Title Page

Protocol Title:
A Study to Compare the Efficacy and Safety of Apixaban to the Standard of Care (SOC) Dalteparin for the Treatment of Venous Thromboembolism in Patients with Cancer.

Protocol Number:

Amendment Number:

[Amendment Scope:

[Country/Region Identifier: International

Compound: Apixaban

Brief Title:
Treatment of cancer-associated venous thromboembolism

Study Phase: Phase 3 / Phase IIIB

[Acronym]: CARAVAGGIO

Sponsor Name:
FADOI / Bristol-Myers Squibb (BMS) / Pfizer

Legal Registered Address:

[Manufacturer]: CATALENT ANAGNI S.R.L.; Pfizer Manufacturing Deutschland GmbH; Swords Laboratories Unlimited Company T/A Bristol-Myers Squibb Pharmaceutical Operations, External Manufacturing; Pfizer Ireland Pharmaceuticals

Regulatory Agency Identifier Number(s):

Registry	ID

[Pediatric Investigational Plan Number]

Approval Date:

Sponsor Signatory:

[Name]	Date
[Title]	

Medical Monitor Name and Contact Information

1. Protocol Summary

1.1 Synopsis

Protocol Title:
A Study to Compare the Efficacy and Safety of Apixaban to the Standard of Care (SOC) Dalteparin for the Treatment of Venous Thromboembolism in Patients with Cancer.

Brief Title:
CARAVAGGIO study

Regulatory Agency Identifier Number(s):

Registry	ID

[Pediatric Investigational Plan Number]:

Objectives, Endpoints, and Estimands:
The trial will be designed to compare the efficacy and safety of apixaban with the standard of care (SOC), dalteparin (a low-molecular-weight heparin, LMWH), for the treatment of acute venous thromboembolism (VTE) in patients with cancer. The study will evaluate apixaban for non-inferiority to dalteparin for the primary outcome of recurrent VTE. Patients with active cancer can be at high risk of both venous thromboembolism and bleeding events, and those who develop VTE are at greater risk for recurrent VTE and early death. When apixaban is considered for DVT or PE treatment in cancer patients, a careful assessment of the benefits against the risks should be made, based on the patient's individual risk for thrombosis and major bleeding after full discussion of the potential benefits and harms. The rationale for this study is based on the hypothesis that apixaban may be an effective and safe option for the treatment of VTE in this population.

Objectives	Endpoints
Primary	
- To assess the non-inferiority of oral apixaban compared to subcutaneous low molecular weight heparin (LMWH) dalteparin for the treatment of newly diagnosed proximal deep vein thrombosis (DVT) and/or pulmonary embolism (PE) in patients with cancer.	-
Secondary	
- To compare the rates of the composite of major and clinically relevant non-major (CRNM) bleeding, and all bleeding events between the apixaban and dalteparin groups. - To assess the incidence of major bleeding (MB) and clinically relevant non-major bleeding (CRNMB). - To evaluate rates of major bleeding in patient subgroups. - To compare the incidence of the Major Venous Thromboembolism (VTE) endpoint, a composite of proximal deep vein thrombosis (DVT), non-fatal pulmonary embolism (PE), and VTE-related death, between apixaban and dalteparin. - To evaluate the efficacy of apixaban versus dalteparin in patient subgroups defined by cancer type and whether the VTE was incidental versus symptomatic. - To evaluate the individual components of the primary efficacy outcome. - To evaluate symptomatic recurrence of VTE. - To evaluate all-cause death. - To evaluate the composite of the primary efficacy outcome plus major bleeding. - To evaluate the composite of the primary efficacy outcome plus all-cause death. - To evaluate the composite of the primary efficacy outcome plus major bleeding plus all-cause death. - To evaluate any major cardiovascular event, fatal or non-fatal, including acute myocardial infarction or ischemic stroke. - To evaluate all venous thromboembolic events, including splanchnic vein thrombosis and cerebral vein thrombosis. - To evaluate permanent early discontinuation of the study drug due to safety reasons. - To assess Quality of Life (QoL) according to the Anti-Clot Treatment Scale (ACTS).	-

Objectives	Endpoints
- To conduct analyses and report on patient subgroups defined by cancer type, cancer treatment, and incidental versus symptomatic VTE.	

Overall Design Synopsis:
This will be an international, multicenter, Phase IIIB/Phase 3, pivotal, interventional clinical study. The design will incorporate a Prospective Randomized Open Blinded End-point (PROBE) approach, where patients and investigators will be aware of treatment assignments, but outcome adjudication will be blinded. The study will also be a pragmatic, open-label, non-inferiority, active-controlled, event-driven, randomized controlled trial. Masking will be applied to the assessor for outcome adjudication, but not to the participant or investigator.

Brief Summary:
The purpose of this study is to compare the efficacy and safety of apixaban with the standard of care (SOC), dalteparin, for the treatment of acute venous thromboembolism (VTE) in patients with cancer.

Study details will include:
- The study duration for each participant will be up to 7 months.
- The treatment duration will be 6 months.
- The visit frequency will include a follow-up visit scheduled at 7 months from randomization.
- Health measurements will include efficacy (recurrent VTE), safety (major bleeding, clinically relevant non-major bleeding, all bleeding), and Quality of Life (QoL).
- The participant population will include patients with cancer-associated VTE, including symptomatic or incidentally diagnosed acute proximal deep vein thrombosis (DVT) or pulmonary embolism (PE). Patients with basal cell or squamous cell skin cancers, primary or metastatic cerebral cancers, known brain metastases, and acute leukaemia will be excluded. Caution with direct factor Xa inhibitors will be warranted in GI and genitourinary malignancies and other settings with high risk for mucosal bleeding.

Number of Participants:
A total of 1,170 patients with cancer and symptomatic or incidental acute proximal deep vein thrombosis (DVT) or pulmonary embolism (PE) will be enrolled in the study.

Study Arms and Duration:
- **Arm 1 (Apixaban):** Patients will receive oral apixaban 10 mg twice daily (bid) for the first 7 days, followed by a maintenance dose of 5 mg bid for six months.
- **Arm 2 (Dalteparin):** Patients will receive subcutaneous (SC) dalteparin 200 IU/kg once daily for the first month, followed by a maintenance dose of 150 IU/kg o.i.d. for the subsequent five months.
The total treatment duration for each participant will be 6 months.

Data Monitoring/Other Committee: [Yes/No]

1.2 Schema

1.3 Schedule of Activities (SoA)

Procedure	Screening (up to specified days before Day 1)	Intervention Period (6 Months)										E/D	Follow-up (Month 7 from randomization)	Notes
		–1	1	2	3	4	5	6	7	8				E/D = Early Discontinuation
Informed consent	X													
Inclusion and exclusion criteria	X													Recheck clinical status before randomization and/or first dose of investigational intervention.
Demography	X													
Full physical examination including height and weight	X											X	X	
Medical history (includes substance use and family history of premature CV disease)	X													

Procedure	Screening (up to specified days before Day 1)	Intervention Period (6 Months)										E/D	Follow-up (Month 7 from randomization)	Notes
		–1	1	2	3	4	5	6	7	8				E/D = Early Discontinuation
Current medical conditions	X													
Pregnancy test (CBP participants only)	X													Refer to Section 8.3.5 Pregnancy Testing for instruction on timepoints.
HIV, Hepatitis B and C screening														
Laboratory tests (include liver chemistries)	X													Includes Hemoglobin, platelet count, creatinine clearance, liver function tests. Repeat testing for clinically significant abnormal values until normalization.
12-lead ECG	X													

Procedure	Screening (up to specified days before Day 1)	Intervention Period (6 Months)										E/D	Follow-up (Month 7 from randomization)	Notes
		–1	1	2	3	4	5	6	7	8				E/D = Early Discontinuation
Vital signs	X		X								X	X	Performed at each visit.	
Randomization (if applicable)		X												
Genetic sample	X													Optional participation with separate consent.
Study intervention			X	X	X	X	X	X	X	X	X	X			Administered for 6 months. Apixaban: 10 mg BID for first 7 days, then 5 mg BID. Dalteparin: 200 IU/kg daily for first month, then 150 IU/kg daily.
AE review			X								X	X	X	X	Monitored continuously from intervention start until the follow-up visit.

Procedure	Screening (up to specified days before Day 1)	Intervention Period (6 Months)										E/D	Follow-up (Month 7 from randomization)	Notes
		–1	1	2	3	4	5	6	7	8				E/D = Early Discontinuation
Solicited administration-site events (if applicable)														
Unsolicited AEs (if applicable)			X								X	X	X	Monitored continuously from intervention start until the follow-up visit.
SAE review			X								X	X	X	Monitored continuously from intervention start until the follow-up visit.
Device deficiencies (if applicable)			X	X	X	X	X	X	X	X	X	X		Monitored throughout the 6-month intervention period for dalteparin pre-filled syringes.
Concomitant medication review	X		X								X	X	X	Reviewed at screening and all subsequent visits.

