Long-term treatment of cancer associated venous thromboembolism: reduced vs full dose of apixaban : API-CAT STUDY for APIxaban Cancer Associated Thrombosis

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Ethical review	Approved WMO
Status	Completed
Health condition type	Coagulopathies and bleeding diatheses (excl thrombocytopenic)
Study type	Interventional

Summary

ID

NL-OMON54840

Source
ToetsingOnline

Brief title
API-CAT

Condition

- Coagulopathies and bleeding diatheses (excl thrombocytopenic)

Synonym
unexpected clotting of blood in veins

Research involving
Human

Sponsors and support

Primary sponsor: Assistance Publique-Hôpitaux de Paris (APHP) delegated to Recherche Clinique et à l'Innovation (DRCI)
Source(s) of monetary or material Support: Bristol Meyer Squibb,Bristol-Myers Squibb

Intervention

Keyword: Cancer, New Anticoaguation drug, Thrombosis

Outcome measures

Primary outcome

The primary efficacy endpoint is the incidence of an adjudicated composite of recurrent symptomatic VTE (proximal and/or distal DVT and/or symptomatic PE and/or upper limb or CVC thrombosis) or incidental VTE (proximal DVT or PE), or death due to PE during the treatment period.

Secondary outcome

The key secondary outcome is the incidence of adjudicated major and clinically relevant non-major bleeding during the treatment period.

Other secondary endpoints:

Adjudicated composite of :

- Recurrent symptomatic VTE ;

- VTE related-death ;

- All-cause death: all deaths will be classified as either VTE-related, cancer death (including all deaths due to the underlying cancer), bleeding-related or others, including all deaths due to a clearly documented other cause, such as for example respiratory failure (e.g., terminal emphysema), infections/sepsis, etc. ;

- Adjudicated major bleeding.

Study description

Background summary

Our objective is to study the extended anticoagulant treatment of cancer associated thrombosis (CAT) in patients who have been receiving at least 6 months of anticoagulant for a venous thromboembolic event (VTE) (index event). The oral route is very attractive in these patients.

Given apixaban at the 5 mg bid dosage is an alternative in the initial treatment of CAT, we aim to assess whether it is possible to reduce the dose of apixaban (2.5 mg bid) in patients with CAT and cancer who have been receiving at least 6 months of anticoagulant therapy and requiring extended anticoagulant therapy (patients with significant life expectancy).

There are 2 conditions to be met: demonstrate the non-inferiority of the 2.5 mg bid regimen of apixaban on the efficacy criterion and then demonstrate the superiority of the 2.5 mg bid regimen compared to the 5 mg bid regimen on the safety criterion.

Study objective

ThThe primary efficacy objective is to determine whether a low-dose regimen of apixaban (2.5 mg bid) is non-inferior to a full-dose regimen of apixaban (5 mg bid) for the prevention of recurrent VTE in patients with cancer who have completed at least 6 months of anticoagulant therapy for treating a documented index event of proximal deep venous thrombosis (DVT) (symptomatic or incidental) or pulmonary embolism (PE) (symptomatic or incidental).

Study design

It will be a multicenter, international, prospective, randomized, parallel-group, double-blind non-inferiority trial with blinded adjudication of outcome events (approximately 160 centers in approximately 9 countries (France, Italy, Spain, Belgium, Greece, Netherlands, UK, Switzerland, Poland). Subjects with active cancer, who have an objectively documented index event of proximal DVT (symptomatic or incidental) or PE (symptomatic or incidental) and have completed at least 6 months of anticoagulant therapy for the treatment of the index event, and have no objectively documented symptomatic recurrence of VTE after the index event, will be eligible for this study. Every attempt should be made to randomize subjects within 7 days after the last dose of their initial treatment.

Randomization will be stratified based on the cancer site and the type of disease treated (PE with/without DVT or DVT alone). If a subject had both symptomatic DVT and symptomatic PE, the subject will be considered as having symptomatic PE.
After completing their initial anticoagulant treatment, subjects will be randomized (1:1 ratio) to Apixaban 5 mg bid (full dose) or Apixaban 2.5 mg bid (reduced dose) for 12 months using Cleanweb e-CRF.

Patients randomized in Apixaban reduced dose group will receive an apixaban 2.5 mg tablet and a placebo of apixaban 5 mg tablet twice daily for 12 months. Patients randomized in the apixaban full dose group will receive an apixaban 5 mg tablet and a placebo of apixaban 2.5 mg tablet twice daily for 12 months.

An independent data monitoring board will monitor the subjects* safety during the study and give recommendations to the steering committee and the sponsor.

Intervention

A urinary pregnancy test will be performed in women of childbearing potential (WOCBP) at the time of inclusion and at every visit during the study (Week 4, M3, M6, M9, M12 visits).

A phone call will be made one month after the end of treatment.

Study burden and risks

Patients in the low-dose apixaban group (Apixaban 2.5 mg bid) are likely to have a higher risk of recurrent VTE compared to patients receiving apixaban 5mg bid. But in this case, we expect this to be offset by a reduction in the risk of bleeding at this dose.

We hypothesized that a reduced dosage regimen of apixaban (2.5 mg bid) is not associated with a lower response for extended treatment of VTE and prevention of recurrence of VTE and is associated with less bleeding than that observed in routine care with a full-dose regimen of apixaban (5 mg bid) in subjects with active cancer, who have been receiving at least 6 months of anticoagulant treatment for the treatment of the index VTE .

