A Randomised, phase II study to Evaluate the sAfety of oraL dabIGatran etexilate in patients after heart valve replacemeNt. (RE-ALIGN)

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The purpose of this study is to confirm/validate predicted dabigatran trough plasma levels gained after individual dose assignment based on simulations by means of PK data from the RE-LY trial. Based on this validation a final appropriate dosing...

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

Summary

ID

NL-OMON39111

Source
ToetsingOnline

Brief title
RE-ALIGN

Condition

- Cardiac valve disorders

Synonym
anticoagulant therapy in mechanical heart valves

Research involving
Human

Sponsors and support

Primary sponsor: Boehringer Ingelheim

Source(s) of monetary or material Support: Boehringer Ingelheim BV

Intervention

Keyword: dabigatran etexilate, direct thrombin inhibitor, mechanical heart valve, warfarin

Outcome measures

Primary outcome

The primary endpoint is the total dabigatran concentration at trough. There are no primary or formal secondary efficacy and safety variables. Clinical efficacy outcome variables, mortality and morbidity enpoints will be evaluated in an exploratory manner. The same goes for safety outcome variables.

Secondary outcome

The following mortality/morbidity clinical endpoints will be examined in an exploratory manner:

• Bleeding events: major, clinically relevant non major, minor and total (major plus minor) during study treatment as defined by ISTH and by Valve Academic Research Consortium (VARC) [R11-0058]

• Heart valve functionality and thrombosis evaluation from clinical routine echocardiography (TTE and/or TEE) and Doppler imaging. TEE should be conducted if there is a clinical suspicion of valve thrombus or valve dysfunction

• Incidence of stroke (including haemorrhagic), SSE and valve thrombosis during study treatment

• Composite of stroke (including haemorrhagic), SSE, valve thrombosis and major bleedings during study treatment

• Composite of stroke (including haemorrhagic), SSE, valve thrombosis, all death

• Individual occurrence of ischaemic stroke (fatal and non-fatal), disabling

stroke (modified Rankin score >=3), haemorrhagic stroke, SSE, pulmonary embolism, valve thrombosis, MI, TIAs, vascular death (including deaths from bleeding), all deaths and hospitalisations

• Incidence of re-operation for mechanical heart valve, para-valvular leakage and endocarditis (per site, per country and overall)

• Net clinical benefit (NCB) as defined by disabling strokes (modified Rankin score >3), life threatening bleeding, vascular death, valve thrombosis and MI.

The main safety endpoint is the composite of major plus CRNMBEs while on treatment. MBE for the composite primary endpoint will be defined by the ISTH bleeding classification. On-treatment will be defined as the time interval from date of randomisation to date of last randomised medication intake plus six days.Additional safety endpoints are total bleeding events (composite of major plus minor bleedings) .

Study description

Background summary

Patients with mechanical heart valves may need lifelong anticoagulant treatment. Treatment of patients with VKAs substantially reduces the risk of thromboembolism, but is associated with a risk of bleeding. Additionally, treatment with VKAs requires regular monitoring and dose adjustment during treatment. Fluctuations in VKA levels increase the risk of haemorrhage and risk of thromboembolism.
There is a need for new oral anticoagulants which may have fewer drug-drug and drug-food interactions, do not require monitoring and which potentially have a better safety and/or efficacy profile. Dabigatran etexilate has been shown to be as effective as LMWH for the primary prevention of VTE after major orthopaedic surgery and it was non-inferior to well-controlled warfarin for the treatment of venous thromboembolic events. Moreover, dabigatran etexilate

(150mg b.i.d.) was recently shown to be superior to warfarin (at a target INR of 2.0-3.0) for the prevention of stroke or SSE in patients with non valvular AF (stroke prevention in atrial fibrillation (SPAF); 35% relative risk reduction of stroke and SSE over warfarin) while resulting in less intracranial haemorrhage and life threatening bleeding. In addition animal models support the use of dabigatran etexilate in thrombus prevention in animals with implanted mechanical heart valves.

