A PROSPECTIVE, RANDOMIZED, OPEN-LABEL, BLINDED ENDPOINT EVALUATION (PROBE) PARALLEL GROUP STUDY COMPARING EDOXABAN VS. VKA IN SUBJECTS UNDERGOING CATHETER ABLATION OF NON-VALVULAR ATRIAL FIBRILLATION

Published: 18-01-2017
Last updated: 12-04-2024

Primary efficacy objective:To compare descriptively the incidence of the composite of all-cause death, stroke (ischemic, hemorrhagic, or undetermined) and MajorBleeding (International Society on Thrombosis and Hemostasis [ISTH] definition) in the…

Ethical review	Not approved
Status	Will not start
Health condition type	Cardiac arrhythmias
Study type	Interventional

Summary

ID

NL-OMON45248

Source
ToetsingOnline

Brief title
ELIMINATE-AF

Condition

- Cardiac arrhythmias

Synonym
atrial fibrillation, irregular heartbeat

Research involving
Human

Sponsors and support

Primary sponsor: Daiichi Pharmaceutical
Source(s) of monetary or material Support: Daiichi Sankyo Europe GmbH

Intervention

Keyword: Catheter ablation, Edoxaban, Non-vavular atrial fibrillation, Vitamin K antagonist

Outcome measures

Primary outcome

Primary efficacy endpoint

Composite of all-cause death, stroke (ischemic, hemorrhagic, or undetermined),

and Major Bleeding (ISTH), analyzed as time to first

occurrence of any component

Primary safety endpoint

Major Bleeding (ISTH), analyzed as time to first occurrence of Major Bleeding

Secondary outcome

Efficacy:

* Composite of all-cause death, stroke (ischemic, hemorrhagic, or undetermined,

according to alternative definition (1); see

Section 7.4.2 for details) and Major Bleeding (ISTH definition)

* Composite of stroke (ischemic, hemorrhagic, or undetermined) SEE, and CV

mortality

* Composite of stroke (ischemic, hemorrhagic, or undetermined) SEE, and

all-cause mortality

* Composite of stroke (ischemic, hemorrhagic, or undetermined) and TIA

* Stroke (ischemic, hemorrhagic, or undetermined)

* Stroke (ischemic)

* Stroke (hemorrhagic)

* Stroke (undetermined)

* SEE

* TIA

* Fatal stroke (ischemic, hemorrhagic, or undetermined)

* Non-fatal stroke (ischemic, hemorrhagic, or undetermined)

* Disabling stroke (ischemic, hemorrhagic, or undetermined)

* Non-disabling stroke (ischemic, hemorrhagic, or undetermined)

Safety:

* Major Bleeding (defined by TIMI, BARC [2 or higher])

* Major and CRNM Bleeding (ISTH definition)

* CRNM Bleeding (ISTH definition)

* Minor Bleeding (ISTH definition)

* Any Bleeding

* ICH

* Life-threatening bleeding

* Fatal Major Bleeding (ISTH definition)

* Non-fatal Major Bleeding (ISTH definition)

* Fatal Major Bleeding (defined by TIMI, BARC [2 or higher])

* Non-fatal Major Bleeding (defined by TIMI, BARC [2 or higher])

* Safety parameters such as AEs, SAEs, laboratory parameters, ECG and vital

signs.

Study description

Background summary

Atrium fibrillation (AF) is the most frequent sustained arrhythmia in clinical practice. Catheter
ablation of AF has been established as an effective therapy for the treatment of symptoms in
these patients. However, this procedure is associated with a significant thromboembolic risk.
The causes of thromboembolic events during and after the ablation are multiple and include (I) char formation at the catheter tip, (II) mobilization of pre-existing left atrial
thrombi, (III) thrombus formation in left atrial sheaths, (IV) the thrombogenic potential of left
atrial endocardial lesions, and (V) electrical cardioversion during the procedure.
Therefore, anticoagulation therapy is required before, during, and for a period after the procedure.
Traditionally, VKAs (eg, coumarins) are used as anticoagulant medications. However, the use of VKAs is complicated by several inherent problems, including a delayed onset of
antithrombotic action, narrow therapeutic index that requires close anticoagulation monitoring
using the INR, unpredictable and variable pharmacological response, and mandatory regular
laboratory monitoring to control its anticoagulant effect and minimize the risk of serious
bleeding.
Therefore, there exists a need for a safer, more effective, and easily manageable oral
anticoagulant (OAC) agent for the prevention of acute stroke in subjects with AF who are
scheduled for catheter ablation. It is expected that edoxaban will provide comparable efficacy to
warfarin (VKA), but with a predictable and faster antithrombotic response and with no need for
laboratory monitoring.

Study objective

Primary efficacy objective:
To compare descriptively the incidence of the composite of all-cause death, stroke (ischemic, hemorrhagic, or undetermined) and Major Bleeding (International Society on Thrombosis and Hemostasis [ISTH] definition) in the edoxaban group against the vitamin K antagonist (VKA) group in subjects undergoing catheter ablation of atrial fibrillation (AF) in the period from the end of the catheter ablation procedure to Day 90/end-of-treatment (EOT).

