STATISTICAL ANALYSIS PLAN

Apixaban for the Treatment of Venous Thromboembolism in Patients with Cancer: A Prospective Randomized Open with Blinded End-Point (PROBE) Study - The Caravaggio Study (Study Code: FADOI 03.2016)

Short Name: **CARAVAGGIO**

IND/EUDRACT NUMBER 2016-003093-40

Authorization Signature Page

Apixaban for the Treatment of Venous Thromboembolism in Patients with Cancer:
A Prospective Randomized Open with Blinded End-Point (Probe) Study.
The Caravaggio Study (Study Code: FADOI 03.2016)

Author:

Claudio Iannacone — 29OCT2019 (Date)
Senior Biostatistician
SPARC Consulting, Milan, Italy

Reviewers:

Federico Montuori — 29 OCT 2019 (Date)
Biostatistician
SPARC Consulting, Milan, Italy

Marco Villa — 29-OCT-2019 (Date)
Clinical Operations Director
EXOM, Milan, Italy

Steering Committee Representative:

Giancarlo Agnelli — 29.Oct.2019 (Date)
Study Chairman
Internal and Cardiovascular Medicine and Stroke Unit, University of Perugia, Perugia, Italy

Table of Contents

1 Distribution list

Name	Title	Affiliation
Claudio Iannacone	Senior Biostatistician	SPARC Consulting, Milan
Federico Montuori	Biostatistician	SPARC Consulting, Milan
Marco Villa	Clinical Operations Director	EXOM Group, Milan
Giancarlo Agnelli	Principal Investigator & Study Chairman	University of Perugia, Perugia

2 Modification history

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Authorized Version
1.0	23MAY2017	Federica Brunero	n.a.
1.1	05SEP2017	Federica Brunero	Previous version not yet approved. Minor changes to the text were made.
1.2	02MAR2018	Federica Brunero	Previous version not yet approved. Minor changes to the text were made.
1.3	29OCT2019	Claudio Iannacone	Previous version not yet approved. Minor changes to the text were made. Added more details about the inferential statistical analysis to be performed.

3 List of abbreviations and definition of terms

The following abbreviations and special terms are used in this document.

Abbreviation	Definition
ACTS	*Anti-Clot Treatment Scale*
AE	*Adverse Event*
AESI	*Adverse Event of Special Interest*
BMI	*Body Mass Index*
CRF	*Case Report Form*
DVT	*Deep Vein Thrombosis*
FADOI	*Italian Federation of Hospital Internists*
FAS	*Full Analysis Set*
HR	*Hazard Ratio*
ITT	*Intention-To-Treat*
LMWH	*Low Molecular Weight Heparin*
MedDRA	*Medical Dictionary for Regulatory Activities*
mITT	*Modified Intention-To-Treat*
NSCLC	*Non-Small Cell Lung Cancer*
PE	*Pulmonary Embolism*
PROBE	*Prospective Randomized Open-label, Blinded End-point*
PP	*Per-Protocol*
PT	*Preferred Term*
SAE	*Serious Adverse Event*
SAP	*Statistical Analysis Plan*
SAS	*Statistical Analysis System (software)*
SCLC	*Small Cell Lung Cancer*
SOC	*System Organ Class*
TEAE	*Treatment Emergent Adverse Event*
TESAE	*Treatment Emergent Serious Adverse Event*
VTE	*Venous ThromboEmbolism*
WHO	*World Health Organization*
WHO-DD	*World Health Organization – Drug Dictionary*

4 Introduction

This document reports on the rules, conventions and table shells to be used in the analysis of data of the clinical study FADOI 03.2016 (short title: CARAVAGGIO) of Fondazione FADOI.

It describes, in details, the data and variables to be summarized and analyzed, including specifics of the statistical analyses to be performed.

5 Study objectives

5.1 Primary objective

To assess whether oral apixaban is non-inferior to the subcutaneous low molecular weight heparin (LMWH) dalteparin for the treatment of acute proximal deep vein thrombosis (DVT) and/or pulmonary embolism (PE) in patients with cancer, with respect to the primary outcome of the study which is objectively confirmed recurrent DVT or PE occurring during the intended study treatment period (6 months), which includes proximal DVT of the lower limbs (symptomatic or incidental), symptomatic DVT of the upper limbs and PE (symptomatic, incidental or fatal).

5.2 Secondary objectives

Secondary objectives of this study are:

Concerning safety

1) To characterize apixaban therapy relative to subcutaneous dalteparin therapy in adjudicated major bleeding during the actual study treatment period plus 72 hours.
2) To characterize apixaban therapy relative to subcutaneous dalteparin therapy in the composite of adjudicated major bleeding and adjudicated clinically relevant nonmajor bleeding during the actual study treatment period plus 72 hours.
3) To characterize apixaban therapy relative to subcutaneous dalteparin therapy in adjudicated clinically relevant nonmajor bleeding during the actual study treatment period plus 72 hours.

Concerning efficacy

1) To assess whether oral apixaban is non-inferior to the subcutaneous dalteparin for the treatment of acute proximal deep vein thrombosis (DVT) and/or pulmonary embolism (PE) in patients with cancer, with respect to one of the following, taken individually:
    a. Recurrence of proximal DVT of the lower limbs (symptomatic or unsuspected)
    b. Recurrence of DVT of the upper limbs (symptomatic)
    c. Recurrence of pulmonary embolism (symptomatic or unsuspected)
2) To assess whether oral apixaban is non-inferior to the subcutaneous dalteparin for the treatment of acute proximal DVT and/or pulmonary embolism (PE) in patients with cancer, with respect to symptomatic recurrence of Venous Thromboembolism (VTE).
3) To assess whether oral apixaban is non-inferior to the subcutaneous dalteparin for the treatment of acute proximal deep vein thrombosis (DVT) and/or pulmonary embolism (PE) in patients with cancer, with respect to confirmed recurrence of proximal DVT or PE plus major bleeding.

4) To compare the overall survival between the two treatment groups (all causes of death).
5) To compare the event free survival between the two treatment groups, where the event is a composite of the primary efficacy outcome plus major bleeding plus death due to all causes.
6) To compare the event free survival between the two treatment groups, where the event is a composite of the primary efficacy outcome plus death due to all causes.
7) To compare oral apixaban with the subcutaneous dalteparin for the treatment of acute proximal deep vein thrombosis (DVT) and/or pulmonary embolism (PE) in patients with cancer, with respect to any fatal or not fatal cardiovascular event (including acute myocardial infarction or ischemic stroke).
8) To compare oral apixaban with the subcutaneous the subcutaneous dalteparin for the treatment of acute proximal deep vein thrombosis (DVT) and/or pulmonary embolism (PE) in patients with cancer, with respect to all venous thromboembolic events (including splancnic vein thrombosis and cerebral vein thrombosis).
9) To compare quality of life evaluation between the two treatment groups (ACTS Scale).

