CLINICAL TRIAL PROTOCOL

COMPOUND: AVE5026

A multinational, randomized, double blind, placebo-controlled study to evaluate the efficacy and safety of AVE5026 in the prevention of venous thromboembolism (VTE) in cancer patients at high risk for VTE and who are undergoing chemotherapy

STUDY NUMBER: EFC6521

STUDY NAME: SAVE-ONCO

Version Number: 2.0 Approved	**Date**: 15-Feb-2008	**EudraCT or IND Number**

NAMES AND ADDRESSES OF

COORDINATING INVESTIGATOR	Name: Address: Tel: Fax: E-mail:	
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SPONSOR	Company: Address:	
OTHER EMERGENCY TELEPHONE NUMBERS		

CLINICAL TRIAL SUMMARY

COMPOUND: AVE5026 STUDY No : EFC6521

TITLE	A multinational, randomized, double blind, placebo-controlled study to evaluate the efficacy and safety of AVE5026 in the prevention of venous thromboembolism (VTE) in cancer patients at high risk for VTE and who are undergoing chemotherapy
INVESTIGATOR/TRIAL LOCATION	Multinational
STUDY OBJECTIVE(S)	**Primary**: To compare the efficacy of once daily (q.d.) subcutaneous (s.c.) injections of 20 mg AVE5026 with placebo in the prevention of venous thromboembolism (VTE) in cancer patients at high risk for VTE and who are undergoing chemotherapy **Secondary**: To evaluate the safety of AVE5026 in cancer patients at high risk for VTE and who are undergoing chemotherapy, to document AVE5026 exposures, to try identifying a metagene predictor of VTE and to assess the survival status at one year in this population.
STUDY DESIGN	This is a multinational, randomized, double blind superiority study, with 2 parallel groups. Cancer patients with high VTE risk i.e. patients with metastatic or locally advanced tumor of the lung, pancreas, stomach, colon/rectum, bladder or ovary, initiating a (new) course of chemotherapy will be randomly assigned to receive once daily s.c. injection of either AVE5026 20 mg or placebo: (i) until change in the initial chemotherapy regimen (i.e. addition or removal of at least one of the initial antineoplastic drugs) if this change occurs after the first 3 months of the study or (ii) at least 3 months and until the regimen ongoing at the 3-month time point (defined as addition or removal of at least one of the antineoplastic drugs of this regimen) is changed; if the change in the initial chemotherapy regimen occurs within the first 3 months of the study and the patient continues on chemotherapy or (iii) until decision is made to stop definitely chemotherapy if it occurs within the first three months of the study whichever comes first . Therefore the study treatment duration is variable, depending on the duration of chemotherapy. In any case, at the latest, study treatment will be discontinued for all patients 6 months after the last patient is randomized (see duration of study period). In order to balance treatment groups with regard to prognostic factors, and geographical region, a dynamic allocation will be used taking into account the three following factors: - Location of the primary site of the tumor (lung, pancreas, stomach, colon/rectum, bladder or ovary) - Stage of the cancer (metastatic, locally advanced) - Geographical region (North America, South America, Western

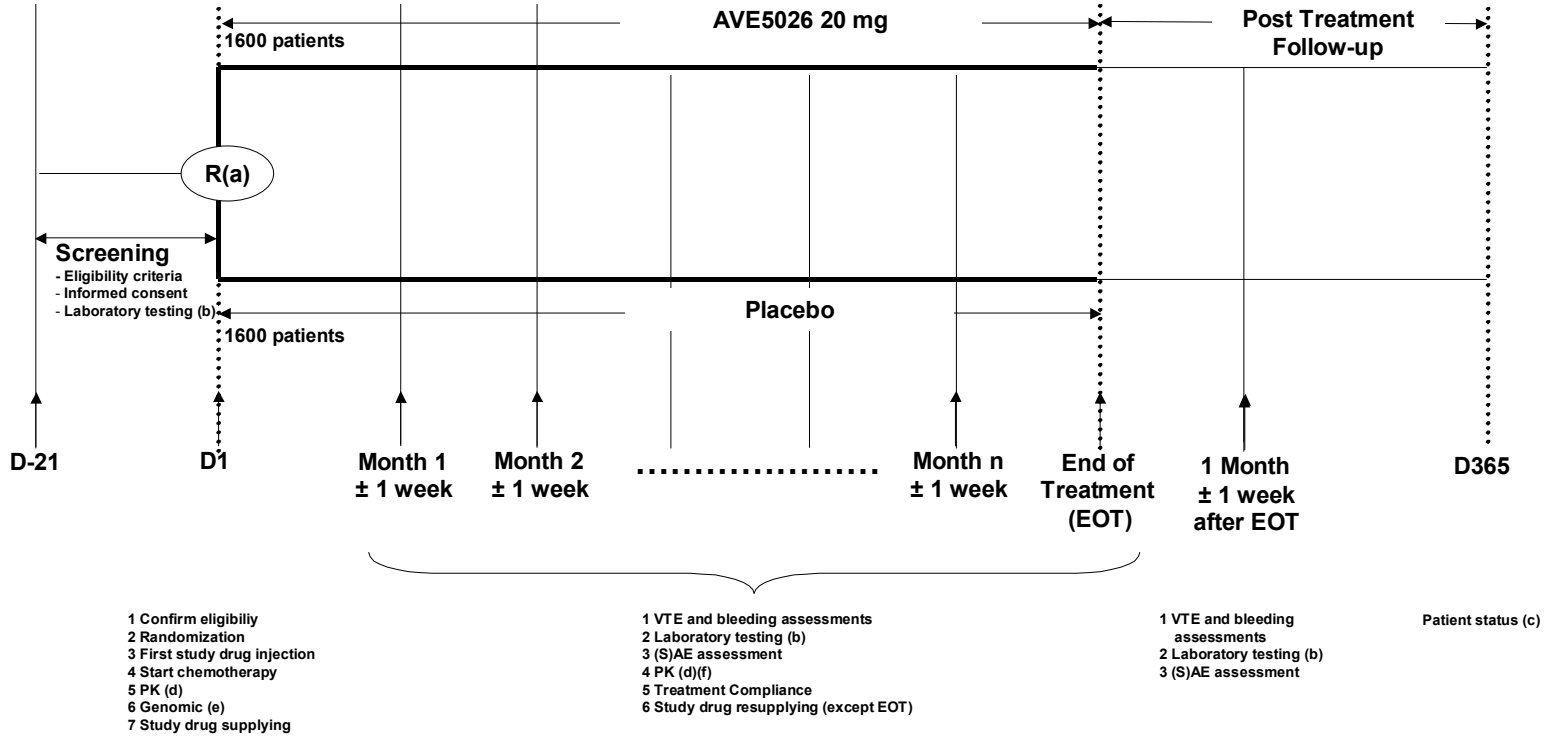
	Europe, Eastern Europe, Asia and Rest of the world).
STUDY POPULATION Main selection criteria: **Total expected number of patients:**	Cancer patients - with metastatic or locally advanced solid tumor of lung, pancreas, stomach, colon/rectum, bladder or ovary - initiating a (new) course of chemotherapy with a minimum intent of 3 months therapy - with an ECOG (Eastern Cooperative Oncology Group) Performance status of 0, 1 or 2 - with an estimated creatinine clearance ≥ 30 mL/min - with a signed informed consent Note: Chemotherapy is defined as any conventional cytotoxic treatment. Biological agents used alone are not considered as chemotherapy but could be associated. Approximately 3200 patients will be randomized, 1600 in each of the two treatment groups
INVESTIGATIONAL PRODUCT(S) **Formulation(s):** **Route(s) of administration:** **Dose regimen:**	• AVE5026: injectable in pre-filled syringes containing 20mg • AVE5026-placebo: injectable in pre-filled syringes Subcutaneous Investigational Product (IP) will be given in a blinded manner Patients will receive once daily either • AVE5026 20 mg s.c. Or • AVE5026-placebo
PRIMARY ENDPOINT(S) AND MAIN SECONDARY ENDPOINT(S)	**The primary efficacy endpoint** is the time-to-first occurrence of any component of the composite endpoint of the following documented outcome results, confirmed by a blinded Adjudication Committee, occurring from randomization up to 3 calendar days after last study drug injection: - Any symptomatic DVT of the lower limbs - Any symptomatic DVT of the upper limbs (including CVC-related thrombosis) - Any non fatal PE - VTE-related deaths (fatal PE or unexplained deaths) Documentation of these events will consist of an investigator's patient summary and, venography or ultrasound for DVT, ventilation/perfusion lung scan or pulmonary angiogram or spiral CT scan for PE, autopsy report if available for death. **Other efficacy outcomes** include each component of the primary efficacy endpoint, from randomization up to 3 calendar days after last study drug and the initiation of curative anticoagulant or thrombolytic treatment by the investigator after local VTE assessment. **Safety parameters** include bleedings (major and clinically relevant non-major as classified by a blinded adjudication committee), transfusions requirements, hemoglobin, platelet count, liver and renal

	laboratory data, serious or non-serious adverse events and deaths (classified as VTE-related, fatal bleeding or other by a blinded Adjudication Committee) up to 3 calendar days after last IP injection and up to the follow-up visit **Pharmacokinetics** 4 blood samples per patient will be drawn in all patients from selected centers to document the AVE5026 exposures in this population. **Genomics** 1 blood sample per patient will be drawn to identify a metagene predictor of VTE in patients who gave informed consent to participate in this sub-study.
ASSESSMENT SCHEDULE	• Screening visit will take place within 3 weeks prior to the start of a (new) course of chemotherapy. • On the first day of chemotherapy, patients will be randomized as close as possible prior to the first IP injection and the start of chemotherapy. • During the study treatment period, visits will be performed monthly (± 1 week). • Efficacy assessments: - At anytime during the course of the study, if patient experiences signs or symptoms evocative of VTE, unscheduled diagnostic test(s) will be performed to confirm or rule out the presence of VTE. For all these events occurring up to 3 calendar days after the last IP injection, a package will be sent to the Blinded Adjudication Committee for review. - In addition, if a PE is discovered incidentally on a lung imaging test for tumor evaluation, a package will be sent to the Blinded Adjudication Committee for review. • Safety assessments: all overt clinically significant bleedings and deaths occurring during the study will be sent to the blinded adjudication committee for review. • An End of treatment visit will be performed within 5 days after last study drug administration. • A follow-up visit is planned one month ± 1 week after the end of the study treatment. • In addition, survival status (alive, dead, or lost to follow up) will be collected one year after randomization or at the end of the study , (i.e.: 7 months following randomization of the last patient at the latest – see duration of study period), whichever comes first. • Dates of admission and discharge of any hospitalization during the study will be recorded.
STATISTICAL CONSIDERATIONS	**Sample size considerations:** [redacted]

	Populations analyzed: • Intent-To-Treat (ITT) population: includes all randomized patients who have given their informed consent. This population will be the basis for the primary analysis on the primary efficacy endpoint. All analyses using this population will be based on the treatment assigned by the IVRS. • All-treated (AT) Population: includes all randomized patients who received at least one dose of study drug. This population will be used for safety analyses and will be based on the treatment actually received. All patients who meet the inclusion criteria will be considered as screened patients. **Primary efficacy analysis:** Death from other causes than VTE will be considered as a competing risk. In order to correct for competing risks in the primary analysis of the primary efficacy endpoint, a cumulative incidence of competing risks approach will be used. Cumulative Incidence Functions (CIF) will be compared between the 2 treatment groups using the test of Gray at a significant level of 0.05 (two-sided) [5]. Patients alive and not having experienced the primary efficacy endpoint event will be censored at last study drug injection plus 3 days. An estimation of the treatment effect (hazard ratio and 95% Confidence Interval) will be given using Fine and Gray regression model for CIFs [6]. For each component of the primary endpoint, CIF will be presented by treatment group; hazard ratio and 95% 2-sided confidence interval will be calculated.
DURATION OF STUDY PERIOD (per Patient)	Duration of study period per patient is variable depending of study treatment duration. A follow-up visit is planned one month after end of treatment. In any case, the study will end at the latest 7 months (6 months randomized treatment period + 1 month follow-up period) following randomization of the last patient (study end date).

1 FLOW CHARTS

1.1 GRAPHICAL STUDY DESIGN



a : Randomization should occur as much as possible just before first dosing of the study drug
b : Hb, Platelets, WBC, AST, ALT, Alkaline Phosphatase, Bilirubin, Creatinine (aPTT, INR and serum albumin at screening only)
c : Patient status will be collected one year after randomization for all patients randomized at least one year before the study end date (7 months following randomization of the last patient)
d : PK sampling will be performed in all patients from selected centers
e : Genomic will be performed in patients who gave informed consent to participate in this sub-study
f : Only at Month 1

1.2 STUDY FLOWCHART

Evaluation	Screening	Treatment						Post treatment	
	D-21 up to D1	D1	W1 to W3 (No visit)	Month 1 ± 1 week	Month 2 ± 1 week	Month n ± 1 week	End of treatment (EOT)	One month ± 1 week after EOT	Day 365 [h]
Study Design:									
Inclusion/Exclusion Criteria	✓								
Previous Medical/Surgical History	✓								
Cancer diagnosis and/or status	✓								
Specific Prior Medication History (including tumor therapy)	✓								
Height (screening only), weight, vital signs	✓	✓		✓	✓	✓	✓	✓	
ECOG Performance status	✓	✓		✓	✓	✓	✓	✓	
Central venous catheter (CVC) status	✓	✓		✓	✓	✓	✓	✓	
Informed Consent /Patient Demography	✓								
Randomization		✓[a]							
IVRS call	✓	✓		✓	✓	✓	✓	✓	
Treatment:									
Investigational Product (IP) injections [b]		←----------						→	
Concomitant Medications		←----------							→
Chemotherapy		✓		✓	✓	✓	✓	✓	
Compliance				✓	✓	✓	✓		
IP supplying		✓		✓	✓	✓			
Efficacy:									
VTE recording [c]		←----------							→
Survival status				✓	✓	✓	✓	✓	✓[g]
Safety:									
AE /SAE recording (if any)	←----------								→
Bleeding recording [c]		←----------							→
Transfusions		✓		✓	✓	✓	✓	✓	
Laboratory Testing (local)[d]:									
Hemoglobin, WBC, neutrophils	✓	✓		✓	✓	✓	✓	✓[h]	
Platelets	✓	✓	✓[e]	✓	✓	✓	✓	✓[h]	
AST, ALT, Alkaline Phosphatase, Bilirubin (total & conj), Albumin (screening only)	✓	✓		✓	✓	✓	✓	✓[h]	
aPTT/INR	✓								
Creatinine	✓			✓	✓	✓	✓	✓[h]	
Pregnancy test [i]	✓						✓		
PK		✓[f]		✓[f]					
Genomics		✓[j]							
HE: hospitalization data if applicable		←----------							→

[a] Verify that the patient continues to meet all inclusion/exclusion criteria
[b] Treatment should be administered once daily approximately 24 hours apart
[c] In case of overt clinically significant bleeding event or death occurring during the study or any suspicion of symptomatic events occurring up to 3 calendar days after the last IP injection or any PE discovered incidentally on a scheduled tumor evaluation imaging during the same period, an adjudication dossier including an investigator's clinical summary and additional relevant documentation such as all relevant films, (venography or ultrasound for DVT, ventilation/perfusion lung scan, pulmonary angiogram or spiral CT lung scan for PE, or autopsy report if available) will be provided for adjudication.
[d] Laboratory tests have to be performed unless already part of the routine care of the patient in the corresponding visit period.
[e] During the first month, platelet count should be performed weekly (no visit)
[f] PK sampling at 0.5-1h and 2-4 h after the first IP injection on Day1 and when patients arrives and leaves the site at the Month 1 visit in all patients of selected centers.
[g] No visit is planned. Only survival status (dead, alive or lost to follow-up) will be collected one year after randomization or at the end of the study, (i.e.: 7 months following randomization of the last patient at the latest), whichever comes first.
[h] Only in case of unresolved abnormal value for these parameters at the end of treatment
[i] Pregnancy test only for women of childbearing potential and to be repeated as required by national law
j Genomic sampling in all patients who gave informed consent to participate in this sub-study

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3 LIST OF ABBREVIATIONS

ACCP	American College of Chest Physicians
AE	Adverse Event
ALT	Alanine Aminotransferase
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
BMI	Body Mass Index
CI	Confidence Interval
CIAC	Central Independent Adjudication Committee
CIF	Cumulative Incidence Function
CSR	Clinical Study Report
CT	Computer Tomography
CUS	Compression UltraSound
CVC	Central Venous Catheter
DMC	Data Monitoring Committee
DRF	Discrepancy Resolution Form
DVT	Deep Vein Thrombosis
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
e-CRF	Electronic Case Report Form
EOT	End of Treatment
FUP	Follow-Up
GCP	Good Clinical Practice
Hb	Hemoglobin
HE	Health Economy
IND	Investigational New Drug
INR	International Normalized Ratio
IP	Investigational Product
IRB/IEC	Institutional Review Board/Independent Ethics Committee
IVRS	Interactive Voice Response System
LFT	Liver Function tests
LLN	Lower Limit of the Normal range
LMWH	Low Molecular Weight Heparin
MI	Myocardial infarction
NSAID	Non Steroidal Anti Inflammatory Drug
PE	Pulmonary Embolism
PI	Package Insert
PK	Pharmacokinetic
q.d.	Quaque Die (once daily)
s.c.	Subcutaneous
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Steering Committee

SD	Standard Deviation
SRI	Severe Renal Impairment
TEAE	Treatment Emergent Adverse Event
UFH	Unfractionated Heparin
ULN	Upper Limit of the Normal range
US	Ultrasound
VTE	Venous Thromboembolic Event
WBC	White Blood Cells

4 INTRODUCTION AND RATIONALE

The association between cancer and thrombosis is well established and was first described by Trousseau in 1867. The mechanisms of thrombosis involve a complex interaction between tumor cells (e.g. release of pro-coagulant factors), the haemostatic system, endothelial cells and the characteristics of the patient (e.g. age, periods of immobilization), promoting a hypercoagulable state [7].