Procedure	Screening (up to specified days before Day 1)	Intervention Period (6 Months)											E/D	Follow-up (Month 7 from randomization)	Notes
		–1	1	2	3	4	5	6	7	8					E/D = Early Discontinuation
Study-specific assessments (e.g., PK, efficacy)											X	X	X	X	Efficacy events (VTE, death) monitored throughout the 6-month intervention period. Final efficacy assessment at Month 6.
PRO assessments	X											X	X	X	Quality of Life (ACTS) assessed. Schedule not specified.

2. Introduction

Apixaban is a potent, oral, reversible, direct, and highly selective active site inhibitor of factor Xa. Its antithrombotic activity does not require antithrombin III. Apixaban inhibits free and clot-bound factor Xa, and prothrombinase activity. Apixaban has no direct effects on platelet aggregation, but indirectly inhibits platelet aggregation induced by thrombin. Through the inhibition of factor Xa, apixaban prevents thrombin generation and subsequent thrombus development. This study will compare apixaban, a direct oral anticoagulant (DOAC), with dalteparin, a low-molecular-weight heparin (LMWH), for the treatment of acute venous thromboembolism in patients with cancer. The risk of bleeding associated with DOACs appears to vary with cancer type and the type of DOAC; a threefold to fourfold higher risk is reported for patients with GI cancers.

2.1 Study Rationale

The trial will be designed to compare the efficacy and safety of apixaban with the standard of care (SOC), dalteparin (a low-molecular-weight heparin, LMWH), for the treatment of acute venous thromboembolism (VTE) in patients with cancer. The study will evaluate apixaban for non-inferiority to dalteparin for the primary outcome of recurrent VTE. The rationale for this study is based on the hypothesis that apixaban will demonstrate a favorable balance between desirable and undesirable effects for the treatment of VTE in patients with cancer, in the context of current evidence and cost-effectiveness considerations.

2.2 Background

The study will enroll patients with cancer-associated venous thromboembolism (VTE). Approximately 5% to 20% of patients with cancer develop a VTE, and approximately 20% of all VTE cases occur in patients with cancer. Patients with active cancer can be at high risk of both venous thromboembolism and bleeding events. Sites of cancer with the highest rates of VTE include the pancreas, kidney, ovary, lung, and stomach. When apixaban is considered for DVT or PE treatment in cancer patients, a careful assessment of the benefits against the risks should be made. It should be noted that patients with basal cell or squamous cell skin cancers, primary or metastatic cerebral cancers, known brain metastases, and acute leukaemia will be excluded from this study.

Apixaban is a potent, oral, reversible, direct, and highly selective active site inhibitor of factor Xa. Its antithrombotic activity does not require antithrombin III. Apixaban functions by inhibiting both free and clot-bound factor Xa, as well as prothrombinase activity. Through the inhibition of factor Xa, apixaban prevents thrombin generation and subsequent thrombus development.

Previous clinical trials have evaluated apixaban against dalteparin for the treatment of VTE in patients with cancer. The direct factor Xa inhibitors apixaban, edoxaban, and rivaroxaban are the only DOACs that were evaluated for the short-term treatment of VTE for patients with cancer, and different DOACs have different drug-drug interactions.

2.3 Benefit/Risk Assessment

2.3.1 Risk Assessment

The main safety endpoint for this trial will be major bleeding. Common adverse reactions expected with these agents include haemorrhage, contusion, epistaxis, and haematoma. Safety endpoints will include major bleeding, a composite of major and clinically relevant non-major (CRNM) bleeding, and all bleeding events. As with other anticoagulants, patients taking apixaban will be carefully observed for signs of bleeding. Caution with direct factor Xa inhibitors will be warranted in GI and genitourinary malignancies and other settings with high risk for mucosal bleeding, as a threefold to fourfold higher risk of bleeding is reported for patients with GI cancers. This study will assess the incidence of bleeding in both treatment groups, including analyses by cancer localization, with a focus on patients with gastrointestinal (GI) and genitourinary (GU) cancer.

2.3.2 Benefit Assessment

This study will assess whether apixaban is non-inferior to dalteparin for the treatment of cancer-associated VTE. The primary efficacy outcome will be the incidence of recurrent VTE at 6 months. The study will also evaluate rates of recurrent VTE in subgroups of patients based on cancer type, such as gynecological cancer, GI cancer, genitourinary cancer, and lung cancer.

2.3.3 Overall Benefit Risk Conclusion

This study is designed to test the hypothesis that apixaban has a favorable benefit-risk profile, demonstrating non-inferiority for VTE recurrence with a similar risk of major bleeding compared to LMWH (dalteparin). The study aims to provide high-quality evidence to support apixaban as a treatment option for VTE in patients with cancer. The choice of treatment must be based on the specific clinical setting to minimize risk, after careful consideration of potential drug-drug interactions, bleeding risk, patient preference, and the availability of treatment options, including cost considerations.

3. Objectives, Endpoints, and Estimands

Objectives	Endpoints
Primary	
- To assess the non-inferiority of oral apixaban compared to subcutaneous low molecular weight heparin (LMWH) dalteparin for the treatment of newly diagnosed proximal deep vein thrombosis (DVT) and/or pulmonary embolism (PE) in patients with cancer.	- **Efficacy:** Incidence of objectively confirmed recurrent Venous Thromboembolism (VTE) at 6 months, a composite of: Proximal Deep Vein Thrombosis (DVT) of the lower limbs, Symptomatic DVT of the upper limb, Pulmonary Embolism (PE). - **Safety:** Incidence of major bleeding at 6 months, as defined by the International Society on Thrombosis and Haemostasis (ISTH) guidelines.
Secondary	
- To compare the rates of the composite of major and clinically relevant non-major (CRNM) bleeding, and all bleeding events between the apixaban and dalteparin groups. - To assess the incidence of major bleeding (MB) and clinically relevant non-major bleeding (CRNMB). - To evaluate rates of major bleeding in patient subgroups. - To compare the incidence of the Major Venous Thromboembolism (VTE) endpoint. - To evaluate the individual components of the primary efficacy outcome. - To evaluate symptomatic recurrence of VTE. - To evaluate all-cause death. - To evaluate the composite of the primary efficacy outcome plus major bleeding. - To evaluate any major cardiovascular event. - To assess Quality of Life (QoL).	- Composite of major bleeding and clinically relevant non-major bleeding (CRNMB). - All bleeding events. - Incidence of major bleeding (MB). - Incidence of CRNMB. - Major Venous Thromboembolism (VTE) endpoint, a composite of proximal DVT, non-fatal PE, and VTE-related death. - Individual components of the primary efficacy outcome. - Symptomatic recurrence of VTE. - All-cause death. - Composite of primary efficacy outcome plus major bleeding. - Any major cardiovascular event, fatal or non-fatal. - Quality of Life (QoL) assessed according to the Anti-Clot Treatment Scale (ACTS).
[Tertiary/Exploratory/Other]	

Objectives	Endpoints
- To conduct a sub-analysis to assess the incidence of bleeding events according to cancer site.	- Incidence of bleeding events (Major Bleeding and CRNMB) according to the primary cancer site (Gastrointestinal, Genitourinary, Lung, Breast, Gynecological, Hematological).

3.1 Estimand(s) for Primary Objective(s)

- **Population:** Patients with cancer and symptomatic or incidentally diagnosed acute proximal deep vein thrombosis (DVT) or pulmonary embolism (PE). Patients with basal cell or squamous cell skin cancers, primary or metastatic cerebral cancers, known brain metastases, and acute leukaemia will be excluded. Careful consideration will be required for patients with GI malignancies due to a higher risk of bleeding and for patients with severe renal impairment (creatinine clearance <30 mL/min) for whom DOACs are generally not recommended [1, 2].
- **Variable (or Endpoint):** The primary efficacy endpoint will be the time to first event of the composite of recurrent VTE over 6 months. The primary safety endpoint will be the incidence of major bleeding over 6 months.
- **Treatment Condition:** Apixaban versus dalteparin over a 6-month treatment period.
- **Intercurrent Events:** Not specified.
- **Population-Level Summary:** The primary outcome analysis will be based on time-to-event data, for which a 95% Confidence Interval (CI) for the hazard ratio will be calculated.
- **Rationale:** The trial will be designed to test for non-inferiority. The non-inferiority design is based on the hypothesis that apixaban will provide a favorable balance between benefits and harms.

Supplementary Estimand(s)

3.2 Estimands for Secondary Objective(s)

Secondary estimand(s) for Secondary Objective

- **Secondary Safety Outcomes:** Clinically Relevant Non-Major Bleeding (CRNMB); Composite of major bleeding and CRNMB; Permanent early discontinuation of the study drug due to safety reasons.

- **Secondary Efficacy Outcomes:** The individual components of the primary efficacy outcome; Symptomatic recurrence of VTE; All-cause death; The composite of the primary efficacy outcome plus major bleeding; Any major cardiovascular event; All venous thromboembolic events.

- **Time-to-Event Measurements:** The primary outcome of recurrent VTE will be assessed over the 6-month trial period.
- **Quality of Life (QoL):** QoL will be assessed according to the Anti-Clot Treatment Scale (ACTS).
- **Subgroup Analyses:** Analyses will be conducted on patient subgroups defined by cancer type, cancer treatment, and whether the initial VTE was incidental versus symptomatic. These analyses will explore if patients with incidental VTE have a different risk profile for recurrence and major bleeding compared to patients with symptomatic VTE.