6 Study design

6.1 General description

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

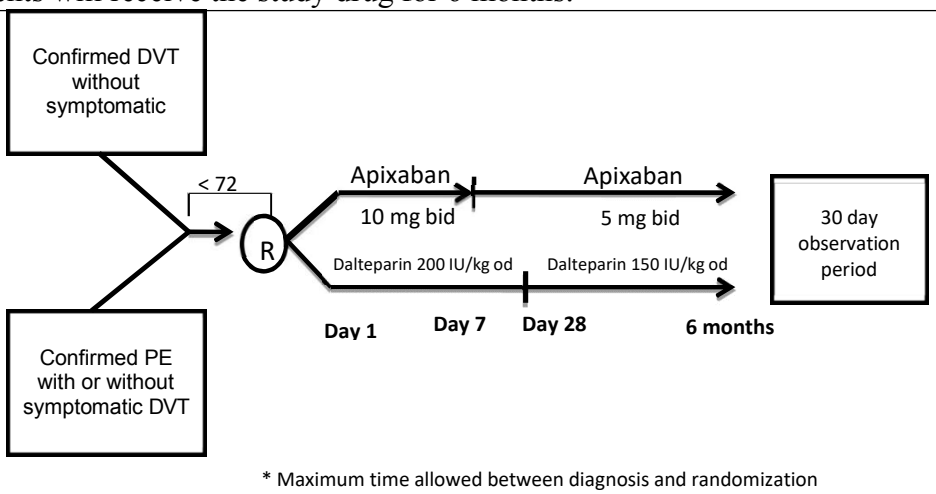
The aim of this study is to assess whether apixaban is non-inferior to the LMWH dalteparin for the treatment of acute proximal deep vein thrombosis (DVT) and/or pulmonary embolism (PE) in patients with cancer.

Patients with cancer and acute 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 and the signature of the informed consent form. Patients will be randomized on a 1:1 basis to receive either:

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 18,000 IU.

Enrolled patients will receive the study drug for 6 months.



* Maximum time allowed between diagnosis and randomization

Randomization will be centralized and stratified by:

1) symptomatic vs. unsuspected VTE

2) active cancer vs. history of cancer

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 symptoms of major bleeding develop. A clinical examination and objective tests will be performed if the patient develops symptoms or signs suggestive of recurrent VTE or major bleeding.

6.2 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 and the signature of the informed consent form. This study planned to enroll a total of about 1,168 patients.

In order to be enrolled, patients had to fulfill the inclusion and exclusion criteria listed in the paragraphs 6.3 (Inclusion criteria) and 6.4 (Exclusion criteria).

6.3 Inclusion criteria

To be eligible for this trial, patients have to meet the following criteria:

1. 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 defect(s) at compression ultrasonography, venography, CT venography or MR venography involving 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 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.

6.4 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) Three 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 of the Study Protocol);

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 higher than 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) Patients 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 participates in the study.

6.5 Stratification

Randomization will be centralized and stratified by:

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

6.6 Treatment

Patients will be randomized in a 1:1 ratio 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.

6.7 Blinding and procedures for unblinding the study

This is an open-label clinical study; therefore, no blinding procedures are applied.

7 Schedule of assessments

The schedule of assessments is reported in the study flow-chart (Table 1).

Table 1: Schedule of assessments

	Visit 1	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Unscheduled Visit (i)**
	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		x	x	x		x
Hematology	x (f)		x (g)	x (g)	x (g)		x
Inclusion/Exclusion criteria	x						
Eligibility criteria		x					
Randomization		x					
Drug dispensation		x	x	x			
Drug return and accountability			x	x	x		
Assess study outcomes (i.e. suspected recurrent VTE, bleeding) (h)			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) At screening: Hematocrit, WBC, Hb, Plts, INR, PTT

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

(h) 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

(i) 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

8 Study procedures

8.1 Administrative procedures

The study will be coordinated by the Internal Emergency and Vascular 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.

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

Exom Group, Milan, Italy, through formal nomination, is the entity allowed to handle data processing and it is in charge of the study analysis.

All analysis results will be exclusively produced in aggregate data and will not in any way referred to individual patients.

8.2 Tracking list / patient consent forms / data entry

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 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 that the primary physician is to be 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.

9 Statistical methods

Deviations from methods described in this document might appear. In case of such deviations, the reason for the deviation will be stated in the statistical report.

9.1 Statistical and analytical plan

This statistical analysis plan is based on the study protocol version 3.0 dated 22 May 2018 and describes the statistical analyses to be conducted for the final assessment of the study data.

9.2 General methodology

All data summaries and listings will be performed using the SAS System version 9.4 under Windows 10 PRO operating system. The statistical analysis will be performed by SPARC Consulting, Milan, Italy on behalf of Exom Group, Milan, Italy.

Continuous-scaled variables will be summarized with means, medians, standard deviations, quartiles, and minimum and maximum values. Categorical variables will be summarized using patient counts and percentages.

Two-sided 95% confidence intervals for proportions and means will also be produced, where clinically appropriate.

The statistical testing will be conducted at the α level of 0.05 (two-sided) unless differently specified (primary end-point analysis). Confidence intervals will be calculated at the confidence level of 95%.

9.3 Sample size

The study has been designed to test the hypothesis that apixaban would be non-inferior to dalteparin with respect to the primary study 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 1,168 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).

9.4 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) assessment 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 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) vs 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.

9.5 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 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)
- 1.8 for AMPLIFY (Apixaban)
- 2.0 for EINSTEIN DVT and EINSTEIN PE (Rivaroxaban)
- 2.75 for RECOVER I and II (Dabigatran)

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

9.6 Adjustments for covariates

All Cox's proportional hazard models and the linear effects models for quality of life evaluation will be performed using treatment group, center, symptomatic vs unsuspected VTE and active cancer vs history of cancer and interaction of stratification factors as dummy covariates.

9.7 Handling of data, dropouts and missing values

For the Burden score of ACTS scale, no imputation on missing data will be applied if ≥ 7 items are incomplete; otherwise, the Burden score is calculated as the mean of the complete items score x 12.

