PROTOCOL
The Jason Study
Final version 1.0 date 23.10.2018

Title of the Study:	The Jason Study: Sulodexide (VESSEL®) for the prevention of recurrent venous thromboembolism in elderly patients after a first episode of venous thrombembolism
Code of the Study	GIASONE (FAAI2.10.2018)
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LISTA DI ABBREVIAZIONI

ACCP	American College of Chest Physician
AE	Adverse event
ASA	AcetylSalicylic Acid (Aspirin)
AVK	Anti-Vitamin K
AT	Anticoagulant Therapy
BID	Bis In Die
CUS	Compression Ultrasonography
DM	Ministerial Decree
DMSB	Data Monitoring and Safety Board
DOAC	Direct Oral Anticoagulant
DVT	Deep Vein Thrombosis
DVT e/o PE	Deep Vein Thrombosis and/or Pulmunary Embolism
eCRF	Elettronic Case Report Form
MB	Major Bleed
NMCRB	non-major clinically relevant bleedin
PE	Pulmunary Embolism
FUP	Follow up
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
HR	Hazard Ratio
IB	Investigator's Brochure
ICH	International Council for Harmonisation
IMPD	Investigational Medical Product Dossier
ISTH	International Society on Thrombosis and Haemostasis
ITT	Intent-To-Treat
mITT	Modified-ITT
LMWH	Low Molecular Weight Heparin
LSU	Lipasemic Unit
NYHA	New York Heart Association
NSAE	Non serius Adverse event
Post-FUP	Post Follow Up
PP	Per-Protocol Population
PTS	Post-Thrombotic Syndrome
QC	Quality Control
RRR	Relative Risk Reduction
FSR	Final Study Report
RVT	Residual Vein Thrombosis
SAE	serius Adverse event
SOP	Standard Operating Procedure
sPAP	Systolic Pulmonary Artery Pressure
SUSAR	Suspected unespected adverese reaction
VTE	Venous ThromboEmbolism

BACKGROUND INFORMATION

Venous Thromboembolism (VTE) in the elderly population

VTE is common in the elderly population, with an incidence that may reach 0.5 cases in 100 per year in subjects older than 75 years of age (1). Following a first VTE event, an anticoagulant therapy of at least 3-6 months (considered as initial and maintenance therapy) is usually prescribed for all patients. Following this period, the extension of anticoagulant therapy (extended therapy) is suggested in patients with idiopathic VTE or associated with a weak and transient risk factor, aimed at avoiding thromboembolism recurrence. The extension of anticoagulant therapy is, however, to be decided in relation to the assessment of the risk / benefit ratio on the basis of the individual analysis of the risk of VTE recurrence and haemorrhage (2). The risk of VTE recurrence is generally higher near the event and tends to decrease with time, while the risk of bleeding in the case of anticoagulant treatment remains unchanged over time (or does not increase in relation to the increase in age-related underlying risk).

The high risk of bleeding in the elderly with VTE if treated with anticoagulants or aspirin (ASA) over a long period of time.

In most cases, patients aged 75 years or older who have suffered a first episode of VTE have a contraindication to the use of anticoagulant therapy as advanced age is in itself a high-risk factor of bleeding.

The latest American College of Chest Physician - ACCP guidelines (2) suggest evaluating individual haemorrhagic risk during an eventual anticoagulant treatment, according to a list of risk factors and a consequent score. According to this score, patients older than 75 years of age have a high haemorrhagic risk if treated with anticoagulants, and even higher in the presence of other morbid conditions among those very common in the elderly (comorbidity, associated pharmacological treatments, etc.). For these reasons, at present, patients aged 75 years or older, with a first idiopathic VTE event, should discontinue the therapy after a 3-6-month treatment with anticoagulant therapy. Sometimes, after having discontinued the anticoagulant therapy, some patients are given a low daily dose of ASA (around 100 mg / day). However, according to a recent study, this procedure is not recommended, as the administration of ASA implies a low efficacy of protection for relapses than the use of anticoagulants, and moreover it is associated with considerable haemorrhagic risk, especially in the elderly.

Difficulty in selecting the elderly with VTE that have a higher risk of recurrence

Measurement of D-dimer levels is considered good clinical practice today. As suggested by the international guidelines (2), in patients with VTE the D-dimer test is used to decide whether to permanently discontinue the anticoagulant treatment, if the test is negative, or to decide to continue

the therapy in those patients with positive D-dimer test considered to be at higher risk of recurrence. For this purpose, the D-dimer test is inserted into the predictive scores of the risk of recurrence. However, a recent DASH score validation study (4), which includes and gives high value to the D-dimer result, has shown that the score is not predictive in elderly patients, as this test is almost always altered in elderly people.

Thrombophilia is considered another risk factor. A recent study showed that thrombophilic alterations (especially mutations such as factor V Leiden and the prothrombin gene mutation) were relatively frequent in elderly people with VTE, with a prevalence of about 14%. However, the presence of these thrombophilic alterations was not associated with the risk of VTE recurrence (5).

The use of direct oral anticoagulant drugs (DOACs) for extended treatment in the elderly population

Recent studies, particularly focused on extensive treatment following VTE, have shown that low doses of apixaban (2.5 mg, 2 daily administrations) or rivaroxaban (10 mg, 1 daily administration) amongst the whole population treated (6)(3) have allowed both good efficacy results in relation to relapses and safety results in relation to the bleeding risk. However, by examining the results of these studies, obtained in different population groups relative to age (additional material available in publications), it should be noted that: a) in both studies, the population with patients older than 75 years was very small (between 11 and 13% of the patients included), and b) the results obtained in this segment of population, both in terms of efficacy and safety, were certainly lower than those in young patients and substantially less satisfactory.

The use of Sulodexide for the extended treatment of VTE

The international, randomized, placebo-controlled Sulodexide for the Prevention of Recurrent Deep Vein Thrombosis (SURVET) (7) study showed that treatment for 2 years with oral Sulodexide (500 LSU, BID) in patients (with an average age of 55) who had suffered from a first idiopathic VTE and had already undergone an adequate period of anticoagulant therapy, has allowed to reduce the risk of thrombotic recurrence by 50% compared to patients treated with placebo, without involving any case of major bleeding. A specific scientific literature to demonstrate the absence of haemorrhagic effect of the oral administration of Sulodexide is already available (8).

RATIONALE

Currently, there are no acceptable criteria for identifying elderly patients with a higher risk of VTE recurrence. Furthermore, efficacy and safety outcomes in the elderly population are not available with regard to the use of DOACs.

In the light of the SURVET study (7) results, the preventive effect of VTE recurrence (even if lower than that achievable with anticoagulant drugs), in association with the absence (or marked decrease)

of the bleeding risk are factors that justify a specific study on the potential role of extended treatment with Sulodexide at the end of a standard period of anticoagulant therapy in elderly patients with VTE.

The study was conceived by creating 3 experimental arms:

1) Treatment A: Sulodexide (Vessel) 2 capsules of 250 LSU x 2 / day. The choice of this dosage is in accordance with that used in the international SURVET study (7) for the prevention of relapses of deep vein thrombosis (DVT) and pulmonary embolism (PE).
2) Treatment B: Sulodexide (Vessel) 1 capsule of 250 LSU and 1 indistinguishable placebo capsule x 2 / day. This treatment is justified for the following reasons:
    A) the dose of 250 LSU x 2 / day is the one recommended in the Summary of Product Characteristics of Sulodexide for the treatment of post-thrombotic syndrome;
    B) elderly patients are often treated with more drugs a day and administering 4 capsules can increase the problems of adherence to therapy;
    C) the daily cost of the drug for future use is reduced.
3) Treatment C: 2 indistinguishable placebo capsules x 2 / day. In compliance with what has been done in the SURVET study and for the safety results obtained.

Aim of the study

This study conducted in elderly outpatients (≥ 75 years old at the time of inclusion)), with at least one of the known bleeding risk factor, who had a first episode of lower extremity proximal DVT and / or PE, idiopathic or associated with weak or removed risk factors, and who have received standard treatment with any oral anticoagulant drug lasting at least 3 months, has the purpose of verifying the efficacy and safety of extended treatment with Sulodexide (Vessel®) in the secondary prevention of DVT / PE recurrence.

