A prospective, randomised, open-label, blinded endpoint evaluation (PROBE) parallel group study comparing edoxaban (DU-176b) with enoxaparin/warfarin followed by warfarin alone in subjects undergoing planned electrical cardioversion of nonvalvular atrial fibrillation

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Cardiac disorders, signs and symptoms NEC
Study type	Interventional

Summary

ID

NL-OMON40676

Source
ToetsingOnline

Brief title
ENSURE

Condition

- Cardiac disorders, signs and symptoms NEC

Synonym
stroke and thromboembolism

Research involving
Human

Sponsors and support

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

Intervention

Keyword: cardioversion, Edoxaban, stroke, thromboembolism

Outcome measures

Primary outcome

endpoints of stroke, systemic embolic event (SEE), myocardial infarction (MI) and cardiovascular (CV) mortality between the edoxaban group and the enoxaparin/warfarin group from randomization to end of follow up (FU).

endpoints of major and clinically-relevant non-major (CRNM) bleeding between the edoxaban group and the enoxaparin/warfarin group from the first administration of study drug to end of treatment + 3 days.

Secondary outcome

endpoints of stroke, SEE, MI, CV mortality and major bleedings between the edoxaban group and the enoxaparin/warfarin group from randomization to end of FU.

Study description

Background summary

AF is a condition that becomes more common as people get older. Patients with AF have a higher risk of having a stroke and other blood clot complications. A stroke happens when a blood vessel begins to leak in the brain or gets a clot in it.
At the present time, patients with AF undergoing a cardioversion procedure are most commonly treated with a medicine called warfarin or sometimes other blood-thinning drugs. Warfarin is a drug to be used in this study. Warfarin is used for the prevention of stroke in patients with AF. People who take warfarin have to have regular blood tests to make sure they are not taking too much or too little medication. Too much warfarin can cause serious bleeding.
Warfarin can also cause interactions when taken along with other common medications. People taking warfarin must avoid certain foods, alcohol, and dietary supplements. Because of these problems Daiichi Sankyo is developing a new drug that is taken in tablet form.
The purpose of this study is to compare this new drug with warfarin to see if it is safe and effective in preventing thromboembolism (formation of a clot (thrombus) in a blood vessel that breaks loose and is carried by the blood stream to block another vessel) and strokes which results when a brain blood vessel becomes blocked by a clot) in patients with AF who have undergone electrical cardioversion.

Study objective

The primary efficacy objective of this study is to:
* Compare the incidences of the composite endpoints of stroke, systemic embolic event (SEE), myocardial infarction (MI) and cardiovascular (CV) mortality between the edoxaban group and the enoxaparin/warfarin group from randomization to end of follow up (FU).

The primary safety objective of this study is to:
* Compare the incidence of the composite endpoints of major and clinically-relevant non-major (CRNM) bleeding between the edoxaban group and the enoxaparin/warfarin group from the first administration of study drug to end of treatment + 3 days.

The secondary objective of this study is to:
* Compare the incidences of the composite endpoints of stroke, SEE, MI, CV mortality and major bleedings between the edoxaban group and the enoxaparin/warfarin group from randomization to end of FU.

Study design

This is a prospective, randomized, open-label, blinded endpoint evaluation (PROBE) parallel group study in subjects with confirmed ongoing AF of no longer than 12 months and in whom electrical cardioversion is planned. This study is designed to compare the incidence of the composite endpoints of stroke, SEE, MI

and CV death and to compare the incidence of major and CRNM bleedings after TEE or non-TEE-guided electrical cardioversion in the edoxaban arm versus the enoxaparin/warfarin arm. Composite endpoints of the key efficacy and safety parameters are also going to be tested.

Stratification
The stratification in the study will be performed on the following levels:
* approach to cardioversion (TEE or non-TEE) as determined by the Investigator;
* subject*s experience in taking anticoagulants at the time of randomization (anticoagulant-experienced or anticoagulant-naïve);

* selected edoxaban dose (full 60 mg or reduced 30 mg dose). A subject with one or more factors (CrCL * 15mL/min and * 50 mL/min, low body weight [* 60 kg], and concomitant use of p-pg inhibitors (excluding amiodarone) will be on the reduced dose (30 mg) of edoxaban if the subject is randomized to the edoxaban group.
Subjects will be randomized in a 1:1 ratio to two treatment groups within each stratum. Enrollment will be managed to achieve the balance of treatment assignment within each stratum. Recruitment will continue until at least 1000 subjects in each arm have undergone cardioversion (spontaneous or electric).