Venous thromboembolism (VTE) occurs more frequently in patients with cancer compared to patients with other diseases. In the MEDENOX study [8] in acutely ill medical patients, the presence of cancer was identified as an independent risk factor for objectively confirmed VTE leading to a significant increase in VTE risk (RR=1.74, 95% CI [1.13-2.68], p=0.02).

A large epidemiological study based on cancer registry data [1] indicates that the thrombosis risk depends on the stage of the disease and on the localization of the tumor. The 1-year VTE incidence rate varies from 0.5 % in localized breast cancer to 20 % in metastatic pancreas cancer. The highest annual incidence rate was observed in metastatic-stage cancer of the pancreas, followed by stomach (11%), bladder (8%), uterus and kidney (6%) and lung (5%).

Chemotherapy can induce direct vascular damage and release of procoagulants and cytokines from damaged tumor cells, further increasing the incidence of VTE [9]. In a population-based case control study to identify the risk factors for VTE [10], in the multivariate logistic analysis, malignant neoplasm alone was associated with a 4 fold increased risk of VTE (OR=4.05, 95% CI [1.93 - 8.52]) while cytotoxic or immunosuppressive chemotherapy increased the malignant neoplasm-associated risk by 6.5 (OR=6.53, 95% CI [2.11 - 20.23]). In a retrospective cohort study on 206 cancer patients treated with chemotherapy (average period of chemotherapy treatment was 22.6 weeks [range: 1-145 weeks]), 15 (7.3%) of these patients had a proven VTE during or within 3 months after chemotherapy. [11]. There is also some data suggesting that the risk of VTE declines once chemotherapy is completed [12].

There is little information about the efficacy of VTE prevention in patients with malignancy and receiving chemotherapy. The best-investigated patient population is women with breast cancer. Only one randomized controlled study has evaluated the role for anticoagulant prophylaxis (low dose warfarin vs. placebo for 6 weeks) in approximately 300 women receiving chemotherapy for metastatic breast cancer [13]. More thrombotic events (7 [4.4%] versus 1) were observed in the placebo group with a RRR of 85% (p=0.031), and there was no difference in terms of bleeding rate.

Long-term central venous catheters (CVC) are commonly used for the administration of chemotherapy (or other uses). The presence of a CVC is an independent risk factor for upper extremity deep vein thrombosis (DVT) in the general population. It is also well-known that cancer patients with indwelling CVCs sometimes develop symptomatic thrombosis of the axillary/subclavian veins, producing arm swelling and discomfort, predisposing them to catheter-related sepsis and the need to replace the catheter as well as serious morbidity such as pulmonary embolism (PE) or post-phlebitic syndrome [14, 15, 4]. The incidence of symptomatic CVC-

related thrombosis is described to be between 3 and 4% in recent clinical studies [3, 2] or from epidemiological data [4].

Despite the consensus that cancer patients undergoing chemotherapy could be considered at high risk for venous thrombosis, guidelines in thrombosis [ACCP guidelines- 16] or in Oncology [NCCN guidelines- 17] do not recommend systematic thromboprophylaxis in patients undergoing chemotherapy unless additional risk factors such as hospitalization are present.

The objectives of study EFC6521 are to evaluate the efficacy and safety of AVE5026 once daily in the prevention of symptomatic venous thromboembolism events in patients with locally advanced or metastatic solid tumors when undergoing chemotherapy. This study is foreseen to coincide the usual clinical care of these patients, and the intent is to evaluate the real case scenario in standard practice of this special population.

Test compound

AVE5026 is a new Ultra Low Molecular Weight Heparin (ULMWH) with a novel antithrombotic profile resulting from a high anti-Xa activity associated with a residual anti-thrombin activity (ratio anti-Xa/anti-IIa >30).

In Phase I clinical development, AVE5026 was well tolerated at a daily dose of 5 20, 60 and 100 mg given 14 days and at a daily dose of 40 mg given for 28 days. Only non-significant bleeding such as epistaxis or haematoma at injection site was reported. Increase in transaminases>2 times the upper limit of the normal, similar to those observed with other Low Molecular Weight Heparin (LMWH) and unfractionated heparin, without any concomitant clinical signs and symptoms have been reported in most of the groups. Liver enzymes returned to normal in all patients within 2 - 3 weeks after study drug discontinuation.

The efficacy and safety of AVE5026 for primary prophylaxis of venous thromboembolism (VTE) was evaluated in a dose-ranging study (DRI6243, TREK).

This was a double-blind, double dummy, stratified (pre-operative injection/no pre-operative injection) dose-ranging study in patients undergoing total knee replacement surgery. Patients were randomized to receive subcutaneously and once daily AVE5026 (5, 10, 20, 40 or 60 mg) or enoxaparin 40 mg used as a positive calibrator for up to 10 days after surgery (treatment was to be maintained at least 5 days after surgery). Depending upon the stratum, the first dose was administered 11-13h before or 7-9h after surgery. A mandatory bilateral venography of the lower limbs was performed 5-11 days after surgery.

Of 678 treated patients, 464 were eligible for the primary efficacy analysis with evaluable venograms. The primary efficacy endpoint was the composite outcome of [1] any DVT diagnosed by mandatory venography; [2] symptomatic VTE and [3] VTE-related deaths. The event rates were: 40.0%, 44.1%, 15.6%, 13.6% and 5.3% for the 5, 10, 20, 40 and 60 mg doses, respectively, demonstrating a clear dose response ($p<0.0001$). The VTE rate in the enoxaparin calibrator arm was 35.8%. The same conclusion applies to proximal DVT with rates decreasing from 7.7% to 0% in the AVE5026 groups ($p=0.0002$). Major bleeding was infrequent in this study (6 patients), increasing from 0% (5 mg group) to 3.4% (60 mg group) with a statistically significant dose

response (p=0.02). At the 20 mg dose of AVE5026, the rates of major bleeding (0.8%) and any bleeding (3.8%) were comparable to enoxaparin 40 mg q.d. at 0% and 5.0%, respectively.

Further details can be found in the Investigator's Brochure, which contains comprehensive information on AVE5026.

Rationale for the AVE5026 dose

Dose selection is based on the results of the above mentioned dose-ranging study (DRI6243, TREK), performed in patients with elective total knee replacement. The selected dose of 20 mg q.d. was very effective in this study and exhibited a bleeding risk comparable to enoxaparin 40 mg q.d.

Rationale for placebo use

As systematic venous thromboprophylaxis is neither recommended nor routinely used in patients undergoing chemotherapy unless there is some additional thrombosis risk and as there is no anti-coagulant drug approved in this indication, this study is placebo-controlled.

Rationale for duration of treatment

Chemotherapy in cancer patients with advanced disease lasts until disease progression, limiting toxicity or death. The rate of symptomatic VTE in ambulatory cancer patients initiating a new chemotherapy regimen and followed during 4 cycles was evaluated to be 0.8%/month, not differing significantly among chemotherapy cycles suggesting the VTE risk remains constant at each cycle [18].

The FAMOUS [19] (survival - one year treatment, versus placebo) and the CLOT [20] (secondary prevention of VTE - 6 month treatment versus a coumarin derivative) studies have demonstrated the feasibility and the safety of long-term administration of LMWH (dalteparin) in patients with advanced cancers. In the FAMOUS study that enrolled 374 patients, the overall bleeding rates were 4.7% in the Dalteparin group (one major and eight minor bleedings) and 2.7% in the placebo group (five minor bleedings).

Because different VTE risk could be associated with different antineoplastic drugs and in order to have appropriate efficacy assessments, the study medication will be administered until decision is made to change the initial chemotherapy regimen (i.e. addition or removal of at least one of the initial antineoplastic drugs) for any reason (disease progression, toxicity) unless this decision is made within the first 3 months of the study. In that case,

- If another chemotherapy regimen is started, the study medication should be continued at least up to 3 months (until end of the regimen ongoing at Month 3 visit)
- If the chemotherapy is stopped definitely, the study medication will be discontinued.

5 STUDY OBJECTIVES

5.1 PRIMARY

The primary objective of this study is to compare the efficacy of AVE5026 20 mg s.c. q.d. with placebo s.c. q.d. for the prevention of venous thrombo-embolism in cancer patients at high VTE risk and undergoing chemotherapy.

5.2 SECONDARY

The secondary objectives of this study are to evaluate the safety of AVE5026 in cancer patients undergoing chemotherapy, to document AVE5026 exposures, to try identifying a metagene predictor of VTE and to assess the survival status at one year in this population.

6 STUDY DESIGN

This is a multinational, multicenter, randomized, double-blind, parallel-group study comparing the efficacy of AVE5026 versus placebo in cancer patients at high VTE risk, defined as patients with a metastatic or locally-advanced solid tumor of the lung, pancreas, stomach, colon/rectum, bladder or ovary and who are undergoing chemotherapy.

6.1 DESCRIPTION OF THE PROTOCOL

Patient eligibility will be determined during the screening period (within 3 weeks prior to the start of the course of chemotherapy) and reviewed the day of randomization (first day of chemotherapy).

Randomized treatment will be allocated to eligible patients through a centralized randomization system using an Interactive Voice Response System (IVRS). In order to balance treatment groups with regard to prognostic factors and geographical region, a dynamic allocation will be used taking into account 3 factors: the localization of the primary site of tumor (lung, pancreas, stomach, colon/rectum, bladder or ovary), the stage of the cancer (metastatic versus locally-advanced) and the geographical region (North America, South America, Western Europe, Eastern Europe, Asia and Rest of the world). The randomization call should occur prior to the start of the chemotherapy and as close as possible prior to the first IP injection.

Study medication will be administered once daily subcutaneously (pre-filled syringes) for the duration of the initial chemotherapy and until decision to change at least one antineoplastic drug (i.e. addition or removal; however, in case of antineoplastic dose adjustment only, study medication will continue as planned) due to disease progression or toxicity unless this decision is made within the first 3 months: in case another chemotherapy regimen is started within the first 3 months, the study medication should be continued at least for 3 months (until the end of the regimen ongoing at Month 3 visit; if the chemotherapy is stopped definitely within the first 3 months, the study medication will be discontinued.

The first injection will be done at the site. The following injections could be done by the patient (self-injection), a relative or a health care professional upon investigator's judgment.

During the study treatment period, visits will be performed monthly ± 1 week (corresponding to scheduled chemotherapy visits). Signs and symptoms of VTE, bleeding, adverse events, specific concomitant medications (including chemotherapy) and compliance will be assessed. Blood samples will be drawn for laboratory tests and in all patients from selected centers for pharmacokinetic purposes. An additional blood sample may be drawn for genomic purposes in patients who gave their inform consent to participate in this sub-study.

At any time during the course of the study, if a patient experiences signs or symptoms evocative of VTE, unscheduled diagnostic test(s) will be performed to confirm or rule out the presence of VTE. For all these events occurring up to 3 calendar days after the last IP injection, a package will be sent to the Blinded Adjudication Committee for review. In addition, if a PE is discovered

incidentally on a lung imaging test for tumor evaluation, a package will be sent to the Blinded Adjudication Committee for review. All bleeding events and deaths reported up to the follow-up visit will also be adjudicated. In all these cases, the adjudication package will consist of relevant documentation such as all relevant films (venography or ultrasound for DVT, ventilation/perfusion lung scan, pulmonary angiogram or spiral CT lung scan for PE) or autopsy report if available.

An end of treatment visit will be done within 5 days after last study drug administration.

A follow-up visit is scheduled one month ± 1 week after last injection of study medication. During this visit, information regarding adverse events (including bleedings and VTE) will be collected. If, for a laboratory parameter collected in the study, an unresolved abnormal value was reported at the end of treatment visit, then a blood sample will be drawn at the follow-up visit to verify this parameter.

In addition, survival status (alive, dead, or lost to follow up) will be collected one year after randomization or at the end of the study , (i.e.: 7 months following randomization of the last patient at the latest), whichever comes first for all patients.

All details can be found in the study flowchart (Section 1.2)

6.2 DURATION OF STUDY PARTICIPATION

The duration of study participation per patient is variable and depends on the duration of study treatment: for a given patient, the duration of study period will be the duration of study treatment followed by a one month follow-up period after the discontinuation of study medication. In addition, patients will be screened within 3 weeks prior to the start of chemotherapy.

In any case, the study end date will be at the latest seven months (6 months treatment period and one month follow-up) following the randomization of the last patient.

Note: Survival status (alive, dead, or lost to follow up) will be collected one year after randomization or at the end of the study, whichever comes first for all patients

6.3 STUDY COMMITTEES

These committees are common to all ongoing AVE5026 studies.

6.3.1 Steering Committee

The Steering Committee (SC) is composed of university-based and Sponsor-based scientists with clinical and methodological expertise. The committee has the overall responsibility for producing and conducting a scientifically sound design and ensuring accurate reporting of the study. In that capacity, the Steering Committee must address and resolve scientific issues encountered during the study.

The primary scientific publication where the study results will be reported is the responsibility of the Steering Committee. Collaborating investigators wishing to prepare secondary publications must submit proposals and manuscripts to the Steering Committee for approval. The Sponsor reserves the right to review manuscripts prior to submission for publication in a scientific journal (see section 24). The final decision on all publications will be the responsibility of the Steering Committee.

6.3.2 Central Independent Adjudication Committee

The Central Independent Adjudication Committee (CIAC) composed of thrombosis and bleeding experts, blinded to study medication assignment, will be responsible for validating all primary VTE outcomes reported up to 3 days after the last injection of study medication as well as bleedings and deaths reported up to the follow-up visit.

A separate adjudication manual prepared under the responsibility of the chairman of the CIAC in order to specify the procedures and criteria used for adjudication of these events is provided as a separate document. The adjudication results will be the basis for final analysis of the efficacy composite endpoints, bleedings and cause of deaths.

6.3.3 Data Monitoring Committee

The Data Monitoring Committee (DMC), composed of clinicians and methodologists who are independent of the Sponsor, the investigators and the Steering Committee and are experienced with clinical trials and can be relied upon to exercise good judgment in weighing the potential risks and benefits to patients as data accumulate in this trial, is responsible for monitoring the safety of the patients exposed to study medication. They will review data on a regular basis.

The DMC will have an Independent Associated Statistician who will receive study data from the Central Database and will remain independent of the trial management team.

The DMC is independent of the sponsor. The chairman of the DMC, in conjunction with the other members, will communicate their recommendations to the chairman of the Steering Committee after each meeting. A DMC charter is displayed in a separate document prepared under the responsibility of the DMC chairman.

7 SELECTION OF PATIENTS

7.1 NUMBER OF PATIENTS PLANNED

The total number of patients to be randomized will be approximately 3200 (approximately 1600 patients per treatment group (see Determination of sample size section 13.1)

7.2 INCLUSION CRITERIA

Cancer patients

1. With metastatic or locally advanced solid tumor of the lung, pancreas, stomach, colon/rectum, bladder or ovary
2. Planned to start a (new) course of chemotherapy with a minimum intent of 3 months therapy
3. With signed informed consent

Note:
Chemotherapy is defined as any conventional cytotoxic treatment.
Biological agents used alone are not considered as chemotherapy but could be associated with cytotoxic agents.