Objectives

1) Verify the efficacy of the treatment with two different doses of Sulodexide (Vessel®) (treatment A and treatment B) compared to the indistinguishable placebo (treatment C), in reducing the incidence of VTE relapses in elderly patients (age ≥ 75 years) who have suffered from a recent episode of DVT (proximal lower extremity) and / or PE, by 35% compared to placebo.
2) Verify the safety of the aforementioned therapy, demonstrating non-inferiority compared to placebo, with an incidence of major bleeding around 1% (upper confidence limit not > 3%)

INVESTIGATIONAL PLAN

Study design

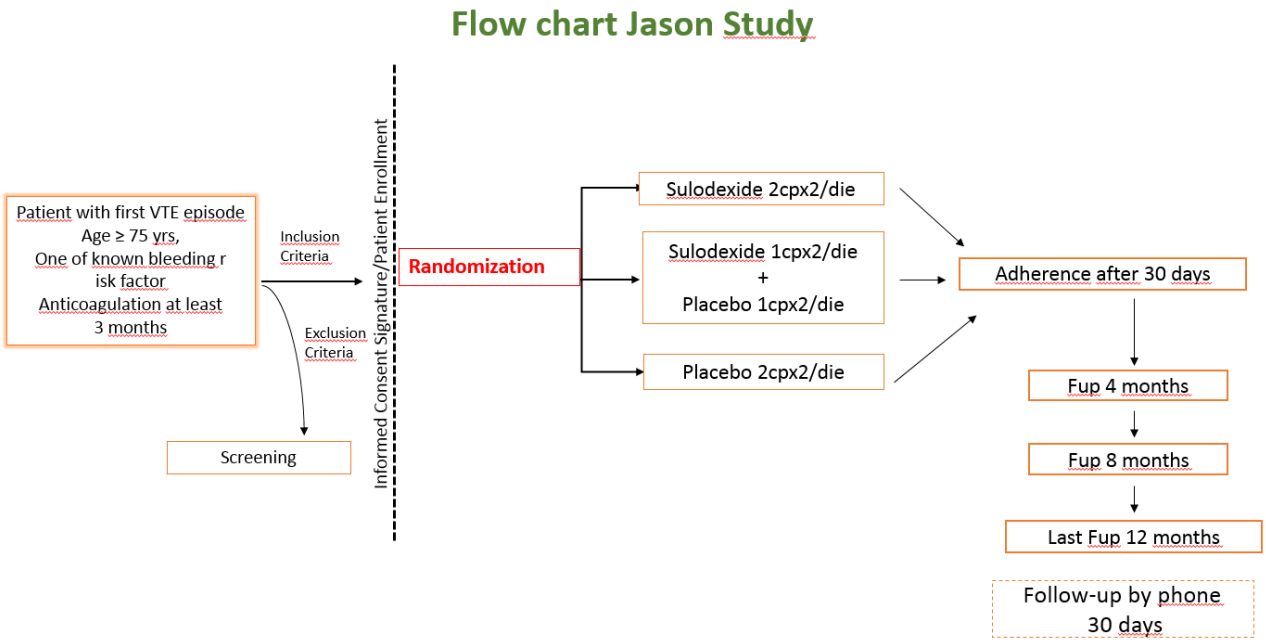
Phase III, national multicentre, randomised to parallel groups,placebo-controlled, double-blind and non-commercial (non-profit) study.

Study settings

The study will be conducted nationwide in hospital facilities and / or university facilities with outpatients. For the participant centre list, refer to the document "Centre List".

These centres have been selected as they meet the following criteria:

- Previous co-authored works
- Experience in the pathology or condition of the study
- Previous participations in clinical trials
- Enrolment capacity
- Availability to conduct the study



Study population

It is expected to enrol 1,455 consecutive outpatients, aged ≥ 75 years, with at least one of the known bleeding risk factor, who have had a first episode of lower extremity proximal DVT and / or PE, idiopathic or associated with weak or removed risk factors, and have completed a period of anticoagulant treatment (whatever the type of medication used) of at least 3 months. Patients are screened when they are still being treated with the anticoagulant. The absence of at least one of the conditions listed in the inclusion criteria or the presence of at least one of the conditions listed in the exclusion criteria , presented below, determines the exclusion of the patient from further evaluations for participation in the study.

Each centre will enrol on average 30 patients, equally distributed among the three treatment groups in balanced blocks.

ELIGIBILITY CRITERIA

Inclusion criteria:

1) Patients with a first event of proximal lower extremity DVT and / or PE, idiopathic or associated with weak or removed risk factors.
2) Patients aged ≥75 years at the time of enrolment
3) Pazienti with at lesast one of the known risk factors of bleeding (APPENDIX 1):
    a. Hypertension
    b. Renal failure
    c. Thrombocytopenia
    d. Diabetes
    e. Antiplatelet therapy (ASA maximum 140 mg/die)
    f. Frequent falls (>2 /years)
    g. Nonsteroidal anti-inflammatory drug
    h. Liver failure
    i. Previous Stroke
    j. Anemia
    k. Poor anticoagulant control
    l. Alcohol abuse
4) Patients of both sexes.
5) Patients who at the time of enrolment have already undergone a period of anticoagulant therapy (AT, with any medication) of at least 3 months and the therapy has not been suspended for more than 30 days.
6) Patients with no other AT indications.
7) Patients capable and able to provide informed consent.

Exclusion criteria:

1) Patients aged <75 years at the time of the recruitment visit.
2) "Provoked" index event, which occurred:
    - Within 3 months of surgery or major trauma,
    - Bed Rest > 4 days,
    - Cast / immobility within 3 months.
3) Index event represented by severe PE, with life threatening risk or treated with thrombolytic therapy.
4) Index event represented by isolated distal DVT or superficial venous thrombosis.
5) Thrombotic event in sites other than the deep proximal veins of the lower limbs.
6) Anticoagulant therapy for less than 3 months at the time of enrolment.
7) Discontinuation of anticoagulant therapy for over thirty days at the time of enrolment
8) Recurrent episodes of DVT ± PE.

9) Presence of severe post-thrombotic syndrome (Villalta score >15 or presence ofvenous ulcer).
10) Presence of other clinical conditions requiring anticoagulant therapy.
11) Active cancer.
12) Presence of Inferior vena cava (IVC) filter.
13) Known bleeding diatheses.
14) Patients treated with antiplatelet drugs other than ASA. The ASA is allowed up to 140 mg / day.
15) All clinical conditions requiring long-term treatment with low molecular weight heparin (LMWH).
16) Presence of Antiphospholipid Antibody Syndrome (according to Sydney criteria) (Appendix 4)
17) Presence of serious thrombophilic alterations
18) Presence of chronic diseases in acute or active phase (e.g.: inflammatory bowel disease)
19) Cardiorespiratory failure (NYHA class 3 or 4).
20) Patients incapacitated or refusing to sign the informed consent.
21) Patients with life expectancy under 1 year.
22) Patients residing in a disadvantaged geographical area.
23) Patient already enrolled in other clinical trials.
24) Patients with systolic pulmonary artery pressure > 40 mm hg (upper limit for elderly).
25) Contraindication to Sulodexide (VESSEL®) and Placebo (see the IMPDs)

STUDY INTERVENTION

After a first VTE event (proximal DVT of a lower limb and / or PE) and anticoagulant treatment (with any medication) for a period of at least 3 months, patients aged ≥ 75 years at the time of enrolment, with at least one of the known risk factor for bleeding, are randomized to receive treatment A, treatment B or treatment C for 1 year.

At each patient will be asked to fill a self-assessment questionnaire for the Villalta score both at the beginning of the treatment and at the end.

Prior to enrollment, and after careful consideration of the intended purposes, methods, expected benefits and risks of the study, the investigator will obtain informed consent from the patients. Patients will discontinue the ongoing anticoagulant therapy (if not already discontinued) and will be randomized to take one of the three treatments under evaluation: Treatment A, Treatment B, Treatment C.

It is recalled that before proceeding to the discontinuation of anticoagulant therapy in a patient who was affected by VTE, the following investigations are usually suggested:

A. **Compression ultrasonography (CUS)**

   Before discontinuing the anticoagulant therapy, as per normal clinical practice, all patients with VTE are subjected to the CUS of both lower limbs, with compression of the femoral vein in the groin, of the superficial femoral vein in the middle of the thigh, and of the popliteal vein (including trifurcation) in the hollow of the knee. The diameter of the residual vein thrombosis (RVT) must be measured. The execution of the CUS at the end of anticoagulant therapy after VTE is recommended by the guidelines as an indispensable tool for the diagnosis of presence or exclusion in cases with suspected recurrent ipsilateral thrombosis.

B. Echocardiographic examination

   For patients who have suffered from pulmonary embolism it is usually suggested to perform echocardiography before discontinuation of anticoagulant therapy. This investigation allows to identify the possible presence of residual systolic pulmonary hypertension that represents a contraindication for the discontinuation of anticoagulant therapy.

C. Villalta score

   Patients with deep vein thrombosis are usually evaluated upon discontinuation of anticoagulant therapy for the presence and level of post-thrombotic syndrome, by applying the Villalta score. (Appendix 2) (9)

INVESTIGATIONAL PRODUCT

The investigational product used in treatment A and B is:

Vessel®: Sulodexide (Vessel®) is a glycosaminoglycan extract with antithrombotic effect and should be administered orally, twice a day throughout the treatment period.

Pharmaceutical form: soft capsules.

Approved therapeutic indications: chronic venous ulcers

Investigational therapeutic indications: prevention of VTE recurrence

For more information on the investigational product of treatment A refer to the Investigational Medicinal Product Dossier (IMPD).

Placebo

Indistinguishable placebo is used in treatment B and C.

Pharmaceutical form: soft capsules. IMPC

Posology and method of administration in treatment A

Dosage: 2 soft capsules of Vessel® 250 LSU BID, without food.

Method of administration: oral route.

Intervention scheme

After signing the informed consent, 485 patients are randomised to receive:

Treatment A: 2 soft capsules of Vessel® 250 LSU BID for 12 months

Indication of daily dose: Vessel® 1,000 LSU

Posology and method of administration in treatment B

Dosage: 1 soft capsule of Vessel® 250 LSU and 1 soft capsule of placebo BDI, without food.

