ISRCTN13973041 https://doi.org/10.1186/ISRCTN13973041

Four-factor prothrombin complex concentrates outcomes in surgery and major bleed

Submission date 14/12/2023	**Recruitment status** No longer recruiting	[_] Prospectively registered [_] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [X] Record updated in last year
Registration date 29/01/2024	**Overall study status** Completed	
Last Edited 17/02/2026	**Condition category** Surgery	

Plain English summary of protocol

Background and study aims
In the event of surgery or a major bleed, where temporary interruption with blood-thinning medication can no longer be used, agents like 4F-PCC can reverse the effects of the blood-thinning medications. Medications such as PROTHROMPLEX TOTAL and 4F-PCC are medications which are generally used to quickly reverse the effects of a blood-thinning medicine during a major bleed, or when there is a need for surgery. The aim of this study is to fill the knowledge gaps of PROTHROMPLEX TOTAL and 4F-PCC treatments in patients presenting for surgery or a major bleed.

Who can participate?
Patients aged 18 years and over who had a surgery or a bleeding episode and were receiving a blood-thinning medication and medications such as PROTHROMPLEX TOTAL or another 4-factor prothrombin complex concentrate (4F-PCC) to reverse the effect of the blood-thinning medication.

What does the study involve?
This is a retrospective chart review study in which the healthcare team at the study site will review patient medical records and collect unidentifiable health information for inputting into a database.

What are the possible benefits and risks of participating?
As this is an observational study, participants will not experience additional risks. Participants will receive no direct individual benefit from participation in this study. The only potential benefit is a better understanding of the use of medications such as PROTHROMPLEX TOTAL or another 4-factor prothrombin complex concentrate (4F-PCC).

Where is the study run from?
Takeda Development Center Americas, Inc. (USA)

When is the study starting and how long is it expected to run for?
June 2022 to May 2026

Who is funding the study?
Takeda Development Center Americas, Inc. (USA)

Who is the main contact?
Angela Simon, Angela.simon@takeda.com

Contact information

Type(s)
Public, Principal investigator

Contact name
Dr Nidhi Guatam

Contact details
Watford General Hospital
60 Vicarage Road
Watford
United Kingdom
WD18 OHB
+44 (0)1923670029
nidhi.gautam@nhs.net

Type(s)
Scientific

Contact name
Ms Angela Simon

Contact details
Takeda Development Center Americas, Inc.
95 Hayden Avenue
Lexington
United States of America
02421
+1 (0)248 990 2390
Angela.simon@takeda.com

Additional identifiers

Integrated Research Application System (IRAS)
331744

Central Portfolio Management System (CPMS)
56352

Protocol serial number
TAK-330-5002

Study information

Scientific Title
A retrospective chart review study evaluating clinical practice, treatment patterns and outcomes of four-factor prothrombin complex concentrates (4F-PCC) in patients treated with Factor Xa (FXa) inhibitors prior to surgery or invasive procedure and those requiring on-demand reversal for a major bleed

Acronym
TAK-330

Study objectives
This study aims to fill knowledge gaps of four-factor prothrombin complex concentrates (4F-PCC) reversal interventions among patients presenting for surgery or a major bleed who are treated with a Factor Xa inhibitor.

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 11/11/2023, East Midlands - Leicester South Research Ethics Committee (2 Redman Place, Stratford, London, E20 1JQ, United Kingdom; +44 (0)207 104 8143; leicestersouth.rec@hra.nhs.uk), ref: 23/EM/0261

Primary study design
Observational

Study design
Retrospective non-interventional multinational multicenter hospital chart review study

Study type(s)
Other

Health condition(s) or problem(s) studied
Blood loss, surgical

Interventions
Data will be collected from the patient's medical records during the pre-treatment period (prior to receiving the first 4F-PCC dose) and post-treatment period (30-90 days after the first 4F-PCC dose). This data from the medical records will be collected based on the routine treatment that this patient is receiving, without any additional tests, procedures, or treatments.

