A Phase 3, Prospective, Randomized, Open-label, Adaptive Group Sequential, Multicenter Trial with Blinded Endpoint Assessment to Evaluate the Efficacy and Safety of TAK-330 for the Reversal of Direct Oral Factor Xa Inhibitor-induced Anticoagulation in Patients Requiring Urgent Surgery/Invasive Procedure

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This study has been transitioned to CTIS with ID 2022-503012-16-00 check the CTIS register for the current data. To evaluate intraoperative efficacy of PROTHROMPLEX TOTAL in comparison with standard of care (SOC) 4F-PCC, for reversal of...

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

Summary

ID

NL-OMON53886

Source
ToetsingOnline

Brief title
TAK-330-3001

Condition

- Other condition

Synonym
Urgent Surgery/Invasive Procedure

Health condition

Urgent Surgery/Invasive Procedure

Research involving
Human

Sponsors and support

Primary sponsor: Takeda
Source(s) of monetary or material Support: the pharmaceutical industry

Intervention

Keyword: Open label, Phase 3, PROTHROMPLEX TOTAL

Outcome measures

Primary outcome

The primary efficacy endpoint of this study is the occurrence of intraoperative effective hemostasis assessed at the end of the surgery/invasive procedure based on the surgeon's assessment using the Four Point Intraoperative Hemostatic Efficacy Scale. At the IA and FA timepoints, the respective one-sided significance level α1*and α2* corresponding to the efficacy crossing boundaries will be calculated, and the primary endpoint will be analyzed as a dichotomous variable as effective or non-effective hemostasis in a noninferiority design. The proportion of subjects achieving intraoperative effective hemostasis will be calculated. Noninferiority will be declared if the lower confidence limit of a two-sided 100*(1-2 αi*)% confidence interval (CI) (i=1 for IA and i=2 for FA) for the difference (between PROTHROMPLEX TOTAL and active comparator 4F-PCC) in the proportion of subjects in both the

Per-Protocol (PP) Set and the mITT Set, respectively, who experience intraoperative effective hemostasis at the end of surgery is greater than a noninferiority margin of -12%. Superiority will be tested only in the mITT Set following a successful test of noninferiority in this set, based on whether the lower limit of the

2-sided 100*(1- 2 αi*)% CI is >0. The CI for the difference in proportion will be calculated by the Wilson score method with continuity correction. The testing for superiority will be exploratory.

Given that the half-life of Factor Xa inhibitors ranges between 5 to 15 hours and based on the fact that anti-Factor Xa levels remain above the recommended threshold for reversal for urgent surgery in all subjects within 15 hours of last Factor Xa inhibitor use, the placebo response rate could be expected to be around 0% within the prerequisite 15-hour study window. Thus, the estimates of the success rates for the 4F-PCC in the 8 studies could be considered as their effect sizes versus placebo (M1). Calculations of the noninferiority margin (M2) have been performed using the fixed margin method and the point estimate method for various scenarios of the fraction of the SOC effect that is assumed to be retained by PROTHROMPLEX TOTAL. There is no clearly established threshold for clinically meaningful difference. Based on clinical judgement, preserving more than 85% of the putative SOC-placebo difference would be an adequately conservative choice. A difference of 12% in the proportion corresponds to the preservation of 85% of the effect and is thus chosen. In an area with limited data, with the 8 studies in the meta-analysis reflecting all that was identified in a systematic literature review approach, Takeda felt appropriate

in choosing the margin based on the meta-analysis results.

Secondary outcome

The analyses of the dichotomous secondary efficacy endpoints of occurrence of postoperative effective hemostasis assessed at 24 hours after the end of investigational product infusion (PROTHROMPLEX TOTAL or comparator 4F-PCC) based on the surgeon's assessment using the Four Point Postoperative Hemostatic Efficacy Scale, occurrence of intraoperative effective hemostasis assessed at the end of the surgery/invasive procedure based on the surgeon*s assessment using the Hemostatic Efficacy Rating Algorithm, usage of blood products or non-study hemostatic agents for bleeding control within 24 hours after the end of investigational product infusion, will be analyzed as dichotomous variables in a noninferiority design as the primary endpoint. The CI for the difference in proportion for each of these secondary endpoints will be calculated by the Wilson score method with continuity correction. For each of these secondary endpoints, noninferiority will be declared if the lower limit of the CI for the difference in proportions is greater than the noninferiority margin of -12%. Superiority will be based on whether the lower limit of the CI is >0. The testing for superiority will be exploratory. The non-dichotomous secondary efficacy endpoint of number of units of PRBCs administered to achieve bleeding control within 24 hours after the end of investigational product infusion will be analyzed using a negative binomial distribution allowing for different shape parameters per treatment arm via SAS PROC GLIMMIX. The CI for the ratio in the number of units per subject per 24 hours of PROTHROMPLEX TOTAL relative to the active comparator 4F-PCC will be reported.

