CLINICAL STUDY PROTOCOL

APIXABAN FOR THE TREATMENT OF VENOUS THROMBOEMBOLISM IN PATIENTS WITH CANCER: A PROSPECTIVE RANDOMIZED OPEN BLINDED END-POINT (PROBE) STUDY - THE CARAVAGGIO STUDY

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SYNOPSIS

EudraCT/IND Number:	2016-003093-40
Protocol Number:	FADOI 03.2016
Investigational Product:	Apixaban (BMS-562247-01)
Study Title:	Apixaban for the treatment of venous thromboembolism in patients with cancer: a prospective randomized open blinded end-point (PROBE) study - the Caravaggio study
Short Title:	Apixaban for venous thromboembolism (VTE) in cancer patients
Study Phase:	Phase IIIb trial
Indication Under Investigation:	Apixaban for venous thromboembolism in cancer patients
Study Aim:	The aim of this study is to assess whether oral apixaban is non-inferior to the subcutaneous low molecular weight (LMWH) dalteparin for the treatment of newly diagnosed proximal deep vein thrombosis (DVT) and/or pulmonary embolism (PE) in patients with cancer.
Study Design:	This is a multinational, prospective, randomized, open-label, blinded end-point (PROBE), non-inferiority study.
Study population:	<u>Inclusion criteria:</u> 1) Consecutive patients 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. 2) Any type of cancer (other than basal-cell or squamous-cell carcinoma of the skin, primary brain tumor or known intracerebral metastases and acute leukemia) that meets at least one of the following: • Active cancer defined as diagnosis of cancer within six months before the study inclusion, or receiving treatment for cancer at the time of inclusion or any treatment for

cancer during 6 months prior to randomization, or recurrent locally advanced or metastatic cancer.
- Cancer diagnosed within 2 years before the study inclusion (history of cancer).

3) Signed and dated informed consent, available before the start of any specific trial procedure.

Exclusion criteria:

Patients are ineligible for the study in case of:

1) age <18 years

2) ECOG Performance Status III or IV;

3) life expectancy of less than 6 months;

related to anticoagulant treatment:

4) administration of therapeutic doses of LMWH, fondaparinux, or unfractionated heparin (UFH) for more than 72 hours before randomization;

5) 3 or more doses of a vitamin K antagonist before randomization;

6) thrombectomy, vena cava filter insertion, or thrombolysis used to manage the index episode;

7) indication for anticoagulant treatment for a disease other than the index VTE episode;

8) concomitant use of strong inhibitors or inducers of both cytochrome P-450 3A4 and P-Glycoprotein (see Appendix 1);

related to bleeding risk:

9) concomitant thienopyridine therapy (clopidogrel, prasugrel, or ticagrelor) or aspirin over 165 mg daily or dual antiplatelet therapy;

10) active bleeding or high risk of bleeding contraindicating anticoagulant treatment

11) recent (in the last 1 month prior to randomization) brain, spinal or ophthalmic surgery;

12) hemoglobin level lower than 8 g/dL (5.0 mmol/L) or platelet count $<75x10^9$/L or history of heparin-induced thrombocytopenia;

13) creatinine clearance < 30 ml /min based on the Cockcroft Gault equation;

14) acute hepatitis, chronic active hepatitis, liver cirrhosis; or an alanine aminotransferase level 3 times or more and/or bilirubin level 2 times or more the upper limit of the normal range;

15) uncontrolled hypertension (systolic BP> 180 mm Hg or diastolic BP > 100 mm Hg despite antihypertensive treatment);

standard criteria:

16) bacterial endocarditis;

17) hypersensitivity to the study drugs or to any of their excipients;

18) Patient's participation in other pharmaco-therapeutic program with an experimental therapy that is known to affect the coagulation system.

19) women of childbearing potential (WOCBP) who do not practice a medically accepted highly effective contraception during the trial and one month beyond. Highly effective contraception methods are:
    a. combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation
    b. progestogen-only hormonal contraception associated with inhibition of ovulation
    c. intrauterine device (IUD)
    d. intrauterine hormone-releasing system (IUS)
    e. bilateral tubal occlusion
    f. vasectomized partner
    g. sexual abstinence;

20) pregnancy or breast feeding

21) any condition that, as judged by the investigator, would place the subject at increased risk of harm if he/she participated in the study.

Efficacy Study Outcomes:	Primary efficacy outcome: objectively confirmed recurrent VTE occurring during the study treatment period, that means the composite of: • proximal DVT of the lower limbs (symptomatic or unsuspected) • DVT of the upper limb (symptomatic) • PE (symptomatic or unsuspected) Secondary efficacy outcomes: • the individual components of the primary efficacy outcome; • symptomatic recurrence of VTE; • all cause death; • the composite of primary efficacy outcome plus major bleeding; • the composite of primary efficacy outcome plus major bleeding plus all cause death; • the composite of primary efficacy outcome 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 vein thrombosis and cerebral vein thrombosis); • Quality of life (QoL) according to Anti-Clot Treatment Scale (ACTS) (see Appendix 2)
Safety Study Outcomes:	Primary safety outcome is major bleeding, defined (as per ISTH guidelines), as acute clinically overt bleeding associated with one or more of the following: • decrease in hemoglobin of 2 g/dl (1.2 mmol/L) or more; • transfusion of 2 or more units of packed red blood cells;

	• bleeding that occurs in at least one critical site [intracranial, intra-spinal, intraocular (within the corpus of the eye; thus, a conjunctival bleed is not an intraocular bleed), pericardial, intra-articular, intramuscular with compartment syndrome, or retroperitoneal];
	• bleeding that is fatal;
	• bleeding that necessitates acute surgical intervention
	
	Secondary safety outcomes include:
	• Clinically relevant non-major bleeding event defined as acute clinically overt bleeding that does not meet the criteria for major and consists of:
	  • any bleeding compromising hemodynamics;
	  • spontaneous hematoma larger than 25 cm^2, or 100 cm^2 if there was a traumatic cause;
	  • intramuscular hematoma documented by ultrasonography;
	  • epistaxis or gingival bleeding requiring tamponade or other medical intervention or bleeding from venipuncture for >5 minutes;
	  • hematuria that was macroscopic and was spontaneous or lasted for more than 24 hours after invasive procedures;
	  • hemoptysis, hematemesis or spontaneous rectal bleeding requiring endoscopy or other medical intervention;
	  • or any other bleeding considered to have clinical consequences for a patient such as medical intervention, the need for unscheduled contact (visit or telephone call) with a physician, or temporary cessation of a study drug, or associated with pain or impairment of activities of daily life.
	
	• Clinically relevant bleeding defined as the composite of major and clinically relevant non-major bleeding
	
	• Permanent early discontinuation of study drug due to safety reasons.

Study treatments and visits:	Patients will be randomized on a 1:1 basis (permuted blocks of four) to receive either apixaban or dalteparin in an open-label fashion. Apixaban group: orally administered, at the dose of 10 mg bid for 7 days, followed by 5 mg bid (total period of treatment: six months) Dalteparin group: subcutaneously administered, at a dose of 200 IU/kg SC o.i.d for 1 month. Thereafter, dalteparin will be administered at a

	dose of 150 IU/kg o.i.d. for 5 months (total period of treatment: six months). The maximum daily dose allowed for dalteparin is 18,000IU. Randomization will be centralized and stratified by: 1) symptomatic vs. unsuspected VTE 2) active cancer vs. history of cancer Apixaban 5mg will be supplied by the Promoter as film-coated tablets. Dalteparin will be supplied by the Promoter as single-use pre-filled syringes. The study requires the following scheduled visits: at enrollment, at 4 weeks, at 3 months, at 6 months, at the end of study treatment whenever it occurs, and at 7 months from randomization. Additional visits will be performed if new symptoms and/or signs of VTE or major bleeding develop. A clinical examination and objective tests will be performed if the patient develops symptoms or signs suggestive of recurrent VTE.
Planned Sample Size:	The study has been designed to test the hypothesis that apixaban would be non-inferior to dalteparin with respect to the primary efficacy outcome. The criteria for non-inferiority require that the upper limit of the two-sided 95% confidence interval of the Hazard ratio is below the pre-specified margin of 2.00. With the use of an estimated incidence of the primary efficacy outcome of 7% at 6 months with dalteparin and an upper non-inferiority margin of 2.00 for the hazard ratio, we calculated that we would need to enroll 934 completer patients for the study to have 80% power to show the non-inferiority of apixaban, at a one-sided alpha level of 0.025. This sample will be increased to 1168 patients to account for up to 20% lost in total patient-years. This estimate is consistent with a drop-out rate of 40% assuming patients discontinued uniformly during the follow-up (mean discontinuation time equal to 3 months)
Statistical Analysis:	Analysis of the Primary Study Outcome The primary efficacy data set will consist of all randomized subjects who received at least one dose of the study drugs (modified intent-to treat population) with a non-missing primary outcome. Subjects will be categorized to the group to which they were assigned at randomization, regardless of the treatment actually received.

The secondary efficacy data sets will consist of a) all randomized subjects (intent-to treat population) and b) the per-protocol population (defined in the SAP).
The safety data set will consist of all treated subjects (randomized subjects who received at least one dose of study drug).
The primary efficacy variable, i.e. the time from randomization to the first recurrent thromboembolic event, will be analyzed after adjusting estimates for the competing risk of death unrelated to VTE.

The evaluation of the primary objective will be done by considering the time from randomization to the first recurrent thromboembolic event (event of interest) or to the occurrence of death unrelated to VTE (nuisance/competing event) or to the last follow-up if neither a recurrent thromboembolic event nor a competing event occurred within the intended 6-month study treatment period (censored time).

Analyses of the primary efficacy endpoint will be performed using the modified intent-to-treat principle, the intent-to treat principle and the per protocol principle. The modified intent-to-treat and the intent-to-treat analyses of the primary endpoint will include endpoints that occur at any time from randomization until the end of their originally intended treatment period regardless of whether subjects were receiving study medication.
A per protocol analysis of the primary endpoint will include endpoints that occur in patients who complete the study fully compliant with the protocol and without any major violation or deviation (defined in the SAP).
For the secondary efficacy outcomes, analyses will be performed using the primary efficacy data set.

The apixaban-to-comparator Hazard Ratio adjusted for the competing risk of death unrelated to VTE will be computed with associated two-sided 95% Confidence Interval by resorting to the Fine & Gray regression model (Fine and Gray, 1999) using treatment group and center as dummy covariates.
Apixaban will be considered non-inferior to the comparator dalteparin if the upper two-sided 95% confidence limit of hazard ratio is < 2.00.
Superiority of apixaban vs. dalteparin will be tested as a secondary analysis of the primary endpoint, only after non-inferiority has been demonstrated for the experimental treatment group (apixaban) relative to the standard treatment group (dalteparin). According to CPMP/EWP/482/99 document entitled: "Points to consider on switching between superiority and non-inferiority", switching the apixaban vs. dalteparin contrast from the non-inferiority objective to the superiority objective is feasible because the trial is properly designed in accordance to the strict requirements of a non-inferiority trial.