Method of administration: oral route

Intervention scheme

After signing the informed consent, 485 patients are randomised to receive:

Treatment B: 1 soft capsule of Vessel® 250 LSU and 1 soft capsule of placebo BID for 12 months

Indication of daily dose: Vessel® 500 LSU

Posology and method of administration in treatment C

Dosage: 2 soft placebo capsules BID, without food.

Method of administration: oral route.

Intervention scheme

After signing the informed consent, 485 patients are randomised to receive:

Treatment C: 2 soft capsules of placebo BID, without food, for 12 months

Indication of the daily dose.

LABELLING AND PACKAGING

EXAMPLE BLISTER AND MODEL OF PRIMARY AND SECONDARY LABELLING

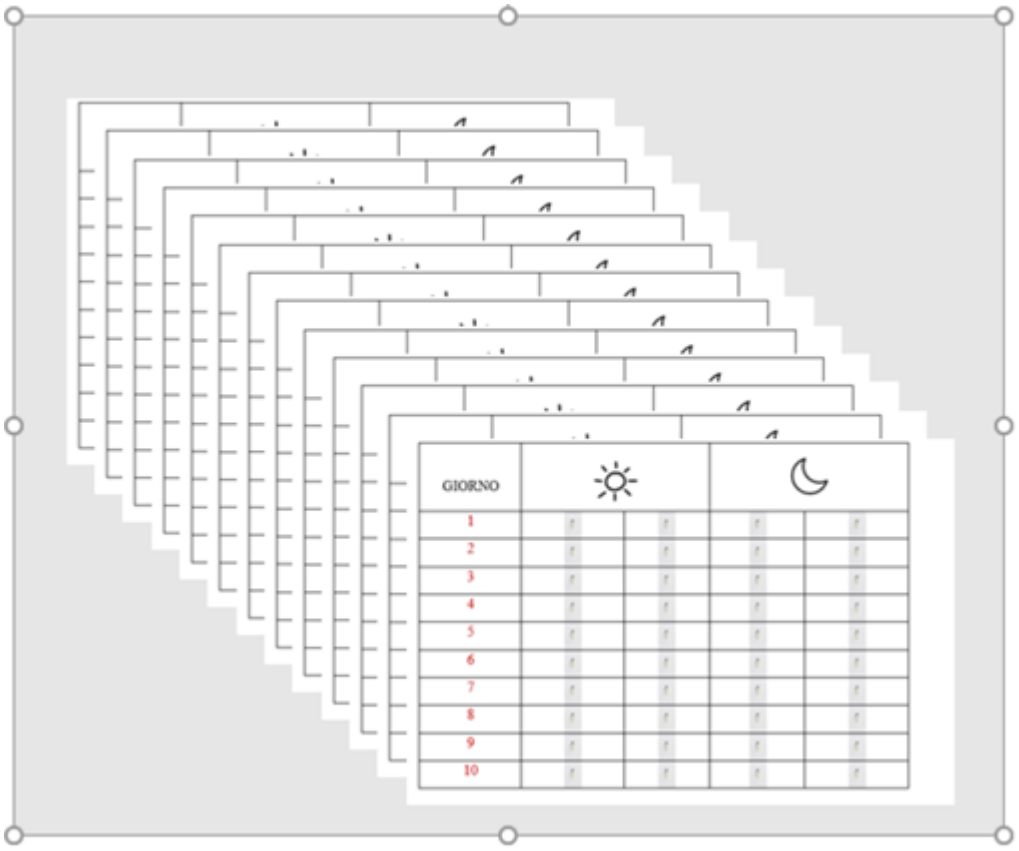
EXAMPLE BLISTER

GIORNO			[redacted]	
1				
2				
3				
4				
5				
6				

7				
8				
9				
10				

EXAMPLE SECONDARY PACKAGING

Each box contains 13 blisters



MODEL LABELLING

PRIMARY LABELLING

Sponsor Fondazione Arianna Anticoagulazione

Via Paolo Fabbri 1/3

40138 Bologna (BO)

Phone 051 341471

Study Code GIASONE (FAAI2.10.2018)

Content: 40 soft capsules, Sulodexide 250 LSU / Placebo

For oral administration

Batch Number.: _____ Code N°: _____ Kit N°.:_____

SECONDARY LABELLING – BOX 1 (kit)

Sponsor: Fondazione Arianna Anticoagulazione

Via Paolo Fabbri 1/3

40138 Bologna (BO)

Phone 051 341471

Phone (Only for medical emergency): +XXXXXXXXX Study Code GIASONE (FAAI2.10.2018)

Content: 40 soft capsules, Sulodexide 250 LSU / Placebo

The box contains 13 blisters. The blisters contain soft capsules Sulodexide (antithrombotic drug) 250 LSU / Placebo

For oral administration

Take 2 capsules in the morning and 2 capsules in the evening (about 12 hours apart), away from meals, taking the capsules from the same blister and following the number on the blister.

Batch Number.: _____ Code N°: _____ Kit N°.:_____

Kit number: _____ __ Exspire date: _____

Randomize N.: _____ (to fill by Investigator)

Site N°: _____ (to fill by Investigator)

Investigator's Name: _____ (to fill by Investigator)

Only for clinical trial.

Not store at temperatures over 30°C.

Return the empty packaging and the unused medicine at the study site. Keep out of reach of children.

TREATMENTS

Treatment initiation

The beginning of the three treatments under assessment must be scheduled a few days later (at least 3 days, to allow the elimination of the effect of the previous anticoagulant treatment - especially for antivitamin K) and no more than 30 days after the discontinuation of anticoagulant treatment.

The investigator:

- Gives the patient the first block of therapy, following the progressive numbering of the randomised blocks of therapy and / or placebo entrusted to the centre; the randomisation list is computer generated for therapy blocks; transcribes the numbering of the therapy block on the treatment labell and in the eCRF and presents the methods of administering and storing the medicinal product and returning the remaining boxes and blisters to the patient;
- Establishes the treatment initiation under assessment, ensuring an interval of at least 3 and not more than 30 days compared to the last uptake of the previous anticoagulant treatment;
- Establishes and agrees with the patient on the date for the 30-day check and the next one when the medicinal product will be replenished and the capsules of the returned treatment will be counted.

Check-up at 30 days with confirmation of adhesion

- The verification can be performed in outpatient or by phone and will be performed after 30 (± 7) days from the beginning of the treatment under assessment, and has the purpose of confirming the need to adhere to the treatment and to respond to any possible questions / concerns of the pacient.

Follow-up

- There are 3 follow-up controls, with periodic supply of the medicinal product every 4 months, of which the last is the final one (end of the treatment period), without dispensing the medicinal product;
- During each check-up, the investigator will provide the relative count of the capsules reported to verify the adherence to the therapy and will record any collateral events that occurred during the treatment period;

During one of the follow-up controls, the investigator may give at his discretion, a questionnaire (Appendix 2b) to be filled in by the patient to evaluate the Villalta score.

It is possible that an unscheduled visit be necessary during the follow-up (also at the request of the patient himself / herself).

After 30 days the conclusion of the study, it is suggested that the investigator makes a control by phone to verify the medical condition of the patients.

Contraindications to the use of Sulodexide: see the IMPD

Contraindications to the use of Placebo: see the IMPD

Investigational product management

The investigational product and the control product will be adequately manufactured, packaged, labelled and will be supplied and distributed free to the hospital pharmacies.

The investigational product will be accompanied by a regular transport document addressed to the pharmacy, containing the product description, quantity, preparation batch, expiry date, any particular storage conditions, the reference of the experimental protocol, the department for which the experimental drug is intended, the name of the investigator. The pharmacy of the centre will deliver the investigational product to the investigator, who will become the consignee upon taken over. The consignee or person delegated thereby, is responsible for keeping a special loading and unloading register, which must be updated constantly. The pharmacy of the participating centre and the investigator will not be able to administer the experimental product to subjects other than the trial patients, and will have to ensure that subjects other than the trial staff do not come into contact with the investigational drug. As for the residual or expired products, the participating centre will use the investigational product provided by the promoter only for the purposes of investigation and in accordance with the protocol, undertaking to return the residual investigational products at the end of the investigation, at the expense of the promoter, and according to the procedures agreed with the promoter.

Any unused and / or expired product will be withdrawn and destroyed at the end of the study.

Adherence to the intervention

Upon check-ups, the investigator will provide the relative count of the capsules reported to verify adherence to the therapy.

Prohibited therapies:

- Therapy with antiplatelet medicinal products other than ASA. ASA is allowed up to 140 mg / day
- Long-term treatment with LMWH
- Treatment with direct oral anticoagulant drugs

Analysis of the potential benefit / risk ratio for the population

The risks for the treated population are those related to oral administration of Sulodexide. Sulodexide has an antithrombotic action both at the arterial and venous level through a series of mechanisms of action such as the inhibition of some factors involved in the coagulation cascade, limiting the anticoagulant action. Therefore, an increase in the risk of bleeding could occur in the treated population, a risk that is considered to be very low according to scientific literature.