The analyses of the secondary efficacy endpoints at the IA and FA timepoints will follow a graphical testing approach. This approach for multiple comparisons will be used to control the type I error (1-sided alpha of 0.025) for the testing of the secondary efficacy endpoints. The approach is based on a sequentially rejective Bonferroni multiple-testing procedure to control the family-wise error rate.

Study description

Background summary

The use of Factor Xa inhibitors has dramatically increased since their introduction in 2010, due to several advantages compared to Vitamin K antagonists, including rapid onset of action and elimination, predictable pharmacokinetics, improved safety profile, and reduced food-drug and drug-drug interactions. However, similar to other anticoagulants, patients using Factor Xa inhibitors are at increased risk of developing major bleeding, and or may suffer from a medical emergency requiring urgent surgery. While published reports suggest interruption of Factor Xa inhibitor therapy for 1 or 2 days depending on the perioperative bleeding risk prior to elective surgery, temporary interruption is not a viable option in patients needing for an urgent intervention associated with a high risk of bleeding.

To date there is no approved drug for reversal of Factor Xa inhibitors for urgent surgery. Clinical practice for Factor Xa inhibitor reversal for urgent surgery is highly variable. Published guidelines and guidance reports recommend the use of prothrombin complex concentrates (PCCs) for Factor Xa inhibitor reversal when a Factor Xa inhibitor specific reversal agent is not available.

Study objective

This study has been transitioned to CTIS with ID 2022-503012-16-00 check the CTIS register for the current data.

To evaluate intraoperative efficacy of PROTHROMPLEX TOTAL in comparison with standard of care (SOC) 4F-PCC, for reversal of anticoagulation in patients receiving direct oral Factor Xa inhibitors and requiring urgent surgery/invasive procedure within 15 hours from the last dose of Factor Xa

inhibitor or at any time after that if their specific DOAC-calibrated (apixaban, rivaroxaban or edoxaban) anti-FXa levels were > 75ng/mL or heparin-calibrated anti FXa assay level of >0.5 IU/mL at screening.

Study design

This is a Phase 3, multicenter, open-label, adaptive group sequential noninferiority study to evaluate the efficacy and safety of PROTHROMPLEX TOTAL in comparison with SOC
4F-PCC for reversal of anticoagulation in patients receiving direct oral Factor Xa inhibitors and requiring urgent surgery/invasive procedure within 15 hours from the last dose of Factor Xa inhibitor.
The study is designed to establish non-inferiority of PROTHROMPLEX TOTAL as compared to investigator-assigned 4F-PCC as a part of SOC, in terms of intraoperative effective hemostasis based on the surgeon's assessment at the end of the surgery/invasive procedure. Subjects will be typically identified in the emergency department or surgical care units of participating hospitals. Determination of whether the patient is being treated with direct oral Factor Xa inhibitors
(eg, apixaban, edoxaban, or rivaroxaban) will be based on information provided by the patient, a patient representative (family member/relative), or the patient*s physician. Initial assessment of the patient will be performed on presentation to a treating facility to confirm the subject*s eligibility for the trial. After a subject is initially considered qualified, informed consent will be obtained. Subjects will be excluded if the time of the last dose of Factor Xa is unknown.

Intervention

Patients will be randomly (like pulling a name from a hat) assigned to receive either the study drug or comparator drug. The chance that the patients will receive the study drug is 1 in 2 patients.
The study drug or comparator drug will be given to patients one time within 1 hour before their scheduled surgery or medical procedure in the form of a drip in a vein in their arm. This is called an intravenous (IV) infusion.
This is an open-label study. The pharmacist, and the doctor who will be giving patients anaesthesia (medicine to numb them or put them to sleep during the surgery) will know which study treatment they are receiving. However, their surgeon will not know which study treatment they are receiving before or during their surgery. They may receive a second dose of the study drug during the surgery, if needed.
Within 1 hour after the surgery is completed, a few tests will be done to check if the study treatment is working.

Study burden and risks

The PROTHROMPLEX TOTAL may help in prevention of bleeding, but this is not certain.
Patients could experience an allergic reaction with the use of study drug or other medicines to treat their condition. Allergic reactions are serious and could be life threatening if not treated promptly. Other medicines patients may be taking could have a negative effect when taken with the study drug.
There is a chance that the study drug may not help to lower patient*s risk of excessive bleeding or it might worsen. Patients may have pain, bleeding, swelling, or bruising around the vein where their blood is collected. There may be a risk of infection from any blood draw. Patients may feel dizzy or patients may feel faint. The procedures in this study may have risks that are not known at this time.