	For the purpose of safety analyses, subjects will be categorized to the group to which they were assigned at randomization unless incorrect study treatment was received throughout the study, in which case the subject will be categorized according to the treatment received. All safety analyses will be conducted on the safety population. The term "treatment period" refers to the period between the first administration of study drug and 48 hours after the last administration of study drug. This period will be the basis for the summaries of safety.
Study Sites and Location:	Approximately 140 study sites in 11 countries are planned to enroll patients in this study

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1. LIST OF ABBREVIATIONS

ACTS	Anti-Clot Treatment Scale
AE	Adverse Event
AESI	Adverse Event of Special Interest
ADR	Adverse Drug Reaction
ALP	Alkaline Phosphatase
ALT	Alanine Transaminase
AST	Aspartate Transaminase
CEC	Clinical Event Adjudication Committee
CK-MB	Creatine Kinase- MB
CrCL	Creatinine Clearance
CRO	Contract Research Organization
DVT	Deep Vein Thrombosis
DSMB	Data Safety Monitoring Board
DSUR	Development Safety Update Report
ECOG	Eastern Cooperative Oncology Group (Performance scale)
eCRF	electronic Case Report Form
FADOI	Italian Federation of Hospital Internists
FAS	Full Analysis Set
ICH-GCP	International Conference on Harmonization – Good Clinical Practice
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISF	Investigator Site File
ISTH	International Society on Thrombosis and Hemostasis
IWRS	Interactive Web-based Randomization System
LMWH	Low molecular weight
MedDRA	Medical Dictionary for Regulatory Activities
PE	Pulmonary Embolism
PIN	Personal Identification Number

PROBE	Prospective Randomized Open Blinded End-Point
RBM	Risk Based Monitoring
QoL	Quality of Life
SAE	Serious Adverse Event
SASR	Serious Adverse Drug Reaction
SAP	Statistical Analysis Plan
SC	Steering Committee
SDEA	Safety Data Exchange Agreement
SOCs	System Organ Classes
SMS	Short Message Service
SUSAR	Suspected Unexpected Serious Adverse Reaction
UFH	Unfractioned Heparin
ULN	Upper Limit of Normal
VTE	Venous Thromboembolism
WBC	White Blood Cells
WHO	World Health Organization
WOCBP	Women of childbearing potential

2. INTRODUCTION

Venous thromboembolism (VTE) is a common clinical event in patients with cancer. The development of VTE is presumed to be due to the production of pro-coagulant molecules by cancer cells and to the pro-coagulant effect of cancer cells spread into the circulation. It should be taken into account that cancer surgery and chemotherapy are associated with a substantial increase in the risk of VTE. Moreover, the risk for recurrence both while on anticoagulant therapy and after its discontinuation was shown to be particularly high in patients with cancer associated VTE (1). The risk for bleeding complications on anticoagulant treatment is also higher in cancer patients than in non-cancer patients such making crucial the balance between benefit and risk (1).

The CLOT study, performed more than 15 years ago, showed that in patients with cancer-associated VTE, anticoagulant treatment with the low-molecular-weight heparin (LMWH) dalteparin was more effective and similarly safe compared to vitamin K antagonists (2). These results were confirmed in studies with a more limited number of patients (3). Thus, current guidelines recommend the use of LMWH, given subcutaneously, for the acute and long-term treatment of VTE in cancer patients (4-5). In the recently published CATCH study in cancer patients, the LMWH tinzaparin was associated with a non-significant 35% risk reduction in recurrence of VTE compared to vitamin K antagonists (6). In the CATCH study, there were no differences in the incidence of major bleeding between the two treatment groups.

Due to the high risk for recurrence, cancer patients who experience VTE are candidates to indefinite treatment duration or to prolong treatment until cancer is completely cured (4-5). The availability of an oral anticoagulant treatment, as effective and safe as LMWH, would be a substantial advantage for patients with cancer who develop VTE. During the last years, new oral anticoagulants given at fixed doses without the need of laboratory monitoring and dose adjustment were shown to be as effective as and probably safer than vitamin K antagonists for the treatment of VTE (7). The results of phase III clinical trials led to their approval for the acute and long-term treatment of VTE. Unfortunately, the clinical trials on the treatment of VTE with the new oral anticoagulants included only a limited number of patients with cancer. Thus, whether the results obtained in the general population of patients with VTE also attain to cancer patients remains undefined.

Subgroup analyses on the efficacy and safety profile of the anti-Xa oral agent apixaban for the treatment of VTE in cancer patients have been recently reported (8-11). In these patients, with all the limitations related to a subgroup analysis, apixaban appeared to be at least as effective as LMWH given with and followed by vitamin K antagonists (10). A recent meta-analysis in cancer patients showed a similar efficacy and safety profile of new oral anticoagulants in comparison with LMWH given with and followed by vitamin K antagonists for the treatment of VTE (12).

3. AIM OF THE STUDY

The aim of this study is to assess whether apixaban is non-inferior to the LMWH dalteparin for the treatment of newly diagnosed proximal deep vein thrombosis (DVT) and/or pulmonary embolism (PE) in patients with cancer.

4. EXPERIMENTAL DESIGN

4.1 Design of the study

This is a multinational, prospective, randomized, open-label, blinded end-point (PROBE), non-inferiority study comparing apixaban to the LMWH dalteparin in the treatment of VTE in patients with cancer.

4.2 Study population

Patients with cancer and newly objectively diagnosed proximal lower-limb DVT, or PE or both will be eligible for the study.
Patients will be included after screening for inclusion and exclusion criteria (see sections 4.2.1 and 4.2.2) and the signature of the informed consent form. Patients will be encouraged to ask any questions regarding the study aims and procedures, to be answered straightforwardly by one of the Investigators.

4.2.1. Inclusion Criteria

Consecutive patients with:

1) 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.

Unsuspected VTE is defined as DVT or PE detected by imaging testing performed not to confirm the suspicion of VTE but for other reasons (e.g. cancer diagnosis or staging).

The diagnosis of DVT requires the evidence of one or more filling defects at compression ultrasonography, venography, CT venography or MR venography involving at least the popliteal vein or more proximal veins.

The diagnosis of PE requires one or more among:
- an intraluminal filling defect at CT pulmonary angiography;
- an intraluminal filling defect, or a new sudden cut-off of vessels more than 2.5 mm in diameter at pulmonary angiogram;

- a perfusion defect of at least 75% of a segment with a local normal ventilation result (high probability) on ventilation/perfusion lung scan (VQ scan);
- in unsuspected PE, there must be one or more filling defect in segmental or more-proximal arteries at chest CT pulmonary angiography.

2) Any type of cancer (other than basal-cell or squamous-cell carcinoma of the skin, primary brain tumor or intracerebral metastases and acute leukemia) that meets at least one of the following:
   - Active cancer defined as diagnosis of cancer within six months before the study inclusion, or receiving treatment for cancer at the time of inclusion or any treatment for cancer during 6 months prior to randomization, or recurrent locally advanced or metastatic cancer.
   - Cancer diagnosed within 2 years before the study inclusion (history of cancer).

3) signed and dated informed consent, available before the start of any specific trial procedure.

4.2.2. Exclusion Criteria

Patients are ineligible for the study in case of:

1) age <18 years

2) ECOG Performance Status III or IV;

3) life expectancy of less than 6 months;

related to anticoagulant treatment:

4) administration of therapeutic doses of LMWH, fondaparinux, or unfractionated heparin (UFH) for more than 72 hours before randomization;

5) 3 or more doses of a vitamin K antagonist before randomization;

6) thrombectomy, vena cava filter insertion, or thrombolysis used to manage the index episode;

7) indication for anticoagulant treatment for a disease other than the index VTE;

8) concomitant use of strong inhibitors or inducers of both cytochrome P-450 3A4 and P-Glycoprotein (see Appendix 1);

related to bleeding risk:

9) concomitant thienopyridine therapy (clopidogrel, prasugrel, or ticagrelor) or aspirin over 165 mg daily or dual antiplatelet therapy;

10) active bleeding or a high risk of bleeding contraindicating anticoagulant treatment;

11) recent (in the last 1 month prior to randomization) brain, spinal or ophthalmic surgery;

12) hemoglobin level lower than 8 g/dL (5.0 mmol/L) or platelet count < $75x10^9$/L or history of heparin induced thrombocytopenia;

13) creatinine clearance < 30 ml /min based on the Cockcroft Gault equation;

14) acute hepatitis, chronic active hepatitis, liver cirrhosis; or an alanine aminotransferase level 3 times or more and/or bilirubin level 2 times or more the upper limit of the normal range;

15) uncontrolled hypertension (systolic BP> 180 mm Hg or diastolic BP > 100 mm Hg despite antihypertensive treatment);

standard criteria:

16) bacterial endocarditis;

17) hypersensitivity to the study drugs or to any of their excipients;

18) Patient's participation in other pharmaco-therapeutic program with an experimental therapy that is known to affect the coagulation system.

19) Women of childbearing potential (WOCBP) who do not practice a medically accepted highly effective contraception during the trial and one month beyond. Highly effective contraception methods are:
    a. combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation
    b. progestogen-only hormonal contraception associated with inhibition of ovulation
    c. intrauterine device (IUD)
    d. intrauterine hormone-releasing system (IUS)
    e. bilateral tubal occlusion
    f. vasectomized partner
    g. sexual abstinence;

20) pregnancy, or breast feeding;

21) any condition that as judged by the investigator would place the subject at increased risk of harm if he/she participated in the study.

Patient has the right to refuse further participation in the study at any time and without providing any reasons. Patients may be withdrawn from the study at any time at the discretion of the investigator; however, in this case, the reason should be fully documented.

5. STUDY OUTCOMES

5.1 Efficacy outcomes

The primary efficacy outcome is objectively confirmed recurrent proximal DVT or PE occurring during the study treatment period, that means the composite of:

a) ipsilateral proximal DVT of the lower limbs (symptomatic or unsuspected):
A recurrent proximal DVT must be distinguished from the original thrombus by comparing serial imaging modalities (compression ultrasonography, venography, CT venography, or MR venography). In order to be classified as a recurrent event, there must be one or more new filling defect evident on the second imaging test not evident on the original images, or an interval imaging test clearly showing thrombus resolution; only in symptomatic patients, if the venous segment was non-compressible at randomization, a substantial increase (4 mm or more) in diameter of the thrombus during full compression.

b) contralateral proximal DVT of the lower limbs (symptomatic or unsuspected):
In order to be classified as a recurrent event, there must be one or more new filling defects at compression ultrasonography, venography, CT venography, or MR venography. Unsuspected thrombus must be evident on the second imaging test and not evident on the original images.

c) DVT of the upper limbs (symptomatic)

In order to be classified as a recurrent event, there must be one or more new filling defects at compression ultrasonography, venography, CT venography, or MR venography.

d) pulmonary embolism (symptomatic or unsuspected):

- Symptoms of PE with one of the following findings:
  - a new intraluminal filling defect at CT pulmonary angiography;
  - a new intraluminal filling defect, or an extension of an existing defect, or a new sudden cut-off of vessels more than 2.5 mm in diameter at pulmonary angiogram;

- a new perfusion defect of at least 75% of a segment with a local normal ventilation result (high probability) on ventilation/perfusion lung scan (VQ scan);
- inconclusive CT pulmonary angiography, pulmonary angiography, or VQ scan evidence of a new or recurrent PE with demonstration of a new or recurrent DVT in the lower extremities by compression ultrasonography or venography.

- Fatal PE defined as PE based on objective diagnostic testing before death or autopsy; death where PE is the most probable cause of a sudden and unexplained death according to central adjudication.

- In unsuspected PE, in order to be classified as a recurrent event, there must be one or more new filling defect in segmental or more-proximal arteries at CT pulmonary angiography evident on the second study not appreciated on previous images or an interval study clearly showing emboli resolution.

