FDA Briefing Document
Oncologic Drugs Advisory Committee Meeting
June 20, 2012

NDA 203213
Semuloparin sodium
Sanofi-aventis

DISCLAIMER STATEMENT

The attached documents contain background material prepared by the Food and Drug Administration (FDA) for the panel members of the Advisory Committee (AC). The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We are presenting the semuloparin NDA with the Applicant's proposed indication, "prophylaxis of venous thromboembolism (VTE) in patients receiving chemotherapy for locally advanced or metastatic solid tumors," and the Applicant-proposed revised indication, "prophylaxis of venous thromboembolism (VTE) in patients receiving chemotherapy for locally advanced or metastatic pancreatic or lung cancer or for locally advanced or metastatic solid tumors with a VTE risk score ≥3" to this Advisory Committee in order to gain the Committee's insights and opinions. This background package may not contain all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all internal reviews have been finalized. The final determination may be affected by issues not discussed at this meeting.

This document is based on the Applicant's original NDA submission and subsequent information as provided up to March 15, 2012.

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List of Abbreviations

AE	Adverse Event
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
BMI	Body Mass Index
CBC	Complete Blood Count
CI	Confidence Interval
CIAC	Central Independent Adjudication Committee
CIF	Cumulative Incidence Functions
CRBE	Clinically Relevant Bleeding Events
CrCl	Creatinine Clearance
CRF	Case Report Form
CRNMB	Clinically Relevant Nonmajor Bleeding
CUS	Compression Ultrasound
CVC	Central Venous Catheter
DVT	Deep Vein Thrombosis
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIT	Heparin-induced Thrombocytopenia
HR	Hazard Ratio
INR	International Normalized Ratio
ISTH	International Society on Thrombosis and Hemostasis
ITT	Intent-to-Treat
IV	Intravenous
LMWH	Low Molecular Weight Heparin
MB	Major Bleeding
MedDRA	Medical Dictionary for Regulatory Activities
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NCRB	Non-Clinically Relevant Bleeding
NDA	New Drug Application
NI	Noninferiority
NME	New Molecular Entity
NNT	Number Needed to Treat
ODAC	Oncologic Drugs Advisory Committee
OR	Odds Ratio
OS	Overall Survival
PE	Pulmonary Embolism
PS	Performance Status
PT	Preferred Term
QD	Daily
RR	Relative risk
SAE	Serious Adverse Event
SC	Subcutaneous
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
ULN	Upper Limit of Normal
US	Ultrasound
VKA	Vitamin K Antagonist
VQ	Ventilation-Perfusion
VTE	Venous Thromboembolism

VTEp	Venous Thromboembolism prophylaxis

1. Proposed Indication

The Applicant is seeking regular approval for the following indication:

Original: Semuloparin is indicated for "prophylaxis of venous thromboembolism (VTE) in patients receiving chemotherapy for locally advanced or metastatic solid tumors."

Revised: Semuloparin is indicated for "prophylaxis of venous thromboembolism (VTE) in patients receiving chemotherapy for locally advanced or metastatic pancreatic or lung cancer or for locally advanced or metastatic solid tumors with a VTE risk score ≥3."

2. Executive Summary

Semuloparin NDA 203213 is a low molecular weight heparin (LMWH) derived from heparin from porcine intestinal mucosa. The Applicant is seeking initial approval of this drug for the indication of prophylaxis of venous thromboembolism (VTE) in patients receiving chemotherapy for locally advanced or metastatic pancreatic or lung cancer or for locally advanced or metastatic solid tumors with a VTE risk score ≥3. The efficacy of semuloparin for this indication is based on the results of a single trial, SAVE-ONCO. SAVE-ONCO was a multinational, Phase 3, randomized, double-blind, placebo-controlled trial of 3,212 patients who were to undergo chemotherapy for locally advanced or metastatic cancer of the lung, pancreas, stomach, colon/rectum, bladder, or ovary. Patients were randomized 1:1 to receive either semuloparin 20 mg daily (QD) subcutaneously (SC) or placebo for a minimum of 3 months while receiving chemotherapy. Randomization was stratified by geographical region, location of primary site of tumor, and stage of cancer. The primary endpoint of Study SAVE-ONCO was a composite endpoint consisting of: symptomatic deep vein thrombosis (DVT), nonfatal pulmonary embolism (PE), and VTE-related death, occurring from randomization up to 3 days after the last study drug injection. Endpoint events were adjudicated and confirmed by a blinded central independent review (CIAC). The primary efficacy analysis was a time-to-event analysis with non-VTE-related death treated as a competing risk.