Study objective

The purpose of this study is to confirm/validate predicted dabigatran trough plasma levels gained after individual dose assignment based on simulations by means of PK data from the RE-LY trial. Based on this validation a final appropriate dosing algorithm for dabigatran etexilate in patients receiving a mechanical heart valve should be developed for further clinical investigation.
In addition, a comparison of pharmacokinetic values at trough as determined by the HPLC-MS/MS method will be compared to other assays for the determination of dabigatran exposure, such as the Hemoclot® thrombin inhibitor assay.

Study design

This is a prospective, randomised, open label, blinded endpoint (PROBE), active comparator trial and the clinical endpoints being adjudicated by an IAC in a blinded fashion. The study will have a stepwise approach. The first cohort of patients (Step 1, n=25 patients) will be recruited from patients considered to be in the low risk stratum only (i.e. aortic valve replacement with no additional individual risk factors). Patients determined to be at intermediate-high risk will be recruited after 25 patients in the low risk stratum have been randomised (Step 2).
Patients will be placed into one of two population strata. They will be either those who have recently undergone surgery for implantation of bileaflet mechanical heart valve(s) (AVR and/or MVR; Step 1 of this trial: single aortic valve replacements with no additional individual risk factors only) and have not yet started oral anticoagulation therapy in the post operative period (Study Population A) or patients who have had surgery for implantation of bileaflet mitral mechanical heart valve (Step 2 of study only) at least 3 months prior to randomisation and are currently taking an oral VKA (Study Population B).

Intervention

Eligible patients, who successfully complete the screening phase and fulfil the inclusion and exclusion criteria, may be randomised. Patients will be randomly assigned to either dabigatran etexilate or warfarin. Patients randomised to dabigatran etexilate will be initially allocated to a pre-defined dabigatran etexilate dose depending on the screening visit (pre surgery) CrCl

measurements. Adjustment of the dose of dabigatran etexilate will be performed based upon the results of a dabigatran plasma level measurement (Hemoclot* assay, Hyphen Biomed, France) once patients are at ss (Day 4-7 after first study drug intake, see Section 4.1.4). Warfarin will be used as recommended in guidelines with at least monthly monitoring required and patients will have one of two target INR ranges as recommended by guidelines. After initiation of warfarin in patients who are commencing warfarin for the first time; INR should be monitored daily for the first four days. Thereafter, measurements should be every two weeks over the first 3 months after surgery.
Study Population A patients randomised to warfarin can initiate their study drug at any time up to seven days post operatively). Patients randomised to receive dabigatran etexilate can initiate study treatment between Days 3 and 7 post operatively. It is expected that patient*s renal function will have returned to the pre-operative (screening) state by this time.

Study burden and risks

Dabigatran etexilate has been shown to be non-inferior to enoxaparin for the prevention of VTEs in patients undergoing major orthopaedic surgery and non-inferior to warfarin for the treatment of deep vein thrombosis (DVT). Dabigatran etexilate has also been shown to be superior to warfarin for the prevention of stroke and SEE in patients with AF (for details see the IB for dabigatran etexilate. In vitro and animal models using dabigatran etexilate with aortic and mitral valves supports the use of dabigatran etexilate in patients with mechanical heart valves Dabigatran etexilate has the potential to be safer, easier to use and at least as effective as the current therapeutic standard
treatment (VKAs, e.g. warfarin) for the prevention of thromboembolic complications in patients following mechanical heart valve replacement.
The potential benefit of dabigatran over warfarin is based on its more rapid onset and offset of action, the absence of a need for routine laboratory monitoring, its lack of drug-food interactions, its low drug-drug interaction potential and the superiority compared to warfarin demonstrated in patients with non-valvular AF for the reduction of stroke and systemic emboli.
Valve thrombosis is considered to be the major risk factor for patients with mechanical heart valves. To reduce the risk of such events, the recruitment into the study will be stepwise; the initial cohort of patients will be those who are considered at low thromboembolic risk. These patients with new generation mechanical bileaflet heart valves in the aortic position and in the absence of additional individual risk factors (such as AF, left ventricular (LV) dysfunction or previous thromboembolism) should receive warfarin to achieve a target INR of 2.0-3.0. Patients with aortic valves and individual risk factors and all patients with mitral valve replacement should receive warfarin at a target INR of 2.5-3.5 as recommended in current guidelines.
Regular measurement of INR (at least every 4 weeks, more frequently at therapy initiation) will be performed to ensure that patients are well-controlled with warfarin. In RE-LY, a dose of 150mg dabigatran etexilate b.i.d. was shown to be