The secondary efficacy outcomes of the study are:

- the individual components of the primary efficacy outcome;
- symptomatic recurrence of VTE;
- all cause death;
- the composite of primary efficacy outcome plus major bleeding;
- the composite of primary efficacy outcome plus major bleeding plus all cause death;
- the composite of primary efficacy outcome plus all cause death;
- any major cardiovascular event, fatal or not fatal (including acute myocardial infarction[1] or ischemic stroke[2]);
- all venous thromboembolic events (including splanchnic vein thrombosis and cerebral vein thrombosis both objectively assessed);
- Quality of Life (QoL), assessed by means of the Anti-Clot Treatment Scale (ACTS) (see Appendix 2).

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[1] An acute myocardial infarction requires the presence of at least 2 out of the 3 following conditions:

- an appropriate clinical situation suggestive of a myocardial infarction (eg, abnormal history, physical examination or new ECG changes)
- elevation of CK-MB or Troponin T or I ≥ 2 x ULN; if no CK-MB or troponin values are available, a total CK ≥2x ULN
- new, significant (≥0.04 seconds) Q waves in ≥ 2 contiguous leads.

[2] An acute stroke is defined as a new, focal neurological deficit of sudden onset, lasting at least 24 hours, that is not due to a readily identifiable non-vascular cause (i.e., brain tumor, trauma). All strokes during the study will be assessed by imaging or autopsy and classified as primary hemorrhagic, non-hemorrhagic, infarction with hemorrhagic conversion, or unknown, as defined by the American College of Cardiology (ACC).

5.2. Safety outcomes

The primary safety outcome is major bleeding, defined (as per ISTH guidelines), as acute clinically overt bleeding associated with one or more of the following:

- a decrease in hemoglobin of 2 g/dl or more;
- a transfusion of 2 or more units of packed red blood cells;
- bleeding that occurs in at least one of the following critical sites [intracranial, intra-spinal, intraocular (within the corpus of the eye; thus, a conjunctival bleed is not an intraocular bleed), pericardial, intra-articular, intramuscular with compartment syndrome, or retroperitoneal];
- bleeding that is fatal (defined as a bleeding event that the independent Clinical Event Adjudication Committee determined was the primary cause of death or contributed directly to death);
- bleeding that necessitates surgical intervention.

Secondary safety outcomes include:

- Clinically relevant non-major bleeding event defined as acute clinically overt bleeding that does not meet the criteria for major and consists of:
  - any bleeding compromising hemodynamics;
  - spontaneous hematoma larger than 25 cm^2, or 100 cm^2 if there was a traumatic cause;
  - intramuscular hematoma documented by ultrasonography;
  - epistaxis or gingival bleeding requiring tamponade or other medical intervention or bleeding from venipuncture for >5 minutes;
  - hematuria that was macroscopic and was spontaneous or lasted for more than 24 hours after invasive procedures;
  - hemoptysis, hematemesis or spontaneous rectal bleeding requiring endoscopy or other medical intervention;
  - or any other bleeding considered to have clinical consequences for a patient such as medical intervention, the need for unscheduled contact (visit or telephone call) with a physician, or temporary cessation of a study drug, or associated with pain or impairment of activities of daily life.

- Clinically relevant bleeding defined as the composite of major and clinically relevant non-major bleeding
- Permanent early discontinuation of study drug due to safety reasons.

6. STUDY PROCEDURES

6.1 Subject information and informed consent

Before being admitted to the clinical trial, the subject must consent to participate after being fully informed about the nature, scope, and possible consequences of the clinical trial.
The documents must be in a language understandable to the subject and must specify who informed the subject.
A copy of the signed informed consent document must be given to the subject. The original signed consent document will be retained by the investigator.
The investigator will not undertake any measures specifically required only for the clinical trial until valid consent has been obtained.
Moreover, the investigator, by the means of the specific template approved by his local EC, should inform the subject's primary physician about the subject's participation in the trial - provided the subject agrees to the primary physician being informed.
After reading the informed consent document, the subject must give consent in writing. The subject's consent must be confirmed by the personally dated signature of the subject and by the personally dated signature of the study doctor conducting the informed consent discussions.
Additionally, in this study, for those centers interested in using it, the Informed Consent administration could be conducted through an electronically managed procedure. In details the study investigator by the means of a tablet, will open the appropriate Informed Consent form and provide it to the patient for reading and understanding. The study investigator will then require an automated generated PIN code that will be directly received by the patient on his/her own personal mobile phone via SMS. Once the patient will have carefully read and/or listened the informed consent text, he/she will sign it electronically by entering the PIN code.
A PDF copy of the electronically signed Informed Consent will be generated for investigator and patient's filing.
No personal patient's contact details (like mobile phone number) will be recorded in the study data-base.

6.2 Randomization

Patients will be randomized to receive:
Apixaban group: orally administered, at the dose of 10 mg bid for 7 days, followed by 5 mg bid;
Dalteparin group: subcutaneously administered, at a dose of 200 IU/kg SC o.i.d for 1 month. Thereafter, dalteparin will be administered at a dose of 150 IU/kg o.i.d. for 5 months. The maximum daily dose allowed for dalteparin is 18,000IU.
Enrolled patients will receive the study drug for 6 months.

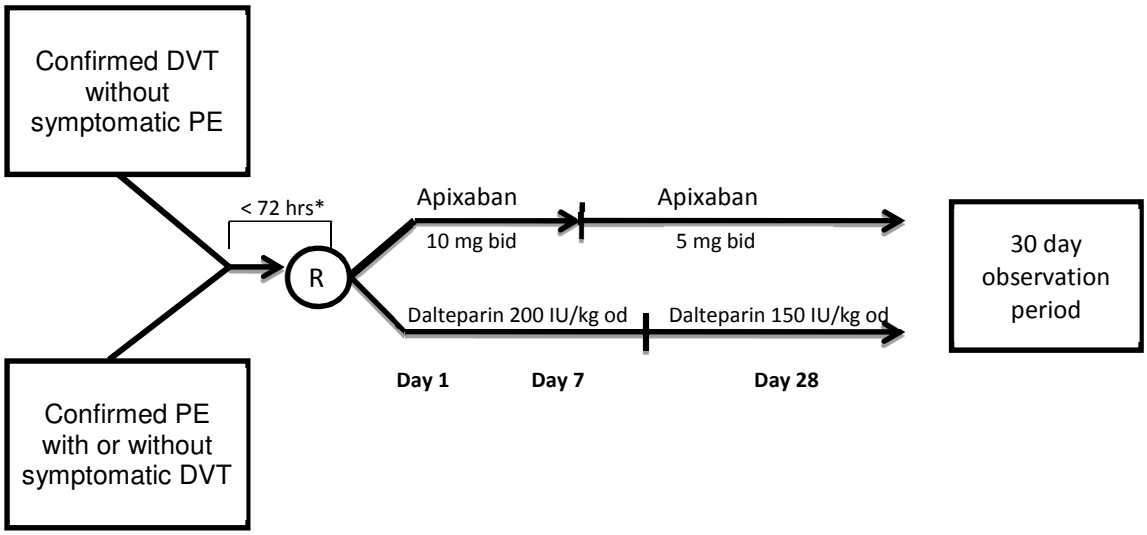

Figure. Study design.

Patients will be randomized on a 1:1 basis (permuted blocks of four) to receive either Apixaban or Dalteparin in an open-label fashion.

Randomization will be centralized and stratified by:

1) symptomatic vs. unsuspected VTE
2) active cancer vs. history of cancer

The maximum proportion of patients entering the study with unsuspected VTE is set at 20% of the overall study population. After this proportion is reached, randomization of patients with unsuspected VTE will not be allowed.
The maximum proportion of patients entering the study with history of cancer is set at 20% of the overall study population. After this proportion is reached, randomization of patients with history of cancer will not be allowed.

6.3. Visits schedule and follow-up

The study requires the following scheduled visits: at enrolment, at 4 weeks, at 3 months, at 6 months, at the end of study treatment whenever it occurs, and at 7 months from randomization.
Additional visits will be performed if new symptoms and/or signs of VTE or major bleeding develop. A clinical examination and objective tests will be performed if the patient develops symptoms or signs suggestive of recurrent VTE.

6.4. Observations and measurements

The investigator or a delegate will complete an electronic Case Report Form (eCRF) to document the study data.
During the screening visit the investigator or delegate will obtain:

- written informed consent;
- relevant medical history;
- information on symptoms of VTE, site and confirmatory tests;
- data on type, site and staging of cancer
- date of cancer diagnosis
- data on type and timing of cancer treatment (chemotherapy, radiotherapy, surgery)
- physical exams and measure of vital signs (e.g. body weight, blood pressure, heart rate)
- pregnancy test (WOCBP only)
- the following local laboratory results:
  - Serum chemistry
    - Total bilirubin (direct and indirect)
    - Alanine transaminase (ALT)
    - Aspartate transaminase (AST)
    - Alkaline phosphatase (ALP)
    - Serum creatinine
    - CrCL
  - Hematology and platelet count
    - Hematocrit
    - White blood cell (WBC) count
    - Hemoglobin
    - Platelet count
    - INR
    - partial prothrombin time;
- concomitant medication use (within 30 days prior to screening visit);
- screening on inclusion/exclusion criteria

Investigators should provide documentation of the index VTE event (qualifying imaging) and cancer (histology reports) during the period that extends from screening period up to two weeks after randomization.

Procedures to be performed at enrollment include:

- determine if subject continues to meet inclusion/exclusion criteria;

- randomize the subject to study medication through the Interactive Web-based Randomization System (IWRS) embedded in the eCRF
- dispense study treatment.

At 4-week and 3-month follow-up visits:
The investigator or delegate will:

- assess study outcomes (i.e. suspected recurrent VTE, bleeding), including subjects who have discontinued study treatment. For subjects who have discontinued study treatment, telephone query of health status (alive, occurrence of efficacy and safety endpoints and AEs/SAEs) is allowed. Subjects who have new symptoms should undergo further assessment as clinically appropriate, preferably at the study site whenever feasible.
- check the following local laboratory results:
  Serum chemistry
  - Total bilirubin (direct and indirect)
  - Alanine transaminase (ALT)
  - Aspartate transaminase (AST)
  - Alkaline phosphatase (ALP)
  - Serum creatinine
  - CrCL

  Hematology and platelet count
  - Hematocrit
  - White blood cell (WBC) count
  - Hemoglobin
  - Platelet count;

- collect study medication dispensed at previous visit;
- assess study medication use;
- measure the body weight;
- dispense study medication assigned for the current visit;
- assess concomitant medication use;
- for patients with study outcomes investigators should provide documentation for the recurrent VTE event (qualifying imaging) within four weeks.

At 6-month follow-up visit or end of study treatment:

The investigator or delegate will:

- assess study outcomes (i.e. suspected recurrent VTE, bleeding), including subjects who have discontinued study treatment. For subjects who have discontinued study

treatment, telephone query of health status (alive, occurrence of efficacy and safety endpoints and AEs/SAEs) is allowed. Subjects who have new symptoms should undergo further assessment as clinically appropriate, preferably at the study site whenever feasible.