The potential benefit for patients treated with Sulodexide is related to the decrease of fibrinogen levels, to the action on altered blood viscosity in patients with vascular diseases and under thrombotic risk.
Furthermore, a decrease of the thromboembolic recurrence risk has been demonstrated, without an increased risk of bleeding.
The medicinal product has shown particular efficacy in elderly patients.
Another indirect benefit is the increase in the knowledge of this experimental product in the treatment of thrombotic diseases.

WITHDRAWAL OF THE SUBJECTS AND MODIFICATIONS OF THE PROCEDURE

Premature discontinuation

The treatment with the investigational product and the control product will be permanently discontinued if one of the following events occurs:

- A serious adverse event that causes premature discontinuation of the treatment
- The occurrence of a pathology requiring treatment with an anticoagulant drug for an indefinite period of time
- Onset of cancer or other pathology requiring the definitive discontinuation of the investigational product and / or control product.
- Withdrawal of the informed consent.
- Decision of the attending physician based on the patient's clinical needs

Temporary discontinuation

A temporary discontinuation of treatments does not imply premature termination of the study.
In particular, each treatment may be temporarily discontinued in case of surgery, invasive procedure. Treatment will be discontinued during treatment with LMWH. It may be discontinued, but not strictly necessary, in the case of minimally invasive manoeuvres (e.g., endoscopy or dental extraction). At the end of the discontinuance period, the treatment can be resumed. The period of interruption will not imply variations of duration in the observation. A period of temporary discontinuance not exceeding 20 days (even non-consecutive) for every 4 months of participation in the study is acceptable for the continuation of the study, thus ensuring an overall discontinuance of treatment not exceeding 20% of the entire expected duration of treatment.

Early termination or discontinuance of the study.

The promoter may interrupt the study at any time on the basis of what will be communicated and recommended by the "Data Monitoring And Safety Board" (DMSB) following the assessment of the results of the scheduled interim analyses upon the first occurrence of any of these conditions: observation of 30 % and 60% of the total events planned for the study, or the achievement of 30% and 60% of the patients concluded, the DMSB will inform the promoter if there are conditions of evident superiority, evident inferiority or futility, for the entire treatment under assessment or for one of the arms in the study, recommending the relative options that could be: early interruption of the entire study; early interruption of one of the arms; continuation as expected. Furthermore, the DMSB may also recommend – with adequate justification - the redistribution of subsequent cases between the study arms or even the change in sample size. In the event of early termination of the study or interruption of an active arm, the promoter will promptly notify the competent authorities, investigators and ethics committees. Patients will be examined as soon as possible and will continue to be followed according to normal clinical practice.

In case of changes to the distribution of the following cases or of recalculation of the sample size, the promoter undertakes to prepare the related amendments to the protocol that will be submitted to the competent authorities and to all the ethics committees for approval before applying the proposed amendment.

Deviations from the protocol

The investigator must not implement any deviations from the protocol or modify it without prior agreement with the Fondazione Arianna Anticoagulazione promoter and without prior review and approval / favourable opinion of the changes by the Regulatory Authorities and the reference ethics committees, except when this is necessary to eliminate an immediate risk for the subjects or when the changes imply only logistic or administrative aspects of the study.

The investigator or his designated person must draw up a document explaining the possible deviation from the approved protocol.

In the event that a change is made to the protocol to eliminate an immediate danger for the participants in the trial without prior approval / favourable opinion of the Regulatory Authorities and the reference ethics committees, the deviation or change implemented, the reasons thereof and, if applicable, the protocol amendments will be sent as soon as possible:

a) To the Regulatory Authorities and to the reference ethics committees for the revision and approval / favourable opinion;
b) To the sponsor for acceptance.

Any deviation from the inclusion and exclusion criteria listed above must be approved, in writing and on a case-by-case basis, by the investigator and promoter before enrolling the subject.

Definition of the conclusion of the study

The study will be concluded for a single patient at 12 months from enrolment (+ 30 days post follow-up), except for any premature withdrawal for the reasons stated above. The study will end, in general, at the last follow-up visit of the last patient enrolled. However, it is suggested an additional observation with a final telephone call 30 days after the discontinuation of therapy to check for any events after the definitive discontinuation of the study therapy. The study report will be drawn up within the next 12 months.

Fondazione Arianna Anticoagulazione is the sole owner of all information deriving from the study and will be responsible for the decision to terminate it.

STUDY ENDPOINTS

Primary endpoints

- Primary efficacy endpoint:
  - cumulative result of: new episodes of venous thromboembolism (proximal DVT and / or PE), overall mortality due to VTE
- Primary safety endpoint:
  - incidence of major bleeding (MB), International Society on Thrombosis and Haemostasis [ISTH] criterion (10)) (see appendix 1)

Secondary endpoints

- Secondary efficacy endpoint:Cardiovascular events that involved hospitalization;
- Death from cardiovascular events (myocardial infarction, ischemic stroke).

- Secondary safety endpoint:
  - Cumulative incidence of MB and non-major but clinically relevant haemorrhages [NMCRB], (11)) (see APPENDIX 3)

STATISTICAL CONSIDERATION

Sample size

Based on available data, the incidence of the primary endpoint (composite of recurrent proximal DVT, new PE events and total mortality attributable to TEEs) is estimated to be 13 per 100 patient-years. Available data (study SURVET [7]) indicate that the relative risk reduction (RRR) of events in the high-dose group (500 U b.d.) should be approximately 0.50. It can be expected that the RRR in the low-dose group (250 U b.d.) is approximately 0.25. The total relative risk reduction among treated subjects can therefore be estimated at approximately 0.38. The expected incidence of events among all examined patients should therefore be approximately 8 per 100 patient-years.

Based on the same information, it is also estimated that the incidence of major bleeding (co-primary endpoint) is approximately 1 per 100 patient-years and is not modified by the study treatments.

Hypotheses

The hypotheses can be formulated as:

Efficacy hypotheses:

a. hierarchically superior hypothesis: $H_0: \pi_{treated} = \pi_{controls}$; $H_A: \pi_{treated} \neq \pi_{controls}$ regardless of dose, where the size of the minimum detectable difference is that indicated above;

b. hierarchically inferior hypothesis (to be examined if the previous null hypothesis is rejected): $H_0: \pi_{250x2} - \pi_{500x2} \geq \delta$; $H_A: \pi_{250x2} - \pi_{500x2} < \delta$, where □ (value expressing the acceptable non-inferiority limit) is set at 0.045. This indicates that the outcome with the low dose is considered not inferior to that of the high dose, if the proportion of events is not greater than that of the high dose increased by 4.5 percentage points.

Safety hypothesis:

the only hypothesis considered is that the incidence of haemorrhagic events among treated patients (regardless of dose) is not superior to that among control and, furthermore, the higher limit of the 95% confidence interval of incidence does not reach 3%. The hypotheses can therefore be expressed as:

$H_0: \pi_{treated} - \pi_{controls} \geq \delta$; $H_A: \pi_{treated} - \pi_{controls} < \delta$, where □ is equal to 0.02. This means that the outcome among treated is considered not inferior compared to that among controls, in case it results in a proportion of haemorrhagic events non greater than that among controls increased by 2 percentage point and, in any case, with upper limit of the 95% confidence interval not greater than 3%.

Multiplicity

The two co-primary endpoints are not correlated consequently do not influence multiplicity. Two other items influence multiplicity: the analyses on the primary efficacy endpoint and the analyses *ad interim* to be supplied to the DMSB.

a) at least 460 patients per group (460 controls and 920 treated) have 80% power to observe with 95.2% confidence (alpha = 0.048 two-tailed) a difference of incidence between treated and controls equal to approximately 5 percentage points, on the assumption of an incidence among controls of 13% [14]

b) the same number is sufficient (minimum required size: approximately 450 cases per group) to have 80% power to observe with 95.2% confidence (alpha = 0.048 one-tailed) the non-inferiority of the low-dose vs. the high-dose group, on the assumption of an incidence of events of

approximately 10% in one group and 6% in the other, accepting a non-inferiority margin of 4.5 percentage points [15]

c) the same number is largely sufficient (minimum required size: approximately 330 cases per group) to have 90% power to observe with 95.35% confidence (alpha = 0.0465 one-sided) the non-inferiority of treated groups combined vs. controls, on the hypothesis of an incidence of haemorrhagic events of 1% among controls and accepting a non-inferiority margin of 2 percentage points [15] and, anyway, accepting an upper limit of the one-sided 95% confidence interval of incidence – determined by exact binomial test - not greater than 3%.

The total sample size should therefore be of approximately 1380 valid cases. Accounting for approximately 5% not assessable cases and for the fact that the total number should be a multiple of 24 – number of cases that can theoretically be assigned to each participating centre to allow randomisation blocks of variable size – the total number of subjects to be recruited should be of approximately 1450 (theoretically, 1464).