Primary safety objective:
To compare descriptively the incidence of Major Bleeding (ISTH definition) in the edoxaban group against the VKA group in the period from date of first intake of study medication to Day 90/EOT.

Study design

This is a multinational prospective, randomized, open-label, blinded endpoint evaluation (PROBE) parallel group phase 3b study comparing edoxaban vs. VKA in subjects undergoing catheter ablation of non-valvular AF. After Screening and randomization, eligible subjects receive 21 days (+7) anticoagulation before being assessed for suitability for the catheter ablation procedure. Subjects will receive 90 days anticoagulation post-procedure and are then followed-up after an additional 30 days. In all subjects, key demographic and risk characteristics of both stroke and bleeding (for example, CHA2DS2-VASc score, HAS-BLED, type of AF, presence of coronary artery disease (CAD), heart failure (HF), diabetes mellitus (DM), and hypertension) will be collected. Subjects will be randomized in a 2:1 ratio to edoxaban vs. VKA.

Intervention

Edoxaban study arm
Subjects will take their first dose of edoxaban in the clinic or hospital and will be required to complete at least 21 (up to +7) days of anticoagulation with edoxaban. Subjects receiving anticoagulants at the time of enrollment will be switched to edoxaban (the switching procedure will follow the edoxaban label and is described in Section 5.2.1.3).
It is mandatory that in the pre-ablation period, the once-daily dose of edoxaban is taken every day in the evening. Edoxaban can be taken with or without food.
If a subject has taken the study drug in the evening, the procedure can be performed in the morning of the next day. The interval between the last intake of edoxaban and the procedure must not exceed 18 hours. After the ablation, study medication must be re-started on the day of procedure but no earlier than 6 hours post-sheath removal and only once adequate hemostasis has been achieved.
Timing of the last dose of edoxaban prior to the catheter ablation procedure

and the first dose after the procedure will be recorded in the electronic case report form (eCRF).

VKA study arm
Subjects enrolled in the VKA study arm will be required to complete at least 21 days (up to +7 days) of anticoagulation treatment with VKA. Subjects will take the VKA according to the direction of the Investigator. Every attempt will be made to bring subjects into the therapeutic target range (INR [International Normalized Ratio] 2.0-3.0) as fast as possible and to maintain the target INR range consistently. INR will need to be measured frequently at the start of the study (unless a subject is receiving an unvarying VKA dose at the time of Before ablation, each subject must be in the INR range of 2.0-3.0 for the last 10 days prior to the catheter ablation. This will need to be documented by frequent INR measurements, at least once per week in the pre-ablation period. On the day of, or the day prior to, the scheduled ablation procedure, subjects INR should be within the range 2.0-3.0. If INR is ¤1.5 and <2.0 or if INR is >3.0 and *3.5 the procedure may be performed at the Investigator's discretion. Otherwise, the subject is not eligible for performing the catheter ablation (the subject will be switched from study medication to standard of care and will enter the 30-day follow-up period).
During the catheter ablation procedure, VKA will be used without interruption and bridging with low molecular weight heparin (LMWH) will not be allowed at this time.

Study burden and risks

The optimal OAC therapy in patients with NVAF undergoing CA is unknown at this time and is subject of this investigation.
Traditionally, Vitamin K antagonists (VKA) are used as anticoagulant medications but regular laboratory monitoring is mandatory to control their anticoagulant effect.
In this study edoxaban will be compared to VKA therapy to investigate on safety and efficacy of treatment groups of oral anticoagulant agent to reduce the risk of thromboembolic complication in subject with NVAF undergoing CA.
Edoxaban has been developed as an alternative to VKA and has already been allowed for clinical use in all study countries, apart from Canada, for the prevention of stroke and systemic embolism in adult patients with NVAF with one or more risk factors, such as congestive heart failure, high blood pressure, age * 75 years, diabetes mellitus, prior stroke or transient ischemic attack (TIA).
In this study, you will receive either edoxaban or VKA therapy. Edoxaban will be compared to a VKA therapy to observe the incidence of bleeding and the incidence of thrombotic complications like stroke

Contacts

Public
Daiichi Pharmaceutical

Zielstattstrasse 48
Munich 81379
DE
Scientific
Daiichi Pharmaceutical

Zielstattstrasse 48
Munich 81379
DE

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Male or female at least 18 years of age with documented history of paroxysmal (lasting *7 days), persistent (lasting >7 days but *12 months) or long-standing [long-lasting] persistent (>12 months) non-valvular AF. Duration of AF can be confirmed by any electrical tracing or a recording in the subject*s medical records (e.g., medical chart, hospital discharge summary).
2. Subject is eligible and is scheduled for either radio frequency (RF) or cryoballoon catheter ablation (both first and repeated procedure included).
3. Signed informed consent form (ICF).