- check the following local laboratory results:

  Serum chemistry
  - Total bilirubin (direct and indirect)
  - Alanine transaminase (ALT)
  - Aspartate transaminase (AST)
  - Alkaline phosphatase (ALP)
  - Serum creatinine
  - CrCL

  Hematology and platelet count
  - Hematocrit
  - White blood cell (WBC) count
  - Hemoglobin
  - Platelet count;

- collect study medication dispensed at previous visit;
- assess study medication use;
- assess concomitant medication use;
- for patients with study outcomes investigators should provide documentation for the recurrent VTE event (qualifying imaging) within four weeks.
- assess Quality of Life (QoL) by means of the Anti-Clot Treatment Scale (ACTS) at the end of the study treatment.

<u>At 7-month after randomization:</u>
The investigator or delegate will:

- assess for AE/SAE(s)
- for patients with study outcomes investigators should provide documentation for the recurrent VTE event (qualifying imaging) within four weeks.
- assess efficacy and safety (i.e. recurrent VTE, major bleeding), including subjects who have discontinued study treatment. Query of health status (alive, occurrence of efficacy endpoints and SAEs) and current anticoagulant treatment by telephone is allowed.

<u>Unscheduled Visit:</u>
An unscheduled visit may occur during the study treatment period, at any time the Investigator considers it might be necessary.

The procedures and assessments performed during an unscheduled visit strictly depends by the reason why such visit occurs.

6.5. Withdrawn/discontinuation of Subjects from Therapy

6.5.1. Reasons for Withdrawal/Early Discontinuation

A subject may discontinue or interrupt study drug for a number of reasons including, but not limited to, those listed below:

- Permanent Discontinuation
  - Death;
  - Withdrawal of consent as defined in Section 6.5.2;
  - Pregnancy
  - Lost to follow-up as defined in Section 6.5.3 (every attempt will be made by the investigator not to have subjects "lost to follow-up");
  - CrCL decrease to < 30 mL/min, confirmed by repeat testing at least 1 week later or need for kidney dialysis;
  - Investigator judgment due to:
    SAE or other safety concern e.g.,
    - Major life-threatening bleeding
    - Onset of clinical jaundice or other overt signs of liver toxicity
    - Unfavorable benefit-to-risk evaluation for continuing anticoagulant treatment
  - Termination of all or part of the study by the DSMB acting in concert with the Promoter.

- Temporary Discontinuation

Temporary discontinuations of apixaban and dalteparin for 3 or more consecutive days will be recorded in the eCRF.
Potential reasons may include:
- Short-term use of prohibited concomitant medications (see Appendix 1);
- Surgical procedures;
- Any medical condition where continuing study drug may expose the subject to an increased hazard;
- New onset of elevated liver enzymes in the absence of a known cause:
  - ALT > 8 × ULN
  - AST or ALT > 5 x ULN for more than two weeks
  - ALT or AST > 3 x ULN, but not reaching the limits in the above criteria, in combination with clinical symptoms suggestive of hepatitis
  - ALT or AST > 3 x ULN with TBL > 2 x ULN
- New onset or deteriorating renal failure <30ml/h

- Platelet count < $50x10^9$/L ($50,000/mm^3$)

In patients receiving Dalteparin who experience platelet counts between 50,000 and $100,000/mm^3$, the daily dose of Dalteparin should not be discontinued but reduced until the platelet count recovers to $\geq 100,000/mm^3$. Please refer to your local product package insert for dosing reduction guidance for this patient population.

During a study drug discontinuation, a subject can be placed on antithrombotic therapy per local guidelines and the investigator's discretion.
Post-randomization changes (other than CrCL decreased to < 30 mL/min or need for kidney dialysis) in health status related to study exclusion criteria should not automatically lead to study drug interruption or discontinuation unless continuing study drug places the subject at undue hazard as determined by the investigator. Such situations should be handled on a case-by-case basis. It is strongly recommended that the investigator consults with the dedicated Medical Support Line (telephone number: +39 0236725581) if a subject has a post randomization change in health status that is associated with an exclusion criterion.
Also, a decision to stop prematurely the overall recruitment in the study and/or intake of study drug can be taken by the Executive Committee/Promoter following advice on safety aspects of the study by the DSMB. The IECs/IRBs will be informed of this decision. The DSMB stopping guidelines will be defined prior to the start of the study. The Promoter has the right to close the study and the right to close a center, at any time, although this should occur only after consultation between involved parties and the Executive Committee. The IECs/IRBs must be informed. Should the site be closed prematurely, all study materials (except documentation that has to remain stored at site) must be returned to the Promoter. The investigator will retain all other documents until notification by Promoter for destruction.
If the subject is withdrawn due to an adverse event, the investigator will follow the subject until the adverse event has resolved or stabilized.

Emergency Surgery

If an urgent surgical intervention is needed, anticoagulant therapy should be discontinued and the surgery should be deferred, if possible, until at least 12 hours and ideally 24 hours after the last administration of anticoagulant therapy. There is no reversal agent for apixaban. Protamine can be used to (partially) reverse the effect of dalteparin. Depending upon the clinical situation and local availability, the use of coagulation factors or other measures can be considered in case of the recent intake of apixaban prior to the surgical procedure. It is recommended to consult the Medical Support Line (telephone number: +39 0236725581) in case of urgent surgery.

Therapeutic Management of Subjects for Planned Interventions

It is advised to withhold apixaban at least 48 hours prior to elective surgery or invasive procedures with a high risk of bleeding. This includes interventions for which the probability of clinically significant bleeding cannot be excluded or for which the risk of bleeding would be unacceptable.
Apixaban should be discontinued at least 24 hours prior to elective surgery or invasive procedures with a low risk of bleeding. This includes interventions for which any bleeding that occurs is expected to be minimal, non-critical in its location or easily controlled.
Apixaban should be restarted after the invasive procedure or surgical intervention as soon as possible provided the clinical situation allows and adequate hemostasis has been established.
Dalteparin should be withhold at least 24 hours prior to the planned intervention. Dalteparin can be resumed upon complete hemostasis and after the assessment of the bleeding risk, i.e., after 6 to 24 hours for most minor procedures and after 2-3 days for most surgical procedures that carry a bleeding risk.
Antithrombotic therapy other than the study drug can be initiated, e.g., a (prophylactic) dose of LMWH, according to the institutional best practice, until re-initiating dosing of the study drug is considered to be appropriate.
It is recommended to consult the Medical Support Line (telephone number: +39 0236725581) in case of any further questions on the management of subjects who need a planned intervention.

Therapeutic Management of Subjects in Other Critical Situations

Other critical situations could be admission to hospital for acute medical illness or active periods of chemotherapy. In these circumstances, gastrointestinal disorders might preclude intake of oral therapy with apixaban and bridging to LMWH is allowed. In case of doubt it is recommended to contact the Medical Support Line (telephone number: +39 0236725581).

6.5.2 Withdrawal of Consent from Study Participation

In accordance with the Declaration of Helsinki and other applicable regulations, a subject has the right to withdraw consent from study participation at any time and for any reason without prejudice to his or her future medical care by the physician or at the institution.
However, it is important to distinguish between withdrawal of consent with regards to continuing on study medication (but continuing to be followed on study) versus withdrawal of consent with regards to discontinuing the study all together (i.e., withdrawal of consent with regards to continuing on study medication and any further study follow-up).
Only subjects who refuse all 4 of the following methods of follow-up will be considered to have withdrawn consent from study participation:

- Participation in the trial follow-up visits per protocol, either in clinic or by telephone;

- Contact by trial personnel even if only by telephone;
- Permission for trial personnel to contact an alternative person (e.g., family member, spouse, partner, legal representative, physician, the anticoagulation clinic, or another healthcare provider) even if only by telephone;
- Permission for trial personnel to access and review their medical information from alternative sources (e.g., doctor's notes, hospital records).

If the subject refuses all 4 of the above methods of follow-up, the investigator should personally speak to the subject to ensure the subject understands all the potential methods of follow-up. If the subject continues to refuse all potential methods of follow-up, the Investigator will document this as a withdrawal of consent in the medical record.
All subjects should be followed for the full duration of the trial using any or all of the above methods, unless there is written documentation by the investigator of the subject's withdrawal of consent to ALL of the above methods of follow-up.
The site will complete and report the observations as thoroughly as possible up to the date of consent withdrawal and including the date of the final dose of study drug. The reason(s) for limited follow-up/data collection will be clearly documented in the medical record and eCRF.
Public databases and subject finder services may be used to determine subject status and to locate potential lost to follow-up patients.

6.5.3 Subjects Lost to Follow-Up

The investigator will make every effort not to have any subjects lost to follow-up. If a subject is potentially lost to follow-up (e.g., missed study visits, unable to be contacted by phone), the investigator will make every effort to contact the subject before the subject is declared lost to follow-up.

6.6. Withdrawal Procedures

Follow-Up of Subjects with Study Drug Discontinuation
The investigator may contact the dedicated Medical Support Line (telephone number: +39 0236725581) in case of any questions regarding how to handle a study drug discontinuation or interruption.
All randomized subjects, including those who temporarily interrupted or discontinued study drug, will be followed for a 7-month period after randomization, except when the study is truncated as noted in Section 6.5.1.
In case of premature discontinuation of treatment, study outcomes can be collected by telephone contact until 7 months after the first dose of study drug. If the subject has an on-site visit at any time after study drug discontinuation, it is expected that a clinical status will be obtained along with any laboratory assessments deemed appropriate by the Investigator.

If the subject and investigator agree that study drug can be resumed without increased hazard to the subject, study medication may be resumed at any time, regardless of the duration of study drug interruption.
Any subject who temporarily interrupts or discontinues study drug due to confirmed liver enzyme abnormalities or jaundice in the absence of a known cause, must have an evaluation to determine the cause of the event. Evaluation may include the following depending on the clinical situation:

- Abdominal ultrasound;
- Hepatitis A, B, C, and E screening (anti-HAV IgM, HbsAg, anti-HCV plus viral titer, and evaluation for Hep E), Antinuclear antibody (ANA) and anti-SmAb, Cytomegalovirus (CMV), Epstein Barr virus (EBV);
- Additional evaluations as deemed appropriate by the investigator to exclude other causes of liver enzyme and bilirubin elevations.

Follow-up of liver enzymes and bilirubin (total and direct) should be performed on a weekly basis until the values return to baseline.
All laboratory results, including local laboratory reference ranges are to be recorded in the eCRF.
All clinically significant hepatic enzyme abnormalities and/or hepatic events are to be documented in the eCRF and prompt submission of the adjudication dossier should also occur when indicated.

7. DATA QUALITY CONTROL AND ASSURANCE

7.1. Requirements for investigational sites and staff

The investigator should be able to demonstrate (e.g., based on retrospective data) a potential for recruiting the required number of suitable subjects within the agreed recruitment period.

The investigator should have sufficient time to properly conduct and complete the trial within the agreed trial period.

The investigator should have available an adequate number of qualified staff trained on protocol procedures and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely.

7.2. Direct access to Source Data/Documents

Original data, also known as source data/records, are those data elements that represent the first recording of study data. Original data contain all the information that is necessary for the reconstruction and evaluation of the study. Examples of original data are 1) subject's information used in a clinical trial whether collected on paper or electronically

at the time of the subject's visit, 2) certified copies of original records, 3) observations, and 4) laboratory data from clinical laboratories. Clinical investigators maintain control over source data from inception to the end of the regulatory retention period. The investigator must permit access to these data during Exom Site Monitor's monitoring visits, audits, ECs reviews, and regulatory inspections.
In addition to original records maintained by the clinical site as part of their standard practices of patient care, this study requires that certified electronic copies of:
a) the index VTE event (qualifying imaging) and of cancer diagnosis (histology reports) during the period that extends from screening period up to two weeks after randomization
b) all suspected outcome events as soon as they occur.
to be uploaded by the investigator into a dedicated eSource repository, independent from the study database, access to which is controlled by the qualified investigative site staff. Only authorized Exom Group users can get access to these eSource documents and provide in an anonymized format, to the Clinical Event Adjudication Committee (CEC) for review and classification, those documents related to clinical events and diagnoses.