For the Benefit score of ACTS scale, no imputation on missing data will be applied if ≥ 2 items are incomplete; otherwise, the Burden score is calculated as the mean of the complete items score x 3.

In the situation where the event date is partial or missing, the date will appear partial or missing in the listings, and any corresponding durations will be presented based on the imputations specified in Section 12 "Partial Date Conventions".

Other missing data will not be replaced.

The number of patients with missing data will be presented under the "Unknown" category.

Missing values will be included in the denominator count when computing percentages.

When continuous data are being summarized, only the non-missing values will be evaluated for computing summary statistics.

9.8 Analysis populations

The following analysis populations will be considered in the statistical analysis:

- The enrolled subjects (ENR) set includes all subjects who signed the informed consent form.
- The Intent-to-Treat (ITT) analysis set includes all randomized subjects. Subjects will be categorized to the group to which they were assigned at randomization, regardless of the treatment actually received.
- The modified Intent-to-Treat set (mITT) includes all randomized subjects who received at least one dose of the study drugs (this is the primary efficacy data set). Subjects will be

categorized to the group to which they were assigned at randomization regardless of the treatment actually received.

- The Safety (SAF) Analysis set includes all randomized subjects with at least one documented administration of any study drug.
- The Per Protocol (PP) analysis set will consist of all patients in the ITT analysis set 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. Major protocol violations are the following:
    - Less than 80% or more than 120% compliance with intended study medications;
    - Use of prohibited concomitant medications (see Appendix 1 of the Study Protocol): dual antiplatelet therapy (any two antiplatelet agents including aspirin plus any other oral or IV antiplatelet drug), oral anticoagulants other than study drug, parenteral anticoagulants (if used contrary to protocol specifications), intravenous fibrinolytics, NSAIDs (if taken for ≥ 4 days per week);
    - Error in treatment dispensing resulting in a subject being dosed with an incorrect treatment.

  The decision whether a protocol deviation is major or not for the classification of patients to the Per-Protocol analysis set will be made case-by case in the blind data review meeting that will be held before the database lock.

9.9 Multicenter studies

Study center is 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.

9.10 Multiple comparisons/multiplicity

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.

9.11 Examination of subgroups

The treatment effects on the primary variable will be characterized for all subgroups outlined in Table 2.

Analyses will be performed on the primary efficacy dataset (mITT) only.

No hypothesis testing will be conducted among the categories of the subgroups.

Statistics presented for each category of the subgroups will include the apixaban-to-comparator Hazard Ratio adjusted for the competing risk of death unrelated to VTE with the associated two- sided 95% CI (by resorting to the Fine & Gray regression model using treatment group, center, symptomatic vs unsuspected VTE, and active cancer vs history of cancer as dummy covariates).

Table 2: Subgroups

Grouping Variable	Category
Index event	Proximal DVT PE
Age	< 65 years old ≥ 65 to < 75 years old ≥ 75 years old
Gender	Male Female
BMI at baseline	≤ 25 kg/m2 >25-≤30 kg/m2 >30 kg/m2
Level of Renal Impairment (by means of creatinine clearance) at baseline	Severe (≤ 30 ml/min) Mild or Moderate (>30-≤ 80 ml/min) Normal (>80 ml/min)
Active Cancer at baseline	Active Cancer Absence of active cancer
Anticancer treatment during the study period	Any CHT/RT No CHT/RT treatment
Symptomatic VTE at Baseline	Symptomatic Unsuspected

9.12 Study endpoints

9.12.1 Primary endpoint

The primary efficacy endpoint is the time from randomization to the first recurrent thromboembolic event.

A thromboembolic event is a confirmed recurrent proximal DVT or PE, 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 seen on the second imaging test but not evident on the original images, or on an interval imaging test 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.

9.12.2 Secondary efficacy endpoints

1. The individual components of the primary efficacy outcome:
   a. Time from randomization to the first recurrent ipsilateral proximal DVT of the lower limbs (symptomatic or unsuspected)
   b. Time from randomization to the first recurrent contralateral proximal DVT of the lower limbs (symptomatic or unsuspected)
   c. Time from randomization to the first recurrent DVT of the upper limbs (symptomatic)
   d. Time from randomization to the first recurrent pulmonary embolism (symptomatic or unsuspected)
2. Time from randomization to the first symptomatic recurrent thromboembolic event.
3. Time from randomization to the composite of primary efficacy outcome plus major bleeding (whichever occurs first).
4. Time from randomization to death (all causes) (Overall Survival).
5. Time from randomization to the composite of primary efficacy outcome plus major bleeding plus death (all causes) (whichever occurs first).
6. Time from randomization to the occurrence of any fatal or not fatal cardiovascular event.
7. Time from randomization to thromboembolic events at sites other than DVT and PE (i.e. ischemic stroke, myocardial infarction, other venous thromboembolic events or other arterial thromboembolic events)
8. Total score and subscales of the Anti-Clot Treatment Scale (ACTS, a Quality of life evaluation).

9.12.3 Primary safety endpoint

The primary safety endpoint is the proportion of subjects with 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.

9.12.4 Secondary safety endpoints

- Proportion of subjects with a 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.
- Proportion of subjects with clinically relevant bleeding defined as the composite of major and clinically relevant non-major bleeding.
- Proportion of subjects who permanently and prematurely discontinued study drug due to safety reasons.

9.13 Replacement policy

No patient prematurely discontinued from the study for any reason will be replaced.

10 Statistical Analysis

10.1 Disposition of patients

Tables and data listings will be presented for ENR population.

The number of subjects enrolled into the study, and the number of subjects enrolled but not randomized together with the reasons for not being randomized will be summarized.

An individual data listing of the patients who did not satisfy the eligibility criteria will be presented (screening log).

The frequency of patients enrolled in each site will be tabulated by randomized treatment group and for all randomized patients combined.

A summary of analysis populations and an individual data listing of the reasons for patients' exclusion from each population will be presented.

The summaries of disposition described below will also be presented by randomization stratification factor - index event.

The number of treated patients, the number of patients who completed 6 months of study treatment, and the number of subjects discontinuing study therapy together with the reasons for discontinuation will be summarized by treatment group.

The reasons for discontinuation will be taken from the End-of-Treatment Status page of the CRF.

Discontinuations from study drug due to AEs will further be summarized by the AE type: ipsilateral proximal DVT lower limbs, contralateral proximal DVT lower limbs, DVT upper limbs, PE, bleeding, acute myocardial infarction (MI), ischemic stroke, other venous thromboembolic events, other arterial thromboembolic events, and other adverse events.