2.1 Efficacy

In the primary efficacy analysis of SAVE-ONCO, symptomatic VTE events were observed in 1.2% of patients in the semuloparin arm and in 3.4% of patients in the placebo arm (HR 0.36 (0.21, 0.60); $p<0.0001$). The relative risk reduction was statistically significant; the absolute risk difference was 2.2%. Although the analysis was conducted in the intent-to-treat (ITT) population, an overall 36% of patients did not complete the study treatment period of at least 3 months. Early discontinuation of patients from study treatment resulted in early censoring of a large percentage (32.5% within the first 3 months) of patient's times in the primary efficacy analysis. No difference between treatment arms was observed in the secondary endpoint, overall survival at 1 year, with 40% observed deaths in the semuloparin arm and 41.5% in the placebo arm (HR= 0.95, 95% CI [0.85, 1.05]; p= 0.31).

2.2 Safety

In Trial SAVE-ONCO, the majority of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) reflected AEs expected from concurrent chemotherapy treatment or were attributable to underlying disease and were balanced between treatment arms. SAEs (26% in both arms) occurring in ≥1% of patients included: malignant neoplasm progression, anemia, neutropenia, and febrile neutropenia. TEAEs (85% in both arms) occurring in >10% of patients included: nausea, malignant neoplasm progression, anemia, diarrhea, vomiting, neutropenia, asthenia, fatigue, decreased appetite, abdominal pain, and constipation.

Major bleeding (MB) occurred in 1.2% of patients in the semuloparin arm compared to 1.1% in the placebo arm. However, 7 patients in the semuloparin arm experienced a major bleeding event into a critical area or organ (2 pericardial, 1 intraocular, 1 splenic, and 3 intracranial), with one case of intracranial bleeding being fatal. No patients in the placebo arm experienced bleeding into a critical area or organ. Adjudicated fatal bleeding AEs occurred in 2 patients receiving semuloparin and 4 patients receiving placebo. An overall higher incidence of clinically relevant bleeding events (CRBE), as adjudicated by blinded independent review, was observed in the semuloparin arm compared to placebo arm (2.8% vs. 2.0%). These were primarily clinically relevant nonmajor bleeding events (CRNMB; 1.6% vs. 0.9%, respectively). Other adverse events that occurred in more patients in the semuloparin arm compared to placebo were: treatment-emergent bleeding AEs (20% vs. 16%), serious bleeding AEs (1.9% vs. 1.5%), and bleeding AEs leading to treatment discontinuation (2.3% vs. 1.6%), respectively.

Additional safety data from other Phase 3 studies of semuloparin for venous thromboembolism prophylaxis (VTEp) in orthopedic and general surgery patients showed that the safety profile of semuloparin, including bleeding AEs, was generally comparable to enoxaparin in the active-control trials in knee replacement, hip replacement, hip fracture surgery, and major abdominal surgery patients.

2.3 Issues with the Submission

1) The Applicant has provided a single pivotal trial for semuloparin for a new indication. The Applicant's reported results from a number of other studies in the clinical development program which included other, better-understood VTE prophylaxis indications (patients undergoing orthopedic and major abdominal surgery, including patients with cancer undergoing oncological surgery) do not provide meaningful support for the approval of semuloparin for the proposed indication. There are no LMWHs or other anticoagulants approved for the indication. Semuloparin is a new LMWH, not currently approved anywhere in the world.
2) The assessment of clinical efficacy is compromised by the early censoring (32.5% within the first 3 months), which undermines confidence in the observed results.
3) The observed clinical efficacy of semuloparin (an absolute risk reduction of 2.2%) appears to be small relative to overall mortality in the population studied.

3. Background

Semuloparin is a low molecular weight heparin (LMWH) obtained by depolymerization of heparin derived from porcine intestinal mucosa. It has an average molecular weight between 2,000 to 3,000 Daltons. Similar to other LMWHs, semuloparin acts by enhancing the activity of endogenous antithrombin, thereby accelerating the inactivation of factor Xa and thrombin, limiting the coagulation process. It has a high anti-factor Xa (anti-Xa) activity relative to anti-IIa activity. The drug is formulated as a solution for subcutaneous injection.

3.1 Prophylaxis of Venous Thromboembolism in Patients with Cancer

No drugs are currently approved for the specific indication of VTE prophylaxis in ambulatory patients with cancer undergoing chemotherapy. Medical practice guidelines in general do not recommend routine prophylactic anticoagulation in this setting in the absence of VTE diagnosis, with the exception of those receiving thalidomide- or lenalidomide-based chemotherapeutic regimens. ASCO 2008 guidelines for VTE prophylaxis in oncology patients recommend in general that patients be considered for prophylactic anticoagulation in the following clinical settings, unless otherwise contraindicated: patients who are hospitalized, patients undergoing major oncological surgery, patients receiving treatment with anti-cancer agents with increased risk of thrombogenicity (thalidomide- or lenalidomide-based chemotherapy regimens), and patients with manifest VTE (recommended for prolonged [≥6 months] anticoagulant therapy) in order to prevent recurrence. These guidelines currently do not recommend the use of prophylactic anticoagulants to improve survival in patients with cancer without manifest VTE, due to inconclusive data.