7.3. Investigator Site File and archiving

The investigator will be provided with an access to an electronic investigator site file (eISF) at the start of the trial. The investigator will archive all trial data and relevant correspondence in the ISF. The ISF, all source data and all documents will be kept filed according to the requirements of the ICH-GCP guidelines not only during the study period but also after its termination.
It is responsibility of the investigator to ensure that the subject-identification sheets and the originally signed informed consent forms are properly stored for at least 15 years beyond the end of the clinical trial.

7.4. Monitoring

Monitoring procedures will be followed, in order to comply with Good Clinical Practice (GCP) guidelines. Three different types of monitoring activities will be performed by the appointed CRO: on site, remote and central monitoring.
Each center will be visited at regular intervals by a CRO Site Monitor to ensure compliance with the study protocol, GCP and legal aspects. This will include on-site checking of the electronic case report forms (eCRF) for completeness and clarity, cross-checking with source documents, and clarification of administrative matters.

The Site Monitor will ensure that the investigator will maintain a list of sub-investigators and other appropriately qualified persons to whom he or she has delegated significant trial-related duties (personnel log). During the on-site monitoring visits, the Site Monitor will review the entries into the eCRF for completeness and correctness and verify the entries on the basis of the source documents. The presence of correct informed consents will be checked for every subject.
The investigator must allow the Site Monitor to look at all relevant documents and must provide support at all times to the Site Monitor.
Moreover, remote monitoring by means of phone calls between investigators and Site Monitors will be done.
The risk for the occurrence of quality and safety issues will be regularly and centrally monitored through the use of a "Risk Based Monitoring & Management" (RBM) platform. For each of following six risk categories: 1) site management quality, 2) data quality, 3) data timeliness, 4) source documents verification, 5) milestone delay, 6) subject safety, study specific risk indicators and related scores will be defined and closely and centrally monitored during the entire study period. This will allow prompt and targeted remedial actions.

8. STUDY ORGANIZATION

The study will be coordinated by the Internal and Cardiovascular Medicine and Stroke Unit of the University of Perugia, Italy and by the Research Department of FADOI Foundation. FADOI Foundation is the Promoter of the study, and owner of the data.
The study will be approved by appropriate Competent Authorities as well as Central IRB, if available, or by Local Ethical Committee of each participating institution. All patients will sign an informed consent form after the explanation of the protocol and the purpose of the study.

8.1 Study Committees

Steering committee

The Steering Committee will consist of the Principal Investigator of the study, the National Coordinators and members of FADOI Foundation and University of Perugia, Italy. This Committee will have the final responsibility for the study design and oversight, as well as data verification and analyses. All the members of the steering committee will have access to the study data, contribute to the interpretation of the results, approve the final version of the manuscript, and make the decision to submit the manuscript for publication, and vouch for the accuracy and completeness of the data reported and the fidelity of the article to the

study protocol. A Writing Committee composed by Steering Committee members will write the first version of the manuscript.

Clinical Event Adjudication Committee

An independent committee, whose members will be unaware of treatment allocation, will adjudicate all suspected outcome events and the qualifying diagnosis, the anatomical extent of the initial DVT or PE.

Data Safety Monitoring Board (DSMB)

An independent Data and Safety Monitoring Board will periodically review the study outcomes having all information available concerning treatment allocation. A DSMB charter will be provided to the board members before the start of the study.

9. ADVERSE EVENTS

9.1 Definition

An **Adverse Event (AE)** is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation subject administered study drug and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of study drug, whether or not considered related to the study drug.

The causal relationship to study drug is determined by a physician and should be used to assess all adverse events (AE). The causal relationship can be one of the following:

- **Related:** There is a reasonable causal relationship between study drug administration and the AE.
- **Not related:** There is not a reasonable causal relationship between study drug administration and the AE.

The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject (in order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs).

9.1.1 Serious Adverse Events

A **Serious Adverse Event (SAE)** is any untoward medical occurrence that at any dose:

- results in death;
- is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe);
- requires hospitalization or causes prolongation of existing hospitalization (see **NOTE** below);
- results in persistent or significant disability/incapacity;
- is a congenital anomaly/birth defect;
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [e.g., medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or seizures that do not result in hospitalization. Potential drug induced liver injury (DILI) is also considered an important medical event.

Although not always serious adverse events by regulatory definition, the following events must be handled as SAEs: pregnancy, overdose, newly diagnosed cancer, exposure (to fetus) during pregnancy, exposure (to infant) during lactation, and paternal exposure, overdose, abuse, misuse, off-label use, occupational exposure, medication error and potential medication error, suspected transmission of an infectious agent (e.g., any organism, virus or infectious particle pathogenic or non-pathogenic, via the medicinal product).

NOTE:

The following hospitalizations are not considered SAEs in FADOI Foundation clinical studies:

- a visit to the emergency room or other hospital department of less than 24-hour duration, that does not result in admission (unless considered an important medical or life-threatening event);
- elective surgery, planned prior to signing consent;
- admissions as per protocol for a planned medical/surgical procedure;
- routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy);
- medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases;
- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing,

economic inadequacy, caregiver respite, family circumstances, administrative reason);

- admission for administration of anticancer therapy in the absence of any other SAEs (applies to protocols involving cancer patients).

9.1.2 Adverse Events of Special Interest (AESI)

In this study, the following adverse events of special interest (AESI) are to be reported to CRO/Promoter immediately, regardless of whether these reports are classified as serious or unexpected:

- potential or suspected cases of liver injury including but not limited to liver test abnormalities, jaundice, hepatitis or cholestasis.

9.1.3 Bleeding Outcomes

All major bleedings defined as:

- a decrease in hemoglobin of 2 g/dl or more;
- a transfusion of 2 or more units of packed red blood cells;
- bleeding that occurs in at least one of the following critical sites [intracranial, intra-spinal, intraocular (within the corpus of the eye; thus, a conjunctival bleed is not an intraocular bleed), pericardial, intra-articular, intramuscular with compartment syndrome, or retroperitoneal];
- bleeding that is fatal (defined as a bleeding event that the independent Clinical Event Adjudication Committee determined was the primary cause of death or contributed directly to death);
- bleeding that necessitates surgical intervention

and all clinically relevant non-major bleedings must be reported and will be reviewed and classified by the CEC.

9.1.4 Adverse Event Severity

The following categories and definitions of intensity as determined by a physician should be used for all FADOI Foundation clinical study AEs:

- Mild (Grade 1) → Event which is well tolerated by the patient and does not interfere with normal daily activities;
- Moderate (Grade 2) → Event which results in discomfort for the patient and impairs his/her normal activities;
- Severe (Grade 3) → Medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling and resulting in substantial impairment of normal activities of the subject;

- Very Severe (Grade 4) → Life-threatening consequences; urgent intervention indicated.

9.1.5 Clarification of the difference in meaning between "serious" and "severe"

The terms “serious” and “severe” are not synonymous but are often used interchangeably. The term ‘severe’ is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor significance (such as severe headache). This is not the same as “serious”, which is based on subject/event outcome or action criteria usually associated with events that pose a threat to a subject’s life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

9.1.6 Adverse Drug Reaction (ADR)

An adverse drug reaction is any noxious and unintended response to an investigational medicinal product (the causal relationship between the medicinal product and the adverse event is at least a reasonable possibility).

9.1.7 Serious Adverse Drug Reaction (SADR)

If there is a causal relationship between a serious adverse event and trial medication, then the event is called serious adverse drug reaction (SADR).

9.1.8 Suspected Unexpected Serious Adverse Reaction (SUSAR)

A SUSAR is a serious adverse reaction which is unexpected. An unexpected serious adverse reaction is any adverse reaction, the nature or severity of which is not consistent with the current Summary of Product Characteristics.

9.1.9 Causality Assessment

The following categories and definitions of causal relationship to investigational product as determined by a physician should be used for all FADOI Foundation clinical study AEs:
• **Certain:** There is a reasonable causal relationship between the investigational product and the AE. The event responds to withdrawal of investigational product (dechallenge), and recurs with rechallenge when clinically feasible.
• **Probable:** There is a reasonable causal relationship between the investigational product and the AE. The event responds to dechallenge. Rechallenge is not required.
• **Possible:** There is reasonable causal relationship between the investigational product and the AE. Dechallenge information is lacking or unclear.

• **Not likely:** There is a temporal relationship to investigational product administration, but there is not a reasonable causal relationship between the investigational product and the AE.
• **Not related:** There is not a temporal relationship to investigational product administration (too early, or late, or investigational product not taken), or there is a reasonable causal relationship between non-investigational product, concurrent disease, or circumstance and the AE.

9.1.10 Action Taken Regarding the Study Product

- 1 = Dose Not Changed → No change in study drug dosage was made;
- 2 = Drug Withdrawn → The study product was permanently stopped;
- 3 = Drug Interrupted → The study product was temporarily stopped.

9.2 Collection, Reporting and Documentation of AEs

This study will follow a targeted approach to AE and SAE collection and reporting.
All AEs occurring after the subject signs the ICF and through Month 6 or the global EOT date, whichever occurs first, whether observed by the Investigator or reported by the subject, will be recorded on the Adverse Events section of the eCRF if they fulfill one of the following criteria:
1) meet seriousness criteria;
2) result in interruption or discontinuation of the assigned study drug;
3) meet criteria as a study outcome; or
4) an event of special interest.
All laboratory, vital sign, or electrocardiogram (ECG) values should be evaluated by the Investigator regarding clinical significance. Isolated abnormal laboratory results or vital sign findings or ECG findings should be reported as AEs if they are symptomatic, result in study drug discontinuation, require corrective treatment, or are otherwise defined as an AE of Special Interest (AESI).
Clinically significant abnormal laboratory findings associated with the subject's cancer or other pre-existing conditions will not be reported as AEs or SAEs unless judged by the Investigator as more severe than expected for the subject's condition and meet the criteria for targeted AE and SAE reporting.
Medical conditions (including laboratory values/vital signs that are out of range) that were diagnosed or known to exist prior to informed consent will be recorded as part of medical history.
All SAEs occurring after informed consent for study participation has been obtained, which are considered not related with the subject's cancer or other pre-existing conditions,

are to be reported according to the procedures for Serious Adverse Event Reporting-Procedure for Investigators.
A preplanned (prior to signing the Informed Consent Form) procedure or treatment requiring hospitalization for pre-existing conditions which do not worsen in severity should not be reported as SAEs.
For deaths, the underlying or immediate cause of death should always be reported as an SAE. When a subject dies from disease progression of pre-existing cancer with no other immediate causes, "disease progression" should be reported as an SAE. In addition, any serious, untoward event that may occur subsequent to the reporting period that the Investigator assesses as related to study drug should also be reported and managed as an SAE.
Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs. If known, the diagnosis of the underlying illness or disorder should be recorded, rather than its individual symptoms. The following information should be captured for all AEs: onset, duration, intensity, seriousness, relationship to investigational product, action taken and treatment required and outcome. If treatment for the AE was administered, it should be recorded on the appropriate eCRF page.
The Investigator's assessment must be clearly documented in the site's source documentation with the Investigator's signature.
Investigator should follow subjects with AEs until the event has resolved or the condition has stabilized.
In case of unresolved AEs including significant abnormal laboratory values at the end of study assessment, these events will be followed up until resolution or until they become clinically not relevant.
The investigator shall supply the Promoter and Ethics Committee with any additional requested information, notably for reported deaths of subjects. Possible additional information on the AE collected/identified during the study will be reported on the eCRF.