Supplementary Estimand(s)

3.3 Estimands for [Tertiary/Exploratory/Other] Objectives

[Tertiary/Exploratory/Other] Estimand(s)
- **Correlation Analyses:** A sub-analysis will be performed to assess the incidence of bleeding events (Major Bleeding and CRNMB) according to the primary cancer site. This analysis will include patients with the following cancer types: Gastrointestinal, Genitourinary, Lung, Breast, Gynecological, and Hematological cancer. This analysis will assess whether the incidence of bleeding is higher in certain cancer types, such as gastrointestinal (GI) and genitourinary (GU) cancer. A further sub-analysis will assess if rates of recurrent VTE vary by cancer type.

Supplementary Estimand(s)

4. Study Design

4.1 Overall Design

This will be an international, multicenter, Phase IIIB/Phase 3, pivotal, interventional clinical study involving approximately 1,170 patients. The study will employ a Prospective Randomized Open Blinded End-point (PROBE) design, where patients and investigators will be aware of treatment assignments, but outcome adjudication will be performed in a blinded manner. It will be characterized as a pragmatic, open-label, non-inferiority, active-controlled, event-driven, randomized controlled trial.

The study will consist of a 6-month treatment period and will include both randomised and preference cohorts. Patients will be randomly assigned to receive either apixaban or a low-molecular-weight heparin (LMWH), dalteparin. The LMWH arm will include the potential for a transition to warfarin. The treatment duration for both arms will be 6 months.

4.2 Scientific Rationale for Study Design

The trial will be designed to compare the efficacy and safety of apixaban with the standard of care (SOC), dalteparin (a low-molecular-weight heparin, LMWH), for the treatment of acute venous thromboembolism (VTE) in patients with cancer. The primary objective will be to assess the non-inferiority of oral apixaban compared to subcutaneous dalteparin for treating newly diagnosed proximal deep vein thrombosis (DVT) and/or pulmonary embolism (PE) in this patient population. The study is designed to test if apixaban meets pre-specified non-inferiority criteria.

Apixaban is a potent, oral, reversible, direct, and highly selective active site inhibitor of factor Xa, which does not require antithrombin III for its antithrombotic activity. It inhibits both free and clot-bound factor Xa, as well as prothrombinase activity. While apixaban has no direct effects on platelet aggregation, it indirectly inhibits thrombin-induced platelet aggregation. By inhibiting factor Xa, apixaban is hypothesized to prevent thrombin generation and subsequent thrombus development.

The ASH guideline panel suggests a DOAC (apixaban, edoxaban, or rivaroxaban) over LMWH for the short-term treatment (3-6 months) of VTE for patients with active cancer (conditional recommendation, low certainty in the evidence of effects). The choice of treatment must be based on the specific clinical setting to minimize risk, after careful consideration of potential drug-drug interactions, bleeding risk, patient preference, and the availability of treatment options, including cost.

4.2.1 Patient Input into Design

This trial will include an option for patients to complete a voluntary ‘Study Participant Feedback Questionnaire’. The purpose will be to collect feedback on their clinical trial experience. Individual participant responses will be anonymous to the investigator and site staff. Coded, aggregated responses will be used by the sponsor to understand where improvements can be made in the clinical trial process. This questionnaire will not collect data about the participant’s disease, symptoms, treatment effect, or adverse events and will be analyzed and reported separately from the clinical study data.

4.3 Justification for Dose

Administration of the investigational product will be discontinued if a severe haemorrhage occurs, or prior to elective surgery or invasive procedures that carry a risk of bleeding.

- Apixaban should be discontinued at least 48 hours prior to elective surgery or invasive procedures with a moderate or high risk of bleeding, or where the risk of bleeding would be un-acceptable.
- Apixaban should be discontinued at least 24 hours prior to elective surgery or invasive

procedures with a low risk of bleeding, where any bleeding is expected to be minimal, non-critical, or easily controlled.
- If surgery or invasive procedures cannot be delayed, appropriate caution should be exercised, taking into consideration an increased risk of bleeding. This risk should be weighed against the urgency of the intervention. Apixaban should be restarted after the procedure as soon as the clinical situation allows and adequate haemostasis has been established.

The main safety endpoint and a potential dose-limiting toxicity for this trial will be major bleeding. The study will assess and compare the rates of major bleeding and clinically relevant non-major bleeding between the apixaban and dalteparin arms. A sub-analysis will evaluate if rates of major bleeding are higher in patients with certain cancer types, such as genitourinary and gastrointestinal (GI) cancers. DOACs should be used carefully for patients with GI cancers because of the higher risk of GI bleeding.

4.4 End-of-Study Definition

The end of the study will be defined as the date of the last visit of the last participant in the study.

A participant will be considered to have completed the study if they have completed the 6-month treatment period and the follow-up visit scheduled at 7 months from randomization. The primary endpoint will be assessed at the conclusion of the 6-month treatment period.

Long-term anticoagulation for secondary VTE prophylaxis should be considered for patients with active cancer. In the absence of contraindications, the benefits of long-term anticoagulation are considered to outweigh the harms. This can be discontinued when patients are no longer at high risk for recurrent VTEs or are entering the last weeks of life. The decision will depend on cancer type and stage, prognosis, risk of VTE and bleeding, comorbidities, costs, and patient preferences.

5. Study Population

The study will enroll a total of 1,170 patients with cancer and symptomatic or incidental acute proximal deep vein thrombosis (DVT) or pulmonary embolism (PE). The randomised cohort is planned to include approximately 671 patients.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, will not be permitted.

5.1 Inclusion Criteria

Participants will be eligible to be included in the study only if all of the following criteria apply:

Age

1. Participant must be greater than 18 years of age.

Type of Participant and Disease Characteristics

2. Must be a consecutive patient with a newly diagnosed, objectively confirmed:
    - Symptomatic or unsuspected proximal lower-limb DVT, or
    - Symptomatic PE, or
    - Unsuspected PE in a segmental or more proximal pulmonary artery.

3. Must have any type of cancer (excluding basal-cell or squamous-cell carcinoma of the skin, primary brain tumor, known intracerebral metastases, and acute leukemia) that meets at least one of the following criteria:
    - **Active Cancer:** Diagnosis of cancer within six months before study inclusion, or receiving treatment for cancer at the time of inclusion, or any treatment for cancer during the 6 months prior to randomization, or recurrent locally advanced or metastatic cancer. Active cancer will also be defined as meeting any of the following criteria: (1) nonsquamous cell or basal cell invasive cancer diagnosed within 6 months before enrollment, (2) cancer treated within the previous 6 months, (3) recurrent or metastatic cancer, or (4) active cancer during the study.
    - **History of Cancer:** Cancer diagnosed within 2 years before study inclusion.

Weight

No specific weight or BMI criteria were provided in the source document.

Sex and Contraceptive/Barrier Requirements

4. Both male and female participants will be eligible. Contraceptive requirements for women of childbearing potential are detailed in the exclusion criteria.

Informed Consent

5. Signed informed consent as described in Appendix 1 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

5.2 Exclusion Criteria

Participants will be excluded from the study if any of the following criteria apply:

Medical Conditions

1. ECOG Performance Status of III or IV.
2. Life expectancy of less than 6 months.
3. Active bleeding or a high risk of bleeding that contraindicates anticoagulant treatment, including active clinically significant bleeding.
4. Lesion or condition if considered a significant risk factor for major bleeding. This may include current or recent gastrointestinal ulceration, presence of malignant neoplasms at high risk of bleeding, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities.
5. Recent (within the last month) brain, spinal, or ophthalmic surgery.
6. Bacterial endocarditis.
7. Uncontrolled hypertension (systolic BP > 180 mm Hg or diastolic BP > 100 mm Hg despite treatment).
8. Hypersensitivity to the study drugs or their excipients.
9. Any condition that, in the investigator's judgment, would place the subject at increased risk of harm.
10. Women of childbearing potential (WOCBP) not practicing a medically accepted, highly effective method of contraception during the trial and for one month beyond. Highly effective methods will include: combined hormonal contraception, progestogen-only hormonal contraception, intrauterine device (IUD), intrauterine hormone-releasing system (IUS), bilateral tubal occlusion, vasectomized partner, or sexual abstinence.
11. Pregnancy or breastfeeding.
12. Patients with a history of thrombosis who are diagnosed with antiphospholipid syndrome.
13. Patients with prosthetic heart valves.

Liver Safety

8. Acute hepatitis, chronic active hepatitis, liver cirrhosis, or an alanine aminotransferase level ≥3 times the upper limit of normal and/or a bilirubin level ≥2 times the upper limit of normal.
9. Hepatic disease associated with coagulopathy and clinically relevant bleeding risk.

Prior/Concomitant Therapy

9. Administration of therapeutic doses of LMWH, fondaparinux, or unfractionated heparin (UFH) for more than 72 hours before randomization.
10. Receipt of 3 or more doses of a vitamin K antagonist before randomization.

