Multicenter, randomized, active comparator-controlled, double-blind, double-dummy, parallel group, dose-finding Phase 2 study to compare the safety of the oral FXIa inhibitor BAY 2433334 to apixaban in patients with atrial fibrillation

Published: 30-10-2019
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To evaluate that the oral FXIa inhibitor BAY 2433334 when compared to apixaban leads to a lower incidence of bleeding in participants with AF

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

Summary

ID

NL-OMON49562

Source
ToetsingOnline

Brief title
PACIFIC-AF

Condition

- Cardiac arrhythmias

Synonym
arrhythmia, atrial fibrillation

Research involving
Human

Sponsors and support

Primary sponsor: Bayer
Source(s) of monetary or material Support: Bayer AG

Intervention

Keyword: atrial fibrillation, FXIa inhibitor

Outcome measures

Primary outcome

Primary Safety Endpoint:

* Composite of International Society on Thrombosis and Hemostasis (ISTH) major

and clinically relevant non-major bleeding.

Secondary outcome

Secundary Safety Enpoints

* All bleeding

* ISTH major bleeding

* ISTH clinically relevant non-major bleeding

* ISTH minor bleeding

Study description

Background summary

Current guidelines recommend long-term oral anticoagulant therapy such as non-Vitamin K oral anticoagulants (NOACs).
Patients receiving NOACs continue to have a significant risk for developing strokes, systemic embolism and CV death. In addition there is still a significant risk for major bleeding. The inhibition of FXIa is expected to not lead to a relevant increase in bleeding and especially major bleeding, while

maintaining the efficacy benefit of NOACs.

Study objective

To evaluate that the oral FXIa inhibitor BAY 2433334 when compared to apixaban leads to a lower incidence of bleeding in participants with AF

Study design

This is a multicenter, randomized, active comparator-controlled, double-blind, double-dummy, parallel-group dose-finding study

Intervention

BAY 2433334 is the sponsor*s study drug under investigation. Apixaban is the drug used as comparator. The following intervention groups are included in the study:
* BAY 2433334 50 mg
* BAY 2433334 20mg
* Apixaban 5 mg or 2.5 mg, according to label

Study duration is between 14 and 16 weeks (max. 2 weeks for screening, 12 weeks of treatment, safety follow up 2 weeks after end of treatment)

Study burden and risks

The safety profile of BAY 2433334 has not yet been established. The following safety and risk information is available:
-Risk for bleeding cannot be excluded in participants with atrial fibrillation.
- Increase in liver enzymes has been oberserved in animal testing.
-Strong CYP3A4 inhibitors should not be taken because exposure to BAY 2433334 and the half-life is enhanced.

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. Participant must be 45 years of age or older at the time of signing the informed consent.
2. Participant with AF documented by ECG evidence with
* CHA2DS2-VASc score **2 if male or CHA2DS2-VASc score **3 if female
* Indication for treatment with an oral anticoagulant in
* any participant currently not treated with an oral anticoagulant (e.g. treatment naïve) or alternatively,
* participant on a NOAC in case of at least one bleeding risk feature (history of a prior bleed within the last 12 months requiring medical attention and*/*or moderate renal dysfunction with eGFR 30-50 ml/min and*/*or current clinically indicated antiplatelet therapy with ASA * 100 mg)

Exclusion criteria

1. Mechanical heart valve prosthesis
2. Any degree of rheumatic mitral stenosis or moderate-to-severe, non-rheumatic mitral stenosis
3. Atrial fibrillation due to a reversible cause, participants in sinus rhythm after successful ablation, or plan for cardioversion or ablation during study conduct
4. Stroke within the last 30 days of screening
5. Uncontrolled hypertension (systolic blood pressure **160 mmHg or diastolic blood pressure **100 mmHg) at randomization

6. Active bleeding; known bleeding disorder
7. Known significant liver disease (e.g. acute hepatitis, chronic active hepatitis, cirrhosis) or hepatic insufficiency classified as Child-Pugh B or C, or ALT/AST >*2.5 x the upper limit of normal, measured between screening and randomization
8. Estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m2, calculated by Modification of Diet in Renal Disease (MDRD) formula, determined between screening and randomization
9. Major surgery during the last 30 days or planned major surgery or intervention within study period (e.g. carotid endarterectomy, coronary artery bypass grafting)
10. Known allergy, intolerance or hypersensitivity to either of the study interventions (active substance or excipients)
11. Any contraindication for the use of an anticoagulant or listed in the local labeling for apixaban
12. Requirement for chronic anticoagulation (for a different indication than AF e.g. mechanical heart valve or cardiac thrombus) or antiplatelet therapy (up to 100 mg ASA is allowed). Anticipated need for chronic (more than 4 weeks) therapy with NSAIDs
13. Treated with a Vitamin K antagonist in the 30 days prior to screening
14. Concomitant use of any of the following therapies within 14 days (or at least five half-lives of the active substance whatever is longer) before randomization and first study intervention administration:
* Strong inhibitors of cytochrome P450 isoenzyme 3A4 (CYP3A4) e.g. human immunodeficiency virus protease inhibitors, systemically used azole-antimycotic agents, clarithromycin or telithromycin
* Strong inducers of CYP3A4, e.g. phenytoin, carbamazepine, phenobarbital, rifampicin or St. John*s wort.
15. Women of childbearing potential (women are considered of childbearing potential if they are not surgically sterile or postmenopausal, defined as amenorrhea for >*12 months). Male participants not willing to use condoms when sexually active with a woman of childbearing potential

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)

Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	24-06-2020
Enrollment:	62
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Eliquis
Generic name:	Apixaban
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	30-10-2019
Application type:	First submission
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	28-02-2020
Application type:	First submission
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	11-05-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	30-06-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	24-12-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-01-2021
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	EUCTR2019-002365-35-NL
CCMO	NL71685.018.19