**MANDATORY SPONSOR INPUTS FOR STUDY PROTOCOL GENERATION**

* **Sponsor Name** FADOI /BMS/PFIZER
* **Study Acronym (if available):** CARAVAGGIO Study
* **Tested IMP :**Apixaban
* **Comparative drug:** Dalteparin
* **Study Type** Interventional
  + Se Study Type = Interventional:
    - **Interventional Study Phase** Phase IIIb
* **Study Design** International, multicenter, Prospective Randomized Open Blinded End-point (PROBE), where both patients and investigators are aware of the treatment assignments, but the outcome assessment is blindedactive-controlled, event-driven, Phase IIIB clinical study comparing the efficacy and safety of Apixaban to the SOC Dalteparin in for the treatment of venous thromboembolism in patients with cancer.
* **Aim of the study**: 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.
* **Target Disease**: VTE (DVT/PE) in cancer patients
* **Type of Randomization**: 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 should be centralized and stratified by:

1) symptomatic vs. unsuspected VTE

2) active cancer vs. history of cancer

* **Tested drugs and dosages**

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.

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.

* **Study Scheduled Patient’s Visits**

The study should foresee 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.

* **Study Objectives**

Primary efficacy outcome:

objectively confirmed recurrent VTE occurring during the study 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)

* **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 cm2, or 100 cm2 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

* **Maximum Sample Size for each arm**

Less than 600 patients for each treatment group

* **Recommended Inclusion Criteria**

Age > 18 years

Both Genders

Signed Informed Consent

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.

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).

* **Recommended Exclusion Criteria**

age <18 years

ECOG Performance Status III or IV;

life expectancy of less than 6 months;

related to anticoagulant treatment:

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

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

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

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

concomitant use of strong inhibitors or inducers of both cytochrome P-450 3A4 and P-Glycoprotein ;

related to bleeding risk:

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

active bleeding or high risk of bleeding contraindicating anticoagulant treatment

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

hemoglobin level lower than 8 g/dL (5.0 mmol/L) or platelet count <75x109/L or history of heparin-induced thrombocytopenia;

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

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

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

standard criteria:

bacterial endocarditis;

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

patients participation in other pharmaco therapeutic program with an experimental therapy that is known to effect the coagulation system.

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 ;

pregnancy, or breast feeding

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