11. Use of thrombectomy, vena cava filter insertion, or thrombolysis to manage the index VTE episode.
12. An indication for anticoagulant treatment for a condition other than the index VTE.
13. Concomitant treatment with any other anticoagulant agent (e.g., UFH, LMWHs, fondaparinux, oral anticoagulants) except under specific circumstances of switching anticoagulant therapy.
14. Concomitant use of strong inhibitors or inducers of both cytochrome P-450 3A4 and P-Glycoprotein.
15. Concomitant thienopyridine therapy (clopidogrel, prasugrel, or ticagrelor), aspirin over 165 mg daily, or dual antiplatelet therapy.

Prior/Concurrent Clinical Study Experience

10. Participation in another pharmacotherapeutic program with an experimental therapy known to affect the coagulation system.

Diagnostic Assessments

11. Creatinine clearance < 30 ml/min based on the Cockcroft-Gault equation. Apixaban is not recommended in patients with creatinine clearance < 15 mL/min, or in patients undergoing dialysis.
12. Hemoglobin level lower than 8 g/dL (5.0 mmol/L) or a platelet count <75x10⁹/L.
13. History of heparin-induced thrombocytopenia.

Other Exclusion Criteria

12. Age less than 18 years.

5.3 Lifestyle Considerations

No specific lifestyle restrictions were provided in the source document.

5.3.1 Meals and Dietary Restrictions

No specific meal or dietary restrictions were provided in the source document.

5.3.2 Caffeine, Alcohol, and Tobacco

No specific restrictions on caffeine, alcohol, or tobacco were provided in the source document.

5.3.3 Activity

No specific activity restrictions were provided in the source document.

5.3.4 Other Restrictions

No other specific restrictions were provided in the source document.

5.4 Screen Failures

A screen failure will occur when a participant who has consented to participate in the clinical study is not subsequently assigned to study intervention. No information regarding rescreening was provided in the source document.

5.5 Criteria for Temporarily Delaying [Enrollment/ Randomization/Administration of Study Intervention]

No information was provided in the source document.

6. Study Intervention(s) and Concomitant Therapy

Study interventions will be all pre-specified, investigational and non-investigational medicinal products, medical devices and other interventions intended to be administered to the study participants during the study conduct.

Table 2. Study Arm(s)

Arm Title	Apixaban Arm	Dalteparin Arm
Arm Type	Experimental	Active Comparator
Arm Description	Patients will receive oral apixaban 10 mg twice daily (bid) for the first 7 days, followed by a maintenance dose of 5 mg bid for six months.	Patients will receive subcutaneous (SC) dalteparin injection at a dose of 200 IU/kg once daily (o.i.d) for the first month, followed by a maintenance dose of 150 IU/kg o.i.d. for the subsequent five months. The protocol may allow for a potential transition to warfarin within this group as per standard practice.
Associated Intervention Labels	Apixaban	Dalteparin

6.1.1 Rescue Medicine

No information was provided in the source document.

6.1.2 Medical Devices

No information was provided in the source document.

6.2 Preparation, Handling, Storage, and Accountability

Apixaban will not require any special storage conditions. Dalteparin should be stored below 30°C and must not be frozen. It will be compatible with isotonic sodium chloride (9 mg/ml) or isotonic glucose (50 mg/ml) infusion solutions in both glass bottles and plastic containers.

For patients who are unable to swallow whole tablets, Apixaban tablets may be crushed and suspended in water, 5% glucose in water (G5W), or apple juice, or mixed with apple puree and immediately administered orally. Crushed Apixaban tablets will be stable in these media for up to 4 hours. Alternatively, Apixaban tablets may be crushed, suspended in 60 mL of water or G5W, and immediately delivered through a nasogastric tube.

Further guidance and information for the final disposition of unused study interventions will be provided in the study reference manual.

6.3 Assignment to Study Intervention

Patients will be centrally and randomly assigned to receive either apixaban or dalteparin.

The protocol will include procedures for switching between treatments:
* **Switching from vitamin K antagonist (VKA) therapy to Apixaban:** When converting patients from VKA therapy to Apixaban, warfarin or other VKA therapy should be discontinued and Apixaban started when the international normalised ratio (INR) is < 2.
* **Switching from Apixaban to VKA therapy:** When converting patients from Apixaban to VKA therapy, administration of Apixaban should be continued for at least 2 days after beginning VKA therapy. After 2 days of coadministration, an INR should be obtained prior to the next scheduled dose of Apixaban. Coadministration should be continued until the INR is ≥ 2.

6.4 [Blinding, Masking]

This will be an open-label study using a Prospective Randomized Open Blinded End-point (PROBE) approach. Patients and investigators will be aware of treatment assignments. However, the outcome adjudication committee will be blinded to treatment allocation to minimize bias.

6.5 Study Intervention Compliance

No information was provided in the source document.

6.6 Dose Modification

- **Apixaban:** No dose adjustment will be necessary for patients with mild or moderate renal impairment. Apixaban will be used with caution in patients with severe renal impairment. For patients with cancer and severe renal impairment (creatinine clearance <30 mL/min), a VKA is generally preferred over LMWH and DOACs.
- **Dalteparin:** Dose modifications will be permitted according to the product label and investigator discretion, based on factors such as patient weight, renal function, and clinical events (bleeding or thrombosis). The dose can be adjusted by increments/decrements of 500 IU or 1,000 IU. Criteria for dose adjustments will include the occurrence of minor bleeding, prolonged access compression time (>10 minutes), or other clinical events.

6.7 Continued Access to Study Intervention after the End of the Study

Following the 6-month treatment period, long-term anticoagulation for secondary VTE prophylaxis should be considered for patients with active cancer. The decision to continue anticoagulation will depend on the type and stage of cancer, overall prognosis, periodic reevaluations of the risk of recurrent VTE and bleeding, comorbidities, costs, and patients' preferences.

6.8 Treatment of Overdose

For this study, any dose of apixaban that results in a higher risk of bleeding may be considered an overdose.

In the event of an overdose or haemorrhagic complications, the investigator should:
- Discontinue treatment and investigate the source of bleeding.
- Consider the initiation of appropriate treatment, such as surgical haemostasis, transfusion of fresh frozen plasma, or administration of a reversal agent for factor Xa inhibitors.
- A specific reversal agent (andexanet alfa) is available for adults. Administration of prothrombin complex concentrates (PCCs) or recombinant factor VIIa may also be considered [3, 4].
- Administration of activated charcoal may be useful in the management of apixaban overdose or accidental ingestion.
- Haemodialysis is unlikely to be an effective means of managing apixaban overdose.

6.9 Prior and Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with the reason for use, dates of administration, and dosage information.

The following restrictions will apply:
- Participants must abstain from taking prescription or nonprescription drugs (including vitamins and herbal supplements) within 7 days (or 14 days for potential enzyme inducers) or 5 half-lives (whichever is longer) before the start of study intervention, unless approved by the investigator and sponsor.
- Concomitant use with other anticoagulants will be contraindicated, except as specified in the protocol for treatment switching.
- Concomitant thienopyridine therapy (clopidogrel, prasugrel, or ticagrelor), aspirin over 165 mg daily, or dual antiplatelet therapy will be prohibited.
- Concomitant use of strong inducers of both CYP3A4 and P-gp (e.g., rifampicin, phenytoin, car-

bamazepine, phenobarbital, St. John's Wort) with apixaban will be prohibited as efficacy may be compromised.

Paracetamol/Acetaminophen at appropriate doses will be permitted. Care is to be taken if patients are treated concomitantly with SSRIs, SNRIs, or NSAIDs, as these may increase bleeding risk. The choice of anticoagulant must be based on the specific clinical setting after careful consideration of potential drug-drug interactions.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

Discontinuation of specific sites or of the study as a whole will be detailed in Appendix 1.

7.1 Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention. If study intervention is permanently discontinued, the participant should, if at all possible, remain in the study to be evaluated for study outcomes. See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

Administration of the investigational product will be discontinued if a severe haemorrhage occurs, or prior to elective surgery or invasive procedures that carry a risk of bleeding. Apixaban should be discontinued at least 48 hours prior to elective surgery or invasive procedures with a moderate or high risk of bleeding, and at least 24 hours prior for those with a low risk of bleeding. Apixaban should be restarted after the invasive procedure or surgical intervention as soon as possible provided the clinical situation allows and adequate haemostasis has been established. Permanent early discontinuation of the study drug due to safety reasons will be a secondary safety outcome.

7.1.1 Liver Event Stopping Criteria

Discontinuation of study intervention for abnormal liver tests will be required by the investigator when a participant meets one of the conditions outlined in the protocol-specified algorithm or in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules if the investigator believes that it is in best interest of the participant.

7.1.2 QTc Stopping Criteria

If a clinically significant finding is identified (including, but not limited to, changes from baseline in QT interval corrected using Bazett's formula [QTcB] or Fridericia's formula [QTcF]) after

enrollment, the investigator or qualified designee will determine if the participant can continue on the study intervention and if any change in participant management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

7.1.3 Temporary Discontinuation

Temporary cessation of the study drug may be required for certain bleeding events considered to have clinical consequences. Lapses in therapy should be avoided as discontinuing anticoagulants places patients at an increased risk of thrombosis. If anticoagulation with apixaban must be temporarily discontinued for any reason, therapy should be restarted as soon as possible.

7.1.4 Rechallenge

This section will describe the procedures for restarting the intervention after stopping criteria have been met.