10.2 Demographic and other baseline characteristics

Demographic and baseline patient characteristics will be summarized by treatment group all patients in the ITT set.

The baseline values are those measured at the Screening Visit and are the following:

- Age (years) – calculated as the difference between the year of informed consent and the year of birth.
- Gender
- Ethnicity (Hispanic or Latino / Not Hispanic or Latino)
- Race (White / Black or African American / Asian / American Indian or Alaska native / Native Hawaiian or other pacific islander / Other / Not applicable (because forbidden by the national law))
- Height (cm)
- Weight (kg)
- BMI (kg/m2)
- Systolic Blood Pressure and Diastolic Blood Pressure (mmHg)
- Heart Rate (bpm)
- ECOG Performance Status (1 / 2 / 3 / 4 / 5)
- Pregnancy test (for females with childbearing potential):

  - Done / Not done
  - Result (Negative / Positive)
- Physical examination:
  - Done / Not done
  - Result (Normal / Abnormal Clinically Significant / Abnormal Not Clinically Significant)

10.3 Cancer diagnosis and history

The following variables on tumor diagnosis and history will be summarized by treatment group with default statistics for all patients in the ITT set:

- Diagnosis of cancer other than basal-cell or squamous-cell carcinoma of the skin or primary tumor or acute leukemia? (Yes / No);
- Intracerebral metastasis? (Yes / No);
- Time of diagnosis (within 6 months before the study inclusion / between 6 months and 2 years before the study inclusion);
- Treatment for cancer (None in the 6 months prior to study inclusion / at study inclusion / during 6 months prior to randomization);
- Recurrent or locally advanced metastatic cancer (Yes / No);
- Time from diagnosis (months), calculated as:
  (Date of screening visit – date of diagnosis + 1) / 30.4.
- Primary Tumor site (Biliary tract / Bladder / Bone-soft tissue / Brain / Breast / Colorectal / Esophagus / Head and neck / Hematological malignancy / Hepatocellular carcinoma / Kidney / Lung / Ovary / Pancreas / Prostate Gland / Skin – Melanoma / Skin – Basal Cell Carcinoma / Skin – Squamous Cell Carcinoma / Stomach / Testicular cancer / Thyroid / Uterus / Other)
- If hematological malignancy:
  - Type of malignancy (Acute lymphocytic leukemia / Chronic lymphocytic leukemia / Acute myeloid leukemia / Chronic myeloid leukemia / Leukemia – other / Non-Hodgkins lymphoma / Hodgkins lymphoma / Multiple myeloma / Other);
  - Complete remission (Yes / No);
- If lung, type of tumor (SCLC / NSCLC / Other)
- Histological type (Adenocarcinoma / Squamous cell carcinoma / Sarcoma / Neuroendocrine / Unknown / Not applicable / Other)
- Staging at study entry (Localized / Regional / Distant / Unknown / Not applicable)

10.4 Venous thromboembolism

The following variables on venous thromboembolism characteristics will be summarized by treatment group with default statistics for all patients in the ITT set:

- Type of VTE (DVT = Deep Vein Thrombosis / PE = Pulmonary Embolism)
- Time from confirmed diagnosis (months), calculated as: (date of screening visit – date of confirmed diagnosis +1)/30.4.

- Symptomatic (Yes / No)
- If type of VTE is DVT:
    - Specific type of DVT (Symptomatic DVT proximal lower limb / Unsuspected DVT proximal lower limb)
    - Location of DVT (Vena Cava, Vena iliaca right / Vena iliaca left / Vena iliaca bilateral, Right femoral vein / Left femoral vein / Bilateral femoral vein, Right popliteal vein / Left Popliteal vein, / Bilateral Popliteal vein, Right Distal vein / Left Distal vein / Bilateral Distal vein, Other)
    - If symptomatic, type of symptoms (Pain, Redness, Calf pain of tenderness, Swelling of extremities, Tenderness along deep vein, Additional relevant DVT findings)
    - Confirmatory tests (Compression ultrasonography, Venography, CT Venography, MR Venography, Other)
- If type of VTE is PE:
    - Specific type of PE (Symptomatic PE / Unsuspected PE in a segmental or more proximal pulmonary artery)
    - Location of PE (Right Pulmonary Artery / Left Pulmonary Artery, Bilateral Pulmonary Artery, Trunk, Right lobar branch / Left Lobal Branch / Bilateral Lobar Branches, Segmentary-Subsegmentary artery, Other)
    - If symptomatic, type of symptoms (Breathing difficulties including dyspnea or tachypnea, Chest Pain, Cough, Hemoptysis, Tachycardia, Fever, Cyanosis, Additional relevant PE findings)
    - Confirmatory tests (CT pulmonary angiography, Pulmonary angiogram, VQ scan, Perfusion scan, Echocardio, Other).

10.5 Medical history and comorbidities

Data will be summarized for ITT analysis set by treatment group with descriptive statistics.

Previous diseases are those reported as "*Not ongoing*" whereas the Concomitant Diseases are those reported as "*ongoing*" in eCRF.

All verbatim terms will be assigned to a Preferred Term (PT) and will be classified by primary System Organ Class (SOC) according to the MedDRA thesaurus version 20.1.

The following data will be presented:

1. a default frequency tabulation of patients who exhibited at least one previous disease by treatment group;
2. a frequency table showing the previous diseases by primary System Organ Class and Preferred Term by treatment group;
3. a default frequency tabulation of patients who exhibited at least one concomitant disease by treatment group;
4. a frequency table showing the concomitant diseases by primary System Organ Class and Preferred Term by treatment group.

10.6 Previous and concomitant medications

All medications will be coded using the WHO-DRL Dictionary (DD) B2-format version 2017 and

classified according to 3rd level ATC subgroup (Primary therapeutic subgroup) and generic name. Concomitant medications are those reported in the eCRF "Concomitant Treatments" form and include all medications with start date on or after the study medication start date and all medications taken prior to the study entry and still taken after the study medication start date.

Previous medications are those reported in the eCRF "Concomitant Treatments" form with end date before the date of first study drug administration.

Previous and concomitant medications will be summarized by treatment group for the ITT set.

Medications started after the date of end of study treatment will be considered as post-study treatments and they will be only listed.

10.7 Study drug

Data will be summarized by treatment group for mITT set with descriptive statistics.

Descriptive analyses will be presented by treatment group for:

- The study drug amount administered (amount dispensed – amount returned);
- The duration of treatment administration (calculated, in weeks, as (date of last dose – date of first dose +1) / 7);
- Compliance (calculated by the system outside the eCRF).