TEE-guided Stratum
Warfarin arm: On the day of randomization (Day -3), subjects assigned to this arm will either be:
a) Naive to anticoagulation or have been taking VKA but have a sub-therapeutic International Normalized Ration (INR) (<2.0) or have been taking anticoagulants other than VKA (e.g. dabigatran, rivaroxaban or apixaban OR parenteral anticoagulants);
b) Have been taking anticoagulants and have an INR *2 at the time of randomization.
Subjects in category a) will start treatment with a minimum of 1 dose each of enoxaparin and warfarin on the day of randomisation and these drugs will be continued until INR *2 has been obtained. After a therapeutic range (TR) is achieved, subjects will discontinue enoxaparin and continue warfarin until end of treatment (Day 28 following the procedure).

Subjects in category b) will not require enoxaparin and will start treatment with warfarin alone. If INR in the subject is >3 at randomisation, the dose of warfarin in the study will be adjusted to achieve and maintain the therapeutic INR level of 2.0-3.0. Please refer to section 16.8 for the detailed instruction on the management of warfarin in the study.
In both categories within the first several days from the start of warfarin treatment, INR measurements will be conducted with a frequency of once every 2-3 days until the value reaches the TR; thereafter subjects will attend theplanned study visits but may have ad hoc INR checks as deemed necessary by the Investigator.
Both TEE and cardioversion may be performed on the day of randomization

providing that the subject has either received at least 1 dose of enoxaparin or for those patients not requiring enoxaparin at randomisation, that the patients INR is in TR (2.0-3.0). In any case cardioversion has to be performed within a maximum of 3 days from randomization.
If no thrombi are identified in the atria by TEE, electrical cardioversion will be conducted and subjects will continue on enoxaparin (if started from randomisation) and warfarin until their INR reaches the TR. In both categories it will be important to aim at achieving the TR of warfarin within 8 days after randomization and to maintain the TR during the study treatment period. Please refer to section 16.8 for the detailed instruction on the management of warfarin in the study. Enoxaparin given beyond 14 days of treatment will trigger automatic notification of the Sponsor.

Edoxaban arm: On the day of randomization, subjects will start treatment with edoxaban and continue treatment until day of TEE/cardioversion (Day 0). If the subject transitions from a prior anticoagulant to edoxaban, this will be done in accordance with the transition algorithm provided in Appendix 16.5.1 (that is, either discontinue VKA and start edoxaban when INR is *2.5 or for novel anticoagulants [NOAC], such as dabigatran, rivaroxaban or apixaban or parenteral anticoagulants (e.g. low molecular weight heparins) start edoxaban when the next dose of the NOAC is due (note that for unfractionated heparin (UFH) start edoxaban 4 hours after the last dose of UFH)). Both TEE and cardioversion may be performed on the same day but cardioversion has to be performed within a maximum of 3 days from randomization.
The cardioversion procedure itself should be performed approximately no earlier than 2 hours and no later than 12 hours after the dose of edoxaban on the day of the procedure.
The next dose of edoxaban will be taken the day after cardioversion and then continued on a 24-hours cycle.
If no thrombi are identified in the atria by TEE, electrical cardioversion will be conducted and the subject will continue with edoxaban until Day 28 following the procedure.

All subjects will be followed-up for safety for 30 days (Day 58) after completing treatment with warfarin/edoxaban in both arms. If thrombi are identified during the TEE procedure; the subject will not be eligible for subsequent cardioversion and may be discontinued from treatment (but the subject will continue to participate in the study including the follow-up period). The Investigators will be encouraged to continue treatment with the drug to which the subject was randomized and repeat the TEE on Day 28 to assess progress of the thrombus. Note that this repeated TEE is not mandatory for continuation in the study.
Subjects with unsuccessful cardioversion or relapse of AF may be cardioverted again at the Investigator*s discretion; however, duration of treatment in the study will be calculated based on the initial cardioversion date. These subjects will be encouraged to remain in the study and continue the study treatment as per the protocol.