7.1.4.1 Study Intervention Restart or Rechallenge After Liver Stopping Criteria Are Met

Study intervention restart or rechallenge after liver chemistry stopping criteria are met will be allowed in this study. If the participant meets liver chemistry stopping criteria, do not restart or rechallenge the participant with study intervention unless:

- Sponsor board approval **is granted**
- Ethics and/or IRB approval is obtained, if required, and
- Separate consent for intervention restart or rechallenge is signed by the participant

> *NOTE: If study intervention was interrupted for suspected intervention-induced liver injury, the participant should be informed of the risk of death, liver transplantation, hospitalization, and jaundice and reconsented before resumption of dosing.*

Refer to Appendix 6 Liver Safety: Suggestions and Guidelines for Liver Events for details on the restart or rechallenge process.

If sponsor board approval to restart or rechallenge the participant with study intervention is **not granted**, then the participant must permanently discontinue study intervention and may continue in the study for protocol-specified follow-up assessments.

7.2 Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at the participant's own request for any reason (or without providing any reason) without any negative consequences.

- A participant may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or compliance reasons.
- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- The participant will be permanently discontinued from the study intervention and the study at that time.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, the participant may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.3 Lost to Follow up

A participant will be considered lost to follow-up if the participant repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule, and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls, and if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, the participant will be considered to have withdrawn from the study.
- Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomized, including those who did not get study intervention. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

8. Study Assessments and Procedures

- Study procedures and their timing will be summarized in the SoA. Protocol waivers or exemptions will not be allowed.
- Adherence to the study design requirements, including those specified in the SoA, will be essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the timeframe defined in the SoA.
- In the event of a significant study-continuity issue (eg, caused by a pandemic), alternate strategies for participant visits, assessments, medication distribution and monitoring may be implemented by the sponsor or the investigator, as per local health authority/ethics requirements.
- Safety, laboratory, or analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.
- Planned timepoints for all assessments will be provided in the SoA.

8.1 Administrative [and General/Baseline] Procedures

At screening, baseline characteristics will be recorded, including hypertension, hyperlipidemia, diabetes, and coronary artery disease. Based on historical data from similar trials (e.g., ADVANCE-3), the expected prevalence of these comorbidities is approximately 46% for hypertension, 10% for hyperlipidemia, 9% for diabetes, and 8% for coronary artery disease.

For context, this trial will exclude patients with basal cell or squamous cell skin cancers, primary brain tumors, known brain metastases, or acute leukemia.

8.2 [Efficacy and/or Immunogenicity] Assessments

Efficacy will be assessed over the 6-month treatment period. Assessments will specifically monitor for recurrent VTE, major bleeding, clinically relevant non-major bleeding, and all-cause deaths.

The primary efficacy endpoint will be the incidence of objectively confirmed recurrent Venous Thromboembolism (VTE), which will be a composite endpoint comprising:
- Proximal Deep Vein Thrombosis (DVT) of the lower limbs (symptomatic or unsuspected).
- Symptomatic DVT of the upper limb.
- Pulmonary Embolism (PE) (symptomatic or unsuspected).

Secondary efficacy outcomes will include the individual components of the primary efficacy outcome, symptomatic recurrence of VTE, all-cause death, major cardiovascular events, and all venous thromboembolic events.

8.3 Safety Assessments

Safety endpoints will be monitored throughout the 6-month treatment period. The main safety endpoint and potential dose-limiting toxicity will be major bleeding. All bleeding criteria will include surgical site bleeding.

8.3.1 Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems. Height and weight will also be measured and recorded.
- A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.3.2 Vital Signs

- Oral, tympanic, rectal, axillary, skin, or temporal artery temperature, pulse rate, respiratory rate, and blood pressure will be recorded (before blood collection for laboratory tests).
- Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions.
- For blood pressure measurements, 3 consecutive blood pressure readings will be recorded at intervals of at least 1 minute. The average of the 3 blood pressure readings will be recorded.

8.3.3 Electrocardiograms

- Triplicate or single 12-lead ECG(s) will be obtained as outlined in the SoA using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Refer to Section 7.1.2 for QTc withdrawal criteria and any additional QTc readings that may be necessary.
- At each timepoint at which triplicate ECGs are required, 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart.

8.3.4 Clinical Safety Laboratory Tests

- See Appendix 2 for the list of clinical laboratory tests to be performed and the SoA (Section 1.3) for the timing and frequency.
- The investigator must review the laboratory results, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory results must be retained with source documents.
- Liver function testing will be performed prior to initiating apixaban.
- Treatment with apixaban will not require routine monitoring of drug exposure. However, a calibrated quantitative anti-Factor Xa assay may be useful in exceptional situations where knowledge of apixaban exposure may help to inform clinical decisions, e.g., overdose and emergency surgery [5, 6].
- All protocol-required laboratory tests, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.
- If laboratory values from non-protocol-specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator, then the results must be recorded.

8.3.5 Pregnancy Testing

Pregnancy will be an exclusion criterion. Women of childbearing potential (WOCBP) must practice a medically accepted, highly effective method of contraception during the trial and for one month beyond. Highly effective methods will include: combined hormonal contraception, progestogen-only hormonal contraception, intrauterine device (IUD), intrauterine hormone-releasing system (IUS), bilateral tubal occlusion, vasectomized partner, or sexual abstinence.

It is unknown whether apixaban or its metabolites are excreted in human milk. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from apixaban therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

8.3.6 Suicidal Ideation and Behavior Risk Monitoring

As apixaban is not considered a CNS-active intervention, specific monitoring for suicidal ideation and behavior (SIB) will not be mandated unless a participant's underlying condition presents an elevated risk. Should a participant experience signs of SIB, a risk assessment will be conducted. All factors contributing to SIB will be evaluated, and consideration will be given to discontinuation of the study intervention. Families and caregivers should be alerted to monitor participants for unusual changes in behavior and report such symptoms immediately to the study investigator.

8.4 Adverse Events (AEs) Serious Adverse Events (SAEs), and Other Safety Reporting

The definitions of adverse events (AEs) and serious adverse events (SAEs) can be found in Appendix 3. Adverse events will be monitored with a particular focus on bleeding and clotting events. Common adverse reactions expected will include haemorrhage, contusion, epistaxis, and haematoma. The use of apixaban may be associated with an increased risk of occult or overt bleeding from any tissue or organ, which may result in posthaemorrhagic anaemia. The investigator and any qualified designees will be responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE.

8.4.1 Time Period and Frequency for Collecting AE and SAE Information

All SAEs and AEs will be collected from the signing of the informed consent form (ICF) until the final follow-up visit at 7 months. The primary monitoring period will cover the 6-month treatment period. Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded as medical history, not as AEs. All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours.

8.4.2 Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant will be the preferred method to inquire about AE occurrences. Patients receiving apixaban will be carefully observed for any signs of bleeding. Specific signs and symptoms of bleeding to monitor for will include bruising or bleeding under the skin, tar-coloured stools, blood in urine, epistaxis, dizziness, tiredness, paleness, weakness, sudden severe headache, and coughing up or vomiting blood.

8.4.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator will be required to proactively follow each participant at subsequent visits/contacts. All SAEs and AEs of special interest (as defined in Section 8.4.8) will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

8.4.4 Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of an SAE will be essential so that legal obligations and ethical responsibilities towards the safety of participants are met.
- The sponsor will have a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation.
- An investigator who receives an investigator safety report describing an SAE will review and then file it and will notify the IRB/IEC, if appropriate according to local requirements.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and sponsor policy and forwarded to investigators within 15 days.

8.4.5 Pregnancy

- Details of all pregnancies in participants able to give birth will be collected after the start of study intervention and until the time period for post-intervention contraception has passed.
- If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the pregnancy.
- While pregnancy itself will not be considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) will be considered SAEs and will be reported as such.
- The investigator will collect follow-up information on the participant, the pregnancy outcome, and the neonate.

8.4.6 Cardiovascular and Death Events

Assessment of any major cardiovascular event (fatal or non-fatal, including acute myocardial infarction or ischemic stroke) and all-cause death will be secondary objectives of this study.

8.4.7 Disease-related Events and/or Disease-related Outcomes Not Qualifying as AEs or SAEs

Certain disease-related events (DREs) that are common in participants with the disease under study may not be reported according to the standard process for expedited reporting of SAEs, even if they meet the SAE definition. However, if the event is of greater intensity, frequency, or duration than expected for the individual, or if the investigator considers there is a reasonable possibility that the event was related to the study intervention, it must be reported as an AE/SAE.

8.4.8 Adverse Events of Special Interest

The primary safety outcome will be the incidence of major bleeding, as defined by the International Society on Thrombosis and Haemostasis (ISTH) guidelines. All bleeding criteria will include surgical site bleeding.