7.3 EXCLUSION CRITERIA

Exclusion criteria related to study methodology

1. Legal lower age limitations (country specific)
2. Life expectancy less than 3 months
3. ECOG (Eastern Cooperative Oncology Group) Performance status of 3 or 4 (see Appendix A)
4. Calculated creatinine clearance <30 mL/min according to Cockroft and Gault formula (21)
5. Any major surgery (i.e. open surgery lasting more than 45 minutes from opening to closure) within the last 6 weeks or planned during the study treatment period
6. Contra-indications to anticoagulation:
   - Active or recent (<3 months) significant bleeding, including gastrointestinal bleeding or peptic ulcer.
   - History of bleeding disorder (congenital, acquired or unexplained repeated bleeding episodes)
   - Uncontrolled arterial hypertension (systolic blood pressure > 180 mm Hg or diastolic blood pressure > 110 mm Hg)
   - Hemorrhagic stroke or recent (in the last 3 months) brain, spinal or ophthalmic surgery

- Known cerebral hemorrhagic lesion
- Primary or metastatic tumor which is at high bleeding-risk according to investigator's judgment
- Known structural damage or other pathologic process involving the central nervous system (brain metastases, vascular malformation…)
- Thrombocytopenia (platelet count < 100 x 10^9/l)
- Activated partial thromboplastin time (aPTT) > 1.5 ULN or International Normalized ratio (INR) >1.5

7. Any treatment with other anti-thrombotic agents within 2 weeks prior to randomization or planned during the course of the study such as:
   - Parenteral anticoagulants (UFH, LMWH: enoxaparin, dalteparin, nadroparin..., or other agents such as fondaparinux, bivalirudin, hirudin)
   - Oral anticoagulants (Vitamin K antagonists)
   - Anti-GPIIb/IIIa: eptifibatide, tirofiban, abciximab
   - Thrombolytic agents

   Note: Chronic treatment with anti-platelet agents such as low dose of aspirin (up to 325 mg/day) or clopidogrel or ticlopidine in patients with coronary artery disease is allowed
8. Subject who requires a systematic venous thromboprophylaxis with anticoagulant or a curative anti-coagulant or thrombolytic treatment
9. Pelvic venous obstruction or superior vena cava syndrome
10. Subject unlikely to comply with protocol, e.g., uncooperative attitude, inability to return for follow-up visits, inability to receive daily injection (self-injection or by relative of patient or by Health care professional) and unlikelihood of completing the study
11. Treatment with any investigational product or investigational device in the last 30 days or 5 half lives (if relevant) prior to randomization
12. Any previous exposure to AVE5026 (e.g.: participation in any previous AVE5026 clinical trial)

Note: A patient could not be randomized in the study more than once

Exclusion criteria related to AVE5026:

13. History of heparin-induced thrombocytopenia
14. Known hypersensitivity to UFH or LMWH
15. Pregnant or nursing woman or women of childbearing potential not protected by highly effective contraceptive method of birth control as defined for contraception in the Informed Consent Form and/or in a local protocol addendum for the duration of the study and/or who are unwilling or unable to be tested for pregnancy**.**

8 TREATMENTS

8.1 INVESTIGATIONAL PRODUCT

Patients will be allocated to one of the 2 study treatments: AVE5026 or placebo of AVE5026.

The AVE5026 syringe will contain 20 mg of AVE5026 in a 0.5 mL pre-filled syringe containing 0.4 mL of a sterile, isotonic solution with sodium chloride 0.9% and water for injection corresponding to a concentration of 50mg/mL.

The matching placebo syringe will be strictly identical in appearance containing the same volume but without active component.

8.1.1 Route and method of administration

AVE5026 or its placebo will be administered subcutaneously. The entire volume of the pre-filled syringe must be injected. Patients should be lying down and study medication should be administered as a deep subcutaneous administration. Administration should alternate between left and right anterolateral and left and right posterolateral abdominal wall. The whole length of the needle should be introduced into a skin fold held between the thumb and forefinger, the skin fold should be held throughout the injection. The product could be administered by self-injection, by a relative of the patient, or by a health care professional.

8.1.2 Timing of administration

Study medication (AVE5026 or its placebo) will start as close as possible after the randomization, which should take place as close as possible to the start of chemotherapy. The first injection will be done at site under direct supervision. The investigator will decide whether injections at home can be performed by the patient (self-injection) or by a relative, or whether it should be supported by a health care professional.

Study medication must be administered once daily s.c. at approximately 24 hours apart. The time of the day is upon investigator's or patient's preference. However it is recommended to keep the same timing during the study. The patient will receive a diary to collect date and time of daily injections.

If by mistake an injection is missed, the patient should not receive two injections on the following day. The number of missed injections will be reported in the e-CRF.

8.1.3 Discontinuations of study treatment

Please also refer to section 11 - handling of patient with temporary or definitive treatment discontinuation and of patient study discontinuation.

As per protocol, the study treatment period will be considered as completed if the study treatment is given:

- until change in the initial chemotherapy regimen (i.e. addition or removal of at least one of the initial antineoplastic drugs; however, in case of antineoplastic dose adjustment only, study medication will continue as planned) if this change occurs after the first 3 months of the study **or**
- at least 3 months and until the regimen ongoing at the 3-month time point (defined as addition or removal of at least one of the antineoplastic drugs of this regimen) is changed, if the change in the initial chemotherapy regimen occurs within the first 3 months of the study and the patient continues on chemotherapy **or**
- until decision is made to stop definitely chemotherapy if it occurs within the first three months of the study

whichever comes first .

Note 1: In case the chemotherapy cycle is delayed (i.e. for toxicity reason), the study treatment will continue unless stopped for other reasons as listed below.

Note 2: The study treatment should not be discontinued between two cycles (or two different chemotherapy regimens if the change in the initial chemotherapy regimen occurs within the first 3 months of the study .

Any of these reasons will be well-documented in the e-CRF.

8.1.3.1 Premature and definite study treatment discontinuations

Study treatment will be stopped prematurely and permanently if any of the following events occurs or is diagnosed:

- Symptomatic DVT or PE before the scheduled end of treatment confirmed locally by diagnosis tests and leading to initiation of any curative anti-coagulant or thrombolytic treatment.
- Any patient's condition (other than symptomatic DVT or PE) that requires the initiation of any anti-coagulant or thrombolytic treatment.
- Clinically significant (at investigator's discretion) symptomatic bleeding meeting the definition of Serious Adverse Event (SAE)
- Occurrence of a Serious Adverse Event warranting premature discontinuation
- Sudden increase in transaminases or bilirubin, of clinical concern as per investigator's judgment and which cannot be explained by intercurrent event, such as but not limited to new metastasis or blockage of biliary conduct in patients with gastro-intestinal cancer
- Platelet count < 50 x 10^9/L which does not correspond to the expected chemotherapy-induced thrombocytopenia profile as per investigator's judgment (see section 10.2)
- Pregnancy

- Patient wishes to terminate study treatment: in that case, it is investigator's responsibility to clarify the exact reason and verify the absence or presence of AE.

8.1.3.2 Temporary study treatment discontinuations

Study treatment should be stopped temporarily if any of the following events occurs:

- Thrombocytopenia (<50 x 10^9/L) corresponding to the expected chemotherapy-induced thrombocytopenia profile as per investigator's judgment until platelet count recovers above 50 x 10^9/L but within 14 days.
- Worsening of renal status: if the creatinine clearance goes below <30 mL/min during study treatment period, the treatment should be discontinued and could be resumed as soon as the creatinine clearance returns to > 30 mL/min but within 14 days.

Note: *If platelets or creatinine clearance do not recover within 14 days, study treatment should be stopped definitely.*

- In case of any invasive procedure (therapeutic or diagnostic), study medication could be discontinued 24 h before the procedure and resumed as early as possible after the procedure and within 7 days.
- In case one single dose of a curative anti-coagulant treatment is initiated for suspicion of VTE but this event is not finally confirmed, the study medication could be resumed.

8.2 DESCRIPTION OF BLINDING METHODS

The study is double blind. Packaging (pre-filled ready to use syringes) and boxes will be strictly identical in appearance for the two treatment arms.

8.3 METHOD OF ASSIGNING PATIENTS TO TREATMENT GROUP

8.3.1 Patient number and treatment number

Patients who meet all inclusion criteria and none of the exclusion criteria are deemed eligible for randomization.

Randomization and treatment allocation(s) will be performed centrally by an interactive voice response system (IVRS). A randomized patient is a patient with a patient number and a treatment kit number allocated by the IVRS.

8.3.2 Allocation of treatment(s)

Treatment will be allocated by the IVRS to either AVE5026 or placebo in a 1:1 ratio.

In order to balance treatment groups with regard to prognostic factors and geographical region, a dynamic allocation will be done by the IVRS center. A stochastic randomization procedure with a

minimization algorithm first proposed by Pocock and Simon [26] and reviewed by Freedman and White [27] will be used taking into account the three following factors:

- Location of the primary site of the tumor (lung, pancreas, stomach, colon/rectum, bladder or ovary),
- Stage of the cancer (metastatic or locally advanced).
- Geographical Region (North America, South America, Western Europe, Eastern Europe, Asia and Rest of the world).

At randomization (D1), the Investigator will be provided by the IVRS with 1 or 2 treatment kit number(s) corresponding to the first month of treatment (up to visit Month 1±1week). The number of dispensed kits will depend upon the chemotherapy cycle frequency and consequently the timing of next visit. Then at each monthly visit until the end of treatment visit, the IVRS will re-supply adequate treatment kit numbers.

8.4 PACKAGING AND LABELING

AVE5026 or its placebo will be supplied in identical boxes (patient kit). Each patient kit will be labeled with a unique kit number.

Each patient kit will contain a 5-week treatment (one monthly patient kit is composed of 5 weekly boxes containing syringes for one week (7 syringes plus one spare syringe)

The content of the labeling is in accordance with the local regulatory specifications and requirements.

8.5 STORAGE CONDITIONS

At site and prior to delivery to the patient, study medication should be stored in a secure and refrigerated 2ºC to 8ºC (36ºF to 46ºF) area.

After dispensation to the patient, the medication can be stored at room temperature not exceeding 30ºC (86ºF) for up to 3 months.

8.6 ACCESS TO THE RANDOMIZATION CODE DURING THE STUDY

Please refer to Section 9.5 - Measures to protect blinding of this trial

In case of an Adverse Event, the code must be broken only in exceptional circumstances when knowledge of the Investigational Product is essential for treating the patient. If possible, contact should be initiated with the Monitoring Team before breaking the code. The IVRS will be used for code-breaking.

If the blind is broken, the Investigator will document the date and reason for code breaking into the e-CRF and the patient hospital file. Whatever the reason of the code-breaking, the patient will

be withdrawn definitely from study medication and must be followed up to one month ± 1 week after last dose of study medication (refer to section 11.2.2 Handling of patients after definitive treatment discontinuation).

The code-breaking material is also kept during the Clinical Trial by the Sponsor or its designee.

8.7 RESPONSIBILITIES

The Investigator, the Hospital Pharmacist, or other personnel allowed to store and dispense Investigational Product will be responsible for ensuring that the Investigational Product used in the clinical trial is securely maintained as specified by the Sponsor and in accordance with the applicable regulatory requirements.

All Investigational Product shall be dispensed in accordance with the protocol and it is the Investigator's responsibility to ensure that an accurate record of Investigational Product issued and returned is maintained.

Any quality issue noticed with the receipt or use of an Investigational Product (deficient IP in condition, appearance, pertaining documentation, labeling, expiry date, etc.) should be promptly notified to the Sponsor, who will initiate a complaint procedure.

Under no circumstances will the Investigator supply Investigational Product to a third party, allow the Investigational Product to be used other than as directed by this Clinical Trial Protocol, or dispose of Investigational Product in any other manner.

8.8 RETRIEVAL AND/OR DESTRUCTION OF TREATMENTS

All partially used or unused treatment kits will be retrieved by the Sponsor or Sponsor’s representative. A detailed treatment log of the returned Investigational Product will be established by the Investigator (or the pharmacist) and countersigned by the Investigator and the Monitoring Team.

The sponsor may initiate a recall procedure if a potential defect in the quality of the Investigational Product is discovered. In this case, the Investigator will be responsible for promptly addressing any request made by the Sponsor, in order to recall Investigational Product and eliminate potential hazards.

8.9 CONCOMITANT TREATMENT

Concomitant medications considered necessary for the patient's welfare and unlikely to interfere with the investigational products may be given at the discretion of the investigator.

Patients must not have received other anti-thrombotic agents 2 weeks prior to randomization and must not receive the following treatments during the total duration of study medication:

- Parenteral anticoagulants (UFH, LMWH: enoxaparin, dalteparin, nadroparin..., or other agents such as fondaparinux, bivalirudin, hirudin), including small amounts such as flushing solutions.
- Oral anticoagulants (Vitamin K antagonists)
- Anti GPIIb/IIIa: eptifibatide, tirofiban, abciximab
- Thrombolytic agents

If treatment with any of these medications is needed according to the investigator's medical judgment during the total duration of study medication, please refer to section 11.2.1 (criteria for definitive treatment discontinuation).

However, if symptom of VTE occur triggering initiation of an anti-coagulant treatment before confirmation by imaging, and eventually the diagnosis is not confirmed, study medication could be resumed if the patient did not receive more than 1 dose of this anti-coagulant.

The use of non steroidal anti-inflammatory drugs (NSAIDs) is discouraged.

Any other concomitant treatment, including chronic treatment with anti-platelet agents such as low dose of aspirin (up to 325 mg/day) or clopidogrel or ticlopidine is allowed.

8.10 POST STUDY TREATMENT

Continuation of venous thromboprophylaxis after the last injection of study medication, and/or therapy with medications considered necessary for the patient's welfare are at the discretion of the investigator and will be recorded in the e-case report form. The first administration of open-label thromboprophylaxis should be performed at least 12h after the last dosing with IP.

8.11 TREATMENT ACCOUNTABILITY AND COMPLIANCE

Study medication should be used in accordance with the protocol under the responsibility of the investigator.

The investigator or any authorized person should maintain a complete and accurate record of the receipt of supplies.

The investigator or any authorized person will keep accurate records of the quantities of the investigational products dispensed to each patient.

At each visit, the patient will return the treatment units whether used (empty box(es)) or unused. The investigator counts the number of unused syringes and the number of weekly boxes for used syringes and fills in the Treatment Log Form. The total of used + unused medication should be equal to the total amount received or dispensed. Any discrepancy should be explained in writing.

9 ASSESSMENT OF INVESTIGATIONAL PRODUCT

9.1 EFFICACY

9.1.1 Primary criteria

The primary efficacy criterion is the time-to-first occurrence of any component of the composite endpoint of the following documented outcome results, confirmed by the CIAC, from randomization up to 3 days after last study treatment administration:

- Any symptomatic DVT of the lower limbs,
- Any symptomatic DVT of the upper limbs (including CVC-related thrombosis),
- Any non-fatal PE
- VTE-related deaths (fatal PE or unexplained deaths)

The VTE diagnosis needs to be confirmed or ruled out by objective investigations.

- **DVT of the lower limbs:** the clinical diagnosis must be confirmed by compression ultrasound (CUS) or venography performed within 72 hours after the clinical suspicion. DVT will be confirmed if:
  - the CUS is abnormal or
  - there is an intraluminal filling defect on the venography
- **DVT of the upper limbs:** thrombosis of the central line is not considered a priori as a suspicion of DVT unless a patient presents symptoms such as arm swelling, erythema, pain, distal paresthesias, neck swelling, headache, and congestion of subcutaneous collateral veins (22). In any case, the clinical diagnosis must be confirmed by ultrasound (US) or venography performed within 72 hours after the clinical suspicion. DVT will be confirmed if:
  - the US is abnormal or
  - there is an intraluminal filling defect on the venography
- **Pulmonary embolism:** the clinical diagnosis must be confirmed by ventilation / perfusion lung scan, pulmonary angiogram or spiral Computer Tomography (CT) lung scan within 72 hours after the clinical suspicion. PE will be confirmed in case of:
  - intraluminal filling defect in (sub)segmental or more proximal branches on a spiral CT scan or
  - intraluminal filling defect on the pulmonary angiogram or
  - a perfusion defect of at least 75% of a segment with a local normal ventilation result (high-probability) on ventilation/perfusion lung scan or
  - an inconclusive spiral CT, pulmonary angiography or lung scintigraphy with demonstration of DVT in the lower extremities by compression ultrasound or venography

- a fatal PE based on autopsy

For any suspicion of VTE occurring up to 3 calendar days after last study drug administration which triggered an unscheduled imaging test, an adjudication package will be prepared by the investigator and sent to the CIAC (see specific manual).

If the diagnosis is not confirmed locally by these investigations, the patient should continue in the study. As stated in section 8.1.3.2, in case one single dose of a curative anti-thrombotic treatment was initiated before the event was ruled out, the study medication could be resumed.

In addition, if a PE is discovered incidentally on a scheduled lung imaging test performed for tumor evaluation up to 3 calendar days after last study drug administration, a package will be sent to the Blinded Adjudication Committee for review.

Note: all deaths will be adjudicated by the CIAC to be classified as VTE-related death, fatal bleeding or other.

9.1.2 Secondary criteria

The secondary criteria include

- the time-to-first occurrence from randomization up to 3 calendar days after last study drug administration of the following events:
  - Any symptomatic DVT of the lower limbs,
  - Any symptomatic DVT of the upper limbs (including CVC-related thrombosis),
  - Any PE
- Initiation of curative anticoagulant or thrombolytic treatment by the investigator after local VTE assessment

9.1.3 Other criteria

Survival status will be collected one year after randomization for all patients until the study end date (7 months after last randomized patient).