All subjects with the CHA2DS2-VASc (or CHADS2)score *2 (refer to Appendix 16.2 for details on calculation) and subjects with CHA2DS2-VASc score =1 (when the use of oral anticoagulants is preferred over aspirin) will require to be transitioned at the end of the study treatment to a standard-of-care anticoagulant which is in accordance with the current European and US guidelines on the anticoagulant treatment of patients with AF22,26,39. These subjects will be transitioned to the treatment chosen by the Investigator and strictly in accordance with the transition algorithms provided in Appendix 16.5.2.

Non-TEE-guided Stratum
Warfarin arm: Subjects assigned to this arm will either:
a) Have taken VKA prior to randomization and have an INR *2 on the day of randomization;
b) Have sub-therapeutic INR at randomization (<2), have taken an anticoagulant other than VKA (e.g. dabigatran, rivaroxaban or apixaban OR parenteral anticoagulants) or are anticoagulant-naïve.
The following algorithms will be implemented:
Subjects in category a) will not require enoxaparin and will start 21 days of warfarin anticoagulation from the day of randomization (Day -21). If INR in the subject is >3 at randomisation, the dose of warfarin in the study will be adjusted to achieve and maintain the therapeutic INR level of 2.0-3.0. Please refer to section 16.8 for the detailed instruction on the management of warfarin in the study.
Patient*s management in this pre-procedural period will be conducted in accordance with the instructions provided in Table 3-1 of the protocol, Section 3.1.1.
Subjects in category b) will receive enoxaparin and daily warfarin until the INR is *2.0. At this time, enoxaparin will be discontinued and warfarin continued for a total minimum of 21 days. Please refer to section 16.8 for the detailed instruction on the management of warfarin in the study.

In both categories within the first several days from the start of warfarin treatment, INR measurements will be conducted with a frequency of once every 2-3 days until the value reaches the TR; thereafter subjects will attend the planned study visits but may have ad hoc INR checks as deemed necessary by the Investigator.
For all subjects, cardioversion will be performed on Day 0, which will occur at a minimum of 21 days following the start of treatment with the study drug or within 3 days thereafter. Refer to Table 3-1 on the guidance of patient management in accordance with the INR value before and on the day of cardioversion.
In subjects who do not have a TR INR (2.0-3.0) on the day of randomization, it will be important to aim at achieving the TR of warfarin within 8 days after randomization and to maintain the TR during the study treatment period. Please

refer to section 16.8 for the detailed instruction on the management of warfarin in the study.
Enoxaparin given beyond 14 days of treatment will trigger an automatic alert to the Sponsor.

Edoxaban arm: After randomization into this study, subjects will receive edoxaban for 21 days before cardioversion followed by cardioversion on Day 0 (or within 3 days thereafter) and an additional 28 days of edoxaban treatment starting from the day of cardioversion. If the subject transitions from a prior anticoagulant to edoxaban, this will be done in accordance with the transition algorithm provided in section Appendix 16.5.1(that is, for VKA discontinue the drug and startedoxaban when INR is *2.5; for novel anticoagulant [NOAC, e.g. dabigatran, rivaroxaban, apixaban] start edoxaban when the next dose of the NOAC is due or for parenteral anticoagulants start edoxaban when the next dose of the anticoagulant is due with the exception of UFH where the first dose of edoxaban will be 4 hours after the last dose of UFH). The count of 21 days will start from the day of the first dose of edoxaban.

Both arms: All subjects will be followed-up for safety for 30 days (Day 58) after completing treatment with warfarin/edoxaban in both arms.
Subjects with unsuccessful cardioversion or relapse of AF may be cardioverted again at the Investigator*s discretion; however, duration of treatment in the study will be calculated based on the initial cardioversion date. These subjects will be encouraged to remain in the study and continue the study treatment as per the protocol.
All subjects with the CHA2DS2-VASc (or CHADS2)score *2 (refer to Appendix 16.2 for details on calculation) and subjects with CHA2DS2-VASc score =1 (when the use of oral anticoagulants is preferred over aspirin) will require to be transitioned at the end of the study treatment to a standard-of-care anticoagulant which is in accordance with the current European and US guidelines on the anticoagulant treatment of patients with AF22,26,39. These subjects will be transitioned to the treatment chosen by the Investigator and strictly in accordance with the transitioning algorithms provided in Appendix 16.5.2.