- **Major Bleeding:** An event will be characterized as acute, clinically overt bleeding associated with one or more of the following criteria:
  - A decrease in hemoglobin of 2 g/dL (1.2 mmol/L) or more.
  - The transfusion of two or more units of packed red blood cells.
  - Bleeding that occurs in at least one critical site (intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, or retroperitoneal).
  - Bleeding that is fatal.
  - Bleeding that necessitates acute surgical intervention.
- **Clinically Relevant Non-Major Bleeding (CRNMB):** An acute, clinically overt bleeding event that does not meet the criteria for major bleeding and consists of one of the following:
  - Any bleeding that compromises hemodynamics.
  - Spontaneous hematoma larger than 25 cm^2, or 100 cm^2 if traumatic.
  - Intramuscular hematoma documented by ultrasonography.
  - Epistaxis or gingival bleeding requiring intervention, or venipuncture bleeding lasting >5 minutes.
  - Macroscopic hematuria that is spontaneous or lasts >24 hours post-procedure.
  - Hemoptysis, hematemesis, or spontaneous rectal bleeding requiring intervention.
  - Any other bleeding event considered to have clinical consequences (requiring medical intervention, unscheduled contact, temporary drug cessation, or associated with pain/impairment).

This study will assess the incidence of major bleeding and CRNMB in both treatment arms, with a particular focus on whether the incidence is higher in patients with gastrointestinal (GI) and genitourinary (GU) cancer.

8.4.9 Medical Device Deficiencies

Medical devices will not be provided for use in this study. This section is not applicable.

8.4.9.1 Time Period for Detecting Medical Device Deficiencies

Not applicable.

8.4.9.2 Follow-up of Medical Device Deficiencies

Not applicable.

8.4.9.3 Prompt Reporting of Device Deficiencies to the Sponsor

Not applicable.

8.4.9.4 Regulatory Reporting Requirements for Device Deficiencies

Not applicable.

8.5 Pharmacokinetics

In patients with chronic renal insufficiency, the mean terminal half-life of anti-Factor Xa activity following a single intravenous dose of 5,000 IU dalteparin was 5.7 ± 2.0 hours, which is considerably longer than in healthy volunteers, suggesting greater accumulation can be expected.

8.6 Pharmacodynamics

While standard clotting tests will be affected as expected by the drug's mechanism of action, these changes will not be recommended for assessing its pharmacodynamic effects. Apixaban prolongs clotting tests such as prothrombin time (PT), INR, and activated partial thromboplastin time (aPTT), but these are subject to a high degree of variability and will not be recommended for routine assessment of the pharmacodynamic effect. The thrombin generation assay may be used to measure the reduction in endogenous thrombin potential.

8.7 Genetics

A blood or saliva sample for DNA isolation will be collected from participants who have consented to participate in the genetic analysis component of the study. Participation will be optional.

Participants who do not wish to participate in the genetic research may still participate in the main study. In the event of DNA extraction failure, a replacement genetic sample may be requested from the participant.

8.8 Biomarkers

Samples will be collected to achieve protocol-specific objectives. Details on sample types, collection schedules, and handling will be provided in the laboratory manual. With participant consent, samples may be stored for a specified number of years after the end of the study for further research to contribute to the understanding of the disease, related conditions, or the development of new treatments.

8.9 Immunogenicity Assessments

Antibodies to the study intervention will be evaluated in plasma/serum samples collected from all participants according to the SoA, including those who discontinue. Samples will be screened for binding antibodies, and the titer of confirmed positive samples will be reported. The detection and characterization of antibodies will be performed using a validated assay method.

8.10 [Health Economics OR Medical Resource Utilization and Health Economics]

For all participants throughout the study, the investigator and study site personnel will collect data about health care resource utilization associated with medical encounters. The data collected will include the reasons and duration of hospitalizations and emergency room visits, and will exclude procedures, tests, and encounters mandated by the protocol. Quality of Life (QoL) will be assessed according to the Anti-Clot Treatment Scale (ACTS).

9. Statistical Considerations

9.1 General Considerations

9.1.1 Decision Criteria/Statistical Hypotheses

The primary objective will be to assess the non-inferiority of oral apixaban compared to subcutaneous low molecular weight heparin (LMWH) dalteparin for the treatment of newly diagnosed proximal deep vein thrombosis (DVT) and/or pulmonary embolism (PE) in patients with cancer [7, 8]. The trial will be designed to test for non-inferiority, and the primary outcome analysis will

be based on time-to-event data. A 95% Confidence Interval (CI) for the hazard ratio will be calculated.

The null and alternative hypotheses will be formulated to support this non-inferiority objective. Nominal significance levels, confidence interval probabilities, and the use of 1- or 2-sided tests will be prespecified.

Previous studies provide context for this non-inferiority framework. For example, the AMPLIFY study for VTE treatment showed apixaban to be non-inferior to enoxaparin/warfarin ($p < 0.0001$). This study will be designed to test for a similar non-inferiority outcome in the specified cancer patient population.

Hypotheses for secondary objectives will also be defined, potentially including both non-inferiority and superiority testing frameworks. The rationale for the non-inferiority margin and its operational evaluation will be detailed.

9.1.2 Multiplicity Adjustment

To control the overall type I error in the trial, a closed testing procedure will be implemented to manage the family-wise error rate [9, 10]. Key secondary endpoints, such as major bleeding and all-cause death, may be tested using a pre-specified hierarchical testing strategy. This fixed sequence testing procedure will ensure that subsequent hypotheses are tested only if the preceding ones are statistically significant at their prespecified levels. The step-by-step hierarchical testing procedures and strategies for Type I error control will be fully defined.

9.1.3 Impact of Intercurrent Events Strategies

Strategies for handling intercurrent events will be defined for the analysis to ensure a robust interpretation of the results.

9.1.4 Handling of Missing Data

Procedures and statistical methods for managing and imputing missing data will be prespecified to minimize bias in the analyses.

9.2 Analysis Sets

For the purposes of analysis, the following analysis sets will be defined:
- **Full Analysis Set (FAS):** All randomized participants.
- **Safety Analysis Set (SAS):** All participants who are exposed to the investigational intervention.

The study will include both randomised and preference cohorts. The randomized cohort will include approximately 671 patients with cancer and either symptomatic or incidentally diagnosed VTE. Efficacy analyses will be conducted on the FAS, with participants analyzed according to their planned investigational intervention. Safety analyses will be conducted on the SAS, with participants analyzed according to the investigational intervention they actually received.

Specific exclusion criteria will be applied to the analysis cohort. Patients with primary or metastatic cerebral cancers and those with acute leukaemia will be excluded. Following the precedent of similar trials, patients with basal cell or squamous cell skin cancers, primary brain tumors, or known brain metastases will also be excluded. Furthermore, patients with lesions or conditions considered a significant risk factor for major bleeding, such as recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, or recent intracranial haemorrhage, will be excluded.

9.3 Analyses Supporting Primary Objective(s)

9.3.1 Primary Endpoint(s)/Estimand(s)

9.3.1.1 Definition of endpoint(s)

Primary Efficacy Endpoint:
The primary efficacy outcome will be the incidence of the first event of the composite of objectively confirmed recurrent Venous Thromboembolism (VTE) or VTE-related death occurring during the study period. This composite endpoint will include:
- Proximal Deep Vein Thrombosis (DVT) of the lower limbs (symptomatic or unsuspected).
- Symptomatic DVT of the upper limb.
- Pulmonary Embolism (PE) (symptomatic or unsuspected).
- VTE-related death.

Primary Safety Endpoint:
The primary safety outcome will be the incidence of major bleeding, as defined by the International Society on Thrombosis and Haemostasis (ISTH) guidelines. A major bleeding event will be an acute, clinically overt bleeding event associated with one or more of the following:
- A decrease in hemoglobin of 2 g/dL (1.2 mmol/L) or more.
- Transfusion of two or more units of packed red blood cells.
- Bleeding that occurs in a critical site (intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, or retroperitoneal).
- Bleeding that is fatal.
- Bleeding that necessitates acute surgical intervention.

9.3.1.2 Main Analytical Approach

The trial will be designed to test for non-inferiority. The primary statistical analysis for the efficacy endpoint, which is the time to the first event of the composite of recurrent VTE, will be a time-to-event analysis. A 95% Confidence Interval (CI) for the hazard ratio will be calculated to assess non-inferiority. This approach is supported by findings from similar trials in related indications.

9.3.1.3 Sensitivity Analyses

Sensitivity analyses will be conducted to assess the robustness of the primary endpoint results under different assumptions and analytical approaches.

9.3.1.4 Supplementary Analyses

Additional supplementary analyses may be performed to further support the primary objectives.

9.4 Analyses Supporting Secondary Objective(s)

9.4.1 Analyses Supporting Secondary Objective [label]

Statistical analyses will be performed for all secondary endpoints.

Secondary Safety Outcomes:
- **Clinically Relevant Non-Major Bleeding (CRNMB):** An acute, clinically overt bleeding event not meeting major bleeding criteria but requiring medical intervention, an unscheduled physician contact, temporary cessation of the study drug, or associated with pain or impairment of daily activities. Specific examples will include spontaneous large hematomas, significant epistaxis, macroscopic hematuria, or gastrointestinal bleeding requiring endoscopy.
- **Composite Safety Outcomes:**
- The composite of major bleeding and CRNMB.
- Permanent early discontinuation of the study drug due to safety reasons.