Intervention Type
Other

Primary outcome(s)
Surgery indication:
1. Intra-operative hemostatic effectiveness will be regarded as effective or ineffective based on a review of intraoperative documentation
2. Post-operative hemostatic effectiveness within 24 hours after index 4F-PCC infusion will be

regarded as effective or ineffective based on a review of postoperative documentation. Absence of post-operative bleeding or oozing will be classified as effective hemostasis.

Bleeding indication:
Hemostatic effectiveness will be measured using the International Society on Thrombosis and Haemostasis (ISTH) criteria, Modified Sarode Criteria, Glasgow Coma Score or NIH Stroke Scale (NIHSS) score within 1 hour, 6 hours, and 24 hours of 4F-PCC infusion.

Change in clinical status over time will be measured using:
1. American College of Surgeons Advanced Trauma Life Support (ATLS) classification of blood loss based on the following signs and symptoms within 1, 6, and 24 hours of index 4F-PCC infusion
2. Clinical opinion based on progress notes for evidence of a change in: a) clinical status and b) amount of bleeding within 1, 6, and 24 hours of index 4F-PCC infusion as worse, no-change (stable), better, or undocumented will be captured for every type of bleed and recurrence of bleeding at the same site as the initial bleed prior to discharge

All outcome measures are collected retrospectively from medical charts

Key secondary outcome(s)

As this is an exploratory study, there are no key secondary outcomes that are powered to address any predefined hypothesis. Secondary outcomes data is abstracted from patient chart data.

The secondary objectives are as follows:

Surgery indication:
1. Baseline characteristics, including FXa inhibitor type, dose, and time of last FXa inhibitor dose prior to procedure, anti-FXa level and assay type (calibrated) indication for anticoagulation, concurrent antiplatelet, anticoagulant, prothrombotic and fibrinolytic therapy, and comorbidities of patients who require 4F-PCC reversal therapy of FXa inhibitor anticoagulation during surgical/interventional procedures.
2. Clinical practice patterns, including procedure type, reversal agent administration characteristics (e.g., administration method [IV push, bolus, infusion], dose, concentration, time between reversal agent infusion and initiation of surgery, use of additional doses of reversal agents, and time of administration), use of other interventions for control of hemostasis, i.e., transfusions (e.g., PRBC, FFP transfusions), other pharmacological agents and invasive procedures, reinitiation of anticoagulant therapy within 30-days of index 4F-PCC infusion (type of anticoagulant, dose, time of re-initiation), and method used to monitor anticoagulant therapy (no monitoring, PT, TT, aPTT, anti-FXa assay, ecarin clotting time [ECT], thrombin generation assay [TGA]).

Bleeding indication:
1. Baseline characteristics, including FXa inhibitor type, dose, and time of last FXa inhibitor dose, Anti-FXa level prior to 4F-PCC infusion, indication for anticoagulation, concurrent antiplatelet, anticoagulant, prothrombotic and fibrinolytic therapy, Glasgow Comma Score, intracerebral hemorrhage (ICH) hematoma volume, and comorbidities of patients who require 4F-PCC reversal therapy of FXa inhibitor anticoagulation for acute major bleeds
2. Clinical practice patterns, including type and location of bleed, reversal agent administration characteristics (e.g., administration method [IV push, bolus, infusion] dose, concentration, use of additional doses of reversal agents, and time of administration), use of other interventions for control of hemostasis, i.e., transfusions, other pharmacological agents and invasive procedures,

re-initiation of anticoagulant therapy within 30 days of on-demand 4F-PCC treatment (type of anticoagulant, dose, time of re-initiation), method used to monitor anticoagulant therapy (no monitoring, PT, TT, aPTT, anti-FXa assay, ECT, TGA)