9.2.1 Serious Adverse Event Collection and Reporting for Investigators

Following the subject's or the legal representative's written consent to participate in the study, all AEs, SAEs, AESIs, bleeding outcomes and study outcomes will be captured in the eCRF.
Study outcomes are clinically anticipated events and will be periodically reviewed by the DSMB to ensure prompt identification of any clinically concerning safety issues. Study outcomes (suspected recurrent DVT or PE, major bleedings, clinically relevant non-major bleedings, MI, stroke, and venous thrombotic events at other locations) will be exempted from expedited safety reports of suspected unexpected serious adverse reactions

(SUSARs) to regulatory authorities, Investigators, IECs, and IRBs. All SAEs resulting in death, regardless of whether they are waived endpoint events, will be captured in the Promoter's global safety database.

The following types of events whether related or not related to study drug, must be reported within 24 hours of the Investigator's awareness, to the Contract Research Organization Exom Group:

- **SAEs**
- **AESIs**
- **Severe Hypersensitivity** (Steven-Johnson Syndrome, Toxic Epidermal Necrolysis)
- **Overdose**
- **Pregnancies**

As a preferred method, all SAEs and Liver Enzyme abnormalities/dysfunction events, must be recorded on the **eSAE Report Form** of the eCRF; while pregnancies on the **ePregnancy Surveillance Form**.

The paper SAE/Pregnancy Surveillance forms are only intended as a back-up option when the eCRF system is not accessible. In this case, the original paper forms are to remain on site and copies are to be transmitted via email or confirmed facsimile (fax) transmission to:

SAE Email Address: caravaggio.phv@exomgroup.com

A **SAE Telephone Contact Number +39 06 9480 1010** is also available, in case of additional support.

The initial SAE Report should be as complete as possible including the essential details of subject's identification (Subject ID), the serious adverse event (medical term, diagnosis), the trial medication and the assessment of the causal relationship between the event and the trial medication. The SAE report must be reviewed and signed by the investigator.

The investigator should provide related additional information on the clinical course and the outcome of each SAE as soon as possible **(eSAE Follow-up Report).**

9.2.2 Notifying Regulatory Authorities, Investigators, and IRB/IEC

The study Promoter FADOI Foundation will ensure that all legal reporting requirements are met, according to local laws and regulations. Further, according to GCP, the study Promoter is responsible for the continuous safety evaluation of the product(s) investigated in the clinical trial.

FADOI Foundation and/or Exom Group will notify the Competent Authorities and Ethics Committees of all SAEs that are suspected (certainly, probably, or possibly related to the investigational product) and unexpected (i.e., not previously described in the Summary of Product Characteristics), the so called Suspected, Unexpected Serious Adverse

Reaction (SUSAR, see Section 9.1.8). Notification of these events will be in the form of an **Expedited Safety Report** (ESR), to be delivered as soon as possible but not later than 15 calendar days if the event is non-fatal and 7 calendar days if it was fatal.
All investigators will be informed, too.
Other important findings which may be reported by the study Promoter as an ESR include:

- increased frequency of a clinically significant expected SAE;
- a SAE considered associated with study procedures that could modify the conduct of the study;
- important safety recommendations from the study Data and Safety Monitoring Board (DSMB, see below), or
- Promoter's decision to end or temporarily halt a clinical study for safety reasons.

During the clinical trial duration, the Promoter will submit to the Ethics Committee(s) and to the Competent Authorities, once a year, a study specific **Development Safety Update Report (DSUR)** including a list of all serious adverse reactions.

FADOI Foundation is also responsible for reporting of safety information to the marketing authorization holders (Bristol-Meyers Squibb and Pfizer) of the two investigational products.

Work flow, procedures and responsibility concerning SAE management will be described in a separate document named SDEA (Safety Data Exchange Agreement)**.**

All potential study outcomes (e.g. DVT, PE) and potentially major or clinically relevant bleedings will be adjudicated by the **Clinical Event Adjudication Committee (CEC).** The result of the adjudication will be a classification of the event as

- primary efficacy or safety endpoint or
- no outcome.

The classification will be recorded in the study database.

A **Data Safety Monitoring Board (DSMB)** will be established for this study, and responsible for monitoring of safety and efficacy during the course of the clinical trial. The recommendations of the DSMB with respect to the study conduct will be presented to the study's **Steering Committee (SC),** in writing.

9.3 Laboratory Test Result Abnormalities

Only laboratory test result abnormalities that meet one of the following criteria:

- clinically significant or meets the definition of a SAE
- requires the subject to have study drug omitted or discontinued

- requires the subject to receive specific corrective therapy

should be recorded in the AE section of the study eCRF and reported immediately (within 24 hours of the Investigator's awareness) as any SAE (see Section 9.2.1) by the means of the eSAE Report Form.
It is expected that wherever possible, the clinical rather than laboratory term would be used by the reporting investigator (e.g., anemia versus low hemoglobin value).

9.4 Pregnancy

If, following initiation of the study drug, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of study drug exposure, including during at least 5 half-lives after product administration, the investigator must immediately notify FADOI Foundation of this event and complete and forward a Pregnancy Surveillance Form to FADOI Foundation within 24 hours and in accordance with SAE reporting procedures.
In most cases, the study drug will be permanently discontinued in an appropriate manner. In the rare event that the benefit of continuing study drug is thought to outweigh the risk, after consultation with FADOI Foundation, the pregnant subject may continue study drug after a thorough discussion of benefits and risk.
Protocol-required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (e.g., x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated.
The Investigator should make every effort to follow the subject until completion of the pregnancy. If the outcome of the pregnancy meets the criteria for immediate classification as a SAE (i.e., post-partum complications, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly, including that in an aborted fetus), the Investigator should follow the procedures for reporting SAEs by the means of the ePregnancy Surveillance Form.
Any pregnancy that occurs in a female partner of a male study participant should be reported to FADOI Foundation as well. Information on this pregnancy will be collected on the ePregnancy Surveillance Form.

9.5 Overdose

All occurrences of overdose must be reported as SAEs.

10. STATISTICAL CONSIDERATIONS

10.1. Sample Size / Power Determinations

The study has been designed to test the hypothesis that apixaban would be non-inferior to dalteparin with respect to the primary efficacy outcome.
The criteria for non-inferiority require that the upper limit of the two-sided 95% confidence interval of the Hazard ratio is below the pre-specified margin of 2.00.
With the use of an estimated incidence of the primary efficacy outcome of 7% at 6 months with dalteparin and an upper non-inferiority margin of 2.00 for the hazard ratio, we calculated that we would need to enroll 934 completer patients for the study to have 80% power to show the non-inferiority of apixaban, at a one-sided alpha level of 0.025. This sample will be increased to 1168 patients to account for up to 20% lost in total patient-years.
This estimate is consistent with a drop-out rate of 40% assuming patients discontinued uniformly during the follow-up (mean discontinuation time equal to 3 months).

		HR Non-inferiority margin					
		1.75	2.0		2.25		
Event rate	6%		1090		796		Sample size (pts)
	7%		934	1250	683	914	
	8%	1250	817		597		
		80%	80%	90%	80%	90%	
		Power					

10.2. Rationale for the event rates in the two treatment arms

Recurrence rate for dalteparin treated arm
An event rate of 7% has been chosen according to the findings of the CLOT and of the CATCH trials.
Both studies used a prospective randomized open blinded end-point (PROBE) design, had warfarin as the comparator vs LMWH, the same definition for active cancer, the same inclusion criteria concerning initial thromboembolic events, and the same treatment duration (6 months). Unlike the CLOT trial, in which dalteparin was given at a reduced dose after the first month, tinzaparin was given at a full dose throughout the study period in the CATCH study. The primary composite efficacy outcome was symptomatic

recurrent VTE in the CLOT trial and symptomatic recurrent VTE plus unsuspected VTE in the CATCH trial.
Reported incidence rates of recurrent VTE with LMWH were slightly different between the two studies, being 8.0% with Dalteparin in the CLOT study and 7.2% with Tinzaparin in the context of the CATCH trial. The incidence of recurrent VTE was higher in patients receiving warfarin in the CLOT trial (15.8%) than in the CATCH trial (10.5%); a risk reduction for recurrent VTE with LMWH as compared with warfarin of 52% and 35% was reported in the two studies, respectively. The 6-month mortality was lower in CATCH compared with CLOT (32% vs 40%).
The lower risk for recurrent VTE observed in the CATCH trial may reflect critical differences in patient populations between the two studies. The prevalence of risk factors for recurrent thrombosis was lower in the CATCH as compared to the CLOT population and in particular fewer patients had metastatic disease (55% in CATCH vs 67% in CLOT), an ECOG performance status of 2 (23% for CATCH vs 36% for CLOT); less patients in the CATCH study received anticancer therapy (53% vs 78%), and had a previous history of thrombosis (6% vs 11%) compared with CLOT study. Moreover, differences in primary tumor sites and associated anticancer treatments, and the 10-year time gap between the 2 trials (during which cancer treatments have evolved) might also have contributed to the different risk for recurrent VTE.
From the timing context point of view, our patient population is presumed to be closer to that of the CATCH study (published in 2015) than to the CLOT study (published in 2003). So it is plausible that patients enrolled in the Caravaggio study will receive less thrombogenic anticancer chemotherapy and improved disease management, as well as they will have less frequently a metastatic disease, due to an earlier diagnosis (screening improvement), like in the CATCH trial.
As a further support to our study hypothesis, the ONCENOX trial, published in 2006, compared Enoxaparin (1.0 mg/kg bid for 5 days + warfarin for 6 months) vs Enoxaparin (1.0 mg/kg bid for 5 days followed by Enoxaparin 1.0 mg/kg od) (low dose – LD) with Enoxaparin (1.5 mg/kg od (high dose - HD) for 6 months) (13). The study was small with limited statistical power, and recurrent VTE was only a secondary objective. However, the rate of this endpoint was 6.9% with the LD and 6.3% with the HD of enoxaparin, therefore comparable to that observed in the CATCH trial.

Recurrence rate for apixaban treated arm

In a post hoc analysis of the Amplify study, 169 patients (3.1%) had active cancer at baseline and 365 (6.8%) had a history of cancer without active cancer at baseline. Among patients with active cancer, recurrent VTE occurred in 3.7% and 6.4% of evaluable patients in the apixaban and enoxaparin/warfarin groups, respectively (relative risk 0.56, 95% confidence interval 0.13-2.37). Among patients with a history of cancer, recurrent VTE occurred in 1.1% and 6.3% of evaluable patients in the apixaban and enoxaparin/warfarin groups, respectively (relative risk 0.17, 95% confidence interval 0.04-0.78). Based on these figures, and taking into account that in the present study more

patients with active cancer will be included, it is expected that the recurrent VTE rate in the apixaban treated patients will not be higher than the 7-8% observed in the LMWH treated groups in CLOT and CATCH studies.