9.2 SAFETY

Safety will be assessed by:

- Adverse events (including bleedings and serious adverse events). They will be collected throughout the study (see study flowchart section 1.2 and section 10).
- Laboratory data for
  - Hematology: White Blood Cells (WBC), Neutrophils, Hemoglobin (Hb) and platelets
  - Biochemistry: creatinine and liver function tests (LFT) : Aspartate and alanine aminotransferase (AST and ALT), total and conjugated bilirubin, Alkaline Phosphatase,

will be sampled at different time points (see study flowchart section 1.2 and section 10) and analyzed locally. Abnormal, clinically significant results will be verified to rule out laboratory error. Persistent relevant abnormal values must be followed up until the cause is determined or until they return to the baseline value.

- Vital signs: systolic and diastolic blood pressures, heart and respiratory rates

The study-specific and general safety criteria are developed in Section 10.1 below.

9.3 PHARMACOKINETICS

Pharmacokinetic samples will be drawn for population PK analysis and descriptive statistics with the objectives of characterizing AVE5026 PK profile in cancer patients undergoing chemotherapy.

Pharmacokinetic evaluation is intended to be done in all patients of selected centers according to the timing described in section 9.3.1.

9.3.1 Sampling time

In PK centers, 4 plasma samples per patient will be collected, two on Day 1 after the first IP injection and two at the following visit (Month 1± 1 week).

Table 1 – Timing of PK sampling

		Timing
D1	PK1	0.5-1h after the first IP injection
	PK 2	2-4 h after the first IP injection
Month 1± 1 week	PK 3	when patient arrives at site (and just before IP injection if done on site)
	PK 4	when patient leaves the site (as late as possible)

9.3.2 PK handling procedure

Please refer to Appendix C.

9.3.3 Bioanalytical method

AVE5026 concentrations will be determined by their anti-Xa activity using an automated chromogenic assay. Analysis will be performed by the sponsor.

- Analyte: AVE5026
- Biological fluid: Plasma

- Lower Limit of quantification: 0.3125 µg/mL (0.05 U/mL)

9.4 GENOMICS

A correlative sub-study is embedded within this trial to develop and validate a metagene predictor of VTE. Please refer to Appendix D.

This sub-study will be open only at sites that permit genomic studies to be conducted in compliance with all applicable laws, rules and regulations and in patients who have given their informed consent for participating specifically to this sub-study.

9.4.1 Sampling time

At anytime on D1 but if possible at the time of another scheduled blood sampling collection, in patients who consent, 5 ml of whole blood will be removed by venipuncture into two, 2.5 ml PAX gene tubes.

9.4.2 Genomics handling procedure

Please refer to Appendix D.

9.4.3 Analytical method

mRNA will be isolated from the peripheral mononuclear cells and submitted for microarray analysis.

9.5 MEASURES TO PROTECT BLINDING OF THIS TRIAL

Please also refer to Section 8.6 - Access to the randomization code during the study.

The following procedures will be implemented to protect blinding:

- Source documents provided to the CIAC members will be blinded. The blinding process will be described in the CIAC charter.
- Any information or unblinding made by the DMC will not be disclosed outside this committee during the whole study conduct, except if decided differently by the DMC members.
- The sponsor will be in charge of the bioassay of AVE5026 and pharmacokinetic analyses. PK assays will be performed blindly and the results of the assays will be unblinded for PK calculation only after database lock.
- The treatment code of any Serious Adverse Event that is unexpected and reasonably associated with the use of the Investigational Product according to either the judgment of the investigator and /or the Company will be unblinded by the sponsor.

10 PATIENT SAFETY

10.1 SAFETY ENDPOINTS ASSESSED IN THIS TRIAL

10.1.1 Clinical safety

Clinical safety will be assessed by bleedings (major bleeding and clinically relevant non-major bleeding as classified by a blinded Adjudication Committee), vital signs, transfusions requirement, hemoglobin, platelet count, liver and renal laboratory data, (S)AEs and deaths (classified as VTE-related death, fatal bleeding or other by a blinded Adjudication Committee) up to 3 calendar days after last IP injection and up to the follow-up visit.

10.1.1.1 Bleeding

During the study period, any bleeding episode should be reported in specific e-CRF pages. In case of bleeding that complies with SAE criteria, it will be also reported as SAE.

A bleeding adjudication package will be prepared for all reported bleedings and sent to the CIAC for adjudication.

The definition of major bleeding is in agreement with the International Society on Thrombosis and Haemostasis (ISTH) recommendation for clinical investigations of antihemostatic products in non-surgical patients (28)

- Fatal bleeding, and/or
- Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome, and/or
- Bleeding causing a fall in hemoglobin level of 2 g/dL (1.24 mmol/L) or more, or leading to transfusion of two or more units of whole blood or red cells

All non-major overt bleedings requiring a medical intervention will be classified as “clinically relevant non-major”.

Medical intervention is defined as any unscheduled contact with the physician due to bleeding or any specific treatment indicated for management of a bleeding episode.

Precise bleeding classifications will be detailed in a specific adjudication manual.

10.1.1.2 Adverse event collection

Adverse events will be collected from the time of informed consent signature and then at each visit until one month after the last dose of study medication.

10.1.1.3 Vital signs

Vital signs including blood pressure (systolic and diastolic), heart and respiratory rates will be collected at screening, at Day 1 prior to start of the study medication, every month until the end of the study medication and one month after the end of the study medication.

10.1.2 Laboratory tests

Standard hematology and chemistry tests will be sampled at different time points (see study flowchart section 1.2 and section 10) i.e. at screening, at Day 1 prior to start the study medication, every month until the end of the study medication and one month after the end of the study medication if applicable. Screening results must be available for eligibility criteria. All laboratory tests requested by the protocol have to be performed unless they are part of the standard care of the patient in the corresponding visit period.

The standard laboratory tests comprise:

- **Hematology:** hemoglobin, White Blood Cells (WBC), neutrophils and platelets. Platelet count will be performed weekly during the first month of treatment.
- **Serum chemistry**: creatinine (except D1), ALT, AST, alkaline phosphatase, total bilirubin.
- **A serum or urine pregnancy test** (in females of childbearing potential) will be performed at screening and at end of treatment visit and repeated as required by national law if necessary

Note: Any abnormal laboratory value will be immediately rechecked for confirmation before making a decision of permanent discontinuation of Investigational Product for the concerned patient

Please also refer to Section 11 below.

10.2 SAFETY INSTRUCTIONS

In the current trial, a significant platelet count reduction is defined as a platelet count $< 50 \times 10^9$/L.

- If the observed thrombocytopenia corresponds to the expected chemotherapy-induced thrombocytopenia profile as per investigator's judgment, study treatment should be temporarily discontinued until platelet count recovers above 50×10^9/L (see section 11)
- In case of suspicion of study drug-induced thrombocytopenia defined as platelet count $< 50 \times 10^9$/L which does not correspond to the expected chemotherapy-induced thrombocytopenia profile as per investigator's judgment, the following procedure should be performed:
  - A repeated test is requested
  - If this test confirms the findings, the treatment with study medication should be stopped permanently and the procedures for the end of treatment should be completed

- A serum sample and a citrated plasma sample should be collected and frozen (2 aliquots of about 1 mL serum and 2 aliquots of about 1 mL plasma) to be analyzed centrally for presence of specific antiplatelet antibodies
- Results of antiplatelet antibodies will be interpreted centrally
- After having considered the responsibility of the study drug or of the chemotherapy, the thrombocytopenia should be managed according to hospital practice and local routine procedures.

The Investigator will provide the Sponsor with a clinical summary of the event followed by a 30 day follow up of the event.

10.3 ADVERSE EVENTS MONITORING

All events will be managed and reported in compliance with all applicable regulations, and included in the final clinical study report.

10.4 DEFINITIONS OF ADVERSE EVENT (AE) AND SERIOUS ADVERSE EVENT (SAE)

An **Adverse Event** is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.
A priori, efficacy endpoints as specified in the protocol will not be considered as AEs except if, because of the course or severity or any other features of such events, the Investigator, according to his/her best medical judgment, considers these events as exceptional in this medical condition see section 10.6).

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

- Results in death or;
- Is life-threatening or;

Note: The term "life-threatening" in the definition of "serious" refers to an event in which the patient 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 prolongation of existing hospitalization or;
- Results in persistent or significant disability/incapacity or;
- Is a congenital anomaly/birth defect;
- Is a medically important event:
  Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above.

Note: Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, convulsions or asymptomatic ALT increase ≥ 10 ULN that does not result in hospitalization, or development of drug dependency or drug abuse.

Note: Transfer of patients to a nursing home or rehabilitation unit will not be considered as a prolonged hospitalization, thus not be reported as SAE. However, when transfer of a patient to a rehabilitation unit is required specifically for treatment of a medical complication, it should be considered as prolonged hospitalization, and reported as SAE.

10.5 OBLIGATION OF THE INVESTIGATOR REGARDING SAFETY REPORTING

10.5.1 Adverse Events

All Adverse Events regardless of seriousness or relationship to Investigational Product, spanning from the signature of the informed consent form up to the last visit (follow-up visit occurring one month ± one week after the end of study medication), are to be recorded on the corresponding screens of the e-CRF.

Whenever possible, diagnosis or single syndrome should be reported instead of symptoms. The Investigator should specify the date of onset, intensity, action taken with respect to Investigational Product, corrective treatment/therapy given, additional investigations performed, outcome and his/her opinion as to whether there is a reasonable possibility that the Adverse Event was caused by the Investigational Product or the chemotherapy.

Laboratory, vital signs or ECG abnormalities are to be recorded as Adverse Events only if they are medically relevant: symptomatic, requiring corrective treatment, leading to discontinuation and/or fulfilling a seriousness criterion.

10.5.2 Serious Adverse Events

In the case of a Serious Adverse Event the Investigator must immediately upon learning of the SAE:

- ENTER (within 1 working day) the information related to the Serious Adverse Event in the appropriate screens of the e-CRF; the system will automatically send the notification to the dedicated Sponsor's representative after approval of the Investigator within the e-CRF.
- SEND (preferably by fax or e-mail) the photocopy of all examinations carried out and the dates on which these examinations were performed, to the representative of the dedicated Sponsor's representative whose name, fax number and email address appear on the Clinical Trial Protocol. Care should be taken to ensure that the patient's identity is protected and the patient's identifiers in the Clinical Trial are properly mentioned on any copy of source document provided to the Sponsor. For laboratory results, include the laboratory normal ranges.
- All further data updates should be recorded in the e-CRF as appropriate, and further documentation as well as additional information should be sent (by fax or e-mail) to the

dedicated Sponsor's representative within 1 working day of knowledge. In addition, any effort should be made to further document each Serious Adverse Event that is fatal or life threatening within the week (7 days) following initial notification.

- The back-up plan should be used (paper copies and forms) when the e-CRF system does not work.

10.5.3 Follow-up

- The Investigator should take all appropriate measures to ensure the safety of the patients, notably he/she should follow up the outcome of any Adverse Events (clinical signs, laboratory values or other, etc.) until they return to normal or consolidation of the patient's condition;
- In case of any Serious Adverse Event, the patient must be followed up until clinical recovery is complete and laboratory results have returned to normal, or until progression has been stabilized. This may imply that follow-up will continue after the patient has left the Clinical Trial and that additional investigations may be requested by the Monitoring Team;
- Any Serious Adverse Event brought to the attention of the Investigator at any time after the clinical trial and considered by him/her to be caused by the Investigational Product with a reasonable possibility should be reported to the Monitoring Team.

10.5.4 Pregnancy

- Pregnancy will be recorded as an AE in all cases. It will be qualified as an SAE only if it fulfills SAE criteria.
- In the event of pregnancy, Investigational Product should be discontinued and the Sponsor/Sponsor representative informed immediately (i.e. within 1 working day), even when not fulfilling a seriousness criterion, using the corresponding screens in the e-CRF, following the same process as described for the Serious Adverse Events
- Follow-up of the pregnancy will be mandatory until the outcome has been determined.

10.5.5 Overdose

An overdose with the Investigational Product is defined as any above the maximal dose to be administered within this clinical trial, i.e. three injections or more actually received on the same calendar day.

Accidental or intentional overdose with the IP, even while not fulfilling a seriousness criterion, is to be reported to the Sponsor/Sponsor representative immediately (within 1 working day) using the corresponding screens in the e-CRF, following the same process as described for the Serious Adverse Events.

10.6 OBLIGATIONS OF THE SPONSOR

During the course of the study, the Sponsor will report in an expedited manner all SAEs that are both unexpected and at least reasonably related to the IP, to the Health Authorities, IECs / IRBs as appropriate and to the Investigators.

In addition, the Sponsor may report in an expedited manner all SAEs that are expected and at least reasonably related to the IPs to the Authorities, according to local regulations.

In this study, the following AEs are considered related to the underlying condition and thus will not be considered unexpected unless their course, intensity or other specific features are such that the Investigator, according to his/her best medical judgment, considers these events as exceptional in the context of this medical condition:

Symptomatic deep vein thrombosis of the lower limbs, Symptomatic deep vein thrombosis of the upper limbs including CVC-related thrombosis, Non-fatal pulmonary embolism and the related hospitalizations are outcome events and components of the primary endpoint of the study. These events will not be reported as (S)AEs but only as efficacy endpoints on specific screens in the e-CRF if they occurred up to 3 days after administration of the last dose of investigational product.
The same events occurring after (and during the follow-up period) should be reported as (S)AEs.

In addition, non-fatal bleedings reported as (S)AE are considered expected for this class of drugs.

Any other AE not listed as an expected event in the Investigator's Brochure and in this protocol will be considered as unexpected.

The Sponsor will report all safety observations made during the conduct of the trial in the CSR.

11 HANDLING OF PATIENT WITH TEMPORARY OR DEFINITIVE TREATMENT DISCONTINUATION AND OF PATIENT STUDY DISCONTINUATION

The investigational product should be continued whenever possible. In case the IP is stopped, it should be determined if the stop can be made temporarily; permanent IP discontinuation should be a last resort. Any IP discontinuation should be fully documented in the e-CRF. In any case, the patient should remain in the study as long as possible.

11.1 TEMPORARY TREATMENT DISCONTINUATION WITH INVESTIGATIONAL PRODUCT(S)

11.1.1 Temporary treatment discontinuation

Temporary treatment discontinuation may be considered by the Investigator because of suspected adverse drug reaction(s). Treatment with the Investigational Product can be re-started under close and appropriate clinical/and or laboratory monitoring once the Investigator has decided that according to his/her best medical judgment it was unlikely that the Investigational Product was responsible for the occurrence of the concerned event and ensured that the selection criteria for the study are still met (refer to Sections 7.2 and 7.3).

All durations for temporary treatment discontinuation should be recorded by the Investigator in the appropriate e-CRF screens when considered as confirmed.

Reasons for temporary treatment discontinuation are the following:

- Thrombocytopenia (<50 x 10^9/L) corresponding to the expected chemotherapy-induced thrombocytopenia profile as per investigator's judgment until platelet count recovers above 50 x 10^9/L but within 14 days.
- Worsening of renal status: if the creatinine clearance goes below <30 mL/min during study treatment period, the treatment should be discontinued and could be resumed as soon as the creatinine clearance returns to > 30 mL/min but within 14 days.

Note: *If platelets or creatinine clearance do not recover within 14 days, study treatment should be stopped definitely.*

- In case of any invasive procedure (therapeutic of diagnostic), study medication could be discontinued 24 h before the procedure and resumed as early as possible after the procedure and within 7 days)
- In case one single dose of a curative anti-coagulant treatment is initiated for suspicion of VTE but this event is not finally confirmed, the study medication could be resumed.

11.2 DEFINITIVE TREATMENT DISCONTINUATION WITH INVESTIGATIONAL PRODUCT(S)

11.2.1 List of criteria for definitive treatment discontinuation

The patients may withdraw from treatment with Investigational Product if they decide to do so, at any time and irrespective of the reason, or this may be the Investigator's decision. All efforts should be made to document the reason for discontinuation and this should be documented in the e-CRF.

As per protocol, the study treatment period will be considered as completed if the study treatment is given

- until change in the initial chemotherapy regimen (i.e. addition or removal of at least one of the initial antineoplastic drugs; however, in case of antineoplastic dose adjustment only, study medication will continue as planned) if this change occurs after the first 3 months of the study or
- at least 3 months and until the regimen ongoing at the 3-month time point (defined as addition or removal of at least one of the antineoplastic drugs of this regimen) is changed, if the change in the initial chemotherapy regimen occurs within the first 3 months of the study and the patient continues on chemotherapy or
- until decision is made to stop definitely chemotherapy if it occurs within the first three months of the study

whichever comes first .