10.8 Analysis of efficacy

10.8.1 Analysis of primary endpoint

Analyses of the primary efficacy endpoint will be performed using the modified intent-to-treat (mITT) analysis set, the intent-to treat (ITT) analysis set and the per protocol (PP) analysis set.

The mITT and the ITT analyses of the primary endpoint will include endpoints that occur at any time from randomization until the end of the originally intended treatment period regardless of whether subjects were receiving study medication.

The analysis performed on the mITT population will be considered as the primary whereas the analyses performed in the ITT and PP population will be seen as supportive (sensitivity analysis).

The primary efficacy variable, i.e. the time from randomization to the first recurrent thromboembolic event (days), will be analyzed after adjusting estimates for the competing risk of death unrelated to VTE. The competing risk analysis will be performed using the SAS procedure PHREG 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). Patients without recurrent thromboembolic event will be censored at 6- month (i.e. Day 180).

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. H0 → E[HR] ≥ 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. Ha → 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 using treatment group, center, symptomatic vs unsuspected VTE and active cancer vs history of cancer 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.

Number and percentage of events of interest, competing events and censored patients will be presented as summary of failure outcome. Degrees of freedom (DF), Wald Chi-square and the associated p-value derived from the PHREG model will be also presented.

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.

10.8.2 Analysis of secondary endpoints

For the secondary efficacy endpoints, analyses will be performed using the mITT analysis set.

- The individual components of the primary efficacy outcome (Proximal DVT of the lower limbs (symptomatic or unsuspected), DVT of the upper limb (symptomatic), and PE (symptomatic or unsuspected): The same competing risk model defined in paragraph 10.8.1 for the analysis of primary efficacy variable will be employed for the analysis of the time (in days) from randomization to the first recurrent event among those included in the primary efficacy outcome recurrent (see Paragraph 9.12.1). 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. If neither the event of interest nor a competing event occurred within the 6-month follow-up, the patient will be censored at 6- month follow-up.
- Symptomatic recurrence of VTE: The same competing risk model defined in paragraph 10.8.1 for the analysis of primary efficacy variable will be employed for the analysis of the time (in days) 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. If neither the event of interest nor a competing event occurred within the 6-month follow-up, the patient will be censored at 6-month follow-up.
- Composite of primary efficacy outcome plus major bleeding: The competing risk model defined in paragraph 10.8.1 for the analysis of primary efficacy variable will be employed for the analysis of the time (in days) from randomization to the composite of primary efficacy outcome (see Paragraph 9.12.1) 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. If neither the event of interest nor a competing event occurred within the 6-month follow-up, the patient will be

censored at 6-month follow-up.

- Death due to any cause (OS): Overall Survival is defined as the time (in days) from randomization to the date of death for any cause. OS will be estimated according to Kaplan-Meier calculating median, first and third quartiles with the respective 95% confidence intervals. Kaplan-Meier plots with a 95% CI will be prepared. OS in the two treatment groups will be also compared by means of a Cox's proportional hazard model with treatment group, center, symptomatic vs unsuspected VTE and active cancer vs history of cancer as dummy covariates. The apixaban-to-comparator Hazard Ratio will be computed with associated two-sided 95% confidence interval. Subjects still surviving at the end of the study will be censored at the date of the last contact.
- Composite of primary efficacy outcome plus major bleeding plus death due to any cause: Event-free-survival is defined as the time (in days) from randomization to the date of event (composite of primary efficacy outcome plus major bleeding plus death due to any cause). Event free survival will be estimated according to Kaplan-Meier calculating median, first and third quartiles with the respective 95% confidence intervals. Kaplan-Meier plots with a 95% CI will be prepared. Event-free-survival in the two treatment groups will be compared by means of a Cox's proportional hazard model with treatment group, center, symptomatic vs unsuspected VTE and active cancer vs history of cancer as dummy covariates. The apixaban-to-comparator Hazard Ratio will be computed with associated two-sided 95% confidence interval. Subjects with no events at the end of the study will be censored at the date of the last contact.
- Composite of primary efficacy outcome plus death due to any cause: Event-free-survival is defined as the time (in days) from randomization to the date of event (composite of primary efficacy outcome plus death due to any cause. 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, center, symptomatic vs unsuspected VTE and active cancer vs history of cancer as dummy covariates. The apixaban-to-comparator Hazard Ratio will be computed with associated two-sided 95% confidence interval. Subjects with no events at the end of the study will be censored at the date of the last contact.
- Any fatal or not fatal cardiovascular event: The competing risk model defined in paragraph 10.8.1 for the analysis of primary efficacy variable will be employed for the analysis of the time (in days) 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. Number and percentage of events of interest, competing events and censored patients will be presented as summary of failure outcome. Degrees of freedom (DF), Wald Chi-square and the associated p-value derived from the PHREG model will be also presented. Subjects with no events at the end of the study will be censored at the date of the last contact.
- All venous thromboembolic events (including splanchnic vein thrombosis and cerebral vein thrombosis): The same competing risk model defined in paragraph 10.8.1 for the analysis of primary efficacy variable will be employed for the analysis of the time (in days) 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. Number and percentage of events of interest, competing events and censored patients will be presented as summary of failure outcome. Degrees of freedom (DF), Wald Chi-square and the associated p-value derived from the PHREG model will be also presented. Subjects with no events at the end of the study will be censored at the date of the last contact.

- Quality of life evaluation (ACTS Scale) (see Appendix 2 of the study protocol): The ACTS is a 17-item, patient-reported measure of satisfaction with anticoagulant treatment. It includes 13 items concerning the burdens of anticoagulant treatment (items 1–12 plus 1 global question about burdens) and 4 items concerning the benefits of anticoagulant treatment (items 14–16 plus 1 global question about benefits). Each of the items is scored on a 5-point Likert scale (1 = not at all; 2 = a little; 3 = moderately; 4 = quite a bit; 5 = extremely). The Burden score was calculated as the sum of questions 1 to 12 subtracted from 60, with a higher score suggesting greater satisfaction with treatment. The Benefit score was calculated as the sum of questions 14 to 16, again with a higher score suggesting greater satisfaction. The Burden subscale can take values of 12-60 and the Benefit subscale score ranges from 3 to 15. Questions 13 and 17 are excluded from the subscale calculations.

  For the Burden score, no imputation on missing data will be applied if ≥ 7 items are incomplete; otherwise, the Burden score is calculated as the mean of the complete items score x 12.