Subjects with spontaneous cardioversion in the pre-procedural period (confirmed by a recording of sinus rhythm) will still need to complete 28 days of treatment from the day that spontaneous cardioversion was noted and 30 days of follow-up (58 days in total).

Intervention

o Warfarin tablets once per day (and with a dose based on your International Normalized Ratio (INR) clotting test results. Some patients in this group may also receive enoxaparin injected just under the skin (subcutaneously).

o Edoxaban once per day 60mg

Study burden and risks

Edoxaban * the investigational study drug

The Sponsor has recently conducted two very large world-wide phase 3 studies using up to 60 mg of edoxaban. As of September 2013, more than 17,500 study subjects had received edoxaban for 12-24 months.
The main known risk associated with taking edoxaban is bleeding. Bleeding events, seen in clinical studies, can occur at any site and have been mostly mild. However, severe bleeding and bleeding into the brain, resulting in stroke or death, has been reported in both edoxaban and warfarin groups. Other side effects seen with edoxaban (based on the concluded studies with edoxaban) included anaemia, skin rash and increased liver enzymes. Edoxaban is an investigational study drug and it may also have unknown side effects.

Warfarin

The main side-effect of warfarin is bleeding. The risk of severe bleeding is small, occurring in approximately 1 or 2 out of 100 patients each year. Other side effects include blackening and dying skin (necrosis) and other tissues, allergic reaction, skin rashes, diarrhoea, hair loss, fever, yellow skin and eyes, and liver problems although these complications are quite rare. Warfarin can also cause interactions when taken along with other common medications. People taking warfarin must avoid certain foods, alcohol, and dietary supplements.

Enoxaparin:

Enoxaparin is in a class of medications called low molecular weight heparins. It works by stopping the formation of substances that cause clots. Enoxaparin is marketed under the trade names Lovenox, Xaparin and Clexane, among others. Enoxaparin is an anticoagulant used to prevent and treat deep vein thrombosis or pulmonary embolism, and is given as a subcutaneous injection. The most common side effects include bleedings, mild reactions or irritation, pain, bruising, and redness of the skin where you have the injection.

Pregnancy:
Edoxaban has not been tested in pregnant women. The effects of this drug on a human foetus (developing baby still in the womb) or a nursing child are unknown.

Contacts

Public
Daiichi Pharmaceutical

Chiltern Place, Chalfon Park .
Gerrads Cross, Buckinghamshire SL9 OBG
GB
Scientific
Daiichi Pharmaceutical

Chiltern Place, Chalfon Park .
Gerrads Cross, Buckinghamshire SL9 OBG
GB

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Signed ICF;
2. Male or female subjects older than the minimum legal adult age (country specific);
3. Ongoing AF lasting for at least 48 hours but * 12 months;
- Ongoing AF at the time of randomization should be confirmed by any electrical tracing (eg, routine 12-lead electrocardiogram (ECG), Holter monitor rhythm strip, intracardiac electrogram, or pacemaker) prior to randomization.
- Duration and proof of AF during the previous 12 months can be confirmed by any electrical tracing or a recording in the subject*s medical records (eg, medical chart, hospital discharge summary).
- Symptomatic subjects with no known history of AF and no prior electrical tracing or recording of/about the cardiac rhythm available for the past 12 months may be randomized into the study if there is reasonable belief that the current episode of AF lasts for at least 48

hours and no longer than 12 months.
4. Subject is planned for electrical cardioversion;
- Subjects with AF following a cardiac surgical procedure will be allowed in the study providing that they meet all the other inclusion criteria AND the time from the surgery to randomization is no less than 30 days. The Investigator will be responsible for assessment of risks relevant to the cardioversion procedure in such subjects.