Secondary Efficacy Outcomes:
- The individual components of the primary efficacy outcome.
- Symptomatic recurrence of VTE.
- All-cause death.
- The composite of the primary efficacy outcome plus major bleeding.
- The composite of the primary efficacy outcome plus all-cause death.
- The composite of the primary efficacy outcome plus major bleeding plus all-cause death.
- Any major cardiovascular event, fatal or non-fatal (including acute myocardial infarction or ischemic stroke).
- All venous thromboembolic events (including splanchnic and cerebral vein thrombosis).
- Major VTE endpoint (composite of proximal DVT, non-fatal PE, and VTE-related death).

Quality of Life (QoL):
- QoL will be assessed using the Anti-Clot Treatment Scale (ACTS).

Subgroup Analyses:
- Analyses will be conducted on patient subgroups defined by cancer type, cancer treatment, and whether the initial VTE was incidental versus symptomatic.

9.5 Analyses Supporting Tertiary/Exploratory/Other Objective(s)

Exploratory analyses will be conducted to further investigate treatment effects. A sub-analysis will assess the incidence of bleeding events (Major Bleeding and CRNMB) according to cancer site, including gastrointestinal, genitourinary, lung, breast, gynaecological, and haematological cancers. This analysis will explore whether the incidence of bleeding is highest in patients with certain cancer types, such as gastrointestinal and genitourinary cancer, particularly if the cancer is not resected. It will also assess if rates of recurrent VTE are highest in specific cancer sub-groups.

Additionally, analyses will be conducted combining patients across treatment arms to identify patient characteristics associated with a higher overall risk of VTE recurrence or major bleeding, recognizing that patients with active cancer are at high risk for both.

9.6 Other Safety Analyses

A comprehensive safety analysis will be performed, comparing rates of bleeding events between the apixaban and dalteparin arms. The main safety endpoint and potential dose-limiting toxicity for this trial will be major bleeding. Safety endpoints monitored throughout the study will include major bleeding, the composite of major and clinically relevant non-major (CRNM) bleeding, and all bleeding events. Common adverse reactions expected will include anaemia, thrombocyt-openia, haemorrhage, contusion, epistaxis, haematoma, and nausea.

Context from previous studies, such as the AMPLIFY VTE treatment study, will inform the safety assessment. In that study, major bleeding occurred in 0.6% of apixaban patients versus 1.8% of enoxaparin/warfarin patients, and the composite of major and CRNM bleeding occurred in 4.3% versus 9.7%, respectively.

9.7 Other Analyses

9.7.1 Other variables and/or parameters

Additional parameters will be analyzed as specified.

9.7.2 Subgroup analyses

Predefined subgroup analyses will be conducted to evaluate the consistency of treatment effects. These will include evaluating rates of major bleeding and the efficacy of apixaban versus dalteparin in patient subgroups defined by cancer type, cancer treatment, and whether the VTE was incidental versus symptomatic.

These analyses will explore whether safety and efficacy are consistent across subgroups and will assess if patients with incidental VTE have a different risk profile for recurrence and major bleeding compared to patients with symptomatic VTE.

Previous large-scale studies have shown the efficacy of apixaban to be generally consistent across subgroups, including age, gender, body mass index (BMI), and renal function. This study will further explore these relationships within the cancer patient population.

9.8 Interim Analyses

An independent Data Monitoring Committee (IDMC) will be established to evaluate interim data. The timing of interim analyses will be based on event-based triggers. The analyses will be conducted using a group sequential design with an alpha spending approach to maintain the overall type I error rate. Conditional power calculations may be performed to assess the probability of study success, and the study may be stopped for futility if this power is low. All procedures will be conducted in a manner that maintains the integrity of the study, with strict blinding protocols for all personnel involved in the interim analysis.

9.9 Sample Size Determination

A total of approximately 1,155 to 1,170 patients will be enrolled in the study. The randomised cohort is planned to include approximately 671 patients. The sample size calculation will be based on the primary efficacy estimand and will provide sufficient statistical power to test the primary hypothesis at a prespecified type-1 error level, using a normal approximation method for a 2-sided test. Assumptions for the calculation, including those related to intercurrent events and expected event rates informed by previous large-scale trials, will be detailed.

For context, similar large-scale trials such as the AMPLIFY study randomized 5,395 patients.

Supporting Documentation and Operational Considerations

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines.
- Applicable ICH Good Clinical Practice (GCP) guidelines.
- Applicable laws and regulations.
- The protocol, protocol amendments, ICF, investigator's brochure, and other relevant documents must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before implementation.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following, as applicable:
- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies conducted in the EU, European Medical Device Regulation 2017/745 for clinical device research, and all other applicable local regulations.

10.1.2 Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators will be responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3 Informed Consent Process

- The investigator or the investigator's representative will explain the nature of the study, including the risks and benefits, to the potential participant or their legally authorized representative and answer all questions regarding the study.
- Potential participants must be informed that their participation is voluntary. They or their legally authorized representatives will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, and privacy and data protection requirements, where applicable.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be reconsented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or their legally authorized representative.
- Specific consent procedures may be required for rescreening, optional exploratory research, and for participants who become pregnant. For complex studies, a 2-step consent process may be utilized.

10.1.4 Recruitment strategy

The study-specific recruitment approach and tools used will be detailed in relevant study documents.

10.1.5 Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that their personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be

explained to the participant who will be required to give consent for their data to be used as described in the informed consent.

- The participant must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The contract between the sponsor and study sites will specify the responsibilities of the parties related to data protection, including the handling of data security breaches and the respective communication and cooperation of the parties.

10.1.6 Committees Structure

An Independent Data Monitoring Committee (IDMC) will be established to oversee the safety of the participants and the integrity of the study data. The IDMC will be composed of independent members with relevant expertise. The committee will operate under a charter that defines its responsibilities, which will include periodic review of accumulating data. The IDMC may recommend modifications to the protocol or early termination of the study, as was the case in the AVERROES study, which was stopped early due to clear evidence of benefit with an acceptable safety profile. An Early Safety Data Review Committee may also be implemented for safety signal detection, with predefined stopping rules based on events such as deaths or specific SAEs.

10.1.7 Dissemination of Clinical Study Data

Study participants will be provided the option of receiving their individual study data. Management of dissemination and the process for providing this option will be in accordance with sponsor policies, laws, and regulations.

10.1.8 Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRFs unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator will be responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source documents.
- Quality tolerance limits (QTLs) will be predefined to identify systematic issues that can impact participant safety and/or reliability of study results.
- Monitoring details describing the strategy (eg, risk-based initiatives such as central, remote, or on-site monitoring), methods, responsibilities, and requirements will be provided in the monitoring plan and/or contracts.

- The sponsor or designee will be responsible for the data management of this study, including quality checking of the data.
- The sponsor will assume accountability for actions delegated to other individuals (eg, contract research organizations).
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for a specified period after study completion as per local regulations or institutional policies.

10.1.9 Source Documents

- Source documents will provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents will be filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The sponsor or designee will perform monitoring to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.10 Study and Site Start and Closure

10.1.10.1 First Act of Recruitment

The study start date will be the date on which the clinical study will be open for recruitment of participants. The first act of recruitment will be defined in the protocol.

10.1.10.2 Study/Site Termination

The sponsor or designee reserves the right to close the study site or terminate the study at any time. Study sites will be closed upon study completion. The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given. Reasons for early closure may include discontinuation of the study intervention development, failure to comply with the protocol, or inadequate recruitment. If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, and the regulatory authorities.

10.1.11 Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This will allow the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors (ICMJE) authorship requirements.

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in the table below will be performed by a central or local laboratory as specified. Local laboratory results may be used if central results are not available in a timely manner for study intervention or response evaluation. Additional tests may be performed as determined necessary by the investigator.

Table 1: Protocol-required Laboratory Tests

Laboratory Tests	Parameters
Hematology	Platelet count, Red blood cell (RBC) count, RBC indices, White blood cell (WBC) count with differential, Hemoglobin, Hematocrit
Clinical chemistry	Blood urea nitrogen (BUN), Potassium, Creatinine, Sodium, Calcium, Glucose, Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), Alkaline phosphatase, Total and direct bilirubin, Total protein
Routine urinalysis	Specific gravity, pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick; Microscopic examination (if blood or protein is abnormal)
Pregnancy testing	Highly sensitive serum or urine human chorionic gonadotropin (hCG) pregnancy test
Other screening tests	Follicle-stimulating hormone (FSH) and estradiol (as needed), Drug screens, Serology (HIV, Hepatitis B, Hepatitis C)

NOTES:

- **Exclusion Criteria:**
- Hemoglobin level < 8 g/dL (5.0 mmol/L) or a platelet count < 75x10⁹/L.
- Creatinine clearance < 30 ml/min (Cockcroft-Gault). Apixaban use will be cautioned in patients with creatinine clearance of 15-29 mL/min and not recommended for those with clearance < 15 mL/min or on dialysis.
- **Liver Safety:**
- Liver function testing will be performed prior to initiating apixaban.
- Patients will be excluded if Alanine aminotransferase (ALT) level is ≥3 times the upper limit of normal (ULN) and/or a bilirubin level is ≥2 times the ULN.
- Apixaban will be contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk.
- **Coagulation Tests:**
- Clotting tests (e.g., PT, INR, aPTT) will be affected by apixaban, but changes are variable. Routine monitoring will not be required, but a calibrated quantitative anti-Factor Xa assay may be useful in exceptional situations like overdose or emergency surgery.
- In studies with dalteparin in patients with end-stage renal failure, no evidence of bioaccumulation of anti-Factor Xa serum levels was observed.