  For the Benefit score, no imputation on missing data will be applied if ≥ 2 items are incomplete; otherwise, the Burden score is calculated as the mean of the complete items score x 3.

  Default summary statistics will be presented for each of the two subscales at Visit 5. For each of the subscales, a linear effects model will be estimated with treatment group, center, symptomatic vs unsuspected VTE and active cancer vs history of cancer as dummy fixed effects. The least square means for Apixaban and Dalteparin, with 95% CIs and p-value will be presented. The difference between the least squares means for Apixaban and Dalteparin will be calculated along the 95% CI and p-value.

10.9 Safety analyses

The analysis of safety will be based on the Safety Population, comparing patients in the two randomized arms: apixaban vs. dalteparin. Analysis of safety will include all events recorded during the treatment period and up to 30 days after the last study dose intake,

To assess the bleeding risk associated with the use of either apixaban or dalteparin, we will include all bleeding events that occur during the on treatment period, which is the classical period for the evaluation of safety. On-treatment bleeding has been defined as occurring during treatment with the assigned study drug or up to 72 hours after the last dose intake.

Concerning bleeding, secondary analyses will be performed:

1) To determine how apixaban compares to dalteparin therapy based on a reduction in major bleeding events over 6 months of therapy;

2) To determine how apixaban compares to dalteparin therapy in the combined endpoint of adjudicated major/CRNM bleeding over 24 weeks of therapy;

3) To determine how apixaban compares to dalteparin therapy based on a reduction in GI bleeding events over 6 months of therapy.

The number and the percentage of patients with bleeding events as well as the number of events will be presented in summary statistical tables.

10.9.1 Adverse events

All adverse events recorded during the treatment period and up to 30 days after the last study dose intake will be summarized by treatment group with descriptive statistics for the Safety population.

All adverse events will be assigned to a Preferred Term (PT) and will be classified by primary System Organ Class (SOC) according to the MedDRA thesaurus version 20.1. Adverse events will be reported on a per-patient basis. This means that even if a patient reports the same event repeatedly (i.e. events mapped to the preferred term) the event will be counted only once. In the latter case, the event will be assigned the worst intensity and the strongest relationship to the study drug.

For summaries, the drug-event relationship will be shown as "*Related*" if relationship with study treatment is assessed as "*Certain*", "*Probable*" or "*Possible*" by the Investigator; otherwise the event is considered as "*Unrelated*". Missing categories will be considered as related.

Treatment emergent events, defined as those AEs that start or worsen after the start of apixaban/dalteparin and up to 30 days after the last study dose intake, 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.

The following listing and tables will be presented:

1) An overview of adverse events with the number of patients who exhibited at least one AE, number of adverse events, number of patients who exhibited at least one TEAE, number of TEAEs, number of patients who reported at least one related TEAE, number of related TEAEs, number of patients who reported at least one treatment-emergent serious adverse event (TESAE), number of TESAEs, number of patients who reported at least one related TESAE, number of related TESAEs, number of patients who reported at least one AESI, number of AESI, number of patients who died, number of patients who temporarily discontinued the study drug due to an adverse event, number of patients with premature

withdrawal due to an adverse event;

2) An overview of adverse events with the number of patients who exhibited at least one TEAE with DVT as study outcome, number of TEAEs with DVT as study outcome, number of patients who exhibited at least one TEAE with PE as study outcome, number of TEAEs with PE as study outcome, number of patients who reported at least one TEAE with bleeding as study outcome, number of TEAEs with bleeding as study outcome, number of patients who reported at least one TEAE with major bleeding as study outcome, number of TEAEs with major bleeding as study outcome, number of patients who reported at least one TEAE with clinically relevant non-major bleeding as study outcome, number of TEAEs with clinically relevant non-major bleeding as study outcome, number of patients who reported at least one TEAE with clinically relevant bleeding as study outcome, number of TEAEs with clinically relevant bleeding as study outcome, number of patients who reported at least one TEAE with myocardial infarction as study outcome, number of TEAEs with myocardial infarction as study outcome, number of patients who reported at least one TEAE with ischemic stroke as study outcome, number of TEAEs with ischemic stroke as study outcome, number of patients who reported at least one TEAE with other venous thrombotic events as study outcome, number of TEAEs with other venous thrombotic events as study outcome, number of patients who reported at least one TEAE with other arterial thrombotic events as study outcome, number of TEAEs with other arterial thrombotic events as study outcome.
3) Summary of all TEAEs by treatment group, primary System Organ Class and Preferred Term;
4) Summary of all TEAEs by treatment group, primary System Organ Class, Preferred Term and Intensity;
5) Summary of all TESAEs by treatment group, primary System Organ Class and Preferred Term;
6) Summary of all non-serious TEAEs by treatment group, primary System Organ Class and Preferred Term (where PT occurred at a frequency of ≥5%);
7) Summary of all Related TEAEs by treatment group, primary System Organ Class and Preferred Term;
8) Summary of all Related TESAEs by treatment group, primary System Organ Class and Preferred Term;
9) Summary of all AESI by treatment group, primary System Organ Class and Preferred Term;
10) Patient Listing of Deaths;
11) List of TEAEs by patient;
12) List of TESAEs by patient;
13) List of Related TEAEs by patient;
14) List of Related TESAEs by patient;
15) List of AESI by patient;
16) List of Patients with Adverse Events Leading to Withdrawal from study drug;
17) List of Patients with Adverse Events Leading to temporary discontinuation of study drug.

The number and the percentage of patients with at least one TEAEs by SOC and Preferred Term, and the number of events will be presented for the statistical summary from the above points #3 to

#9.

Adverse events with start date before the first study dose intake or after 30 days the last study dose intake will be only listed.

10.9.1.1 Safety study outcomes

Possible safety study outcomes are: DVT, PE, bleeding, acute myocardial infarction, ischemic stroke, other venous thrombotic events, other arterial thrombotic events.

A frequency table on safety study outcomes will be produced. Details of each category of the study outcomes will be summarized by treatment group with default statistics: number and percentage of patients with the study outcomes and the number of events reported will be presented.