TIMING OF THE STUDY

Enrollment	24 months
Duration of Treatment	12 months
Maximum duration of the study for each patients	12 months
Total duration of the study	36 months
First enrolled patients	September 2019
Last enrolled patients	October 2022
Data Lock	April 2023
Final report	September 2023

Inclusion visit to the study

All patients aged 75 years or older who submit to observation with a first VTE event should be evaluated and included in the screening list. Patients who meet the inclusion criteria and who have no exclusion criteria must complete a period of at least 3 months of anticoagulant therapy (irrespective of the medicinal product used) before being enrolled in the study.

At screening, the participant centre physician:

1. Checks the clinical condition of the patient aged 75 years or older ,candidate for the study, and checks the general tests (valid within 3 months from the date of the check) that are routine for patients who have undergone anticoagulation treatment;
2. Checks the inclusion and exclusion criteria. In the presence of even one exclusion criterion, fills out the patient screening sheet and excludes him / her from the study;

3. In the event that any exclusion criterion is absent, prior to enrolment, and after adequate information about the aims, methods, expected benefits and foreseeable risks of the study, the investigator will obtain informed consent from the patients. Patients will discontinue the current anticoagulant therapy, if not already suspended, and will be randomised to take one of the three treatments
4. Then keeps the informed consent in the appropriate folder;
5. Records the required information in the eCRF and writes the study code that connects to the patient's name in the file.

Treatments

After signing the informed consent, the enrolled patients are randomised to receive:

- Approximately 485 patients: treatment A: Sulodexide Vessel®, 2 capsules of 250 LSU BID for 12 months
- Approximately 485 patients: treatment B: Sulodexide Vessel®, 1 capsule of 250 LSU and 1 capsule placebo BID for 12 months
- Approximately 485 patients: C treatment: 2 indistinguishable placebo capsules BID for 12 months

Conduct of the study

Treatment initiation

The beginning of treatment should be scheduled a few days later the last assumption of the ongoing anticoagulant treatment, especially for VKA 3 days, to allow the removal of the effect of the previous treatment, and no more than 30 days after the withdrawal of previous anticoagulant treatment.

The researcher

1. Gives the patient the first block of therapy, following the progressive numbering of the randomised therapy blocks (drug and / or indistinguishable placebo) entrusted to the centre; the randomisation list is computer generated for the therapy blocks; transcribes the numbering of the therapy block in the eCRF and highlights the methods of administering and storing the drug and returning the remaining capsules to the patient;
2. Establishes the beginning of the treatment under assessment, guaranteeing an interval of at least 3 and not more than 30 days compared to the last administration of the previous anticoagulant treatment;
3. Establishes and agrees with the patient on the date for the 30-day check and the next check when the medicinal product will be replenished and the capsules of the returned treatment will be counted.

First contact

1. The first subsequent contact will take place after 30 (± 7) days following the beginning of the treatment under assessment, and has the purpose of confirming the need for adherence to the treatment and responding to any questions / doubts from the pacient;
2. Any adverse events occurring during the treatment period are recorded

Follow-up controls

1. There are 3 follow-up visits, with periodic supply of the drug every 4 months, of which the last is the final one (end of the treatment period);
2. At each visit, the investigator will provide the relative count of the capsules reported to verify the adherence to the therapy and will record any adverse events occurring during the treatment period;
3. During any of the follow-up checks, the investigator, at his discretion, will be able to deliver a questionnaire to be filled in by the patient to evaluate the Villalta score. The score will be included in the eCRF;
4. A fourth check-up (also by telephone) must be scheduled after 30 days from the end of the therapy period (post follow-up);
5. At each follow-up visit the appropriate eCRF form must be filled in, as well as for the final visit and post follow-up check.

Unscheduled check-ups

It is possible that an unscheduled visit be necessary during the follow-up (also requested by the patient himself / herself). The visit and its result must be recorded in the eCRF. If the visit shows that a primary endpoint has occurred, the visit coincides with the end of the study for that patient, and then the end-study section of eCRF must also be filled in.

End of study

The end-study section must be filled in for:

a) Patients who have completed the planned treatment period (including post follow-up control);
b) Patients for which the unblinding has occurred.
c) Patients in whom an established endpoint has occurred;
d) Patients who withdraw their consent for participation in the study;
e) Patients who ha signed informed consent and refused the assigned treatment
f) Patients in whom any circumstances occur that prevent their participation in the study (lost to follow-up, patient transfer, death due to causes other than VTE, etc.);
g) Patients who need to start treatment with VKA or DOAC;

All events occurring during follow-up and post follow-up, including VTE recurrence, major bleeding, non-major but clinically relevant bleeding and death from any cause, will be objectively documented and recorded in accordance with current guidelines.

All events will be awarded by a central adjudication committee (see below) unaware of the type of treatment received by patients (investigational product or placebo). In addition, patients are advised to immediately contact the enrolling centre upon occurrence of signs or symptoms compatible with venous thromboembolism or other complications (such as bleeding episodes).

Each patient, based on the sequential enrolment order, will receive one of the three planned treatments, based on a randomisation list for each of the participating centres. The treatments will be identified exclusively through a unique randomisation number and will be distributed in randomized blocks. Each treatment will be accompanied by a sealed opaque envelope containing the decoding of the treatment assigned for any urgent need for decoding. The opening of the code must be reported immediately to the promoter and leads to the patient leaving the study.

The treatment of patients is discontinued upon the occurrence of:

- A primary event, whether related to efficacy (e.g., recurrence of VTE, death) or safety (e.g., major haemorrhage);
- The patient withdraws his / her informed consent to the study;
- The premature discontinuation of the study (see "withdrawal of subjects and changes to the procedure").

In the case of premature discontinuation without reaching the primary event, the patient is classified as censorised at the time of the last valid observation. In such cases, however, the researcher will use his best endeavours so as to obtain - except for those who have withdrawn their consent - information on the patient's status at the scheduled time for the 2-month check-up following the theoretical 12 months of treatment.

Assignment of the intervention

The investigator must follow the procedures concerning the assignment of treatments in a randomised manner. Please note that the code can be opened exclusively in the circumstances that are described in the next paragraph and only in accordance with the protocol. Furthermore, the investigator should promptly document and explain to the promoter the circumstances that led to any premature opening of the code (e.g., accidental opening, opening due to a serious adverse event).

The progressive numbering of the randomised therapy blocks (drug or indistinguishable placebo) entrusted to the centre is generated by a computer. To avoid the likelihood of predicting the random sequence, the details of each block are provided in a separate document not accessible to the investigator who recruits patients and assigns the interventions.

To avoid any selection bias regarding the masking of the assignment, a centralised office distributes patients by groups, the investigational drug and the indistinguishable placebo and the numbering will be such as not to predict the random sequence.

Opaque and sequentially sealed envelopes will be used as a mechanism for implementing the allocation sequence. The list must remain inaccessible and the envelopes must be opened sequentially after enrolling the patient and obtaining the consent.

The allocation ratio is 2:2:2 .

The investigator or his delegate is responsible for enrolling patients and assigning them to each intervention group.

Masking the treatments and conducting the blind study

The subjects enrolled in the study, the experimenters, and the members of the Steering Committee, Adjudication Committee, Data Monitoring and Safety Board will not be aware of the assignment of the 3 treatments following their distribution.

The unblinding and the possibility of revealing the assignment of the treatment is permitted only in the following circumstances:

- The occurrence of an AE for which the investigator needs to unblind the treatment
- The discontinuance of only one of the study arms by the DMSB
- The remodulation of the sample size (with the need to provide a new randomisation for subsequent cases)

Table Timeline of the Study

Procedure	**Enrollement**	**Control 30 days**	**Control 4 months**	**Control 8 months**	**Last Control 12 months**
Eligibility Assessments					
Informed Consent	X				
Inclusion/Exclusion Criteria	X				
Medical History	X				
Safety Assessments					
Physical Examination	X				X
Adherence to treatment		X	X	X	X
Clinical Drug Supplies					
Dispense Study Treatment	X		X	X	
Drug accountability			X	X	X
Efficacy End Points					
Primary		X	X	X	X
Secondary		X	X	X	X
Safety End Points					

Procedure	Enrollement	Control 30 days	Control 4 months	Control 8 months	Last Control 12 months
Primary		X	X	X	X
Secondary		X	X	X	X

DATA MANAGEMENT

Data collection in electronic case report form

Upon enrolment, the investigator of the participating centre will collect in the electronic case report form (eCRF):

- The personal data, pseudo-anonymised, of the patient inserted
- The general and clinical characteristics of the patient, including laboratory and instrumental examinations
- The type, location and characteristics of the thromboembolic event
- The type of treatment for the index event
- Will assign one of the three treatments to the patient and insert the randomisation code into the eCRF

At follow-up checks, the researcher doctor will collect in the eCRF:

- Verification of adherence to therapy
- Recording of adverse events or other complications
- Evaluation of the villata score using a questionnaire (APPENDIX 2B). The delivery of the questionnaire is at the discretion of the investigator

At the post follow-up call, the research doctor will collect in the eCRF:

- Adverse events or other complications occurring after discontinuation of treatment

For further details on the data collected, refer to the data collection form submitted together with the protocol.

Fondazione Arianna Anticoagulazione will provide an eCRF to all participating investigators.

The investigator will access eCRF exclusively for the insertion of the clinical data of his patients, which are collected according to this protocol. To safeguard the integrity and confidentiality of data, each investigator will be provided with a personal account that will allow access to relevant data on the individual centre, blocking any unauthorised intrusion attempt.

