Research involving
Human

Sponsors and support

Primary sponsor: Forest Research Institute
Source(s) of monetary or material Support: Forest Research Institute;Inc.

Intervention

Keyword: Azimilide, cardiovascular, ICD, Ventricular arrhythmia

Outcome measures

Primary outcome

The primary efficacy endpoint is the time-to-first-event of unplanned

cardiovascular

hospitalizations, unplanned cardiovascular emergency department visits, or

cardiovascular death.

Secondary outcome

The secondary efficacy endpoints are:

• Time-to-first all-cause shock; and

• Time-to-first unplanned physician-office visits that resulted in a change in

therapy

(reprogramming ICD or change in medication as it relates to ICD findings).

Study description

Background summary

Implantable cardioverter defibrillators detect and terminate ventricular arrhythmias by
rapidly pacing the heart (antitachycardia pacing [ATP]) or delivering electrical shocks.
Numerous randomized clinical studies have established ICDs as the treatment of choice
to prevent sudden cardiac death in patients at high risk for such arrhythmia (primary
prevention) or in patients with documented sustained ventricular tachycardia (VT) or
ventricular fibrillation (VF) (secondary prevention).

Symptomatic arrhythmias and ICD shocks are a frequent cause of cardiac-related emergency department/hospital visits.

Antiarrhythmic drugs have been used concomitantly with ICD therapy to reduce the recurrence of non-sustained and sustained ventricular arrhythmia. The usefulness of
antiarrhythmics for patients with an ICD is reflected in the fact that over time, 30% to
50% of ICD recipients receive antiarrhythmic drug therapy to prevent symptomatic tachyarrhythmias and to reduce the number of device therapies,17,18,19 even though there is presently no antiarrhythmic therapy approved for this indication.
The potential benefits of antiarrhythmic drugs as adjunctive therapy in patients with an ICD are reductions in the recurrence of arrhythmia, leading to fewer symptoms, fewer ICD-delivered therapies, and consequently fewer visits to emergency department and fewer hospitalizations overall.

There is an unmet medical need for an antiarrhythmic drug that lacks beta-blocking activity, reduces the frequency of symptomatic arrhythmias and the ICD therapies they trigger (through reducing the frequency of VT/VF and VT storms), and has a side effect profile that is compatible with long-term therapy in patients with an ICD.

The results from a previous study (the SHIELD-1 study) showed that 75 mg daily doses of azimilide delivered a clinically meaningful benefit to patients with an ICD by significantly reducing clinically relevant endpoints.
This study (AZM-MD-302) will be undertaken to confirm the effectiveness of a once-daily oral dose of 75 mg azimilide on the reduction of unplanned emergency department visits and hospitalizations observed in the SHIELD-1 study and to provide

additional evidence of efficacy.

Study objective

This study (AZM-MD-302) will be undertaken to confirm the effectiveness of a once-daily oral dose of 75 mg azimilide on the reduction of unplanned cardiovascular emergency
department visits and hospitalizations or cardiovascular death in patients with an ICD. Analysis of efficacy will be done by comparing the effect of azimilide versus placebo on the time-to-first-occurrence of a qualifying event.

Study design

This is an event-driven randomized, multi-center, double-blind, placebo-controlled,
parallel-group study of the safety and efficacy of a once-daily oral dose of 75 mg
azimilide on the incidence of cardiovascular hospitalizations, cardiovascular emergency
department visits, or cardiovascular death in patients with a transvenous ICD who have
had a life-threatening ventricular arrhythmia. Patients are to be randomly assigned in a
1:1 ratio to receive daily oral doses of placebo or 75 mg azimilide.
It is anticipated that approximately 890 patients (445 patients per arm) will be randomized and treated for up to 365 days (1 year). As an event-driven study, the actual number of patients may be less than or greater than 890. The Investigators will be encouraged to maintain the patient on study drug throughout the remaining study visits even after the patient experiences a primary endpoint event that is confirmed by the treatment-blinded Clinical Events Committee (CEC), up to a 1-year treatment period.
No patient should be kept on the study drug if the Investigator determines that the
patient*s clinical status requires that the study drug be discontinued.
Enrollment will be discontinued when at least 330 patients have had confirmed events); this trigger for enrollment cessation is intended to result in 388 patients with confirmed primary endpoint events at study end.
The CEC will adjudicate/confirm all protocol-defined primary efficacy endpoints. When patients experience a protocol-defined primary efficacy endpoint, the patient will remain in the study to be observed for protocol-defined secondary efficacy endpoints. The study treatment period for each patient will be a maximum of 365 days (1 year) or a minimum of 6 months after cessation of enrollment (ie, the last patient enrolled will be observed for 6 months for protocol-defined efficacy endpoints).
Patients will be evaluated at screening, baseline, Weeks 2, 4, 6, 8, and 10; at Months 3, 6, and 9; and at Month 12 or the Withdrawal visit. In addition,

patients will be followed for 30 days after withdrawal or completion of study-drug treatment for safety and adverse events but not efficacy endpoints. At all scheduled visits after baseline, patients will be asked if they were hospitalized or had a visit to an emergency department.