Default frequency tabulations (n,%) will be provided for the following categorical variables characterizing the safety study outcomes:

DVT

- Specific type of DVT (Symptomatic / Unsuspected);
- Location of DVT (Upper limbs, Vena Cava, Vena iliaca right / Vena iliaca left / Vena iliaca bilateral, Right femoral vein / Left femoral vein / Bilateral femoral vein, Right popliteal vein / Left Popliteal vein / Bilateral Popliteal vein, Right Distal vein / Left Distal vein / Bilateral Distal vein, Other);
- If symptomatic, type of symptoms (Pain, Redness, Calf pain of tenderness, Swelling of extremities, Tenderness along deep vein, Additional relevant DVT findings);
- Confirmatory tests (Compression ultrasonography, Venography, CT Venography, MR Venography, Other);
- Event resulting in discontinuation or interruption of patient's cancer treatment (Yes / No).

PE

- Specific type of PE (Symptomatic / Unsuspected);
- Location of DVT (Right pulmonary artery / Left pulmonary artery / Bilateral pulmonary artery, Trunk, Right lobar branch / left lobar branch / Bilateral lobar branch, Segmentary-subsegmentary artery, Other);
- If symptomatic, type of symptoms (Breathing difficulties including dyspnea and tachypnea, Chest pain, Hemoptysis, Tachycardia, Fever, Cyanosis, Other);
- Confirmatory tests (CT pulmonary angiography, pulmonary angiogram, VQ scan, perfusion scan, echocardio, other);
- Event resulting in discontinuation or interruption of patient's cancer treatment (Yes / No).

Bleeding

- Single episode / Repetitive bleeding. If repetitive bleeding and main duration of each episode known: duration (hours)
- Major bleeding (Yes / No).

  If major:

  - Decrease in hemoglobin of 2 g/dl (1.2 mmol/L) or more (Yes / No);
  - Transfusion of 2 or more units of packed red blood cells (Yes / No);

  - Bleeding that occurs in at least one critical site (Yes / No);
    - Intracranial (Yes / No);
    - Intra-spinal (Yes / No);
    - Intra-ocular (Yes / No);
    - Pericardial (Yes / No);
    - Intra-articular (Yes / No);
    - Intramuscular with compartment syndrome (Yes / No);
    - Retroperitoneal (Yes / No).
  - Fatal bleeding (Yes / No);
  - Surgical intervention needed (Yes / No).
- Clinically relevant non-major bleeding (Yes / No).

  If yes:
  - Bleeding compromising hemodynamics (Yes / No);
  - Spontaneous hematoma larger than 25 cm^2 (no traumatic cause) (Yes / No);
  - Spontaneous hematomas larger than 100 cm^2 (traumatic cause) (Yes / No);
  - Intramuscular hematoma documented by Ultrasonography (Yes / No);
  - Epistaxis requiring tamponade or other medical intervention (Yes / No);
  - Gingival bleeding (Yes / No);
  - Bleeding from venipuncture for > 5 minutes (Yes / No);
  - Spontaneous macroscopic hamtura (Yes / No);
  - Macroscopic hematuria which lasted for more than 24 hours after invasive procedures (Yes / No);
  - Hemoptysis requiring endoscopy or other medical intervention (Yes / No);
  - Hematemesis requiring endoscopy or other medical intervention (Yes / No);
  - Spontaneous rectal bleeding requiring endoscopy or other medical intervention (Yes / No).

Ischemic stroke

- Duration of symptoms (less than 24 hours / more than 24 hours);
- Assessment by imaging or autopsy (Yes / No). If yes, Non-hemorrhagic / Infarction with hemorrhagic conversion);
- Therapeutic intervention (Yes / No).

Myocardial infarction

- CK-MB ≥ 2 x ULN (Yes / No / Not available);
- Troponin T ≥ 2 x ULN (Yes / No / Not available);
- Troponin I ≥ 2 x ULN (Yes / No / Not available);
- Total CK ≥ 2 x ULN (Yes / No / Not available);
- ECG performed (Yes / No). If yes, new significant Q-waves ≥ 0.04 seconds in ≥ 2 contiguous leads? (Yes / No).

Other venous thrombotic events

- Clinical sign (Yes / No);
- Location (splanchnic vein thrombosis, cerebral vein thrombosis, genitourinary vein thrombosis, other)

Other arterial thrombotic events

- Clinical sign (Yes / No);
- Location (carotid artery thrombosis, femoral artery thrombosis, iliac artery thrombosis, renal artery thrombosis, retinal artery thrombosis, other).

Analysis will be performed on the Safety analysis set.

10.9.2 Laboratory evaluation

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;

(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.

Presentations will use SI Units.

To convert from the conventional unit to the SI unit, multiply by the conversion factor:

Parameter	**Conventional Unit**	**Conversion Factor**	**SI Unit**
Hematocrit	%	0.01	Proportion of 1.0
Hemoglobin	g/dL	10	g/L
RBC count	x 10^6/µL	0.1	x 10^{12}/L
WBC count	x 10^3/µL	1	x 10^9/L
Platelets count	x 10^3/µL	1	x 10^9/L
Creatinine	mg/dL	76.25	µmol/L
Total Bilirubin	mg/dL	17.10	µmol/L
Direct Bilirubin	mg/dL	17.10	µmol/L
Indirect Bilirubin	mg/dL	17.10	µmol/L
ALT	U/L	1	U/L
AST	U/L	1	U/L
ALP (Alkaline Phosphatase)	U/L	1	U/L

Partial Prothrombin Time (PPT)	Seconds	1	Seconds

10.9.3 Vital Signs

Vital signs measurement (systolic BP, diastolic BP, heart rate and, for dalteparin group, body weight) and their changes from baseline will be summarized by visit and treatment group. Individual vital signs measurement will be listed.

10.9.4 Interim analyses

Not foreseen.

10.9.5 Protocol deviations

An individual data listing of patients who did not satisfy the eligibility criteria will be produced.

A summary table and an individual data listing of major protocol deviations will be prepared.

10.9.6 Data and Safety Monitoring Board (DSMB)

An independent DSMB periodically reviews the study outcomes with all information available concerning treatment allocation. A DSMB charter was provided to the board members before the start of the study. The DSMB is composed of three expert clinicians with experience in the conduction and monitoring of clinical trials.

11 Programming Conventions for Outputs

DATES & TIMES

Depending on data available, dates and times will take the form DDMMMYYYY (i.e. 01JAN2019) and hh:mm (i.e. 10:35)

SPELLING FORMAT

English UK

PRESENTATION OF TREATMENT GROUPS

For outputs, treatment groups will be represented as follows and in that order:

Treatment Group	For Tables and Listings
Apixaban	Apixaban
LMWH Dalteparin	Dalteparin

PRESENTATION OF VISITS

For outputs, visits will be represented as follows and in that order:

Long Name (default)	Short Name	Day
Screening	V1	Day -3 or less
Enrolment	V2	Day 1
Week 4	V3	4-week after enrolment
Month 3	V4	3-month after enrolment
End of study Treatment	V5	6-month after enrolment or early withdrawal
End of Study	V6	7-months after randomization

LISTINGS

All listings will be ordered by the following:

- Treatment group
- Site ID
- Patient ID
- Visit/date/hour (where applicable).