Study treatment will be stopped prematurely and permanently if any of the following events occurs or is diagnosed:

- Symptomatic DVT or PE before the scheduled end of treatment confirmed locally by diagnosis tests and leading to initiation of any curative anti-coagulant or thrombolytic treatment.
- Any patient's condition (others than symptomatic DVT or PE) that requires the initiation of any anti-coagulant or thrombolytic treatment.
- Clinically significant (at investigator's discretion) symptomatic bleeding meeting the definition of Serious Adverse Event (SAE)
- Occurrence of a Serious Adverse Event warranting premature discontinuation
- ALT $\geq$ 5 times the Upper Limit of Normal range (ULN) or ALT $\geq$ 3 times (ULN) with total bilirubin > 2 ULN
- Platelet count < 50 x 10^9/L which does not correspond to the expected chemotherapy-induced thrombocytopenia profile as per investigator's judgment (see section 10.2)
- Pregnancy
- Investigator's judgment

- Patient wishes to terminate study treatment

Any treatment unblinding by the Investigator will lead to permanent treatment discontinuation.

11.2.2 Handling of patients after definitive treatment discontinuation

Patients will be followed up according to the study procedures as specified in this protocol up to the scheduled date of study completion (one month after discontinuation of study medication), or up to recovery or stabilization of a followed-up AE, whichever comes last.

All definitive treatment discontinuation should be recorded by the Investigator in the appropriate pages when considered as confirmed.

If possible, and after the permanent discontinuation of treatment, the patients will be assessed using the procedure normally planned for the last dosing day with the Investigational Product.

The single main reason for premature treatment discontinuation should be recorded on the appropriate e-CRF page. At the time of permanent treatment discontinuation, a blood sample will be drawn for measurement of Hb, WBC, neutrophils, Platelets, AST, ALT, Alkaline phosphatase, Bilirubin (total and conjugated), Creatinine. In addition a serum or urine pregnancy test (for women of childbearing potential) will be performed.

11.3 PROCEDURE FOR WITHDRAWAL OF PATIENTS FROM STUDY FOLLOW-UP SCHEDULE

The patients may withdraw from the study follow-up schedule, before study completion if they decide to do so, at any time and irrespective of the reason:

- All study withdrawals should be recorded by the Investigator in the appropriate e-CRF pages and in the patient's medical records when considered as confirmed (at least date of withdrawal and reason for);
- If possible, the patients will be assessed using the procedure normally planned for the end-of-study visit

The Investigator should make every effort to contact the patient, to identify the reason why he/she failed to attend the visit, and to determine his/her health status, including VTE and the occurrence of any bleeding or at least his/her vital status. Attempts to contact such patients must be documented in the patient's records (e.g., times and dates of attempted telephone contact, receipt for sending a registered letter).

The statistical analysis plan will specify how these patients lost to follow-up for their primary endpoints will be considered.

11.4 CONSEQUENCE

Patients who have been withdrawn from the study cannot be re-included in the study. Their inclusion and treatment number must not be reused.

12 STUDY PROCEDURES

12.1 VISIT SCHEDULE

12.1.1 Screening period

The screening period will take place within 21 days prior to randomization (i.e.: Day 1, corresponding also to the initiation day of the chemotherapy and the study medication).

Cancer patients with metastatic or locally advanced solid tumor of the lung, pancreas, stomach, colon/rectum, bladder or ovary, with an ECOG Status of 0, 1 or 2 and planned to start a (new) course of chemotherapy are potentially eligible for the study. Eligibility will be assessed by the absence of the exclusion criteria. Potentially eligible patients will be asked to provide written informed consent. All patients who meet the inclusion criteria will be considered as screened patients. Investigator should call the IVRS for registering screened patients into the IVRS database.

The following information/procedures should be obtained/performed to determine patient eligibility:

- Date of informed consent's signature
- Patient demography
- Weight, Height, vital signs
- ECOG status
- Prior medical and surgical history,
- Cancer localization and status at time of diagnosis and at screening
- Central venous catheter information (if any)
- Prior antitumor therapy
- Specific prior and concomitant medications within 7 days prior to the start of study treatment
- AE (including SAE) assessment occurring since time of signature of informed consent
- A blood sample is collected for:
  - Hematology: hemoglobin, WBC, neutrophils and platelet count
  - Biochemistry: albumin, serum creatinine, AST, ALT, bilirubin (total and conjugated), alkaline phosphatase
  - Coagulation tests: aPTT, INR
- Urine or serum Pregnancy test in women of childbearing potential

These screening laboratory samples analyzed locally will be drawn for all patients who signed the informed consent, unless the results of tests performed as routine evaluation during the 21 days screening period are already available. If this is the case, it is highly recommended to obtain informed consent as close as possible prior to the randomization.

12.1.2 Study Treatment period

From first study medication administration to end of study, patients should be assessed carefully for any symptoms of DVT of the upper or lower limbs and PE. In case of suspicion of one of these events, objective tests must be performed to confirm or rule out the diagnosis (see section 9.1.1). Occurrence of bleedings should also be followed carefully.

From Day 1 (Randomization) to end of study, information on all hospitalizations will be recorded in the CRF. This includes the date of admission, the date of discharge and the number of days in Emergency Room and/or Intensive Care Unit.

12.1.2.1 Day 1 (Randomization)

Randomization should occur the day of initiation of the chemotherapy, as close as possible prior to the first administration of study treatment after verification that the patient continues to meet eligibility criteria.

All the information obtained to determine patient eligibility (see Section 12.1.1) will be recorded in the e-CRF for all randomized patients. For the screened patients who will not be randomized, only the baseline demographic characteristics and exclusion criteria that have been met will be recorded in the e-CRF.

If the patient continues to meet the eligibility criteria, randomization will be done by calling the IVRS (see section 8.3) and 1 or 2 treatment kits numbers (depending of the frequency of chemotherapy cycles) will be allocated.

The following information/procedures should be obtained/performed:

- ECOG status
- Weight, vital signs
- Central venous catheter information (if any)
- Concomitant medications (including chemotherapy)
- Transfusions: number of prescribed blood units
- (S)AE assessment
- Laboratory evaluation consisting in Hb, WBC, neutrophils, platelets and LFT should be done prior to the first study medication administration and the start of chemotherapy.
- If applicable, the sampling for genomic sub-study should be done at the same time

- The first IP administration should be done at site as close as possible to the start of the chemotherapy to allow easier timing of PK sampling (if applicable).
- If applicable, the two PK sampling should be done at 0.5 to 1h and 2 to 4h after the first IP administration.
- When the patient leaves the center, s/he will receive:
  - Study medication kit(s)
  - Precise information on how and when to inject study drug
  - A diary to collect the date/time of the daily injections prior to next visit
  - A prescription for a weekly platelet count
  - A document detailing symptoms suggestive of DVT/PE or bleeding and an emergency card that will include a medical contact person with an emergency call number. The patient will be asked to immediately contact the investigator if any of these events occurred or if the weekly platelet count performed during the first month is below 50×10^9/L.

12.1.2.2 Monthly visits

For all randomized patients, visits will be performed monthly ± 1 week (i.e. corresponding to a scheduled chemotherapy visit) until discontinuation of study medication (see section 8.1.3). Adjustment of the antineoplastic dose for toxicity will not lead to study medication discontinuation.

At each visit, the following information/procedures will be systematically checked:

- ECOG status
- Weight, vital signs
- Central venous catheter information (if any)
- Concomitant medications (including chemotherapy)
- Transfusions: number of prescribed blood units
- Whenever applicable, specific forms (Procedures, Transfusions, unscheduled laboratory tests) will be completed.
- Occurrence of bleeding
- VTE recording
- (S)AE occurrence
- IP injection if the usual timing of the daily injection is within the period spent at the center.
- Laboratory evaluation: Hb, WBC, neutrophils, platelets, LFT and serum creatinine unless they are part of the routine care of the patient and sampled within 7 days prior to the visit.

- If applicable, and at the first monthly visit only, two PK sampling should be done when patient arrives at site (and just before IP injection if done on site) and when patient leaves the site (as late as possible).
- Compliance with study drug (as specified in section 8.11)
- If the patient was hospitalized, record date of admission, date of discharge, and the number of days in Emergency room and/or Intensive Care Unit if applicable
- IVRS will be called for IP-resupplying

12.1.2.3 End of treatment visit

This visit will be performed when the study drug is discontinued, either because the study medication is completed as per protocol (see section 8.1.3) or for any other reason leading to premature study drug discontinuation as listed in section 8.1.3.1. The visit should take place no later than 5 days after study drug discontinuation.

At this visit, the following information/procedures will be systematically checked:

- Reason for study drug discontinuation
- ECOG status
- Weight, vital signs
- Central venous catheter information (if any)
- Reasons for changing/Stopping chemotherapy if applicable
- Concomitant medications (including chemotherapy if applicable)
- Transfusions: number of prescribed blood units
- Whenever applicable, specific forms (Procedures, Transfusions, unscheduled laboratory tests) will be completed.
- Occurrence of bleeding
- VTE recording
- (S)AE assessment
- Laboratory evaluation: Hb, WBC, neutrophils, platelets, LFT and serum creatinine unless they are part of the standard care of the patient and sampled within 7 days prior to the visit, serum or urine pregnancy test for women of childbearing potential.
- Compliance with study drug as specified in section 8.11.
- If the patient was hospitalized, record date of admission, date of discharge, and the number of days in Emergency room and/or Intensive Care Unit if applicable
- The IVRS should be called for registering the patient as having completed the treatment period.

12.1.3 Follow-Up period

The follow-up period starts at the last dose of study medication and ends at the follow-up visit to be performed one month ± 1 week after study drug discontinuation.

The following information/procedures will be systematically checked:

- ECOG status
- Weight, vital signs
- Concomitant medications (including chemotherapy if applicable)
- Transfusions: number of prescribed blood units
- Occurrence of bleeding
- VTE recording
- S(AE) assessment
- Laboratory tests in the following cases:
  - Hb if previous bleeding detected or not recovered at end of treatment visit and/or drop of Hb
  - Platelets if thrombocytopenia not recovered at end of treatment visit
  - LFT if increase in one of the parameter not recovered at end of treatment visit
  - Serum creatinine if increase not recovered at end of treatment visit
- If the patient was hospitalized, record date of admission, date of discharge, and the number of days in Emergency room and/or Intensive Care Unit if applicable
- The IVRS should be called for registering the patient as having completed the study.

12.1.4 Survival status

In addition, survival status (alive, dead, or lost to follow up) will be collected one year after randomization or at the end of the study, whichever comes first (study end date is defined as 7 months following randomization of the last patient at the latest) for all patients. No patient visit is necessary: this information could be retrieved during phone call, routine visit, etc…

12.2 DEFINITION OF SOURCE DATA

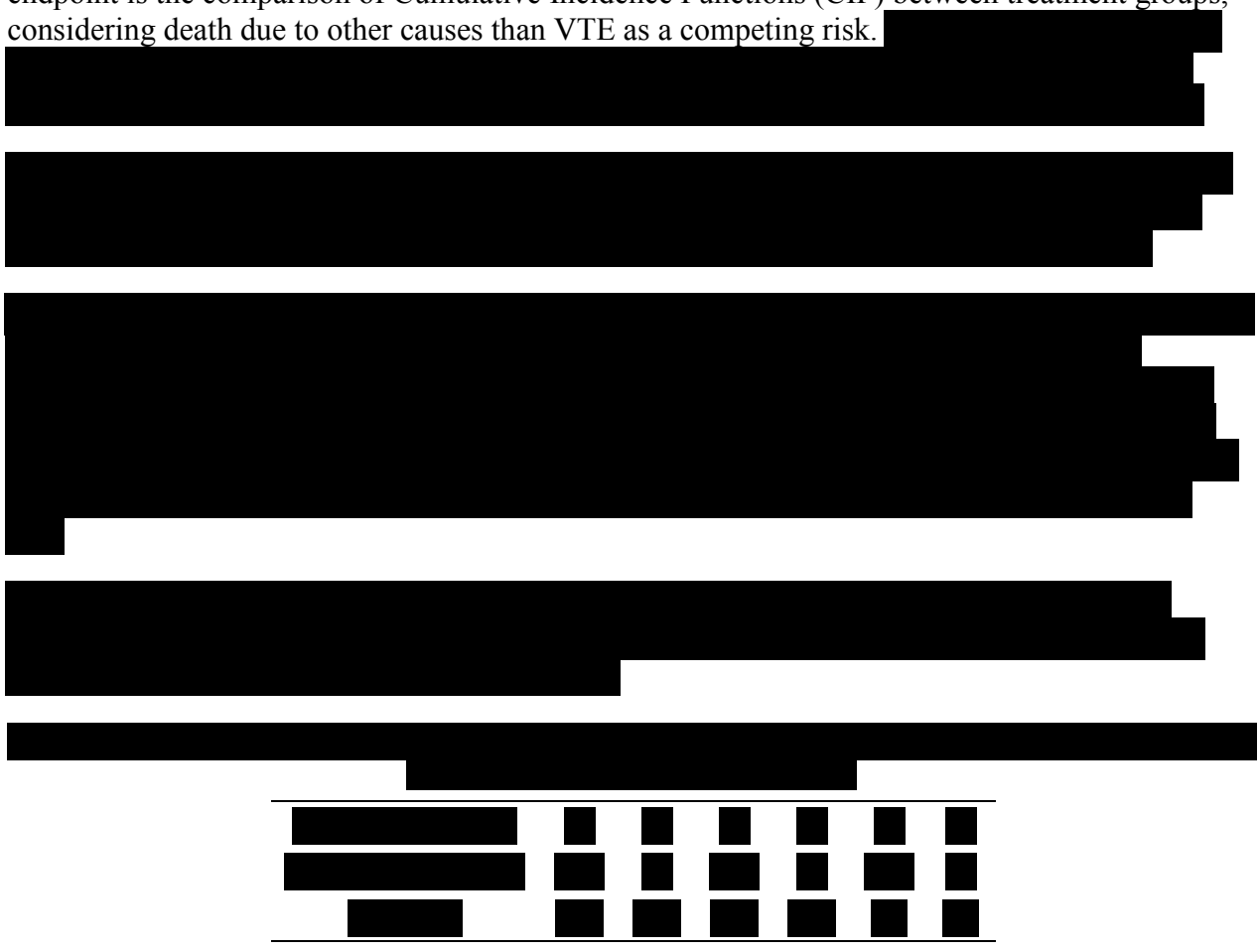
In this study, source data will comprise the medical records/chart and results of laboratory and other diagnostic examinations, e.g. US, venography, CT lung scan… that document the efficacy and safety outcomes. Actual dates and times of injections reported in the patient's diary/calendar will be considered as source data.

13 STATISTICAL CONSIDERATIONS

The material of this Section is the basis for the Statistical Analysis Plan for the study. This plan may be revised during the study to accommodate Clinical Trial Protocol amendments and to make changes to adapt to unexpected issues in study execution and data that affect planned analyses. These revisions will be based on blinded review of the study and data, and a final plan will be issued at the latest 8 weeks before final database lock.

13.1 DETERMINATION OF SAMPLE SIZE

In this population of cancer patients undergoing chemotherapy, the mortality rate during the chemotherapy treatment is not negligible: in the analysis of the primary endpoint, death from other reasons than VTE should be considered as a competing risk event, i.e. as an event whose occurrence precludes the occurrence of the event of interest. The primary analysis of the primary endpoint is the comparison of Cumulative Incidence Functions (CIF) between treatment groups, considering death due to other causes than VTE as a competing risk.



13.2 ANALYSIS VARIABLES

13.2.1 Demographic and baseline characteristics

Demographic data will include gender, race, age (years), weight (kg), height (cm), estimated creatinine clearance (mL/min) using Cockroft and Gault formula (21) in class (≥ 30 - < 50 mL/min, ≥ 50 - < 80 mL/min, ≥ 80 mL/min), and calculated body mass index (BMI) (<30 and ≥ 30 kg/m^2).

Baseline cancer characteristics will include location of the primary site of the tumor, TNM staging at time of initial diagnosis and at screening, ECOG performance status, prior anti-tumor therapy, and time (weeks) from cancer diagnosis up to randomization.

Other baseline data will include previous medical/surgical history and prior medication (see section 8.9).

13.2.2 Efficacy variables

The efficacy analysis period is defined as the period from the randomization up to last study drug injection plus 3 days.

13.2.2.1 Primary efficacy variable(s)

The primary efficacy variable is the time in days elapsed from the randomization to the first occurrence of any component of the composite endpoint of the following documented outcome results, confirmed by the CIAC, occurring from randomization up to last study drug injection plus 3 days:

- Any symptomatic DVT of the lower limbs,
- Any symptomatic DVT of the upper limbs (including CVC-related thrombosis),
- Any non fatal PE
- VTE-related deaths (fatal PE and unexplained deaths)

The dates to consider will be the assessment date of the confirmed episode of VTE by the CIAC.