The investigator medical doctor will insert the data on the eCRF, in a strictly anonymised form and the subject will be identified only with a code generated automatically with a progressive number of insertion.
The adopted database is mySQL and it will be produced by Softime90 Snc company.
Data anonymously entered in the eCRF will be recorded and stored in the server of the Arianna Anticoagulazione Foundation in Bologna.
Each access to the eCRF will be managed by personal user name and a password.
The security system requires that the password be changed at the first access; it requires a length of at least 8 characters and provides for a periodic 3-month expiry.
It is obviously possible to disable the login, if it is deemed necessary by the system administrator.
Investigators can have full access only to their patient's data. Every night the data backup is automatically performed.

Monitoring

The study monitor, commissioned by Fondazione Arianna Anticoagulazione, will monitor the progress of the study remotely, with the aim of ensuring that it is performed, recorded and reported in compliance with the protocol, the SOP, the GCP and the applicable regulatory provisions.
The monitor will contact the centres in advance to schedule the monitoring visit and inform them of the documents to be made available for the monitoring day.
The monitor will show the investigator and his staff the operational details of the protocol and the eCRF.
The monitor will also check the eCRFs and assess its completeness and consistency by remote monitoring.
All entries, corrections and changes must be made by the responsible investigator. Roles and rights of the personnel responsible for entering clinical data in the eCRF will be determined in advance. If further corrections are necessary, the monitor or data manager will start a query.
The clinical case researcher will respond to the queries sent.
During the study, the investigator should allow the monitor to check the progress of the study and provide the missing data.
All the personal data is handled confidentially.
The Study Monitor will send blind to the Safety Committee the data of the occurred events and all the necessary related information for their assessment.

For any data transfer, all data protection measures will be undertaken (art 32 GDPR 2016/679), preventing disclosure to unauthorised third parties and ensuring that confidentiality is maintained at all times.

Data monitoring

Fondazione Arianna Anticoagulazione has established a DMSB to supervise the study.
The main purpose of the DMSB is the protection of patients enrolled in the study.
For details on the role and DMSB activity, please refer to the study committee chapter below.

STUDY FEASIBILITY

We expect that at each participating site at least 30 patients/18 months, in average 18 months will be enrolled. Thus, with the participation of 40-50 Italian centers we plan to complete enrolment in 24 months. With the last patient in completing the study follow-up in 18 months, study completion is expected in 3 years.

DATA QUALITY CONTROL

The promoter ensures that appropriate quality control (QC) procedures are implemented for adequate protection of enrolled patients and data quality.
Professor Angelo Bignamini (Milan), Medical Doctor Alberto Tosetto (Vicenza) and Medical Doctor Lorenza Bertù (Vasere) will assist the promoter in the statistical analysis of the study.

STATISTICAL PLAN

Populations examined

In principle, all randomised subjects will be examined for efficacy and safety. Only those subjects who, after having signed the informed consent and having been randomised to treatment, refused to receive the assigned medication, will be excluded from all analysis and will be classified as screening failures.
The safety analyses (haemorrhages, adverse events, vital signs) shall be performed on all properly randomised subjects, excluding only the screening failures. These subjects represent the safety population.
The efficacy analyses will be performed on all properly randomised subjects (Intent-To-Treat population; ITT). However, from the ITT population could be excluded, in addition to the screening failures, also those subjects presenting violations of the admission criteria, such to make the individual case inappropriate for the study. The not assessable cases will equally be excluded, Not assessable means those subjects who had been properly followed during the whole observation

period, had the final evaluation but this evaluation was inconclusive as to the efficacy endpoints and cannot be repeated.
Exclusion of a subject from the ITT population will be decided jointly by the Steering Committee and the Adjudication Committee (see below). The Committees will take their decision having available the complete CRF for the individual case, but still blinded.
The resulting population (modified ITT; mITT) will be the population submitted to the efficacy analyses.
The Steering Committee will identify the subjects among the mITT population for whom the documentation is available, validated by the Adjudication Committee, demonstrating that one of the primary endpoints had been reached, or showing that the planned observation had been concluded without any primary event (recurrence, death, severe haemorrhage); who had a compliance with treatment of at least 75% of the theoretical amount; and had no protocol violation that the same Committee considered major. The analysis of the primary endpoints in this population (per-protocol population, PP) will be used as sensitivity analysis for efficacy and safety.

Descriptive analyses

Data collected at recruitment will be analysed on the mITT population and, only if necessary, also on the safety and PP populations. It is expected that separate analyses will be considered appropriate if the difference in number between populations exceeds 10%.

All collected data will be described as central tendency and dispersion for continuous variables (mean with standard deviation and 95% confidence interval if normally distributed; median with range interquartile and 95% CI in case of substantial deviation from normal distribution). Nominal variables will be described as absolute and relative frequency tables. The results will be expressed by treatment group. Formal statistical analysis of the baseline variables is not planned, except for those variables that, at the descriptive analysis, will suggest potential differences of clinical relevance. In such cases the appropriate tests will be applied: analysis of variance (ANOVA) complemented with the Tukey and Dunnet tests for normally distributed continuous variables; Kruskal-Wallis test for continuous or pseudo-continuous variables not normally distributed; chi square test for nominal variables.

Primary endpoints analyses

The primary endpoints of this study are events that can be expressed as frequencies (number of events in relation to the observed subjects) and as time to the event occurrence.
The primary analysis of the primary efficacy endpoint will be the survival analysis according to Cox, using as sole covariate the treatment to estimate the hazard ratio, the relevant 95% confidence

interval and the associated P value. Subsequently, other covariates may be analysed in the same model of proportional risk according to Cox, adding to the treatment, if appropriate, the age (in decades), sex, the type of index event (PE – alone or associated with DVT – or DVT alone), the duration of exposure to anticoagulation (<6 months / ≥6 months), the renal function (glomerular filtration rate [GFR] ≥60/<60) the body weight (BMI ≥30/<30) and, if appropriate, the level of compliance (<75% / ≥75%). This analysis will be applied to the mITT population and, for what applicable, to the PP population.

The results of the primary efficacy endpoint will also be examined as frequencies. Since it is possible that in the mITT population there will be censored cases (those who left prematurely the study without having reached an endpoint), procedures will have to be applied to replace the missing outcome. Two procedures are anticipated: a) a "worst case" classification, in which all censored cases will be classified as failure (endpoint reached); b) if appropriate, attribution to the missing outcomes of the outcome seen in the nearest neighbour case, estimated by the propensity score computed using the same predictors used for the Cox model, with and without the predictor "treatment". These results will be analysed with the exact Fisher's test, estimating the relative risk and the relevant 95% confidence interval. The analysis will be applied to the mITT and PP populations. In this latter, by definition, the missing data replacement will not be required.

If the comparisons of the primary efficacy endpoint will allow to detect that the treatment, regardless of dose, produced a significant effect, then the two doses will be compared, using the Cox model for the analysis of the time to the events, and the exact Fisher's test for the analysis of frequencies. These analyses will be performed using the one-sided confidence intervals, in accordance with the hypotheses expressed in the sample size calculation. For this analysis the reference population will be the PP population, since the estimation of the true effect of different doses is affected by the level of compliance.

The primary safety endpoint (severe haemorrhages) will be analysed in the same way as the primary efficacy endpoint, using however one-sided tests in accordance with the non-inferiority hypothesis expressed in the sample size calculation.

Secondary endpoints analyses

The secondary endpoints will be examined on the mITT population without replacement of missing data, using the same techniques indicated for the analyses of the primary endpoints.

The compliance is considered a secondary endpoint. The measure of compliance is the proportion of presumably consumed medication vs. expected, given the interval between date delivered and date returned. Results will be expressed as compliance percent considered as continuous variable,

and as proportion of subjects with compliance ≥75%. If appropriate, compliance will be compared between groups with the analysis of variance and the chi square test.
Another secondary endpoint is the Villalta score [9], which will be analysed as continuous variable and as nominal variable, using the cut-off >5 to identify the post-thrombotic syndrome and the cut-off >14 to classify the syndrome as severe. The distribution of the continuous variable will be analysed with the general linear model for repeated measures, the distribution of the nominal variable will be analysed by contingency tables.

Safety analyses

Safety analyses will be performed on the safety population, without replacement of missing values. The analysis of continuous variables, if appropriate, will compare treatment groups using the general linear model for repeated measures if possible, otherwise comparing by ANOVA the changes between the last available measurement and the baseline value.
Adverse events will be tabulated by organ/system, split by treatment groups. No formal analyses will be performed, unless the frequency distribution across groups suggests clinically relevant differences. In such cases, the specific event will be compared as frequency (subjects with event, regardless of the number of events per subject) by groups using the chi square test.
If appropriate, the number of subjects with at least one event; with at least one serious event; with at least one event leading to treatment interruption; with at least one event considered potentially treatment-related, will by tabulated by treatment groups and, if needed, compared with the chi square test.
Deaths will be individually described, but the analysis of the relevant frequency was already considered among the efficacy endpoints.