For listings where non-randomized subjects are included, these will appear in a category after the randomized treatment groups labelled “Not Randomized”.

TEXT CASE

- For titles and column labels, capitalize important words, i.e. nouns, pronouns, verbs, adverbs and adjectives but not articles, conjunctions or prepositions
- All Footnotes will be in sentence case format.
- All symbols used in body of outputs will be footnoted.

12 Partial Date Conventions

Imputed dates will NOT be presented in the listings.

ALGORITHM FOR TREATMENT EMERGENCE OF ADVERSE EVENTS:

START DATE	STOP DATE	ACTION
Known	Known	If start date < study med start date, then not TEAE If start date >= study med start date but ≤ study med end date+30, then TEAE
	Partial	If start date < study med start date, then not TEAE If start date >= study med start date but ≤ study med end date+30, then TEAE
	Missing	If start date < study med start date, then not TEAE If start date >= study med start date but ≤ study med end date+30, then TEAE
Partial, but known components show that it cannot be on or after study med start date	Known	Not TEAE
	Partial	Not TEAE
	Missing	Not TEAE
Partial, could be on or after study med start date	Known	If stop date < study med start date, then not TEAE If stop date >= study med start date but ≤ study med end date+30, then TEAE
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, then not TEAE If stop date >= study med start date but ≤ study med end date+30, then TEAE
	Missing	Assumed TEAE
Missing	Known	If stop date < study med start date, then not TEAE If stop date >= study med start date but ≤ study med end date+30, then TEAE
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, then not TEAE If stop date >= study med start date but ≤ study med end date+30, then TEAE
	Missing	Assumed TEAE

ALGORITHM FOR PRIOR / CONCOMITANT MEDICATIONS:

START DATE	STOP DATE	ACTION
Known	Known	If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of treatment, assign as concomitant If stop date >= study med start date and start date > end of treatment, assign as post study
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of treatment, assign as concomitant If stop date >= study med start date and start date > end of treatment, assign as post treatment
	Missing	If stop date is missing could never be assumed a prior medication If start date <= end of treatment, assign as concomitant If start date > end of treatment, assign as post treatment
Partial	Known	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of treatment, assign as concomitant If stop date >= study med start date and start date > end of treatment, assign as post treatment
	Partial	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown) and impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of treatment, assign as concomitant If stop date >= study med start date and start date > end of treatment, assign as post treatment
	Missing	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date is missing could never be assumed a prior medication If start date <= end of treatment, assign as concomitant If start date > end of treatment, assign as post treatment
Missing	Known	If stop date < study med start date, assign as prior If stop date >= study med start date, assign as concomitant Cannot be assigned as 'post treatment'
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date, assign as concomitant Cannot be assigned as 'post treatment'
	Missing	Assign as concomitant

13 References

Fondazione FADOI, Study Protocol, Protocol no. FADOI 03.2016, Short title The CARAVAGGIO Study, Version 3.0 dated 22 May 2018.

SAS Institute Inc., Cary, NC, USA, version 9.4.

Fine JP, Gray RJ. A Proportional Hazards Model for the Subdistribution of a Competing Risk. J Am Statist Ass 1999; 94: 496-509

Campigotto F, Neuberg D, Zwicker JI. Accounting for death as a competing risk in cancer-associated thrombosis studies. Thromb Res. 2012;129 Suppl 1:S85-7.

Agnelli G, Buller HR, Cohen A, Gallus AS, Lee TC, Pak R, Raskob GE, Weitz JI, Yamabe T. Oral apixaban for the treatment of venous thromboembolism in cancer patients: results from the AMPLIFY Trial. J Thromb Haemost 2015;13:2187–91.

Coleman, C. I., Haas, S., Turpie, A. G.G., Kuhls, S., Hess, S., Evers, T., Amarenco, P., Kirchhof, P., Camm, A. J. and on behalf of the XANTUS Investigators (2016), Impact of Switching From a Vitamin K Antagonist to Rivaroxaban on Satisfaction With Anticoagulation Therapy: The XANTUS-ACTS Substudy. Clin Cardiol, 39: 565–569. doi:10.1002/clc.22565

Hokusai-VTE Investigators, Büller HR, Décousus H, Grosso MA, Mercuri M, Middeldorp S, Prins MH, Raskob GE, Schellong SM, Schwocho L, Segers A, Shi M, Verhamme P, Wells P. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. N Engl J Med. 2013;369:1406-15.

Agnelli G, Buller HR, Cohen A, Curto M, Gallus AS, Johnson M, Masiukiewicz U, Pak R, Thompson J, Raskob GE, Weitz JI; AMPLIFY Investigators. Oral apixaban for the treatment of acute venous thromboembolism. N Engl J Med. 2013;369:799-808

EINSTEIN Investigators. Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med. 2010;363:2499-510

EINSTEIN Investigators. Oral Rivaroxaban for the Treatment of Symptomatic Pulmonary Embolism. N Engl J Med. 2012; 366: 1287-97

Schulman S, Kearon C, Kakkar AK, Mismetti P, Schellong S, Eriksson H, Baanstra D, Schnee J, Goldhaber SZ; RE-COVER Study Group. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. N Engl J Med 2009;361:2342-52.

Schulman S, Kakkar AK, Goldhaber SZ, Schellong S, Eriksson H, Mismetti P, Christiansen AV, Friedman J, Le Maulf F, Peter N, Kearon C; RE-COVER II Trial Investigators. Treatment of acute venous thromboembolism with dabigatran or warfarin and pooled analysis. Circulation. 2014;129:764-72
Guideline on the choice of the non-inferiority margin, Doc. Ref. EMEA/CPMP/EWP/2158/99; Statistical principles for clinical trials, ICH harmonised tripartite guideline E9; Points to consider on multiplicity issues in clinical trials, CPMP/EWP/908/99.

EMEA, Points to consider on multiplicity issues in clinical trials, CPMP/EWP/908/99

14 Tables, line listings and figures shells

The shells of statistical analysis tables, individual data listings and figures to be produced for the final statistical analysis of the study data are reported in the document “TLF Shells” version 1.1 dated 30 October 2019.