13.2.2.2 Secondary efficacy variable(s)

Each component of the primary efficacy endpoint will be analyzed separately as a secondary analysis of the primary endpoint (see section 13.4.3.1).

Secondary efficacy variables include the initiation of curative treatment by the investigator after VTE.

13.2.2.3 Other efficacy variable(s)

The patient survival status will be reported one year after randomization until study end date (7 months following randomization of the last patient).

13.2.3 Safety variables

The main safety analysis period is defined as the period from the first study drug injection up to the last study drug injection plus 3 days. This analysis period is afterwards called "on-treatment period".

The baseline safety variables value for each patient is defined as the last available value prior to the first study drug injection and to the chemotherapy. It should be noted that the dates of the baseline evaluation could be different within the different parameters.

13.2.3.1 Bleeding assessment

Any unusual bleeding reported up to the last study drug injection plus 3 days will be centrally reviewed by the CIAC according to the adjudication manual and classified according to the adjudication manual as:

- Major bleeding
- Clinically relevant non-major bleeding
- Non-clinically relevant bleeding

Any major, any clinically relevant non-major, and any major or clinically relevant non major bleedings will be summarized.

Any bleeding episodes reported by the investigators but considered by the CIAC as non-clinically relevant (major or non-major) bleedings according to a priori defined criteria in the CIAC manual will not be taken into account in the adjudicated bleeding statistical analysis. Such bleedings will be tabulated separately as non-clinically relevant bleeding.

Time in days elapsed from the first study drug injection and the first occurrence of bleeding, up to last study drug injection plus 3 days will be analyzed.

13.2.3.2 Related bleeding criteria

The related bleeding criteria variables include:

- Blood transfusion from first study drug injection up to last study drug injection plus 3 days: number of patients with at least one prescribed blood unit
- Hemoglobin level from first study drug injection up to last study drug injection plus 3 days: number of patients with (1) at least one post-baseline value <7g/dL, (2) a decrease from baseline ≥ 2g/dL.

13.2.3.3 Adverse events

Bleeding events are always considered as AEs.

Before the database lock, all AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) using the current version at that time.

Each AE is classified as treatment-emergent AE, pre-treatment emergent AE or post-treatment emergent AE, as follows:

- Treatment-Emergent AEs (TEAEs) are defined as AEs that developed or worsened in intensity or became serious during the on-treatment period.
- Pre-treatment emergent AEs are defined as AEs that developed or worsened in intensity or became serious before the first study drug injection.
- Post-treatment emergent AEs are defined as AEs that developed or worsened in intensity or became serious after the on-treatment period.

13.2.3.4 Laboratory safety variables

Hematology, biochemistry and hemostasis are assessed locally and include the following parameters:

- Hematology: Hemoglobin, WBC, neutrophils and platelets
- Biochemistry:
  - Liver function: AST, ALT, Alkaline phosphatase, Total and conjugated bilirubin
  - Renal function: Creatinine

13.2.4 Pharmacokinetic variables

AVE5026 plasma concentration is assessed at specified time points in all patients of selected centers.

Four plasma samples per patient will be collected (see section 9.3.1 for exact timing).

Plasma concentration obtained from patients in the AVE5026 group is classified C_{trough} if time interval between last study drug injection before sampling and sample time is 24 ± 2 hours.

Samples with missing date and/or time and/or missing date and/or time of the previous study drug injection are discarded. Concentrations below the Limit Of Quantification (LOQ) of 0.3125 µg/mL (0.05 U/mL) are set to 0 or to 0.156 µg/mL depending on the analysis (Population pharmacokinetic modeling or descriptive statistics on observed data respectively).

13.3 ANALYSIS POPULATIONS

Screened patients are defined as patients who meet the inclusion criteria.

Allocation of randomized treatment to eligible patients (patients who meet all inclusion/exclusion criteria) will be centrally performed using an IVRS. A patient is considered as randomized as soon as there is confirmation of successful allocation of a randomization number through the IVRS. Patients allocated outside the IVRS will not be taken into account in any of the analyses.

13.3.1 Efficacy populations

The primary efficacy population is the Intent-To-Treat (ITT) population which includes all randomized patients. The patients will be analyzed in the treatment group to which they will be allocated by the IVRS (i.e. “as randomized” regardless of treatment actually received).

13.3.2 Safety population

The All-Treated (AT) population includes all randomized patients who received at least one dose of the study drug. The patients will be analyzed in the treatment group actually received (i.e. “as treated”), i.e. as soon as a patient will receive any study drug injection of AVE5026, he/she is considered as an AVE5026 treated patient.

13.3.3 Pharmacokinetic population

The pharmacokinetic population considered for descriptive statistics includes all randomized and treated patients in the AVE5026 group with C_{trough} plasma concentration (see Section 13.2.4). In addition, patients under AVE5026 treatment and in whom PK samples are drawn are included in the PK subset for population pharmacokinetic modeling.

13.3.4 Disposition of patients

Non-randomized patients will be summarized by number and percentage on the all screened patients according to the reason for not being randomized.

The number and percentage of patients included in each population will be summarized by treatment group. Summaries by region, country and treatment group and then according to the location of the primary tumor site, the stage of the cancer and the treatment group will be also provided.

Randomized patients who never received any study drug injection will be listed.

The number of patients either completing or prematurely discontinuing the study drug (according to the main reason) will be summarized by treatment group. The incidence of premature study drug discontinuation (whatever the reason) will be presented graphically, using Kaplan-Meier method.

13.4 STATISTICAL METHODS

Summary tables will be provided by treatment group and stratification stratum (when relevant).

Quantitative variables will be summarized with number of observations, mean, standard deviation (SD), median, minimum and maximum values.

Qualitative variables will be summarized with counts, percentage and number of missing data (if relevant).

Two dates will be used as reference dates (Day 1) according to the purpose of the analyses: the day of randomization and the day of the first study drug injection. In all tables and listings the reference date(s) will be clearly identified.

13.4.1 Demographic and baseline characteristics

All analyses described in this section will be performed on the ITT population.

Demographic data:

Gender, race, calculated BMI and baseline estimated creatinine clearance will be summarized as qualitative variables. Age and weight will be summarized as quantitative variables as well as qualitative variables. Height will be summarized as quantitative variable. In addition weight and height will be summarized by gender.

Previous medical/surgical history:

Number and percentage of patients with any previous medical/surgical history including risk factors for VTE will be tabulated.

Cancer diagnosis, status and staging, ECOG performance status

Cancer diagnosis, TNM staging at diagnosis and at screening, prior anti-cancer therapy and ECOG performance status at screening will be summarized as qualitative variables. Time from cancer diagnosis up to randomization will be summarized as quantitative variable.

Prior medications:

Number and percentage of patients with specific prior medications will be tabulated.

13.4.2 Extent of study treatment exposure, compliance and concomitant medications

All analyses described in this section will be performed on the All-Treated population.

13.4.2.1 Investigational product

The extent of exposure variable is defined as the duration in months elapsed from the first study drug injection up to the last study drug injection, ignoring temporary periods without treatment (date of last study drug injection minus date of fist study drug injection plus 1 day).
Categorization of the extent of exposure (months) is also defined as follows: < 1, [1-3[, [3-6[, ≥ 6 months.

Compliance to study drug variable is determined on an individual basis corresponding to the ratio of the number of study drug injections actually taken from the first study drug injection to the last study drug injection over the theoretic number of injections q.d. from the day of first study drug injection to the day of last study drug injection. Result will be expressed in percentage for each patient.

Duration of treatment exposure as well as treatment compliance will be summarized as quantitative and qualitative variables.

13.4.2.2 Concomitant medication/therapy

Chemotherapy exposure (duration of dosing in months and drugs administered) will be summarized by treatment group. Duration of dosing is defined as the time from the first chemotherapy administration up to the last chemotherapy administration, ignoring temporary periods without treatment.

Number and percentage of patients with other specific concomitant medications will be tabulated.

13.4.3 Analyses of efficacy variables

All analyses described in this section will be performed on the ITT population, unless otherwise specified.

13.4.3.1 Analysis of primary efficacy variable(s)

Primary analysis

In order to correct for competing risks, a cumulative incidence approach will be used [24]. Competing risks considered will be deaths from cause other than VTE-related death. Patients alive and not having experienced the primary efficacy endpoint will be right censored at last study drug injection plus 3 days.

The primary analysis of the primary endpoint will consist of the comparison of the 2 treatment groups (AVE5026 and placebo) using the two-sample test of Gray for comparing Cumulative Incidence Functions (CIF), at a significant level of 0.05 (2-sided) [5]:

- H0: CIF of AVE5026 group = CIF of placebo group
- H1: CIF of AVE5026 group ≠ CIF of placebo group

CIFs will be estimated separately for the two treatment groups with Prentice non-parametric estimator using a model of cause-specific hazards [23]; corresponding 95% 2-sided Confidence Intervals (CIs) will be computed by Keiding and Andersen formula with variance computed using the delta method [25].

An estimation of the treatment effect (hazard ratio and 95% CIs) will be given using Fine and Gray regression model for CIFs (proportional marginal mean model) [6].

Secondary analysis

In order to examine the consistency of the results between the different components of the primary endpoint, the time-to-first occurrence of each primary endpoint component, from randomization up to 3 calendar days after last study drug administration, will be analyzed separately. For each time-to-event definition, the components not defined as the event of interest will be considered as competing risk events. CIF will be presented by treatment group and hazard ratio and 95% 2-sided confidence interval will be calculated.

13.4.3.2 Analyses of secondary efficacy variables

For curative treatment therapy initiated based on the investigator's assessment of VTE, the number and percentage of patients who received a curative anticoagulant or thrombolytic treatment following VTE assessment will be presented according to the treatment received.

13.4.3.3 Analyses of other efficacy variables

Patient survival status will be summarized using Kaplan-Meier estimates and compared between the two treatment groups using a two-sided Log-rank test in the ITT population.

An estimation of the treatment effect (hazard ratio with corresponding 2-sided 95% CI) will be given using Cox regression model with treatment group as the only term; acceptability of proportional hazards assumption will be checked graphically.

13.4.4 Analyses of safety data

All analyses described in this section will be performed on the All-Treated population.

13.4.4.1 Analyses of bleeding assessment

Bleeding events centrally reviewed and classified by the CIAC as major bleeding or clinically relevant non-major bleeding will be summarized by treatment arm.

Any bleeding episodes reported by the investigators but considered by the CIAC as non-clinically relevant (major or non-major) bleedings according to a priori defined criteria in the CIAC manual will not be taken into account in the adjudicated bleeding statistical analysis. Such bleedings will be tabulated separately as non-clinically relevant bleeding

In addition, in order to correct for competing risks, a cumulative incidence approach will be used. Competing risks considered are deaths from cause other than fatal bleeding.

Patients alive and not having experienced any bleeding event will be right censored at last study drug injection plus 3 days. Cumulative Incidence Functions will be presented separately for the two treatment groups. Hazard ratio and 95% 2-sided confidence interval will be calculated using the Fine and Gray regression model for CIF.

13.4.4.2 Analyses of related bleeding criteria

Number and percentage of patients requiring blood transfusion (in prescribed blood unit) will be tabulated as qualitative variable.

Number and percentage of patients with at least one post-baseline hemoglobin value <7g/dL will be tabulated. Number and percentage of patients with hemoglobin decrease from baseline ≥2g/dL during the on-treatment period will be tabulated.

Additional analyses of hemoglobin are presented in section 13.4.4.4.

13.4.4.3 Analyses of adverse events

The overall frequency of TEAEs, serious TEAEs, TEAEs leading to death, TEAEs leading to permanent treatment discontinuation will be summarized by primary System Organ Class (SOC) and Preferred Term (PT) within SOC, using counts and percentages. TEAEs will also be summarized by relationship to study drug, to distinguish TEAEs related to the study drug from other TEAEs (in particular TEAEs related to the background chemotherapy).

The adjudicated causes of death will be summarized by treatment group.

13.4.4.4 Analyses of laboratory variables

Number and percentage of patients presenting at least one post-baseline Potentially Clinically Significant Abnormality (PCSA) will be provided by laboratory parameter.

Shift table between baseline value status and post-baseline value status will be provided for hemoglobin, ALT, AST and estimated creatinine clearance parameters.

Additional analyses including NCI grading may be provided.

13.4.5 Analyses of pharmacokinetic variables

Descriptive statistics (number of observation, arithmetic mean, SD, coefficient of variation (CV), geometric mean, median, minimum and maximum) will be presented for AVE5026 C_{trough} (see section 13.2.4). Concentrations below the LOQ will be replaced by the value of the LOQ/2. If the median, the minimum, and/or a calculated mean will be below the LOQ then the result will be provided as "< LOQ".

13.5 DATA HANDLING CONVENTIONS

Missing data will not be included in the calculation of the percentages, unless otherwise specified. Imputation rules will be defined in the SAP.

14 ETHICAL AND REGULATORY STANDARDS

14.1 ETHICAL PRINCIPLES

This Clinical Trial will be conducted in accordance with the principles laid down by the 18th World Medical Assembly (Helsinki, 1964) and all applicable amendments laid down by the World Medical Assemblies and the ICH guidelines for Good Clinical Practice (GCP).

14.2 LAWS AND REGULATIONS

This Clinical Trial will be conducted in compliance with all international laws and regulations, and national laws and regulations of the country(ies) in which the Clinical Trial is performed, as well as any applicable guidelines.

14.3 INFORMED CONSENT

The Investigator (according to applicable regulatory requirements), or a person designated by the Investigator, and under the Investigator's responsibility, should fully inform the Patient of all pertinent aspects of the Clinical Trial including the written information giving approval/favorable opinion by the Ethics Committee (IRB/IEC). All participants should be informed to the fullest extent possible about the study, in language and terms they are able to understand.

Prior to a patient’s participation in the Clinical Trial, the written Informed Consent Form should be signed, name filled in and personally dated by the patient or by the patient’s legally acceptable representative, and by the person who conducted the informed consent discussion. A copy of the signed and dated written Informed Consent Form will be provided to the patient.

- Participants who can read the Assent Form will do so before writing their name and dating or signing and dating the form.
- Participants who can write but cannot read will have the assent form read to them before writing their name on the form.
- Participants who can understand but who can neither write nor read will have the assent form read to them in presence of an impartial witness, who will sign and date the Assent form to confirm that assent was given.

The Informed Consent Form and the Assent Form used by the Investigator for obtaining the Patient’s Informed Consent must be reviewed and approved by the Sponsor or the Sponsor’s representative prior to submission to the appropriate Ethics Committee (IRB/IEC) for approval / favorable opinion.

14.4 INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE (IRB/IEC)

As required by local regulation, the Investigator or the Sponsor must submit this Clinical Trial Protocol to the appropriate Ethics Committee (IRB/IEC), and is required to forward to the respective other party a copy of the written and dated approval/favorable opinion signed by the Chairman with Ethics Committee (IRB/IEC) composition.

The Clinical Trial (study number, Clinical Trial Protocol title and version number), the documents reviewed (Clinical Trial Protocol, Informed Consent Form, Investigator's Brochure, Investigator's CV, etc.) and the date of the review should be clearly stated on the written (IRB/IEC) approval/favorable opinion.

Investigational Product will not be released at the study site and the Investigator will not start the study before the written and dated approval/favorable opinion is received by the Investigator and the Sponsor.

During the Clinical Trial, any amendment or modification to the Clinical Trial Protocol should be submitted to the Ethics Committee (IRB/IEC) before implementation, unless the change is necessary to eliminate an immediate hazard to the patients, in which case the IRB/IEC should be informed as soon as possible. It should also be informed of any event likely to affect the safety of patients or the continued conduct of the Clinical Trial, in particular any change in safety. All updates to the Investigator's Brochure will be sent to the Ethics Committee (IRB/IEC).

A progress report is sent to the Ethics Committee (IRB/IEC) at least annually and a summary of the Clinical Trial's outcome at the end of the Clinical Trial.

15 STUDY MONITORING

15.1 RESPONSIBILITIES OF THE INVESTIGATOR(S)

The Investigator(s) undertake(s) to perform the Clinical Trial in accordance with this Clinical Trial Protocol, ICH guidelines for Good Clinical Practice and the applicable regulatory requirements.

The Investigator is required to ensure compliance with all procedures required by the Clinical Trial Protocol and with all study procedures provided by the Sponsor (including security rules). The Investigator agrees to provide reliable data and all information requested by the Clinical Trial Protocol (with the help of the Case Report Form [e-CRF], Discrepancy Resolution Form [DRF] or other appropriate instrument) in an accurate and legible manner according to the instructions provided and to ensure direct access to source documents by Sponsor representatives.

The Investigator may appoint such other individuals as he/she may deem appropriate as Sub-Investigators to assist in the conduct of the Clinical Trial in accordance with the Clinical Trial Protocol. All Sub-Investigators shall be appointed and listed in a timely manner. The Sub-Investigators will be supervised by and work under the responsibility of the Investigator. The Investigator will provide them with a copy of the Clinical Trial Protocol and all necessary information.