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

• Signed Written Informed Consent
• Any cancer diagnosed histologically (other than basal-cell or squamous-cell carcinoma of the skin, primary brain tumor or intra-cerebral metastasis)
• Active cancer defined as the presence of measurable disease or ongoing (or planned) chemotherapy, radiotherapy, hormonotherapy, targeted therapy, immunotherapy at inclusion.
• Objectively documented index event of :
symptomatic or incidental proximal lower-limb, iliac, inferior vena cava DVT or symptomatic or incidental PE in a segmental or larger pulmonary artery
(1) Proximal DVT is defined as DVT that involves at least the popliteal vein or a more proximal vein, demonstrated by imaging with compression ultrasound (CUS), including grey-scale or color-coded Doppler, or ascending contrast venography or contrast enhanced computed tomography or magnetic resonance imaging.
(2) PE has to be demonstrated by imaging as follows:
* an intraluminal filling defect in segmental or more proximal branches on contrast enhanced chest computed tomography or on computed tomography pulmonary

angiography ; or
* an intraluminal filling defect or a sudden cutoff of vessels more than 2.5 mm in diameter on the pulmonary angiogram; or
* a perfusion defect of at least 75% of a segment with a local normal ventilation result (high-probability) on ventilation/perfusion lung scan (VPLS)
(3) Incidental VTE is defined as proximal DVT or PE detected by imaging incidentally when a patient undergoes imaging studies as standard of care for the management of his or her malignancy or other reasons but not for a VTE suspicion(e.g. cancer diagnosis or staging).• At least 6 months of anticoagulant therapy at therapeutic dosage (whatever the drug and the dosing), or completed assigned clinical trial study treatment, for the treatment of the index event; and patient still receiving anticoagulant treatment after occurrence or the index VTE .
• No objectively documented symptomatic recurrence of VTE between the index event and randomization.

Exclusion criteria

• WOCBP who are unwilling or unable to use an acceptable method of birth control [such as oral contraceptives, other hormonal contraceptives (vaginal products, skin patches, or implanted or injectable products), or mechanical products such as an intrauterine device or barrier methods (condoms)] to avoid pregnancy for the entire study • Women who are pregnant or breastfeeding • Women with a positive pregnancy test on enrollment or prior to investigational product administration • Isolated sub-segmental (incidental or symptomatic) PE without associated DVT • Isolated distal DVT of the legs • Isolated upper-extremity DVT or superior vena cava thrombosis • Isolated visceral thrombosis • Isolated catheter thrombosis • Objectively documented symptomatic recurrence of VTE after the index event under anticoagulant treatment • VTE during anticoagulant treatment given at therapeutic dosage • Subjects with indications for long-term treatment with a VKA, such as: - Mechanical heart valve - Antiphospholipid syndrome • Subjects with indication for long-term anticoagulation with a VKA or a DOAC at therapeutic dosage • Conditions increasing the risk of serious bleeding - intracranial or intraocular bleeding within the 6 months - major surgery within 2 weeks prior to randomization - overt major bleeding at time of randomization • Life expectancy < 12 months • Eastern Cooperative Oncology Group (ECOG) level 3 or 4 • Bacterial endocarditis • Uncontrolled hypertension: systolic blood pressure >180 mm Hg or diastolic blood pressure >110 mm Hg • Platelet count < 75,000/mm3 • Hemoglobin < 8g /dl • Creatinine clearance < 30 ml /min based on the Cockcroft Gault equation (see Section 5.7.4) • Acute hepatitis, chronic active hepatitis, liver cirrhosis; or an alanine aminotransferase level 3 times or more and/or bilirubin level 2 times or more higher the upper limit of the normal range • Subjects requiring ASA >165 mg/day at randomization or thienopyridine therapy (clopidogrel, prasugrel, or ticagrelor) • Subjects

requiring dual anti-platelet therapy (such as acetylsalicylic acid plus clopidogrel or acetylsalicylic acid plus ticlopidine) at randomization. Subjects who transition from dual antiplatelet therapy to monotherapy prior to randomization will be eligible for the trial • Concomitant use of strong inhibitors of both cytochrome P-450 3A4 and P Glycoprotein (e.g. human immunodeficiency virus protease inhibitors or systemic ketoconazole) or strong inducers of both cytochrome P-450 3A4 and P Glycoprotein (e.g. rifampicin, carbamazepine, or phenytoin) • Prisoners or subjects who are involuntarily incarcerated • Subjects who are compulsorily detained for treatment of either a psychiatric or physical (e.g. infectious disease) illness • Hypersensitivity to apixaban • Subjects participating in another pharmaco therapeutic program with an experimental therapy that is known to affect the coagulation system • Under 18 years old • Patients under legal protection (guardianship; court decision)

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	18-12-2019
Enrollment:	110
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	ELIQUIS 2.5mg
Generic name:	APIXABAN

Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	ELIQUIS 5mg
Generic name:	APIXABAN
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	04-03-2019
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	03-08-2019
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	19-02-2020
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	10-03-2020
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	05-11-2020
Application type:	Amendment

Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	19-11-2020
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	30-11-2020
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	11-01-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	09-04-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	28-05-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	12-08-2021
Application type:	Amendment

Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	30-09-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	19-04-2022
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	25-11-2022
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	09-12-2022
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	11-06-2023
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

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	EUCTR2017-003342-25-NL
ClinicalTrials.gov	NCT-03692065
CCMO	NL68781.098.19