Exclusion criteria

1. AF considered to be of a transient or reversible nature (such as in myocarditis, post-

surgery, ionic disturbances, thyrotoxicosis, pneumonia, severe anemia etc.).
2. Subject post stroke, or with a systemic thromboembolic event within the past 6 months prior to randomization.
3. Subject has a thrombus in the left atrial appendage (LAA), left atrium (LA), left ventricle (LV), or aorta, or an intracardial mass.
4. Subject had a myocardial infarction (MI) within the 2 months prior to randomization or coronary artery bypass graft (CABG) surgery within 3 months prior to the randomization.
5. Subject has signs of bleeding, history of clinically-relevant bleeding according to ISTH, or conditions associated with high risk of bleeding such as past history of intracranial (spontaneous or traumatic), or spontaneous intraocular, spinal, retroperitoneal, or intra-articular bleeding; overtgastrointestinal (GI) bleeding or active ulcer within the previous year; recent severe trauma, major surgery, or deep organ biopsy; active infective endocarditis; uncontrolled hypertension (blood pressure [BP] above 170/100 mmHg); or hemorrhagic disorder including known or suspected hereditary or acquired bleeding or coagulation disorder in the last 12 months prior to randomization.
6. Subjects with mechanical heart valves, subjects with moderate to severe mitral stenosis and subjects who have new implantation (within 3 months prior to randomization) of a bioprosthetic heart valve, with or without AF.
7. Subjects with a history of LAA occlusion/exclusion (either by surgery or by a procedure).
8. Subjects with any contraindication for edoxaban, VKA, LMWH, heparin therapy.
9. Subjects receiving dual antiplatelet therapy (DAPT, i.e., aspirin and P2Y12 antagonist) or planned to receive DAPT during the study
10. Subjects who require chronic use of medicines affecting hemostasis such as higher doses of aspirin (acetylsalicylic acid [ASA]) (ASA up to 100 mg per day allowed) or chronic oral or parenteral intake of non-aspirin non-steroidal anti-inflammatory drugs (NSAID) on *4 days/week (use of NSAIDs via other routes is not restricted)
11. Subjects with active liver disease or persistent (confirmed by repeat assessments at least a week apart) elevation of liver enzymes/bilirubin:
* Alanine transaminase (ALT) or aspartate transaminase (AST) *2 times the upper limit of normal (ULN)
* Total bilirubin (TBL) *1.5 times the ULN (subjects whose elevated TBL is due to known Gilbert*s syndrome may be included in the study)
* Hepatic disease associated with coagulopathy and clinically relevant bleeding risk.
12. Subjects with kidney failure (calculated creatinine clearance [CrCL] <15 mL/min).
13. Subjects with hemoglobin <10 g/dL or platelet count <100,000 cells/*L or white blood cell (WBC) count <3000 cells/*L.14. Subjects with pre-planned invasive diagnostic or therapeutic procedures/interventions (other than endoscopy) during the study period in which bleeding is anticipated.
15. Participation in any other interventional trial (subjects who received any investigational drug or device within 30 days prior to randomization, or plan to receive such investigational therapy during the study period).
16. Previous randomization in this study.
17. Female subjects of childbearing potential without using adequate contraception (female of childbearing potential is defined as one who has not been postmenopausal for at least one year, or has not been surgically sterilized, or has not had a hysterectomy at least 3 months prior to the start of this study [Visit 1]). Females taking oral contraceptives should have been on therapy for at least 3 months. Adequate contraceptives include hormonal intra-uterine

devices, hormonal contraceptives (oral, depot, patch or injectable), and double barrier methods such as condoms or diaphragms with spermicidal gel or foam.
18. Pregnant or breast-feeding subjects.
19. Subjects with the following diagnoses or situations:
* Active cancer undergoing chemotherapy, radiation or major surgery within the next 5 months
* Significant active/uncontrolled concurrent medical illness
* Life expectancy <6 months.
20. Subjects who are unlikely to comply with the protocol (e.g., uncooperative attitude, inability to return for subsequent visits, and/or otherwise considered by the Investigator to be unlikely to complete the study).
21. Subjects with a known drug or alcohol dependence within the past 12 months prior to randomization as judged by the Investigator.
22. Subjects with any condition that, in the opinion of the Investigator, would place the subject at increased risk of harm if he/she participated in the study.
23. Planned procedure using laser catheter ablation or other forms of catheter ablation different from RF or cryoballoon (i.e. high intensity focused ultrasound [HIFU], microwaves, hot balloon, etc)

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	25
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Lixiana
Generic name:	Edoxaban
Product type:	Medicine
Brand name:	Phenprogamma 3
Generic name:	Phenprocoumon
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Previscan
Generic name:	Fluindione
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Warfarin
Generic name:	Warfarin

Ethics review

Approved WMO Date:	18-01-2017
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Not approved Date:	24-04-2017
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	EUCTR2016-003069-25-NL
ClinicalTrials.gov	NCT02942576
CCMO	NL59845.091.17