15.2 RESPONSIBILITIES OF THE SPONSOR

The Sponsor of this Clinical Trial is responsible to Health Authorities for taking all reasonable steps to ensure the proper conduct of the Clinical Trial Protocol as regards ethics, Clinical Trial Protocol compliance, and integrity and validity of the data recorded on the Case Report Forms. Thus, the main duty of the Monitoring Team is to help the Investigator and the Sponsor maintain a high level of ethical, scientific, technical and regulatory quality in all aspects of the Clinical Trial.

At regular intervals during the Clinical Trial, the site will be contacted, through monitoring visits, letters or telephone calls, by a representative of the Monitoring Team to review study progress, Investigator and patient compliance with Clinical Trial Protocol requirements and any emergent problems. These monitoring visits will include, but not be limited to, review of the following aspects: patient informed consent, patient recruitment and follow-up, Serious Adverse Event documentation and reporting, AESI documentation and reporting, AE documentation, Investigational Product allocation, patient compliance with the Investigational Product regimen, Investigational Product accountability, concomitant therapy use and quality of data.

15.3 SOURCE DOCUMENT REQUIREMENTS

According to the ICH guidelines for Good Clinical Practice, the Monitoring Team must check the Case Report Form entries against the source documents, except for the pre-identified source data

directly recorded in the e-CRF. The Informed Consent Form will include a statement by which the patient allows the Sponsor's duly authorized personnel, the Ethics Committee (IRB/IEC), and the regulatory authorities to have direct access to original medical records which support the data on the e-CRFs (e.g., patient's medical file, appointment books, original laboratory records, etc.). These personnel, bound by professional secrecy, must maintain the confidentiality of all personal identity or personal medical information (according to confidentiality rules).

15.4 USE AND COMPLETION OF CASE REPORT FORMS (E-CRFS) AND ADDITIONAL REQUEST

It is the responsibility of the Investigator to maintain adequate and accurate e-CRFs designed by the Sponsor or the Sponsor's representative to record (according to Sponsor instructions or the Sponsor's representative instructions) all observations and other data pertinent to the clinical investigation. All e-CRFs should be completed in their entirety in a neat, legible manner to ensure accurate interpretation of data. Data should be entered in the system within 72 h of visit completion. Any initial data entry or data update should be signed electronically by the investigator.

The computerized handling of the data by the Sponsor or the Sponsor's representative after receipt of the e-CRFs may generate additional requests (DRF) to which the Investigator is obliged to respond by confirming or modifying the data questioned. The requests and the responses will be managed through and documented in the e-CRF.

15.5 USE OF COMPUTERIZED SYSTEMS

Computerized systems used during the different steps of the study are:

- For data management activities, the CRO in charge of the study will use a RDC Oracle Clinical system. The whole data will be transferred from the CRO database to the Sponsor Oracle Clinical Database.
- For pharmacokinetic activities, NONMEM V
- For statistical activities, SAS version 8.2 or higher.
- The Sponsor pharmacovigilance team will manage SAE information in the Sponsor Clintrace database.
- Part 11 compliant document management system for clinical documentation activities.

16 ADMINISTRATIVE RULES

16.1 CURRICULUM VITAE

A current copy of the curriculum vitae describing the experience, qualification and training of each Investigator and Sub-Investigator will be provided to the Sponsor prior to the beginning of the Clinical Trial.

16.2 RECORD RETENTION IN STUDY SITES (S)

The Investigator must maintain confidential all study documentation, and take measures to prevent accidental or premature destruction of these documents.

It is recommended that the Investigator retain the study documents at least fifteen (15) years after the completion or discontinuation of the Clinical Trial.

However, applicable regulatory requirements should be taken into account in the event that a longer period is required.

The Investigator must notify the Sponsor prior to destroying any study essential documents following the Clinical Trial completion or discontinuation.

If the Investigator's personal situation is such that archiving can no longer be ensured by him/her, the Investigator shall inform the Sponsor and the relevant records shall be transferred to a mutually agreed upon designee.

17 CONFIDENTIALITY

All information disclosed or provided by the Sponsor (or any company/institution acting on their behalf), or produced during the Clinical Trial, including, but not limited to, the Clinical Trial Protocol, the e-CRFs, the Investigator's Brochure and the results obtained during the course of the Clinical Trial, is confidential, prior to the publication of results. The Investigator and any person under his/her authority agrees to undertake to keep confidential and not to disclose the information to any third party without the prior written approval of the Sponsor.

However, the submission of this Clinical Trial Protocol and other necessary documentation to the Ethics Committee (IRB/IEC) is expressly permitted, the IRB/IEC members having the same obligation of confidentiality.

The Sub-Investigators shall be bound by the same obligation as the Investigator. The Investigator shall inform the Sub-Investigators of the confidential nature of the Clinical Trial.

The Investigator and the Sub-Investigators shall use the information solely for the purposes of the Clinical Trial, to the exclusion of any use for their own or for a third party's account.

18 PROPERTY RIGHTS

All information, documents and Investigational Product provided by the Sponsor or its designee are and remain the sole property of the Sponsor.

The Investigator shall not mention any information or the Product in any application for a patent or for any other intellectual property rights.

All the results, data, documents and inventions, which arise directly or indirectly from the Clinical Trial in any form, shall be the immediate and exclusive property of the Sponsor.

The Sponsor may use or exploit all the results at its own discretion, without any limitation to its property right (territory, field, continuance). The Sponsor shall be under no obligation to patent, develop, market or otherwise use the results of the Clinical Trial.

As the case may be, the Investigator and/or the Sub-Investigators shall provide all assistance required by the Sponsor, at the Sponsor's expense, for obtaining and defending any patent, including signature of legal documents.

19 DATA PROTECTION

The patient's personal data and Investigator's personal data which may be included in the Sponsor database shall be treated in compliance with all applicable laws and regulations;

When archiving or processing personal data pertaining to the Investigator and/or to the patients, the Sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

20 INSURANCE COMPENSATION

The Sponsor certifies that it has taken out a liability insurance policy covering all clinical trials under its sponsorship. This insurance policy is in accordance with local laws and requirements. The insurance of the Sponsor does not relieve the Investigator and the collaborators from maintaining their own liability insurance policy.

An insurance certificate will be provided to the Ethics committees/IRB or Health Authorities in countries requiring this document.

21 SPONSOR AUDITS AND INSPECTIONS BY REGULATORY AGENCIES

For the purpose of ensuring compliance with the Clinical Trial Protocol, Good Clinical Practice and applicable regulatory requirements, the Investigator should permit auditing by or on the behalf of the Sponsor and inspection by regulatory authorities.

The Investigator agrees to allow the auditors/inspectors to have direct access to his/her study records for review, being understood that these personnel is bound by professional secrecy, and as such will not disclose any personal identity or personal medical information.

The Investigator will make every effort to help with the performance of the audits and inspections, giving access to all necessary facilities, data, and documents.

As soon as the Investigator is notified of a planned inspection by the authorities, he will inform the Sponsor and authorize the Sponsor to participate in this inspection.

The confidentiality of the data verified and the protection of the patients should be respected during these inspections.

Any result and information arising from the inspections by the regulatory authorities will be immediately communicated by the Investigator to the Sponsor.

The Investigator shall take appropriate measures required by the Sponsor or Sponsor representative to take corrective actions for all problems found during the audit or inspections.

22 PREMATURE DISCONTINUATION OF THE STUDY OR PREMATURE CLOSE-OUT OF A SITE

22.1 DECIDED BY THE SPONSOR IN THE FOLLOWING CASES:

- If the information on the product leads to doubt as to the benefit/risk ratio;
- If the Investigator has received from the Sponsor all Investigational Product, means and information necessary to perform the Clinical Trial and has not included any patient after a reasonable period of time mutually agreed upon;
- In the event of breach by the Investigator of a fundamental obligation under this agreement, including but not limited to breach of the Clinical Trial Protocol, breach of the applicable laws and regulations or breach of the ICH guidelines for Good Clinical Practice;
- If the total number of patients are included earlier than expected;

In any case the Sponsor or Sponsor representative will notify the Investigator of its decision by written notice.

22.2 DECIDED BY THE INVESTIGATOR

The Investigator must notify (30 days' prior notice) the Sponsor or Sponsor representative of his/her decision and give the reason in writing.

In all cases (decided by the Sponsor or by the Investigator), the appropriate Ethics Committee(s) (IRB/IEC) and Health Authorities should be informed according to applicable regulatory requirements.

22.3 DECIDED BY THE STEERING COMMITTEE

A decision to stop the overall recruitment in the study and/or study treatment in all patients could be taken by the Steering Committee following the recommendation of the Data Monitoring Committee on safety aspects of the study (see section 6.3.3). Stopping guidance is defined prior to the study start.

23 CLINICAL TRIAL RESULTS

The Sponsor will be responsible for preparing a Clinical Study Report and to provide a summary of study results to Investigator.

When the data from all investigational sites have been fully analyzed by the Sponsor, the latter will communicate the results of the Clinical Trial to the Investigator(s).

24 PUBLICATIONS AND COMMUNICATIONS

The Investigator undertakes not to make any publication or release pertaining to the Study and/or results of the Study the Sponsor's prior written consent, being understood that the Sponsor will not unreasonably withhold its approval.

The Sponsor agrees that, consistent with scientific standards, first presentation or publication of the results of the Study shall be made only as part of a publication of the results obtained by all sites performing the Protocol. However, if no multicenter publication has occurred within twelve (12) months of the completion of this Study at all sites, the Investigator shall have the right to publish or present independently the results of this Study patient to the review procedure set forth herein (see section 6.3.1). The Investigator shall provide the Sponsor with a copy of any such presentation or publication derived from the Study for review and comment at least thirty (30) days in advance of any presentation or submission for publication. In addition, if requested by the Sponsor, any presentation or submission for publication shall be delayed for a limited time, not to exceed ninety (90) days, to allow for filing of a patent application or such other measures as the Sponsor deems appropriate to establish and preserve its proprietary rights. The Investigator shall not use the name(s) of the Sponsor and/or its employees in advertising or promotional material or publication without the prior written consent of the Sponsor. The Sponsor shall not use the name(s) of the Investigator and/or the collaborators in advertising or promotional material or publication without having received his/her and/or their prior written consent(s).

The sponsor has the right at any time to publish the results of the study.

25 CLINICAL TRIAL PROTOCOL AMENDMENTS

All appendices attached hereto and referred to herein are made part of this Clinical Trial Protocol.

The Investigator should not implement any deviation from, or changes of the Clinical Trial Protocol without agreement by the Sponsor and prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to Clinical Trial Patients, or when the change(s) involves only logistical or administrative aspects of the trial. Any change agreed upon will be recorded in writing, the written amendment will be signed by the Investigator and by the Sponsor and the signed amendment will be filed with this Clinical Trial Protocol.

Any amendment to the Clinical Trial Protocol requires written approval/favorable opinion by the Ethics Committee (IRB/IEC) prior to its implementation, unless there are overriding safety reasons.

In some instances, an amendment may require a change to the Informed Consent Form. The Investigator must receive an IRB/IEC approval/favorable opinion concerning the revised Informed Consent Form prior to implementation of the change.

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27 APPENDICES

Appendix A ECOG (Eastern Cooperative Oncology Group) PERFORMANCE STATUS*

GRADE	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

* As published in Am. J. Clin. Oncol.: Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

Appendix B Table of Critical Creatinine Values corresponding to a creatinine clearance of 30mL/min (Cockroft-Gault Formula)

The serum creatinine clearance (CLCR, expressed as mL/min), is yielded by the Cockroft and Gault formulas, relating serum creatinine, with age (expressed as years) and body weight (expressed as Kg).

According to the units used for expressing serum creatinine (micromoles/L, or mg/dL) and the gender of patients, the formula is as follows:

$$Cl_{CR} \text{ for men : } \frac{\textbf{(140 - age) x (weight)}}{\textbf{0.814 x (creatinine concentration, µmol/L)}}$$

$$Cl_{CR} \text{ for women : } \frac{\textbf{140 - age) x (weight)}}{\textbf{0.814 x (creatinine concentration, µmol/L)}} \textbf{ x 0.85}$$

$$Cl_{CR} \text{ for men : } \frac{\textbf{(140 - age) x (weight)}}{\textbf{72 x (creatinine concentration, mg/dL)}}$$

$$Cl_{CR} \text{ for women : } \frac{\textbf{(140 - age) x (weight)}}{\textbf{72 x (creatinine concentration, mg/dL)}} \textbf{ x 0.85}$$

The following tables provide the creatinine value corresponding to a creatinine clearance of 30 mL/min according to age, sex and body weight.

Relation between age, body weight, serum creatinine, and creatinine clearance of 30 mL/min

		Serum Creatinine			
		Men		Women	
Age	Body Weight (kg)	mg/dL	µmol/L	mg/dL	µmol/L
20	40	2.2	198	1.9	168
	50	2.8	247	2.4	210
	60	3.3	296	2.8	252
	70	3.9	346	3.3	294
	80	4.4	395	3.8	336
	90	5.0	444	4.3	378
	100	5.6	494	4.7	420
	110	6.1	543	5.2	462
	120	6.7	593	5.7	504
	130	7.2	642	6.1	546
	140	7.8	691	6.6	588
	150	8.3	741	7.1	630
25	40	2.1	189	1.8	161
	50	2.7	237	2.3	201
	60	3.2	284	2.7	241
	70	3.7	331	3.2	282
	80	4.3	379	3.6	322
	90	4.8	426	4.1	362
	100	5.3	473	4.5	402
	110	5.9	521	5.0	442
	120	6.4	568	5.4	483
	130	6.9	615	5.9	523
	140	7.5	663	6.3	563
	150	8.0	710	6.8	603
30	40	2.0	181	1.7	154
	50	2.5	226	2.2	192
	60	3.1	272	2.6	231
	70	3.6	317	3.0	269
	80	4.1	362	3.5	308
	90	4.6	407	3.9	346
	100	5.1	453	4.3	385
	110	5.6	498	4.8	423
	120	6.1	543	5.2	462
	130	6.6	588	5.6	500
	140	7.1	634	6.1	539
	150	7.6	679	6.5	577
35	40	1.9	173	1.7	147
	50	2.4	216	2.1	184
	60	2.9	259	2.5	220
	70	3.4	302	2.9	257
	80	3.9	346	3.3	294
	90	4.4	389	3.7	331
	100	4.9	432	4.1	367
	110	5.3	475	4.5	404
	120	5.8	519	5.0	441
	130	6.3	562	5.4	477
	140	6.8	605	5.8	514
	150	7.3	648	6.2	551

Relation between age, body weight, serum creatinine, and creatinine clearance of 30 mL/min

		Serum Creatinine			
		Men		Women	
Age	Body Weight (kg)	mg/dL	µmol/L	mg/dL	µmol/L
40	40	1.9	165	1.6	140
	50	2.3	206	2.0	175
	60	2.8	247	2.4	210
	70	3.2	288	2.8	245
	80	3.7	329	3.1	280
	90	4.2	370	3.5	315
	100	4.6	412	3.9	350
	110	5.1	453	4.3	385
	120	5.6	494	4.7	420
	130	6.0	535	5.1	455
	140	6.5	576	5.5	490
	150	6.9	617	5.9	525
45	40	1.8	156	1.5	133
	50	2.2	195	1.9	166
	60	2.6	235	2.2	199
	70	3.1	274	2.6	233
	80	3.5	313	3.0	266
	90	4.0	352	3.4	299
	100	4.4	391	3.7	332
	110	4.8	430	4.1	366
	120	5.3	469	4.5	399
	130	5.7	508	4.9	432
	140	6.2	547	5.2	465
	150	6.6	586	5.6	498
50	40	1.7	148	1.4	126
	50	2.1	185	1.8	157
	60	2.5	222	2.1	189
	70	2.9	259	2.5	220
	80	3.3	296	2.8	252
	90	3.8	333	3.2	283
	100	4.2	370	3.5	315
	110	4.6	407	3.9	346
	120	5.0	444	4.3	378
	130	5.4	481	4.6	409
	140	5.8	519	5.0	441
	150	6.3	556	5.3	472
55	40	1.6	140	1.3	119
	50	2.0	175	1.7	149
	60	2.4	210	2.0	178
	70	2.8	245	2.3	208
	80	3.1	280	2.7	238
	90	3.5	315	3.0	268
	100	3.9	350	3.3	297
	110	4.3	385	3.7	327
	120	4.7	420	4.0	357
	130	5.1	455	4.3	387
	140	5.5	490	4.7	416
	150	5.9	525	5.0	446

Relation between age, body weight, serum creatinine, and creatinine clearance of 30 mL/min