Exclusion criteria

1. AF considered to be of a transient or reversible nature (such as in myocarditis, post-surgery [unless the duration of AF post-cardiac surgery is >30 days, refer to inclusion criterion #4], ionic disturbances, thyrotoxicosis, pneumonia, severe anemia, etc);;2. Subjects with moderate or severe mitral stenosis, mitral valve rheumatic disease, unresected atrial myxoma, or a mechanical heart valve (subjects with bioprosthetic heart valves and/or valve repair can be included) and/or other conditions, such as PE, considered to be formal indication for conventional anticoagulation;;a. However subjects with AF and valvular heart diseases such as mitral valve prolapse, mitral valve regurgitation, and aortic valve disease are allowed in the study;;3. Subjects with a history of LAA closure (either by surgery or by a procedure);;4. Known presence of a thrombus in LAA, LA, left ventricle, aorta or intracardial mass;;5. Subjects with acute myocardial infarction (MI), stroke, acute coronary syndrome (ACS), or percutaneous coronary intervention within the previous 30 days or receiving DAPT regardless of when the event has occurred;;6. Subjects with any contraindication to anticoagulant agents;;7. Signs of bleeding or conditions associated with high risk of bleeding including major surgeries or biopsies in the last 10 days;;8. Subjects with 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; overt gastrointestinal (GI) bleeding or active ulcer within the previous year; recent severe trauma, major surgery, or deep organ biopsy within the previous 10 days; 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;;9. Subjects receiving dual antiplatelet therapy (eg, aspirin plus thienopyridine such as clopidogrel, prasugrel or ticagrelor) or anticipated to receive such therapy;;10. Subjects receiving prohibited concomitant medications (fibrinolytics, non-study anticoagulants other than those used as a bridge to/from study drug), chronic oral or parenteral Non-Aspirin/Non-Steroidal Anti-Inflammatory Drugs (NSAID) use for * 4 days/week;;11. Subjects receiving chronic cyclosporine therapy;;12. Subjects with active liver disease or persistent (confirmed by repeat assessments at least a week apart) elevation of liver enzymes/bilirubin:
- ALT or AST * 3 x ULN;
- TBL * 2 x ULN (however, subjects whose elevated TBL is due to known Gilbert*s syndrome may be included in the study);;13. Subjects with renal failure (end stage renal disease, calculated CrCL < 15 mL/min);;14. Subjects with hemoglobin < 10 g/dL or platelet count < 100000 cells/mcL or white blood cell count < 3000 cells/mcL;;15. Subjects with pre-planned invasive procedures (other than routine endoscopy) or surgeries in which bleeding is anticipated during the study period;;16. 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;;17. Women of childbearing potential without proper contraceptive measures, and women who are pregnant or breast feeding;Note: Childbearing potential without proper contraceptive measures (i.e., a method of contraception with a failure rate < 1 % during the course of the study (including the observational period). These methods of contraception according;to the note for guidance on non-clinical safety studies for the conduct of human trials for pharmaceuticals (CPMP/ICH/286/95, modification) include consistent and correct use of hormone containing implants and injectables, combined oral contraceptives, hormone containing intrauterine devices, surgical sterilization, sexual abstinence, and vasectomy for the male partner);;18. Subjects with the following diagnoses or situations:
- Active cancer undergoing chemotherapy, radiation or major surgery within the next 3 months;
- Significant active concurrent medical illness or infection;
- Life expectancy < 6 months;;19. Subjects who are unlikely to comply with the protocol (eg, uncooperative attitude, inability to return for subsequent visits, and/or otherwise considered by the Investigator to be unlikely to complete the study);;20. Subjects with a known drug or alcohol dependence within the past 12 months as judged by the Investigator;;21. 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.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	11-12-2014
Enrollment:	178
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	EDOXABAN
Generic name:	EDOXABAN
Product type:	Medicine
Brand name:	Warfarine
Generic name:	Warfarine

Ethics review

Approved WMO Date:	17-04-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-08-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-09-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-09-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-10-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-11-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	04-12-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-01-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-02-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-07-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2013-003148-21-NL
CCMO	NL47944.018.14