superior to warfarin (INR level 2.0-3.0) in preventing thromboembolic events and non-inferior with regard to MBE. Patients randomised to receive dabigatran etexilate will receive a dose which results in comparable exposure to that shown to be superior in RE-LY.
Data will be scrutinised on an ongoing basis by an independent external DSMB (no representation from the Sponsor will participate). All data (for both dabigatran etexilate and warfarin patients), both adjudicated and non adjudicated will be reviewed by the DSMB in an ongoing fashion,
Following positive DSMB opinion once adequate patient data has been reviewed (to be detailed in the DSMB charter), patients who have undergone mechanical valve replacement in the mitral position or have aortic valve replacement with additional underlying risk factors will be recruited into the study. Taking the more consistent and predictable anticoagulant effect of dabigatran into account, an exposure comparable to that achieved in RE-LY with 150mg b.i.d. is considered to be sufficient to provide similar outcomes as with warfarin at a target range of INR of 2.5-3.5 (as recommended per guidelines for patients at intermediate- to high thromboembolic risk).
Heart valve patients are expected to have good renal function and to be on average 10 years younger than patients in RE-LY. Therefore, in order to achieve an appropriate exposure of dabigatran, higher doses of dabigatran etexilate, greater than 150mg b.i.d., may be required (see section 4.1.3 for dose selection). Addition of an antiplatelet, such as ASA (permissible in this trial), may increase the risk of bleeding to a similar extent as it is known for concomitant treatment with warfarin.

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. Male and female patients aged >= 18 years and <= 75 years
2. For study population A - undergone elective implantation of bileaflet mechanical heart valve(s) in the aortic and/or mitral posion during the current hospital stay and not started oral coagulation, or
For study population B - undergone elective implantation of bileaflet mechanical heart valve(s) in the mitral position more than three months prior to randomisation.
Patients (Population A and B) receiving CABG concomitantly with the valve replacement may be included.
3. The patient must be able to give informed consent in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines and local legislation and/or regulations.

Exclusion criteria

1. Patients who have undergone prior valve surgery before the index surgery defined for this study.
2.Patients undergoing aortic root surgery and/orreplacement of the ascending aorta at the time of valve replacement.
3. Patients undergoing bioprosthetic or mechanical tricuspid or pulmonary valve replacement
4. Tricuspid valve repair prior or at index valve replacement in a patient with double valve replacement (AVR+MVR)
5.Clinically relevant paravalvular leak related to vavle replacement surgery.
6. Active infective endocarditis.
7. Complex congenital heart abnormality.
8. Acute coronary syndrome within 1 month prior to randomisation.
9. Uncontrolled hypertension (systolic blood pressure (SBP) >180 mmHg and/or diastolic blood pressure (DBP) > 100 mmHg.
10. Emergency surgery or major trauma within three months of randomisation.
11.Planned surgery or intervention within 1 months post randomisation.
12. Any history of haemorrhagic stroke or any of the following intracranial pathologies: bleeding, neoplasm, AV malformation or aneurysm.