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. Subject or legally authorized representative willing to sign e-consent/written informed consent form.
2. Subjects >=18 years of age at enrollment.
3. Subject currently on treatment with oral Factor Xa inhibitor (rivaroxaban, apixaban, edoxaban).
4. In the opinion of the surgeon, the subject requires urgent surgery/procedure that is associated with high-risk of intraoperative bleeding within 15 hours of the last Factor Xa inhibitor dose and requires a reversal agent for suspected direct oral Factor Xa inhibitor-related coagulopathy. In subjects who are beyond the 15-hour window,
eligibility requires proof of elevated plasma anti FXa levels using either specific DOAC-calibrated (apixaban, rivaroxaban or edoxaban) anti-FXa levels of > 75ng/mL, or heparin-calibrated anti-FXa assay levels of > 0.5 IU/mL at screening.
5. Women of childbearing potential should have a negative pregnancy test documented prior to enrollment.

Exclusion criteria

1. The subject has an expected survival of less than 30 days, even with best available medical and surgical care.
2. Recent history (within 90 days prior to screening) of venous thromboembolism, myocardial infarction (MI), DIC, ischemic stroke, transient ischemic attack, hospitalization for unstable angina pectoris or severe or critical coronavirus 2 (SARS-CoV-2) infection.
3. Active major bleeding defined as bleeding that requires surgery or transfusion of >2 units of PRBC or intracranial hemorrhage with the exception of subacute and chronic subdural hemorrhages with a Glasgow Coma Score (GCS) >= 9
4. Polytrauma for which reversal of Factor Xa-inhibition alone would not be sufficient to achieve hemostasis.
5. Known prothrombotic disorder including primary antiphospholipid syndrome, antithrombin-3 deficiency, homozygous protein C deficiency, homozygous protein S deficiency, and homozygous factor V Leiden.
6. Known bleeding disorder (eg, platelet function disorder, hemophilia, Von Willebrand disease, or coagulation factor deficiency).
7. Platelet count <50,000/µL.
8. History of heparin-induced thrombocytopenia.
9. Administration of procoagulant drugs (eg, non-study prothrombin complex concentrates (PCCs), recombinant Factor VIIa) or blood products (transfusion of whole blood, fresh frozen plasma, cryoglobulins, plasma fractions, or platelets) within 7 days before enrollment. (Note: administration of PRBCs for

hemoglobin correction,
tranexamic acid or aminocaproic acid are not exclusion criteria).
10. Planned use of procoagulant drugs (eg, Vitamin K, non-study PCCs, recombinant Factor VIIa) or blood products
(transfusion of whole blood, fresh frozen plasma, cryoglobulins, plasma fractions, or platelets) after enrollment but before the investigational product infusion is initiated (Note: administration of PRBCs for hemoglobin correction tranexamic
acid or aminocaproic acid are not exclusion criteria)
11. Administration of unfractionated heparin within 2 hours before randomization or low molecular weight heparin within 26hours before randomization.
12. Hypersensitivity to PCC constituents, or any excipient of TAK-330.
13. Patients with history of confirmed immunoglobulin A (IgA) deficiency with hypersensitivity reaction and antibodies to IgA.
14. Septic shock as defined by persistent hypotension requiring vasopressors to maintain mean arterial pressure (MAP) >= 65mmHg and having blood lactate > 2 mmol despite adequate volume resuscitation.
15. Acute or chronic liver failure (hepatic cirrhosis Child-PUGH score C).
16. Renal failure requiring dialysis.
17. Any other condition that could, in the opinion of the investigator, put the subject at undue risk of harm if the subject were to participate in the study.
18. Participation in another clinical study involving an investigational product or device within 30 days prior to study enrollment, or planned participation in another clinical study involving an investigational product or device during the course of this study.
19. The use of PROTHROMPLEX TOTAL as SOC 4F-PCC.
20. Women who are breastfeeding at the time of enrollment.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	30-11-2022
Enrollment:	35
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	PROTHROMPLEX TOTAL
Generic name:	Human Coagulation Factors II, VII, IX, and X

Ethics review

Approved WMO Date:	25-04-2022
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	25-07-2022
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	28-12-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	04-01-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	06-03-2023

Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	07-03-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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
EU-CTR	CTIS2022-503012-16-00
EudraCT	EUCTR2021-004138-12-NL
ClinicalTrials.gov	NCT05156983
CCMO	NL81011.056.22

Study results

Date completed: 11-04-2024

Summary results
Trial ended prematurely