Interim analyses

In this study, the periodic assessments will be preformed when reaching the first among the following conditions:

a) 30% and 60% of concluded cases, i.e., when 485 and, respectively, 970 patients will have reached the end of the observation, regardless of the number of events, or

b) 30% and 60% of the primary events (composite of recurrence of proximal DVT, new PE episodes, total mortality attributable to TEEs), i.e., when 46 and, respectively, 92 primary events will have been confirmed by the Adjudication Committee.

Impact of interim analyses on the alpha error

Performing two interim analyses in addition to the final analysis implies and increase of the alpha error that, estimated with the O'Brien-Fleming function, imposes to decrease the nominal alpha

value for the final analysis from 0.05 to 0.048 (two-tailed) for the primary efficacy endpoint [13]. This correction was already considered in the sample size calculation.

Similarly, the critical alpha value (one-sided) to be considered for the final analysis of the safety endpoint will change from 0.05 to 0.0465 for the effect of the interim analyses. This correction as well was already considered in the sample size calculation.

SAFETY AND REPORTING

DEFINITIONS

SERIOUS ADVERSE EVENTS

A **S*erious 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 participant 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 were more severe)
- requires inpatient 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 [eg, 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 convulsions that do not result in hospitalization.)
- Suspected transmission of an infectious agent (eg, pathogenic or nonpathogenic) via the study drug is a SAE.

The following hospitalizations are not considered SAEs:

- a visit to the emergency room or other hospital department < 24 hours, 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 (eg, 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 (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason).

ADVERSE EVENTS

An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation participant 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 investigational product, whether or not considered related to the investigational product.

The causal relationship to study drug is determined by a physician and should be used to assess all adverse events (AE). The casual 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

NONSERIOUS ADVERSE EVENT

A ***non-serious adverse event*** is an AE not classified as serious.

- Non-serious Adverse Events (AE) are to be provided in aggregate via interim or final study reports as specified in the agreement or, if a regulatory requirement as part of an annual reporting requirement.

SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTION – SUSAR

SUSAR is defined as an untoward and unintended response to a study drug, which is not listed is the applicable product information, and meets one of the following serious criteria: results in death, is life-threatening, requires hospitalisation or prolongation of an existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect.

Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiograms, X-rays, and any other potential safety assessments, whether or not these procedures are required by the protocol, should also be recorded as a non-serious or serious AE, as appropriate, and reported accordingly.

ADVERSE EVENTS REPORTING

Serious Adverse Events (SAEs) Collecting and Reporting

Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures and reported in e-CRF

A SAE report should be completed for any event where doubt exists regarding its status of seriousness.

SAEs must be recorded on the SAE and pregnancy Forms and have to be reported to the farmacovigilance referent within 24 hours.

SAE indirizzo mail: farmacovigilanza-noprofit@neurofarba.it
SAE numero Fax: 055 2758205
SAE telefono fisso: 055 2758303
SAE telefono mobile: 392 3176384:

Primary and secondary endpoints do not have to be reported to the farmacovigilance referent

If only limited information is initially available, follow-up reports are required. If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours to the Sponsor using the same procedure used for transmitting the initial SAE report.
All SAEs should be followed to resolution or stabilization.

Non-Serious Adverse Events (NSAEs) Collecting and Reporting
The collection of non-serious adverse event (NSAE) information should begin at initiation of study drug. Nonserious adverse event information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects. Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious. Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study drug, or those that are present at the end of study treatment as appropriate. Nonserious Adverse Events are reported in CRF

SAE Reconciliation
The investigator will reconcile the clinical database SAE cases sento to Sponsor Reconciliation will occur every six months and once just prior to database lock/Final Study Report (FSR). The investigator will request a safety data reconciliation report

ADMINISTRATIVE ISSUES

Support of the study

The study was supported by a grant from ALFASIGMA; ALFASIGMA kindly provided and distributed the treatments. Participation in the Jason Study is entirely voluntary and no form of remuneration or refund is given to the investigators.

No profit study

This study has all the necessary requirements according to the Ministerial Decree of 17 December 2004 (Art.1, subparagraph 1 and 2) for the definition of "clinical trials designed to improve clinical practice as an **integral part of health care and not for industrial purposes".**

Insurance

All subjects participating in the study will be covered by an insurance policy taken out by Fondazione Arianna Anticoagulazione, which is in accordance with applicable laws and/or regulations (D.M. 14 Luglio 2009).

STUDY COMMITTEES

The scientific integrity of this study will be supervised and publicly assured by four managing Committees: Steering Committee, Adjudication Committee, Data Monitoring and Safety Board and Writing Committee

Steering Committee

The Steering Committee:

a. supervises the course of the study and ensures that the protocol is carefully followed by each participant. To exert this responsibility, the Steering Committee is supported by the Monitor(s); is informed of all the monitoring activities and receives – and should take into appropriate consideration – the reports of the Data Monitoring and Safety Board as detailed below;
b. proposes amendments to the protocol to resolve, clarify and implement potential doubts, questions or practical difficulties that may onset during the study;
c. proposes amendments to protocol that may become necessary upon the scientific progress in the specific therapeutic segment, to ensure the maintenance of the scientific validity of the study;
d. solves doubts concerning possible protocol violations, deciding whether individual cases have to be classified as minor deviation, major deviation or violation proper and, consequently, whether the specific subject is to be included into the safety population only or also into the mITT population or event into the PP population. To this aim, the Steering Committee will have anonymous and rigorously blinded access to all data relevant to the specific case;
e. participates to the Writing Committee;F. Assisting the Adjudication Committee in case of irremediable disagreement among the members of this committee in expressing their judgment.

The Steering Committee consists of [Palareti, Ageno, Bignamini, Legnani, Lodigiani, Pengo, Poli, Testa, Tosetto]

Adjudication Committee

The Adjudication Committee is responsible of validating the efficacy and safety outcomes reported by the Investigators, and of classifying the doubtful event of recurrence and/or bleeding as outcome or non-outcome. The evaluation by the Adjudication Committee will be blind, with blinded access to all data available onto the database for the specific case. The data will be completely anonymous. If considered necessary, the Adjudication Committee has the right to request additional information, not available onto the database, to the Investigator responsible for the case. All data supplied to the

Adjudication Committee will anyway be completely anonymous or, where necessary, anonymised before being conferred to the Committee. The Investigators participating to the study, for the simple fact of accepting this protocol also accept the possibility of receiving such requests for additional information and accept to supply what requested, if possible and without prejudice for the respect of confidentiality.

The judgement of the Adjudication Committee is taken by consensus among its member. In case of irreconcilable disagreement, the judgement will be deferred to a joint meeting with the Steering Committee, in which the decision will be taken by majority.

The Adjudication Committee is composed of Profs. Domenico Prisco (Florence), Davide Imberti (Piacenza) and Franco Piovella (Pavia).

Writing Committee

The Writing Committee is composed of the Steering Committee, Gualtiero Palareti (Bologna), Walter Ageno (Varese) , Angelo Bignamini (Milano), Cristina Legnani (Bologna), Corrado Lodigiani (Milano), Vittorio Pengo (Padova), Daniela Poli (Firenze), Sophie Testa (Cremona), Alberto Tosetto (Vicenza), complemented with Elisabetta Bigagli (Firenze) and one Investigator indicated by each centre having recruited at least 24 patients.

The Writing Committee:

a. prepares the publication of the main study results;

b. decides additional and subsequent publications of planned and unplanned study results;

c. requests additional statistical analyses of study data in relation to the publications indicated above;

d. defines the list of authors for each publication;

e. manages the contacts with the journals and the responses to possible queries for clarifications and modifications to the publications sent.

Data Monitoring and Safety Board

This study will be supervised by a specifically instituted Data Monitoring and Safety Board (DMSB).

The main aim of the DMSB is the patients' protection, in first instance of those enrolled in the study, but also of other patients with the examined disorder. The second responsibility of the DMSB is to ensure the integrity of the study, in relation to the compliance with procedures indicated in the protocol to guarantee the data credibility.

The DMSB is composed of Profs. Angelo Bignamini (Milan), Alberto Tosetto (Vicenza), Gualtiero Palareti (Bologna) and Lorenza Bertù (Varese).

To exert its function the DMSB performs periodical evaluations on the data, writes a report with its recommendations and submits the recommendations to the Steering Committee. These reports are not binding, however, in case the Steering Committee decides not to implement decisions recommended by the DMSB, this latter is free to communicate its recommendation to the Ethics Committees who approved the protocol.

Procedures

The DMSB periodically receives from the study monitor a detailed evaluation of:

- frequency of primary events
- frequency of serious adverse events
- frequency of treatment interruptions
- frequency of subjects lost to follow-up without having incurred into a primary event
- frequency of potential protocol violations.

The evaluations presented to the DMSB will, in principle, not be stratified by treatment group. Only when the classification by treatment group could imply a decision to interrupt the study or the suggestion of a major protocol modification, the results will be stratified by treatment group, always blinded as to which treatment. Unblinding, with the attending consequences under the statistical and procedural viewpoint, will occur only in the case the DMSB intends to recommend the interruption of one study arm only or to recalculate the sample size (with the need to provide a new randomisation for the following cases).