13. History of intraocular, spinal, retroperitoneal or atraumatic intra-articular bleeding unless the causative factor has been permanently eliminated or repaired (e.g. by surgery).
14. Gastrointestinal (GI) hemorrhage within the past year, unless the cause has been permanently eliminated (e.g. by surgery) or symptomatic or endoscopically documented gastroduodenal ulcer disease in the previous 30 days.
15.Haemorrhagic disorder or bleeding diathesis (e.g. von Willebrand disease, hemophilia A or B or other heriditary bleeding disorder, history of spontaneous intra-articular bleeding, history of prolonged bleeding after surgery/intervention).
16. History of thrombocytopenia, including heparin-induced thrombocytopenia or a platelet count <100X10 9/L at screening (visit 1).
17. Renal impairment (estimated CrCl calculated by Cockcroft-Gault equation) < 40mL/min at screening.
18. Liver disease as indicated by one of the following:
• Prior and persistent ALT or AST or AF > 3 X ULN, and/or
• Active hepatitis C (as evidenced by positive hepatitis C virus ribonucleic acid assay by sensitive polymerase chain reaction (PCR) based assay, such as Roch Monitor or Bayer TMA assay) and/or
• Active hepatitis B1 (HBs antigen + or anti HBc IgM+) and/or
• Active hepatitis A
19. Patients who will continue to require treatment with dual antiplatelet therapy.
20. Ongoing or planned treatment with long-term oral anticoagulants for alternative indications during the course of the study (e.g. treatment of VTE, secondary prevention of VTE) with the exception of anticoagulation for stroke prevention in patients with preexisting AF. Patients with prior use of oral anticoagulants for SPAF or for prevention of thromboembolic events due to the presence of a mechanical heart valve will e allowed to participate in this trial.
21. Need for continued treatment with ticlopidine, ticagrelor, prasugrel, systemic ketoconazole, itraconazole, posaconazole, cyclosporine, tacrolimus, dronedarone, rifampicin, carbamazepine, st John's wort or any cytotoxic/myeolosuppressive therapy.
22. Recent malignancy or radiation therapy (<=6 months) unless the malignancy was a basal cell carcinoma that was completely removed.
23. Patients with a known allergy to dabigatran etexilate or to the excipients used for the capsule of the drug.
24. Patients with a known allergy to warfarin tablets ow who in teh Investigator"s opinion should not be treated with warfarin.
25. Pre-menopausal (last menstruation <= 1 year prior to screening) sexually active women who:
• are pregnant or nursing
• are not surgically sterile
• are of child bearing potential and not practicing an acceptable method of birth control, or do not plan to continue practising an acceptable method of birth control throughout the trial (acceptable methods include intrauterine devices (IUD), oral, implantable or injectable contraceptives, double barrier or vasectomised partner).
26. Patients weighing less than 40 kg.
27. Patients who have participated in another trial with an investigational drug or device within the past 30 days preceding the screening visit or are participating in another trial.
28. Patients not willing or able to comply with the protocol requirementsor considered

unreliable by the Investigator concerning the requirements for follow-up during the study and/or compliance with study drug administration, has a life expectancy less than the expected duration of the trial due to concomitant disease, or has any condition which in the opinion of the Investigator, would not allow safe participation in the study (e.g. drug addiction, alcohol abuse).
the opinion of the investigator, would not allow safe participation in the study (e.g. drug addiction, alcohol abuse).
29. Previously randomised to receive study medication in this study.

Study design

Design

Study phase:	2
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):	05-03-2012
Enrollment:	25
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	niet van toepassing
Generic name:	Warfarin
Product type:	Medicine
Brand name:	Pradaxa
Generic name:	dabigatran etexilate

Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	11-07-2011
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	05-10-2011
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	22-11-2011
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	23-11-2011
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	23-12-2011
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	21-02-2012
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	08-03-2012
Application type:	Amendment

Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	17-07-2012
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	25-07-2012
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	06-08-2012
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	07-08-2012
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	20-08-2012
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	30-08-2012
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	18-09-2012
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO	

Date:	24-09-2012
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	26-11-2012
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	13-12-2012
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	20-12-2012
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	17-01-2013
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	01-03-2013
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	08-03-2013
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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	EUCTR2010-022685-27-NL
CCMO	NL33617.060.11
Other	nog niet toegekend