Investigators must document their review of each laboratory safety report.

10.3 Appendix 3: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definition of AE

10.3.1.1 AE Definition

- An AE will be any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

10.3.1.2 Definition of Unsolicited and Solicited AE

- An unsolicited AE will be an AE that was not solicited using a participant diary and that is communicated by a participant or their representative.

- Solicited AEs will be predefined local and systemic events for which the participant is specifically questioned.

10.3.1.3 Events Meeting the AE Definition

- Any abnormal laboratory test results or other safety assessments considered clinically significant by the investigator.
- Exacerbation of a chronic or intermittent pre-existing condition.
- New condition detected or diagnosed after study intervention administration.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction or overdose.
- Common adverse reactions expected with the study agents will include haemorrhage, contusion, epistaxis, haematoma, anaemia, thrombocytopenia, and nausea. The use of apixaban may be associated with an increased risk of occult or overt bleeding from any tissue or organ, which may result in posthaemorrhagic anaemia.

10.3.1.4 Events not Meeting the AE Definition

- Abnormal findings associated with the underlying disease, unless more severe than expected.
- The disease being studied or its expected progression, unless more severe than expected.
- A medical or surgical procedure itself; the condition leading to the procedure will be the AE.
- Hospital admission for social or convenience reasons.
- Anticipated day-to-day fluctuations of pre-existing conditions that do not worsen.

10.3.2 Definition of SAE

An SAE will be defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:

a. **Results in death**
b. **Is life threatening**
c. **Requires inpatient hospitalization or prolongation of existing hospitalization**
d. **Results in persistent or significant disability/incapacity**
e. **Is a congenital anomaly/birth defect**
f. **Is a suspected transmission of any infectious agent via an authorized medicinal product**
g. **Other situations:** Important medical events that may not be immediately life-threatening but may jeopardize the participant or require intervention to prevent one of the other serious outcomes.

10.3.3 Recording and Follow-Up of AE and/or SAE

10.3.3.1 AE and SAE Recording

- When an AE/SAE occurs, the investigator must review all related documentation and record all relevant information. The investigator will attempt to establish a diagnosis of the event. Adverse events will be monitored throughout the duration of the study, with a particular focus on bleeding and clotting events.

10.3.3.2 Assessment of Intensity

The investigator will assess the intensity of each AE and SAE as:
- **Mild:** Usually transient, minimal or no treatment required, does not interfere with daily activities.
- **Moderate:** Alleviated with specific intervention, interferes with daily activities.
- **Severe:** Interrupts daily activities, significantly affects clinical status, or requires intensive intervention.

10.3.3.3 Assessment of Causality

- The investigator must assess the relationship between the study intervention and each AE/SAE, considering alternative causes and the temporal relationship. A *reasonable possibility* of a relationship will suggest a causal link. The investigator will consult the IB and/or product information. This assessment will be crucial for regulatory reporting.

10.3.3.4 Follow-up of AEs and SAEs

- The investigator will be obligated to perform supplemental evaluations as medically indicated to elucidate the nature and/or causality of the AE or SAE. If a participant dies, a copy of any postmortem findings will be provided to the sponsor. New or updated information will be recorded, and any updated SAE data will be submitted to the sponsor within 24 hours of receipt.

10.3.4 Reporting of SAEs

10.3.4.1 SAE Reporting to the Sponsor via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to the sponsor will be the electronic data collection tool. If the electronic system is unavailable, the site will use the paper SAE data collection tool to report the event within 24 hours. The site will enter the SAE data into the electronic system as soon as it becomes available.

10.3.4.2 SAE Reporting to the Sponsor via Paper Data Collection Tool

- In the event the electronic system is unavailable, facsimile transmission of the paper SAE data collection tool will be the preferred method. Notification by telephone will be acceptable in rare circumstances but will not replace the need to complete and sign the SAE data collection tool within the designated reporting timeframes.

10.4 Appendix 4: Contraceptive and Barrier Guidance

10.4.1 Definitions

Women of childbearing potential (WOCBP) will be defined as those who are biologically capable of becoming pregnant.

10.4.2 Contraception Guidance

- WOCBP must practice a medically accepted, highly effective method of contraception during the trial and for one month after the last dose of the study drug.
- Highly effective methods will include: combined (estrogen and progestogen containing) hormonal contraception, progestogen-only hormonal contraception, intrauterine device (IUD), intrauterine hormone-releasing system (IUS), bilateral tubal occlusion, a vasectomized partner, or true sexual abstinence.
- Pregnancy or breastfeeding will be exclusionary criteria for study participation. There are no data from the use of apixaban in pregnant women; as a precautionary measure, it is preferable to avoid its use during pregnancy. It is unknown if apixaban or its metabolites are excreted in human milk; therefore, a decision must be made whether to discontinue breastfeeding or to discontinue/abstain from the study drug.
- Animal studies with apixaban have shown no effect on fertility.

10.5 Appendix 5: Genetics

Where local regulations and IRB/IEC allow, a sample will be collected for DNA analysis from consenting participants. DNA samples will be used for research related to the study intervention, the indication, and related diseases. This may include pharmacogenomic analysis, candidate gene analysis, or genome-wide analysis to understand how genetic variation impacts drug response, disease susceptibility, and progression [11, 12]. Samples will be stored securely to protect confidentiality and will be retained for a specified period as per local requirements.

10.6 Appendix 6: Liver Safety: Suggestions and Guidelines for Liver Events

- Patients will be excluded from the study if they have acute hepatitis, chronic active hepatitis, or liver cirrhosis.
- Patients will also be excluded if their alanine aminotransferase (ALT) level is ≥3 times the upper limit of normal (ULN) and/or their bilirubin level is ≥2 times the ULN.
- Apixaban will be contraindicated in patients with hepatic disease associated with coagulopathy and a clinically relevant bleeding risk. It will not be recommended for patients with severe hepatic impairment and should be used with caution in those with mild or moderate hepatic impairment (Child Pugh A or B).
- Liver function testing will be performed prior to initiating apixaban.

10.7 Appendix 7: Medical Device AEs, ADEs, SAEs, SADEs, USADEs and Device Deficiencies: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting in Medical Device Studies

- The definitions and procedures detailed in this appendix will be in accordance with ISO 14155 and the European Medical Device Regulation (MDR) 2017/745 for clinical device research (if applicable).

10.7.1 Definition of Medical Device AE and ADE

- A medical device AE will be any untoward medical occurrence in a clinical study participant, user, or other person, temporally associated with the use of a study device.
- An adverse device effect (ADE) will be an AE related to the use of an investigational medical device, including events from use error or malfunction.

10.7.2 Definition of Medical Device SAE, SADE and USADE

- A Medical Device SAE will be an AE that led to death, serious deterioration in health (life-threatening illness, permanent impairment, hospitalization), or fetal distress/death/ congenital abnormality.
- An SADE will be an ADE that has resulted in any of the consequences characteristic of an SAE, or a device deficiency that might have led to an SAE.

- An USADE will be an SADE that, by its nature, incidence, severity, or outcome, has not been identified in the current version of the risk analysis report.

10.7.3 Definition of Device Deficiency

- A device deficiency will be an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. This will include malfunctions, use errors, and inadequate information from the manufacturer.

10.7.4 Recording and Follow-Up of Medical Device AE and/or SAE and Device Deficiencies

10.7.4.1 Medical Device AE, SAE, and Device Deficiency Recording

- The investigator will record all relevant AE/SAE/device deficiency information in the participant's medical records and on the appropriate form. For device deficiencies, any corrective or remedial actions taken must be described.

10.7.4.2 Assessment of Intensity

- Intensity will be assessed as Mild, Moderate, or Severe.

10.7.4.3 Assessment of Causality

- The investigator will assess the relationship between the study device and each event, using clinical judgment and consulting the investigator's brochure or instructions for use.

10.7.4.4 Follow-up of Medical Device AE/SAE and device deficiency

- The investigator will perform supplemental evaluations as needed to elucidate the nature and causality of the event. Updated information will be recorded and submitted to the sponsor promptly.

10.7.5 Reporting of Medical Device SAEs

- SAEs will be reported to the sponsor within 24 hours, primarily via an electronic data collection tool, with a paper-based system as a backup.

10.7.6 Reporting of SADEs

- Any device deficiency associated with an SAE must be reported to the sponsor within 24 hours. The sponsor will review these events and report them to regulatory authorities and IRBs/IECs as required.

10.8 Appendix 8: Country-specific Requirements

This appendix will detail any country-specific requirements or regional regulatory adaptations that cannot be addressed by flexible language within the main body of the protocol.

10.9 Appendix 9: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment will be located before the table of contents. This appendix will contain the history of all previous amendments. Amendments will be classified as substantial or non-substantial based on criteria set forth in regulations such as EU No 536/2014. The rationale for changes will be documented, and a clear numbering system for global, country-specific, and site-specific amendments will be maintained.

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