10.3. Rationale for Non-inferiority margin (delta) choice

The goal of this trial is to test a drug that could lead to the more convenient oral route of administration and a trend towards better safety than the currently recommended LMWH treatment for cancer patients with VTE (14), thus fulfilling a gap within this therapeutic indication. In this situation, the choice of a relatively "large" delta for efficacy might be accepted in exchange for the possible safety and compliance benefits, provided that a putative superiority to placebo is not left in doubt (*EMEA/CPMP/EWP/2158/99 Document. Guideline on the choice of non-inferiority margin. July 27, 2005*). Based on these assumptions, the upper limit of the two-sided 95% confidence intervals of the Hazard ratio below the pre-specified margin of 2.00 planned for our study seems to us acceptable from a clinical and methodological point of view.
Further, it's worth reminding that the non-inferiority margins used in pivotal trials on VTE therapy with direct oral anticoagulants were the following:

- 1.5 for HOKUSAI-VTE (Edoxaban) (15)
- 1.8 for AMPLIFY (Apixaban) (16)
- 2.0 for EINSTEIN DVT and EINSTEIN PE (Rivaroxaban) (17-18)
- 2.75 for RECOVER I and II (Dabigatran) (19-20)

All the above mentioned studies were considered valid by EMA and FDA for registration of direct oral anticoagulants for the indication "treatment of VTE".

10.4. Analysis Populations

The Full Analysis Set (FAS) consists of all randomized patients.
The primary efficacy data set will consist of all randomized subjects who received at least one dose of the study drugs (modified intent-to treat population). Subjects will be categorized to the group to which they were assigned at randomization, regardless of the treatment actually received.
Secondary efficacy data sets will consist of a) all randomized subjects (intent-to treat population) and b) the per-protocol population. The per-protocol population will be defined in the SAP.
The safety data set (as-treated) will consist of all treated subjects (randomized subjects who received at least one dose of study drug). For the purpose of safety analyses, subjects will be categorized to the group to which they were assigned at randomization unless incorrect study treatment was received throughout the study, in which case the subject will be categorized according to the treatment received.

A Per Protocol (PP) population will consist of all patients in the FAS population who complete the study fully compliant with the protocol and without any major violation / deviation. Patients in the PP population will be analyzed according to the treatment they actually received. Efficacy analyses based on PP population will be considered supportive. The Safety population will consist of all randomized patients with at least one documented administration of any study drug. It will be the basis for the analyses of safety. Patients in the Safety population will be analyzed according to the treatment they actually received. Of note, a statement that a patient experienced no adverse events also constitutes a safety assessment.

10.5. Demographic and Baseline Data

Demographic and baseline patient characteristics will be summarized by treatment group for all patients in the FAS. Continuous-scaled variables (e.g., age) will be summarized with means, medians, standard deviations, quartiles, and minimum and maximum values. Categorical variables (e.g., sex) will be summarized using patient counts and percentages. Baseline medical histories and pre-existing conditions will be summarized by treatment group based on mapping to system organ classes (SOCs) and preferred terms in the Medical Dictionary for Regulatory Activities (MedDRA). Medications taken after the informed consent form is signed and before randomization will be summarized by treatment group, based on mapping to drug classes and generic terms in the WHO Drug Dictionary.

10.6. Efficacy Analyses

<u>Analysis of Primary Endpoint</u>
Analyses of the primary efficacy endpoint will be performed using the modified intent-to-treat and the intent-to treat principle and the per protocol principle. The modified intent-to-treat and the intent-to-treat analyses of the primary endpoint will include endpoints that occur at any time from randomization until the end of their originally intended treatment period regardless of whether subjects were receiving study medication.
The primary efficacy variable, i.e. the time from randomization to the first recurrent thromboembolic event, will be analyzed after adjusting estimates for the competing risk of death unrelated to VTE (21). The competing risk analysis will be performed using the SAS macro %PSHREG (22) while the probabilities of failure for the event of interest (first recurrent thromboembolic event) are displayed using cumulative incidence plots which do account for the competing risk (death unrelated to VTE).
The null hypothesis to be tested will be that apixaban is inferior to dalteparin in the prevention of recurrent thromboembolic events during 6-month follow-up; i.e. $H_0 \rightarrow E[HR] \geq 2.00$.

The alternative hypothesis will be that apixaban is non-inferior to dalteparin in the prevention of recurrent thromboembolic events during 6-month follow-up; i.e. $H_a \rightarrow E[HR] < 2.00$.
Where: E[HR] is the Expected (E) apixaban-to-comparator Hazard Ratio (HR), while 2.00 is the prefixed non-inferiority threshold.
The evaluation of the primary objective will be done by considering the time from randomization to the first recurrent thromboembolic event (event of interest) or to the occurrence of death unrelated to VTE (nuisance/competing event) or to the last follow-up if neither a recurrent thromboembolic event nor a competing event occurred within the 6-month follow-up (censored time). The apixaban-to-comparator Hazard Ratio adjusted for the competing risk of death unrelated to VTE will be computed with associated two-sided 95% confidence interval by resorting to the Fine & Gray regression model (23) using treatment group and center as dummy covariates. Apixaban will be considered non-inferior to the comparator dalteparin if the upper two-sided 95% confidence limit of Hazard ratio is < 2.00.
Superiority of apixaban vs. dalteparin will be tested as a secondary analysis of the primary endpoint, only after non-inferiority has been demonstrated for the experimental treatment group (apixaban) relative to the conventional treatment group (dalteparin). According to CPMP/EWP/482/99 document entitled: "Points to consider on switching between superiority and non-inferiority", switching the apixaban vs. dalteparin contrast from the non-inferiority objective to the superiority objective is feasible because the trial is properly designed in accordance to the strict requirements of a non-inferiority trial.

<u>Analysis of Secondary Endpoints</u>
For the secondary efficacy endpoints, analyses will be performed using the primary efficacy data set.

- *The individual components of the primary efficacy outcome:* The same competing risk model (23) defined above for the analysis of primary efficacy variable will be employed for the analysis of the time from randomization to the first recurrent event among those included in the primary efficacy outcome recurrent (see 4.1). The apixaban-to-comparator Hazard Ratio adjusted for the competing risk of death unrelated to VTE will be computed with associated two-sided 95% confidence interval.

- *Symptomatic recurrence of VTE:* The same competing risk model (23) defined above for the analysis of primary efficacy variable will be employed for the analysis of the time from randomization to the first symptomatic recurrent thromboembolic event. The apixaban-to-comparator Hazard Ratio adjusted for the competing risk of death unrelated to VTE will be computed with associated two-sided 95% confidence interval.

- *Composite of primary efficacy outcome plus major bleeding:* The same competing risk model (23) defined above for the analysis of primary efficacy variable will be employed for the analysis of the time from randomization to the composite of primary

efficacy outcome plus major bleeding. The apixaban-to-comparator Hazard Ratio adjusted for the competing risk of death unrelated to VTE or major bleeding will be computed with associated two-sided 95% confidence interval.

- *All cause of death:* Event free survival will be estimated according to Kaplan-Meier and the event free survival in the two treatment groups will be compared by means of a Cox's proportional hazard model with treatment group and center as dummy covariates. The apixaban-to-comparator Hazard Ratio will be computed with associated two-sided 95% confidence interval.

- *Composite of primary efficacy outcome plus major bleeding plus all cause death:* Event free survival will be estimated according to Kaplan-Meier and the event free survival in the two treatment groups will be compared by means of a Cox's proportional hazard model with treatment group and center as dummy covariates. The apixaban-to-comparator Hazard Ratio will be computed with associated two-sided 95% confidence interval.

- *Composite of primary efficacy outcome plus all cause death:* Event free survival will be estimated according to Kaplan-Meier and the event free survival in the two treatment groups will be compared by means of a Cox's proportional hazard model with treatment group and center as dummy covariates. The apixaban-to-comparator Hazard Ratio will be computed with associated two-sided 95% confidence interval.

- *Any fatal or not fatal cardiovascular event:* The same competing risk model (23) defined above for the analysis of primary efficacy variable will be employed for the analysis of the time from randomization to the occurrence of any fatal or not fatal cardiovascular event. The apixaban-to-comparator Hazard Ratio adjusted for the competing risk of death unrelated to cardiovascular event will be computed with associated two-sided 95% confidence interval.

- *All venous thromboembolic events (including splanchnic vein thrombosis and cerebral vein thrombosis):* The same competing risk model (23) defined above for the analysis of primary efficacy variable will be employed for the analysis of the time from randomization to thromboembolic events at sites other than DVT and PE. The apixaban-to-comparator Hazard Ratio adjusted for the competing risk of death unrelated to venous thromboembolic events will be computed with associated two-sided 95% confidence interval.

- *Quality of life evaluation (ACTS Scale)* (see Appendix 2)*:* For the total score and for each of the subscales, a linear effects model will be estimated with treatment group and center as dummy fixed effects. Results will be reported as Least-Square Means together with associated two-tailed 95% CI and p-value. ITT Analyses will be performed with missing data imputed using conventional LOCF.

<u>Multiplicity</u>

No adjustment for multiplicity is required for the primary efficacy analysis because it is focused on a single time point (6-month) at which only two treatments are being compared.

Center-to-center variability

Study center and treatment-by-center interactions are included in each of the analyses described above. To assess center-to-center variability, forest plots will be generated to display the results at each center.

Due to the possibility of small numbers of patients at some study sites, some sites may be combined in order to bring the numbers of patients in each pooled site to at least 12. Upon completion of the study and prior to unblinding, study statisticians in consultation with the Steering Committee will determine the pooling based on enrolment numbers and geographical proximity.

10.7. Safety Analyses

The analysis of safety will be based on the Safety Population, comparing patients in the two randomized arms: apixaban vs. dalteparin. AEs will be mapped to system organ classes and preferred terms in MedDRA. Treatment emergent events, defined as those that start or worsen after the start of apixaban/dalteparin AEs, will be summarized by treatment group, system organ class, and preferred term, and also by event severity and by the event's relationship to study treatment. At each level of summation, patients will be counted only once, under the greatest severity and strongest study-drug relationship (as reported by the investigator). Clinical laboratory data will be summarized for each treatment group at each measurement time point and for each patient's final post-baseline measurement in the following ways: (1) with descriptive statistics (mean, standard deviation, median, and range) for each measurement time point; (2) with descriptive statistics for the change from baseline in the measurements at each post-baseline time point; and (3) with shift tables summarizing the frequencies of patients below, within, and above the normal ranges at each time point as compared with baseline. All clinical laboratory values collected during the study will be listed, with values outside the normal ranges flagged for clinical evaluation. Concomitant medications will be summarized by treatment group based on mapping to drug classes and generic terms in the WHO Drug Dictionary.

10.8. Subgroup Analyses

Pre-specified subgroup analyses will be planned and reported in the statistical analysis plan before the un-blinding of the study.

Interim Analyses

No interim analysis is planned.

10.9. Detailed Statistical Analysis Plan

A detailed statistical analysis plan will be drafted, reviewed and approved by the Steering Committee prior of the un-blinding of the data.

11. FEASIBILITY

Overall, about 140 study centers in Europe and USA, will participate in the study. Each study center is expected to recruit not less than 10 patients in the 18-month recruitment period. The overall study duration (first patient in/last patient out) is estimated to be 25 months.

12. INSURANCE

All subjects participating in the study will have insurance coverage by the Promoter, which is in line with applicable laws and/or regulations.

13. PROMOTER

The Promoter of the study is FADOI Foundation.