Intervention

Patients will take the study drug (placebo or azimilide 75 mg tablets) orally, once daily, at any time during the day, but at approximately the same time every day. Doses may be taken without regards to meals.

Study burden and risks

The most frequent side effects associated with the use of azimilide have included:
• stuffy nose
• diarrhea
• weakness
• slow heart rate
• feeling faint or fainting
• rash
• allergic-type reaction
• higher than normal level of eosinophils (type of disease-fighting white blood cell)
• mild and passing changes in liver tests
• changes in kidney tests (although these were mostly seen at a dose higher than is used in this study)

Additional, more serious side effects which have been reported with the use of azimilide and drugs of this class are:
• azimilide has been associated with a low incidence of neutropenia
• Emergence of new, and often serious, heartbeat abnormalities, caused by azimilide and other drugs in this class.

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. Men or women at least 18 years of age with a left ventricular ejection fraction (LVEF) <= 40% as determined by echocardiography (ECHO), nuclear scan, left ventriculography, or cardiac magnetic resonance (CMR) imaging within 120 days;prior to randomization;;2. Have an ICD implanted that meets the following criteria:;a. generates a biphasic waveform discharge;;b. stores intracardiac electrograms;;c. has both anti-tachycardia pacing and anti-bradycardia pacing capabilities;;d. has a minimum of 2 anti-tachycardia detecting zones and a ventricular fibrillation zone; and;e. has arrhythmia-discriminating algorithms (eg, high rate or sudden onset or rate stability).;3. Patients who had their qualifying event before their first ICD implantation (*New ICD Patient*): must have had a documented episode of spontaneous sustained VT or VF (ventricular arrhythmia >= 150 bpm lasting at least 30 seconds or;requiring intervention during the sustained VT), or cardiac arrest, or VF during the 42 days preceding their first ICD implantation and be randomized during the 60 days immediately following their OR;4. Patients who had their qualifying event after their first ICD implantation or any subsequent re-implantation (*Existing ICD Patient*): must have had an ICD shock triggered by a spontaneous VT or VF after implantation and be randomized;during the 180 days following this shock;5. Must have their ICD programmed in the following manner:;a. Antitachycardia pacing must be programmed *on* for all patients at the time of randomization (see exception in 4[b]).;b. The device will be set for a minimum of 2 attempts of ATP in the lowest detection zone. Every attempt should be made to leave the ATP programmed *on* during the study unless, in the Investigator*s judgment, it is medically necessary to turn;ATP *off.* If ATP is turned *off,* the reason must be recorded on the

eCRF.;c. The first shock will be delivered no lower than the lowest successful defibrillation energy at implantation or immediately before randomization.;d. Programming of the ventricular tachycardia detection rate (the detection zone in which ATP will be given) should follow the parameters shown below, with adaptation dictated by the patient*s clinical condition and the Investigator*s judgment (VT = ventricular tachycardia):;*If the slowest VT rate is <= 150 bpm, then the floor should be 10 bpm less than the VT rate and the ceiling should be 200 bpm;*If the slowest VT rate is 151 to 194 bpm, then the floor should be 20 bpm less than the VT rate and the ceiling should be 200 bpm ;*If the slowest VT rate is >= 195 bpm or cardiac arrest with no documented VT rate, then the floor should be Ventricular rate: 175 bpm and the ceiling should be 200 bpm;e. For dual chamber devices, at least 1 VT discriminator should be enabled (eg, for;dual chamber devices, AV dissociation detection).;5. Women who meet one of the following:;a. Women of childbearing potential with a negative serum pregnancy test at;screening who are not breast feeding, do not plan to become pregnant during the;study, and agree to use one or more approved methods of birth control during the;study as judged to be appropriate by the Investigator. Approved methods of birth;control are: oral, patch, injectable, or implantable hormonal contraception;;intrauterine device; diaphragm plus spermicide; or female condom plus;spermicide. Abstinence, partner*s use of condoms, and partner*s vasectomy are;not acceptable methods of contraception.;b. Women who have been postmenopausal for at least 1 year (with amenorrhea for;at least 1 year) or have had a hysterectomy, bilateral salpingo-oophorectomy, or;tubal ligation at least 6 months prior to signing the informed consent.