Based on these evaluations, the DMSB decides by majority which recommendation shall be sent to the Steering Committee: continue the study as planned in the protocol; implement further verifications of adequacy and quality of the applied procedures (to decrease the risks of protocol violations and/or facilitate maintaining in the study the recruited patients); interrupt the study for manifest superiority or manifest inferiority or futility; interrupt one of the study arms because of the of indicated reasons; modify the sample size of the whole study or of one of the arms.

Interim analysis

In this study, the periodic assessments will be preformed when reaching the first among the following conditions:

a) 30% and 60% of concluded cases, i.e., when 485 and, respectively, 970 patients will have reached the end of the observation, regardless of the number of events, or

b) 30% and 60% of the primary events (composite of recurrence of proximal DVT, new PE episodes, total mortality attributable to TEEs), i.e., when 46 and, respectively, 92 primary events will have been confirmed by the Adjudication Committee.

Impact of interim analyses on alpha error

Performing two interim analyses in addition to the final analysis implies and increase of the alpha error that, estimated with the O'Brien-Fleming function, imposes to decrease the nominal alpha value for the final analysis from 0.05 to 0.048 (two-tailed) for the primary efficacy endpoint [13]. This correction was already considered in the sample size calculation.

Similarly, the critical alpha value (one-sided) to be considered for the final analysis of the safety endpoint will change from 0.05 to 0.0465 for the effect of the interim analyses. This correction as well was already considered in the sample size calculation.

DMSB decisional criteria

Interruption due to manifest superiority

"Manifest superiority" means that one of the groups (treated regardless of dose, or controls) showed at one of the interim analyses a rate of the composite primary efficacy endpoint so largely superior compared with the other group, that continuing the study as planned will have very small probability to change the result. Furthermore, this result invalidates the principle of equipoise among treatments, making unethical the continuation of the study.

Since the considered hypothesis was two-tailed, the criterion to suggest interrupting the study for manifest superiority is that the analysis yields a Z-test value of 3.929 or more at the first interim analysis, or of 2.670 or more at the second interim analysis.

Interruption due to manifest inferiority

"Manifest inferiority" means that one of the groups (treated regardless of dose, or controls) showed at one of the interim analyses a rate of bleedings so largely greater compared with the other group, that continuing the study as planned will have very small probability to change the result. Furthermore, this result exposes to unacceptable risks one of the groups, making unethical the continuation of the study.

Since the considered hypothesis was one-tailed, the criterion to suggest interrupting the study for manifest inferiority is that the analysis yields a Z-test value of 3.393 or more at the first interim analysis, or of 2.281 or more at the second interim analysis.

Interruption due to futility

"Futility" means that the data collected at the time of the analysis suggest that the study as planned will have little probability of reach its primary objectives. This condition can occur because the rate of events among controls is less than expected and/or the risk reduction among treated is less than expected. If at the first interim analysis the number of events among controls is 14 or less and, at the same time, the number of events among treated (regardless of dose) is 19 or more, in absence of factor that could justify such deviations from the expected, continuing the study will have very

small probability of reaching the planned objectives. The same conclusion will be reached if, at the second interim analysis, the number of events among controls will be 28 or less and, at the same time, the number of events among treated (regardless of dose) will be 37 or more.

Alternative decisions

In case one the interruption criteria will be reached, or even without reaching one of such criteria but in presence of deviations considered relevant by the DMSB in relation to the study objectives, the Committee could require that the interim analysis is repeated, stratifying the results by treatment group. In case one group presents sufficient evidence of deviating from expected, the DMSB could suggest to the Steering Committee:

- to recalculate the sample size based on the effectively observed incidence of events;
- to interrupt one the treatment arms based on the deviation of the incidence of events actually observed vs. that expected;
- a combination of both the above suggestions.

ETHICS

The study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and in compliance with the protocol and ICH-GCP.

The protocol and any amendments and the informed consent form (or information/non-opposition letter, as allowed by local regulations) will have to obtain Institutional Review Board or Ethics committee (IRB/EC) approval prior to initiation of the study.

Informed consent forms

Participation in this study is entirely voluntary. Informed consent will be obtained in accordance with the Declaration of Helsinki, ICH GCP and local regulations. A properly executed, written, informed consent will be obtained from each subject prior to entering the subject into the trial. Information should be given in both oral and written form and subjects (or their legal representatives) must be given ample opportunity to inquire about details of the study. If appropriate and required by the local IRB/IEC, assent from the subject will also be obtained. If a subject is unable to sign the informed consent form (ICF) a legal representative may sign for the subject. A copy of the signed consent form will be given to the subject or legal representative of the subject and the original will be maintained with the subject's records.

Once a patient has been enrolled in the study, he/she may withdraw his/her consent to participate in the study at any time without prejudice. Patients will not be entered in the database if the informed consent has not been obtained.

Direct access to source data/document

The subjects will be informed in writing that representatives of Fondazione Arianna Anticoagulazione, EC/IRB, or regulatory authorities may inspect their records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws. If the results of the study are published, the subject's identity will remain confidential. The investigator will retain a secure list to enable the patients' records to be identified.

Confidentiality

All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.

The promoter of the study will provide the measures to safeguard the subject's privacy and the protection of personal data according to the EU GDPR 2016/679

Institutional review board / independent ethics committee

Before study initiation, the investigator must have obtained written and dated approval from the Institutional Review Board/ Independent Ethics Committee (IRB/EC) for the protocol, the patient informed consent form (or information/non-opposition document, as allowed by local regulations), subject recruitment materials/process (e.g. advertisements), and any other written information to be provided to subjects. The investigator or promoter should provide the IRB/EC with reports, updates and other information (e.g. amendments) according to regulatory requirements or institution procedures of each country. Protocol amendments, except where necessary to eliminate an immediate hazard to subjects, will be issued by Fondazione Arianna Anticoagulazione. Agreement from the investigator must be obtained for all protocol amendments and amendments to the patient informed consent form (or information/non-opposition document, as allowed by local regulations). The IRB/EC must be informed of all amendments and give written approval, which must be provided to Fondazione Arianna Anticoagulazione.

Publication

Role of Promoter and Investigators

The Promoter and the investigators may suggest specific analysis, regarding all or some data of the central database. The authorship of the article must provide who proposed the analysis, who performed the data analysis, who took part in writing the article.

Data handling and record keeping

All data and results and all intellectual property rights to the data and results derived from the study will be the property of the Promoter Fondazione Arianna Anticoagulazione according to D.M. 17 Dicembre 2004. This study is a No Profit Study (D.M. 17 Dicembre 2004, Art. 1, comma 2, lettera c).

Archiving of data

The investigator should arrange for the archiving of the study documentation file and the raw data from the hospital for the longest of the following period of time. At least 7 years after completion/discontinuation of the study. Patient hospital files and other source data should be kept for not less than 7 years.

Final report and publication

Within 12 months from the completion of the trial and in accordance with ICH-GCP, the promoter provides the IRB/IEC with a summary of the trial's outcome, and the regulatory authority(ies) with any reports required. This study will be registered on the site www.clinicaltrials.gov (_____). All data and results and all intellectual property rights to the data and results derived from the study will be the property of Fondazione Arianna Anticoagulazione, who may utilize the data in various ways, such as for submission to government regulatory authorities or disclosure to other investigators. All publication or communication (oral or written) will respect the international requirements: "Uniforms requirements for Manuscripts Submitted to Biomedical Journals".

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APPENDIX 1

Known risk factors of bleeding (adapted from Kearon J et al, CHEST 2016)

a. Hypertension
b. Renal failure
c. Thrombocytopenia
d. Diabetes
e. Antiplatelet therapy (ASA maximum 140 mg/die)
f. Frequent falls (>2 /years)
g. Nonsteroidal anti-inflammatory drug
h. Liver failure
i. Previous Stroke
j. Anemia
k. Poor anticoagulant control
l. Alcohol abuse

APPENDIX 3

BLEEDING EVENTS

Major bleeding event

A major bleeding event was defined as a bleeding event (as per International Society on Thrombosis and Haemostasis guidelines [11]), as follows.

- Acute clinically overt bleeding accompanied by 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, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal
  - ✓ fatal bleeding.

Clinically relevant non-major bleeding event

The definition of clinically relevant non-major bleeding (from Kaatz et al. Definition of clinically relevant non-major bleeding in studies of anticoagulants in atrial fibrillation and venous thromboembolic disease in non-surgical patients: communication from the SSC of the ISTH. J Thromb Haemost 2015; 13: 2119-2126)

Any sign or symptom of hemorrhage (e.g., more bleeding than would be expected for a clinical circumstance,including bleeding found by imaging alone) that does not fit the criteria for the ISTH definition of major bleeding but does meet at least one of the following criteria:
i requiring medical intervention by a healthcare professional
ii leading to hospitalization or increased level of care
iii prompting a face to face (i.e., not just a telephone or electronic communication) evaluation

Minor bleeding events

All acute clinically overt bleeding events not meeting the criteria for either major bleeding or clinically relevant non-major bleeding were classified as minor bleeding.

Fatal bleeding event

A fatal bleeding event was defined as a bleeding event that the adjudication committee determined was the primary cause of death or contributed directly to death.