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15. APPENDICES

Appendix 1 – Concomitant medications

1. Prohibited Concomitant Medications

Specifically excluded concomitant medications and cautions regarding other concomitant medications are provided below. The list in this appendix reflects exclusionary concomitant medications at the beginning of the study. If there are changes to this list during the study, the changes will be provided as an update to this appendix, but will not be considered a protocol amendment.

1.1. Antiplatelet Drugs

Dual antiplatelet therapy (any 2 antiplatelet agents including aspirin plus any other oral or IV antiplatelet drug) is prohibited while on study drug. If a clinical indication for dual antiplatelet therapy arises after randomization (eg, placement of an intracoronary stent), study drug should be interrupted and use of open-label LMWH/VKA is permitted at the physician's discretion.

Use of any antiplatelet medication, including aspirin, as single agent antiplatelet therapy is allowed while on study drug.

It is strongly encouraged to restrict the dose of aspirin (if indicated) to ≤ 100 mg daily, although higher doses are permitted for a strong clinical indication (eg, development of an acute MI).

Examples of non-aspirin oral antiplatelet agents include the following:

- Thienopyridines: clopidogrel (Plavix®), ticlopidine (Ticlid®), prasugrel
- (Effient™)
- Dipyridamole: Persantine®, Aggrenox®
- Pentoxifylline (Trental®)

- Sulfinpyrazone (Anturane®)
- Ticagrelor (Brilinta®)
- Cilostazol (Pletal®)

IV antiplatelet agents include the following:

- Glycoprotein IIb/IIIa inhibitors: Abciximab (ReoPro™), Eptifibatide
- (Integrilin®), Tirofiban (Aggrastat®)
- PGY12 Inhibitor: Cangrelor
- Dextran

1.2. Oral Anticoagulants Other Than Study Drug

Oral anticoagulants including vitamin K antagonists (eg, warfarin), Factor IIa inhibitors (eg, dabigatran), and FXa inhibitors (eg, rivaroxaban, edoxaban) after randomization are prohibited (unless used to bridge a temporary study drug interruption). The only allowed oral antithrombotics are the study drugs.

1.3. Parenteral Anticoagulants

Parenteral anticoagulants such as heparin, LMWHs, direct thrombin inhibitors, and FXa inhibitors are prohibited except as specifically outlined in the protocol. For instance, LMWHs are allowed as lead-in therapy prior to edoxaban administration. Examples of prohibited parenteral anticoagulant medications, when used contrary to protocol specifications, include the following:

- Low molecular weight heparins: dalteparin (Fragmin®), tinzaparin (Innohep®,
- Logiparin®), reviparin (Clivarin®), nadroparin (Fraxiparine®), ardeparin (Normiflo®), certoparin (Sandoparin®), parnaparin (Fluxum®)
- Direct thrombin inhibitors: bivalirudin (Angiomax®), argatroban (Acova®), desirudin (Ipravask®), lepirudin (Refludan®)

- FXa inhibitors: fondaparinux (Arixtra®)

1.4. Intravenous Fibrinolytics

Examples of fibrinolytics include the following:

- Tissue plasminogen activator (alteplase, Activase®)
- TNK (tenecteplase, TNKase®)
- rPA (reteplase, Retavase®)
- Streptokinase (Streptase®)
- Anistreplase (Eminase®)

If a subject requires treatment with a fibrinolytic agent, then study drug must be interrupted while the subject is taking the fibrinolytic drug and at least 24 hours after administration of a fibrinolytic agent.

1.5. NSAIDs (Excluding Aspirin)

While on study drug, NSAIDs cannot be taken for ≥ 4 days per week. Less frequent use of NSAIDs is permitted while on study drug. However, the Investigator should weigh the benefit/risk of NSAID use in combination with an oral anticoagulant for the individual subject. Examples of NSAIDs include the following:

1.6. COX-2 Inhibitors

While on study drug, COX-2 inhibitors cannot be taken for ≥ 4 days per week. Less frequent use of COX-2 inhibitors is permitted while on study drug. However, the Investigator should weigh the benefit/risk of COX-2 inhibitor use in combination with an oral anticoagulant for the individual subject.

1.7. Strong inhibitors of both CYP3A4 and P-gp:

- atazanavir
- boceprevir
- clarithromycin
- conivaptan
- darunavir
- darunavir/ritonavir
- erythromycin
- indinavir
- indinavir/ritonavir
- itraconazole
- ketoconazole
- lopinavir/ritonavir
- nelfinavir
- nefazodone
- posaconazole
- ritonavir
- saquinavir
- telaprevir
- telithromycin
- voriconazole

1.8. Strong inducers of both CYP3A4 and P-gp:

- avasimibe
- carbamazepine
- fosphenytoin
- phenytoin
- phenobarbital
- primidone
- rifampicin
- St John's wort

Appendix 2 – Quality of Life assessment / Anti-Clot Treatment Scale (ACTS)

During the past 4 weeks…

1. How much does the possibility of bleeding as a result of anti-clot treatment limit you from taking part in vigorous physical activities? (e.g. exercise, sports, dancing, etc.).

2. How much does the possibility of bleeding as a result of anti-clot treatment limit you from taking part in your usual activities? (e.g. work, shopping, housework, etc.).

3. How bothered are you by the possibility of bruising as a result of anti-clot treatment?

4. How bothered are you by having to avoid other medicines (e.g. aspirin) as a result of anti-clot treatment?

5. How much does anti-clot treatment limit your diet? (e.g. food or drink, including alcohol).

6. How much of a hassle (inconvenience) are the daily aspects of anti-clot treatment? (e.g. remembering to take your medicine at a certain time, taking the correct dose of your medicine, following a diet, limiting alcohol, etc.).ù

7. How much of a hassle (inconvenience) are the occasional aspects of anti-clot treatment? (e.g. the need for blood tests, going to or contacting the clinic/doctor, making arrangements for treatment while travelling, etc.).

Now I want to ask you about daily and occasional aspects of your anticoagulation therapy during the past 4 weeks

8. How difficult is it to follow your anti-clot treatment?

9. How time-consuming is your anti-clot treatment?

10. How much do you worry about your anti-clot treatment?

11. How frustrating is your anti-clot treatment?

12. How much of a burden is your anti-clot treatment?

13. Overall, how much of a negative impact has your anti-clot treatment had on your life?

14. How confident are you that your anti-clot treatment will protect your health? (e.g. prevent blood clots, stroke, heart attack, DVT, embolism)

15. How reassured do you feel because of your anti-clot treatment?

16. How satisfied are you with your anti-clot treatment?

17. Overall, how much of a positive impact has your anti-clot treatment had on your life?

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Appendix 3 – Schedule of assessments

	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Unscheduled Visit (j)
	Screening	**Enrolment**	**4-Wks**	**3-mos**	**End of Study Treatment**	**End of Study**	**UNSCH**
	-72 hrs or less	**Day 1**	**4-week after enrolment (± 7 days)**	**3-month after enrolment (± 7 days)**	**6-month after enrolment or Early withdrawal (± 7 days)**	**7 months after Randomization (± 7 days)**	**Any time during the Study Treatment period**
Informed consent	x						
Demography	x						
Medical History	x						
VTE Diagnosis (a)	x						
Cancer History (b)	x						
Cancer treatments (c)	x						
Physical Examination and Vital Signs (d)	x		x	x			x
Pregnancy test (for women of childbearing age)	x						
Serum chemistry (e)	x (f)		x	x	x		x
Hematology	x (g)		x (h)	x (h)	x (h)		x
Inclusion/Exclusion criteria	x						
Eligibility criteria		x					
Randomization		x					
Drug dispensation		x	x(k)	x			
Drug return and accountability			x	x	x		
Assess study outcomes (i.e. suspected recurrent VTE, bleeding) (i)			x	x	x	x	x
Anti-Clot Treatment Scale (ACTS)					x		
Prior and Concomitant Medications	*From 30 days prior to screening visit*						x
AE / SAE		*From first study drug administration to 30 days after the last dose of study drug administration*					*x*

(a) Symptoms of VTE, site and confirmatory tests

(b) Type, site and staging of cancer; date of diagnosis

(c) Data on type and timing of cancer treatment (chemotherapy, radiotherapy, surgery)

(d) Blood pressure, heart rate will be collected during at Screening and, if deemed necessary by the Investigator, during the unscheduled visit(s). Body weight will be collected at Screening and, for patients randomized to dalteparin, at Visit 3 and 4 (and Unscheduled, if any occurs), to correctly evaluate the drug dosage

(e) Total Bilirubin (Direct and Indirect), ALT, AST, ALP, Serum creatinine, Creatinine clearance (Cockcroft Gault equation)

(f) Samples obtained as part of routine care outside study auspices may be analyzed by local laboratories and the results used to qualify the subject provided the tests were performed within 72 hours of randomization

(g) At screening: Hematocrit, WBC, Hb, Plts, INR, PTT. Samples obtained as part of routine care outside study auspices may be analyzed by local laboratories and the results used to qualify the subject provided the tests were performed within 72 hours of randomization

(h) At 4-wks, 3-mo, 6-mo: Hematocrit, WBC, Hb, Plts

(i) For subjects who have discontinued study treatment, telephone query of health status (alive, occurrence of efficacy and safety endpoints and AEs/SAEs) is allowed. Subjects who have new symptoms should undergo further assessment as clinically appropriate, preferably at the study site whenever feasible

(j) Unscheduled Visit(s): may occur at any time, during the study treatment period. Based on the specific reason why performing an unscheduled visit, the Investigator may decide if perform or not all the assessments marked in the table above

(k) Applicable for Dalteparin patients only (Apixaban will not be dispensed at V3)

Appendix 4 – Protocol Signature Page (protocol writers)

Protocol Title:

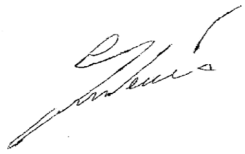
APIXABAN FOR THE TREATMENT OF VENOUS THROMBOEMBOLISM IN PATIENTS WITH CANCER: A PROSPECTIVE RANDOMIZED OPEN BLINDED END-POINT (PROBE) STUDY (**CARAVAGGIO**)

The present research protocol was subject to critical review and has been approved in the present version by the persons who undersigned. The information contained is consistent with the moral, ethical and scientific principles governing clinical as set out in the Declaration of Helsinki and the principles of ICH/GCP.

Signatures:

_____ Date: May 22nd, 2018

Giancarlo Agnelli MD, Study Chairman
University of Perugia, Italy



_____ Date: May 22nd, 2018

Giorgio Vescovo MD, FADOI

_____ Date: May 22nd, 2018

Mauro Campanini MD, FADOI

_____ Date: May 22nd, 2018

Andrea Fontanella MD, FADOI

Appendix 5 – Protocol Signature Page (principal investigator)

Protocol Title:

APIXABAN FOR THE TREATMENT OF VENOUS THROMBOEMBOLISM IN PATIENTS WITH CANCER: A PROSPECTIVE RANDOMIZED OPEN BLINDED END-POINT (PROBE) STUDY (**CARAVAGGIO**)

Declaration of Principal Investigator
I have read the present research protocol and agree to conduct the study according to the protocol.
I will enroll the first subject only after all ethical and regulatory requirements are fulfilled.
I pledge to obtain written consent for study participation from all subjects.
I pledge to retain all study-related documents and source data as described.

Principal Investigator (Head of the study center):

Name: _____

Study Center: _____

Signature: _____Date: _____