		Serum Creatinine			
		Men		Women	
Age	Body Weight (kg)	mg/dL	µmol/L	mg/dL	µmol/L
60	40	1.5	132	1.3	105
	50	1.9	165	1.6	131
	60	2.2	198	1.9	157
	70	2.6	230	2.2	184
	80	3.0	263	2.5	210
	90	3.3	296	2.8	236
	100	3.7	329	3.1	262
	110	4.1	362	3.5	289
	120	4.4	395	3.8	315
	130	4.8	428	4.1	364
	140	5.2	461	4.4	392
	150	5.6	494	4.7	420
65	40	1.4	123	1.2	105
	50	1.7	154	1.5	131
	60	2.1	185	1.8	157
	70	2.4	216	2.1	184
	80	2.8	247	2.4	210
	90	3.1	278	2.7	236
	100	3.5	309	3.0	262
	110	3.8	340	3.2	289
	120	4.2	370	3.5	315
	130	4.5	401	3.8	341
	140	4.9	432	4.1	367
	150	5.2	463	4.4	367
70	40	1.3	115	1.1	98
	50	1.6	144	1.4	122
	60	1.9	173	1.7	147
	70	2.3	202	1.9	171
	80	2.6	230	2.2	196
	90	2.9	259	2.5	220
	100	3.2	288	2.8	245
	110	3.6	317	3.0	269
	120	3.9	346	3.3	294
	130	4.2	374	3.6	318
	140	4.5	403	3.9	343
	150	4.9	432	4.1	367
75	40	1.2	107	1.0	91
	50	1.5	134	1.3	114
	60	1.8	160	1.5	136
	70	2.1	187	1.8	159
	80	2.4	214	2.0	182
	90	2.7	241	2.3	205
	100	3.0	267	2.6	227
	110	3.3	294	2.8	250
	120	3.6	321	3.1	273
	130	3.9	348	3.3	296
	140	4.2	374	3.6	318
	150	4.5	401	3.8	341

Relation between age, body weight, serum creatinine, and creatinine clearance of 30 mL/min

		Serum Creatinine			
		Men		Women	
Age	Body Weight (kg)	mg/dL	µmol/L	mg/dL	µmol/L
80	40	1.1	99	0.9	84
	50	1.4	123	1.2	105
	60	1.7	148	1.4	126
	70	1.9	173	1.7	147
	80	2.2	198	1.9	168
	90	2.5	222	2.1	189
	100	2.8	247	2.4	210
	110	3.1	272	2.6	231
	120	3.3	296	2.8	252
	130	3.6	321	3.1	273
	140	3.9	346	3.3	294
	150	4.2	370	3.5	315
85	40	1.0	91	0.9	77
	50	1.3	113	1.1	96
	60	1.5	136	1.3	115
	70	1.8	158	1.5	135
	80	2.0	181	1.7	154
	90	2.3	204	1.9	173
	100	2.5	226	2.2	192
	110	2.8	249	2.4	212
	120	3.1	272	2.6	231
	130	3.3	294	2.8	250
	140	3.6	317	3.0	269
	150	3.8	340	3.2	289
90	40	0.9	82	0.8	70
	50	1.2	103	1.0	87
	60	1.4	123	1.2	105
	70	1.6	144	1.4	122
	80	1.9	165	1.6	140
	90	2.1	185	1.8	157
	100	2.3	206	2.0	175
	110	2.5	226	2.2	192
	120	2.8	247	2.4	210
	130	3.0	267	2.6	227
	140	3.2	288	2.8	245
	150	3.5	309	3.0	262
95	40	0.8	74	0.7	63
	50	1.0	93	0.9	79
	60	1.3	111	1.1	94
	70	1.5	130	1.2	110
	80	1.7	148	1.4	126
	90	1.9	167	1.6	142
	100	2.1	185	1.8	157
	110	2.3	204	1.9	173
	120	2.5	222	2.1	189
	130	2.7	241	2.3	205
	140	2.9	259	2.5	220
	150	3.1	278	2.7	236

Relation between age, body weight, serum creatinine, and creatinine clearance of 30 mL/min

		Serum Creatinine			
		Men		Women	
Age	Body Weight (kg)	mg/dL	µmol/L	mg/dL	µmol/L
100	40	0.7	66	0.6	56
	50	0.9	82	0.8	70
	60	1.1	99	0.9	84
	70	1.3	115	1.1	98
	80	1.5	132	1.3	112
	90	1.7	148	1.4	126
	100	1.9	165	1.6	140
	110	2.0	181	1.7	154
	120	2.2	198	1.9	168
	130	2.4	214	2.0	182
	140	2.6	230	2.2	196
	150	2.8	247	2.4	210

Appendix C PHARMACOKINETICS HANDLING PROCEDURE

The accuracy of AVE5026 concentration measurements in plasma is entirely dependent on the quality of phlebotomy, plasma preparation and storage.

In all cases, the actual date and time of the blood sampling and of the first IP injection at D1 and the three preceding injections of study drug at Month 1 visit will be accurately recorded on the requisition forms..

The following procedure should be applied by centers participating in the pharmacokinetic sampling:

- Collect 2.7 mL of blood using BD vacutainer tubes containing 3.2 % citrate (0.109 mol/L) for each sampling time point. Blood collection for PK samples will be performed after the first drops of blood are discarded, in order to avoid collection of blood rich activated coagulation factors present near the cannula. Then, gently invert tube at least 3 to 5 times permitting specimen to mix with tubes anticoagulant.
- The exact time of sample collection should be recorded on the Requisition Form.
- Within 60 minutes of collection, incubate sample in an ice/water bath for 15 minutes and then centrifuge at 3000 g for 5 minutes at room temperature. If 3000g is not available, 2200g is equivalent.
- Immediately following the centrifugation, transfer the top layer of human plasma into the number of pre-labeled storage tubes; minimum plasma volume of 0.5 mL per tube, being careful not to transfer blood cells.
- All of the resulting plasma (approx. 1.5 mL) will then be transferred into 2 polypropylene screw-cap tubes PK AVE5026 Xa, PK AVE5026 IIa ; about >0.5 mL plasma per tube.
- Ensure that all sample tubes are clearly and appropriately labeled.
- Immediately cap tubes and freeze the plasma in an upright position at -20°C for storage. Samples must be stored on dry ice if freezer is not immediately available.

Appendix D GENOMIC PREDICTORS OF VENOUS THROMBOEMBOLISM (VTE) IN PATIENTS WITH CANCER TREATED WITH CHEMOTHERAPY: the EFC6521 genomic sub-study

[redacted] **U.S.A.**

BACKGROUND AND RATIONALE

VTE is the second leading cause of death in cancer patients. The probability of death in cancer patients with VTE is higher than that of patients with cancer alone or VTE alone. According to a population based study by Sorenson et al., the 1-year survival rate in patients diagnosed with cancer at time of VTE is 12% compared to 36% in patients with cancer that have no VTE. Risk factors for VTE in cancer patients include surgery, hospitalization, and chemotherapy.

The underlying mechanisms of VTE in cancer patients are not completely understood. Cancer patients who develop VTE typically do not demonstrate findings of any particular hypercoagulable state; however, putative mechanisms include excess Tissue Factor (TF) or another cancer procoagulant produced by tumor cells, as well as increased platelet activation by tumor cells, promoting VTE. In addition to VTE, recent studies from several laboratories have linked malignant transformation (oncogenesis), tumor angiogenesis and metastasis to the generation of clotting intermediates (e.g. TF, factor Xa and thrombin) (Rickles FR, Pathophysiol Haemost Thromb. 2006;35(1-2):103-10). Randomized controlled studies suggest that prophylaxis with low molecular weight heparin versus placebo or coumadin may result in improved clinical outcomes in patients with advanced solid tumor malignancies (Kakkar AK, et al J Clin Oncol. 2004 May 15;22(10):1944-8; Lee AY, et al. J Clin Oncol. 2005 Apr 1;23(10):2123-9.).

Protocol EFC6521 represents a new initiative to test whether the use of a novel ultra low molecular weight heparin (AVE5026) can prevent the occurrence of VTE associated with chemotherapy. When thrombosis occurs secondary to the use of chemotherapy, no clear mechanism of action has yet been identified. Overall, the expected event rate of symptomatic VTE is thought to be 4% in the placebo arm for this study. The study will enroll 3200 patients.

Regardless of the outcomes of this study, identifying predictive factors for VTE in this population will be critically important. A predictive model for risk of VTE from chemotherapy may support the extrapolation of this data into other patient populations including patients with other tumor types and/or earlier stages of disease (i.e. adjuvant chemotherapy settings). In addition, it is possible in a selected patient population that AVE5026 demonstrates a survival advantage that may not be seen in an unselected patient population.

The challenge is in identifying a priori the most likely source for such a predictive model. In the past, attempts at individual candidate biomarkers have not yielded positive results. However, recently we have shown that patterns of gene expression in RNA isolated from peripheral blood obtained from patients with antiphospholipid syndrome (APS) another thrombogenic condition, can predict for patients at “high risk” for thrombotic events (Potti A, et al. Blood. 2006 Feb 15;107(4):1391-6). Specifically, gene expression patterns that characterize APS as well as

thrombosis in the presence of antiphospholipid antibody (aPLA) were identified by hierarchical clustering and binary regression methods. Gene-expression profiles identified and predicted individuals with APS from patients with VTE without aPLA, as well as those patients with aPLA at high risk for thrombotic events. We propose to extend these observations to patients with cancer receiving chemotherapy with and without subsequent VTE, in other words, to determine if gene expression patterns can characterize cancer patients who subsequently develop thrombosis on chemotherapy from similarly matched patients who do not develop thrombosis.

HYPOTHESES

Patients with advanced cancer who subsequently develop a symptomatic VTE on chemotherapy will have a distinct gene expression profile from similarly matched patients with cancer and chemotherapy who do not develop VTE. Gene expression profiles from peripheral blood collected from patients with locally advanced or metastatic cancer may have prognostic significance.

AIM

Identify a metagene predictor for VTE in patients with cancer receiving systemic chemotherapy using peripheral blood PAXgene samples for gene expression analysis.

PRELIMINARY DATA

Preliminary microarray analyses of a subset of patients with non-small cell lung cancer (NSCLC) as well as patients with ovarian cancer have been performed, and we have determined that patients with and without VTE had distinct gene expression profiles. Also, biologically relevant genes within the metagene distinguished the two comparator groups (VTE versus no VTE), including p53, H-ras, Factor X, and tissue factor. We seek to extent this preliminary data to other tumor types and patient populations with high VTE risk as well as to expand our study to use peripheral blood samples to create a metagene for prediction of VTE in cancer patients. This would be a more scalable tool for clinical practice and study.

STUDY DESIGN AND METHODOLOGY

Study Methods

The following procedures should be applied in patients who have consented to participate in EFC6521 and who voluntarily have given written informed consent for genomic sub-study.

- At a scheduled blood sample collection time on Day 1 (day of randomization), approximately 5 ml of peripheral whole blood will be collected into two 2.5 mL PAXgene™ Blood RNA tubes. Then the tubes need to be gently inverted 8-10 times and rested at room temperature for 2-72 hours before transferring to a freezer (-20°C).
- Each patient will be assigned a sub-study number that will be recorded on the tubes as well as on a requisition form. Each tube will be labeled with the date of draw and patient study number. The sample collection form will contain both the patient study identification number and their sub-study number.

- Samples will be centralized from sites to a central laboratory (and then shipped on a regular basis to a central location at (USA). The samples will be stored by sub-study number and microarray analysis will be performed in selected samples after study completion. All samples will be destroyed no later than 10 years from the date the sample is collected.

Study Design

Specimens from patients with cancer and VTE, and a similarly sized population of case controlled matched patients with cancer and no VTE will undergo microarray laboratory analyses. Half of the specimens (1/2 N) from patients with cancer and VTE, and half of the specimens from patients with cancer and no VTE will be used for testing for the training subset; the remaining specimens will constitute the validation sample.

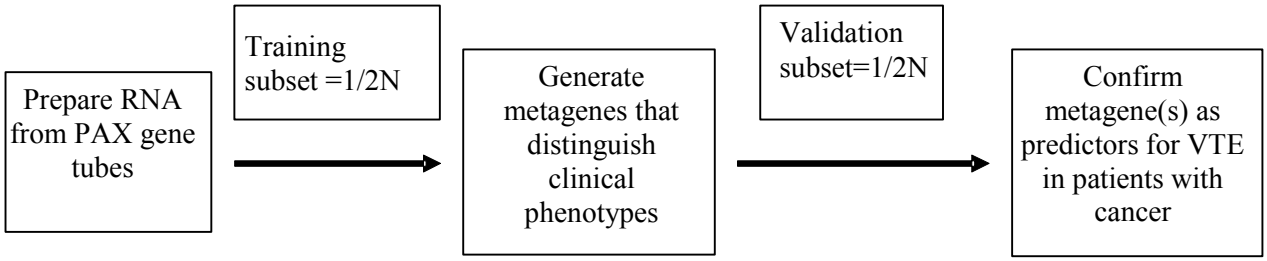

Figure 1 : Proposed study design for a nested case controlled study using patients with VTE, half of which will be in training set and half will be in a validation set

Additional samples may be tested to explore the prognostic significance of gene expression profiles in this patient population.

Specimen storage

On arrival at the (USA), samples will be stored at -80°C under the supervision, rules and regulations of .

SELECTION OF SUBJECTS

Whole blood sample collection for genomic profiling will be performed at EFC6521 sites that permit genomic studies to be conducted in compliance with all applicable laws, rules, and regulations. Subjects enrolled in EFC6521 at sites that have appropriate Institutional Review Board/Ethics Committee approval will be asked to participate voluntarily in the genomic research sub-study. Subjects will be asked to read, understand, and sign an informed consent form designed for the purpose of collecting a one time blood sample for genomic research. Subjects will be informed that they will not be excluded from the EFC6521 study if they do not wish to participate in the Genomic Blood Sample Sub-study.

ETHICS

The Genomic Blood Sample Sub-study can only be implemented where consistent with local law and only when the local IRB/Ethics Committee and Clinical Investigator have agreed to allow study subjects to participate in this portion of the study.

WITHDRAWAL OF SUBJECTS FROM THE SUBSTUDY

Subjects have, at any time, the option to withdraw consent for participation from the Genomic Blood Sample Sub-study independent of the EFC6521 protocol. Subjects who wish to withdraw their consent from the Genomic Blood Sample Sub-study (i.e., have their blood samples destroyed) should contact the investigator in writing. The investigator will fax a Sample Withdrawal Form to the country sponsor's representative. Upon receipt of the Sample Withdrawal Form, the country sponsor's representative will forward the sample withdrawal form either to [redacted], depending on the location of the samples. [redacted] will then destroy all of the remaining blood sample and material obtained from the patient's blood sample. A copy of the genetic sample withdrawal form is provided in Appendix E. After all patient's samples have been destroyed, [redacted] will provide the investigator with confirmation of the samples destruction by sending back the genetic withdrawal form dully completed.

STATISTICAL CONSIDERATIONS

Sample Size Justification

No pre-determined number of study subjects is required for this genomic analysis. This is an exploratory analysis that will depend both upon the number of patients enrolled onto the sub-study as well as the event rate for VTE in this population.

Genetic analysis

The genetic analysis will be performed at [redacted] USA.

Scientists performing the genetic analysis will be blinded to the patient identity as well as to the EFC6521 patient identification number. Clinical demographics and outcomes will be associated with genomic profiles for analyses only using the sub-study number.

ADMINISTRATION

Informed Consent

An informed consent independent of the EFC6521 consent form describes the rationale, objectives, study methodology and data analysis for this sub-study.

Confidentiality

[redacted] will ensure that the confidentiality of research subjects who volunteer to participate is maintained and that the genomic analyses are conducted in compliance with all applicable laws, rules and regulations.

Appendix E Sample withdrawal procedures of the EFC6521 Genomic Sub-study

FAX TRANSMITTAL SHEET

FAX THIS COMPLETED PAGE TO:

COUNTRY SPONSOR'S REPRESENTATIVE

WITHDRAWAL OF PERMISSION FOR USE OF SPECIMENS OF THE EFC6521 genomic sub-study

This section is to be completed by either the investigator or the coordinator at the institution.

The study subject indicated below (only identify the study subject using the sub-study subject number; **DO NOT** provide any other identifying information such as the study subject's name or social security number) initially provided informed consent for his/her samples to be used for genomic research. After discussion with a study staff member at our institution, he/she has now indicated that he/she wants to withdraw consent for future genomic research and have his/her sample destroyed.

PROTOCOL NUMBER: EFC6521 Genomic Sub-Study

EFC6521 SUB-STUDY SUBJECT NUMBER	
INVESTIGATOR NAME	
INVESTIGATOR FAX	
INVESTIGATOR SIGNATURE	

This section is to be completed by [redacted] and faxed back to the investigator.

CONFIRMATION OF GENETIC SAMPLE DESTRUCTION

The blood and related material derived from the blood sample obtained from the study subject indicated above has been destroyed. Please notify the study subject that this has occurred.

VERIFIED BY: _____ **DATE:**_____

PRINT NAME: _____