Exclusion criteria

1. Have New York Heart Association (NYHA) Class IV CHF or have decompensated CHF at the time of randomization;;2. Have unstable angina pectoris or a myocardial infarction within 30 days of randomization;;3. Have a history of Torsade de Pointes or heart transplantation;;4. Have chronic atrial fibrillation or atrial fibrillation/flutter, that is not adequately rate-controlled in the judgment of the Investigator, at screening;;5. Have an electrocardiogram (ECG) with a QTc value > 460 msec (with a QRS <= 120 msec), or a JTc value > 340 msec (with a QRS > 120 msec) (QT and JT intervals corrected by Bazett*s formula for heart rate) recorded during screening;;6. Have abnormalities (at screening) in the following clinical laboratory parameters: creatinine > 2.5 mg/dL (221 µmol/L); serum alanine aminotransferase, aspartate aminotransferase, or gamma-glutamyltransferase >= 3 · upper limit of normal (ULN),;or bilirubin >= 2 · ULN; potassium < 4.0 mEq or > 5.5 mEq, or magnesium below the lower limit of normal (potassium and magnesium levels can be adjusted back to normal range if judged by the Investigator, in consultation with the Study Medical Monitor, to be stabilized before randomization);;7. Have an absolute neutrophil count (ANC) < 1000/µL prior to randomization;;8. Are currently taking systemic Class I or other Class III antiarrhythmic drugs (must be off for >= 5 dosing-intervals prior to randomization), including but not limited to quinidine, procainamide, disopyramide, systemic lidocaine, phenytoin, mexiletine, dofetilide, ibutilide, dronedarone, propafenone, moricizine, ranolazine, and sotalol; see exclusion criterion 11 regarding amiodarone;;9. Are currently taking systemic drugs that prolong the QT interval (must be off for 5 half-lives before dosing), including but not limited to clarithromycin, azithromycin, erythromycin, hydroxyzine, phenothiazines, and probucol;;10.

Are currently taking or have taken immune-modulating drugs (eg, azathioprine, methotrexate, tumor necrosis factor alpha modifying drugs, or similar drugs which could affect the immune system or white blood cells) within 90 days before randomization;;11. Have taken oral amiodarone within 60 days before randomization or intravenous amiodarone within 14 days before randomization; or if amiodarone treatment (oral or IV) was <= 24 hours, have taken it within 5 days before randomization;;12. Use ticlopidine 30 days before randomization;;13. Have uncontrolled or untreated hypertension (systolic > 170 mm Hg, diastolic > 100 mm Hg). If a patient is receiving medical therapy for hypertension, his or her blood pressure should be stable for at least 1 week before randomization;;14. If female, are currently pregnant or breast feeding, or plan to become pregnant during the course of the study;;15. Have neoplasia, immune, infectious, or degenerative diseases that are likely to cause death or significant morbidity during the clinical study;;16. Have a systemic disease that, in the opinion of the Investigator, could impact compliance or study results;;17. Have qualifying ventricular fibrillation (episode that justified ICD implantation) during the acute phase (within 48 hours) of a myocardial infarction;;18. Are taking an investigational new drug, or have participated in any investigational study (with an approved or non-approved drug) within 30 days of randomization;;19. Have a non-approved ICD system (lead or generator);;a. Have an ICD system (lead or generator) under current *recall* by the manufacturer; if a component of the ICD system is under *intensive monitoring*;status by the manufacturer, the case should be discussed with the study*s medical monitor prior to randomization.;b. Have an ICD pulse generator with a battery level of ERI (elective replacement indicator), EOL (end-of-life), or other indication of replacement need likely to occur in the 12 months following randomization.;20. Have a current diagnosis of psychosis;;21. Have known drug-induced organ toxicity;;22. Evidence of active hepatic disease, or any of the following: positive human immunodeficiency virus antibodies, positive hepatitis C antibody, positive hepatitis B surface antigen;;23. Use illicit drugs, or abuse alcohol (per Investigator*s judgment); or;24. Are unwilling or unable to give or understand informed consent.

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):	05-03-2013
Enrollment:	35
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Azimilide Dihydrochloride
Generic name:	nvt

Ethics review

Approved WMO Date:	12-01-2012
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-10-2012
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	01-03-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	04-04-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	EUCTR2011-004376-11-NL
ClinicalTrials.gov	NCT01464476
CCMO	NL39046.078.12