All outcome measures are collected retrospectively from medical charts

Completion date
29/05/2026

Eligibility

Key inclusion criteria
Surgery indication:
1. Patient was >18 years of age at the time of surgery/invasive procedure
2. Patient was on treatment with an oral FXa inhibitor (rivaroxaban, apixaban, edoxaban) at time of surgery/invasive procedure
3. Patient admitted for a high-bleeding risk surgery (e.g., intra-abdominal surgery [e.g., bowel or visceral organ resection]), intra-thoracic surgery (e.g., lung resection), major orthopedic surgery (e.g., hip/knee replacement], arterial revascularization (e.g., abdominal aortic aneurysm repair, vascular bypass), urologic surgery (e.g., prostatectomy, bladder tumor resection), any other surgery lasting ≥ 1 hour, or major invasive procedure with high bleeding risk (e.g., colonic polyp resection, biopsy of kidney or prostate)
4. Patient received Takeda PROTHROMPLEX TOTAL or other 4F-PCC (e.g., Beriplex/Kcentra, Octaplex, Cofact, Uman Complex, Kanokad, Kedcom) reversal infusion during surgery or an invasive procedure as their first reversal agent type to control intra-operative bleeding in patients admitted for surgery/invasive procedure

Major bleed indication:
1. Patient was >18 years of age at time of admission for an acute major bleed
2. Patient was on treatment with an oral FXa inhibitor (rivaroxaban, apixaban, edoxaban) at the time of major bleed
3. Patient received a 4F-PCC reversal infusion (e.g., Beriplex/Kcentra, Octaplex, PROTHROMPLEX TOTAL, Cofact, Uman Complex, Kanokad, Kedcom) for a major bleed as their first on-demand reversal agent type
4. Acute major bleeding, defined as bleeding that is potentially life-threatening, that requires an emergent surgery or invasive procedure, or requires transfusion of ≥1 units of PRBCs or is associated with a decrease in Hg of >2.0 g/dL, or bleeding in a critical area or organ such as intraspinal, pericardial, or intracranial. Acute bleeding associated with a Hg level of ≤8 g/dL if no baseline Hg is available is also considered major.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
18 Years

Upper age limit
100 Years

Sex
All

Total final enrolment
0

Key exclusion criteria
Surgery indication:
Cohort 1: Real-world patients undergoing reversal with 4F-PCC
1. Patient presented with an acute bleed that required on-demand therapy with 4F-PCC
2. Patient underwent a low-bleeding risk surgery/invasive procedure (gastrointestinal endoscopy [with or without biopsy], cardiac catheterization [with or without percutaneous coronary intervention], permanent pacemaker or internal defibrillator insertion, dental surgery or other dental procedure, dermatologic surgery or other dermatologic procedure, cataract removal or other ophthalmologic procedure, any other surgery or procedure lasting < 1 hour)
3. Participation in a clinical study involving an investigational product or device within 30 days prior to or after initiation of 4F-PCC reversal

Bleeding indication:
Cohort 2: Real-world patients undergoing on-demand reversal with 4F-PCC for major bleeding
1. Patient with acquired/congenital hemostatic disorders, e.g., hemophilia A and B, platelet function disorder, fibrinogen deficiency, Von Willebrand disease, coagulation factor deficiency, acute or chronic liver failure (hepatic cirrhosis Child-PUGH score C (1)), confirmed or suspected sepsis
2. Patient with minor bleeding (e.g., epistaxis, hematuria)
3. Peri-operative reversal with 4F-PCC to control intra-operative bleeding in patients admitted for surgery/invasive procedure
4. Participation in a clinical study within 30 days post initiation of 4F-PCC on-demand reversal

Date of first enrolment
01/01/2024

Date of final enrolment
30/04/2026

Locations

Countries of recruitment
United Kingdom

England

Austria

Belgium

Germany

Greece

Netherlands

Poland

Spain

Study participating centre
West Hertfordshire Teaching Hospitals NHS Trust
Trust Offices
Watford General Hospital
Vicarage Road
Watford
England
WD18 0HB

Study participating centre
West Suffolk NHS Foundation Trust
West Suffolk Hospital
Hardwick Lane
Bury St. Edmunds
England
IP33 2QZ

Sponsor information

Organisation
Takeda (United States)

ROR
https://ror.org/03bygaq51

Funder(s)

Funder type
Not defined

Funder Name
Takeda Development Center Americas, Inc.

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Data sharing statement to be made available at a later date