Several approved agents are available for VTE prophylaxis in a variety of treatment settings. Approved indications include, VTE prophylaxis in the orthopedic setting (patients undergoing knee and hip replacement surgery, hip fracture surgery), patients undergoing abdominal surgery, medical patients with severely restricted mobility during acute illness, patients who are at risk of developing thromboembolic disease, and extended treatment of symptomatic VTE to reduce recurrence in patients with cancer.

For each approved drug, the prescribing information (labeling) provides guidance on the indications studied, the benefits demonstrated, and general recommendations for use. The labels allow for clinician judgment to match individual patient needs with options for therapy and with safety factors to consider for each drug and each patient.

Drugs approved in the U.S. for VTE prophylaxis are listed in the following table.

Table 1: Drugs Approved in the U.S. for VTE Prophylaxis

Drug	Year	Class	Indicated Population
Heparin sodium	1939	Unfractionated heparin	Patients at risk of developing thromboembolic disease
Coumadin (warfarin sodium)	1954	Vitamin K antagonist	Patients needing DVT/PE prophylaxis
Lovenox (enoxaparin sodium)	1993	LMWH	• Knee replacement surgery • Hip replacement surgery • Abdominal surgery • Medical patients with severely restricted mobility during acute illness
Fragmin (dalteparin sodium)	1994	LMWH	• Hip replacement surgery • Abdominal surgery • Medical patients with severely restricted mobility during acute illness • Extended treatment of symptomatic VTE to reduce the recurrence in patients with cancer
Argatroban	2000	Direct Thrombin Inhibitor	Patients with heparin-induced thrombocytopenia (HIT)
Arixtra (fondaparinux sodium)	2001	Synthetic pentasaccharide Factor Xa inhibitor	• Knee replacement surgery • Hip replacement surgery • Hip fracture surgery (including extended prophylaxis) • Abdominal surgery
Iprivask (desirudin recombinant)	2003	Direct Thrombin Inhibitor	Hip replacement surgery
Xarelto (rivaroxaban)	2011	Direct Factor Xa inhibitor	• Knee replacement surgery • Hip replacement surgery

3.2 Regulatory History

The IND for semuloparin was opened in March 2006. On November 16, 2007, an End-of-Phase 2 meeting was held with the Applicant. On May 4, 2011, a pre-NDA Meeting was held for the VTE prophylaxis indication in patients with cancer. NDA 203213 was subsequently received on September 30, 2011.

On January 31, 2012 (post-submission), the Applicant submitted a revised proposed indication for semuloparin for: “prophylaxis of venous thromboembolism (VTE) in cancer patients receiving chemotherapy for locally advanced or metastatic pancreatic or lung cancer or for locally advanced or metastatic solid tumors with a VTE risk score ≥3.”

4. Clinical Studies

The Applicant's clinical development program for semuloparin is listed in the table below. SAVE-ONCO is the only trial for the indication under review. However, the following other Phase 3 studies are included here for completeness and relevance to the use of semuloparin for VTE prophylaxis.

Table 2: Phase 3 Clinical Trials of Semuloparin for VTE Prophylaxis

Trial	N	Population	Comparator	Sponsor's 1° Efficacy Findings
SAVE-ONCO EFC6521	3212	Patients receiving chemotherapy for locally advanced or metastatic solid tumors	Placebo	Met 1°EP (superiority)
SAVE-KNEE EFC10571	1150	Knee replacement surgery	Enoxaparin	Did not meet 1ºEP (superiority)
SAVE-HIP1 EFC10342	2326	Hip replacement surgery	Enoxaparin	Met 1ºEP (superiority) [Note: Proportion of patients with less than planned dosing was greater in enoxaparin arm than in semuloparin arm].
SAVE-HIP2 EFC10343	1003	Hip fracture surgery	Enoxaparin	Did not meet 1ºEP (superiority)
SAVE-ABDO EFC6520	4413	Major abdominal surgery	Enoxaparin	Did not meet 1ºEP (noninferiority)
SAVE-VEMED EFC10572	421	Acutely ill medical patients	Enoxaparin	Discontinued Early
SAVE-HIP3 EFC10636	469	Extended prophylaxis in hip fracture surgery	Placebo	Met 1ºEP(superiority)

Tx Dur= Treatment duration; 1ºEP= Primary endpoint
Reviewer's table based on information in Applicant's tables

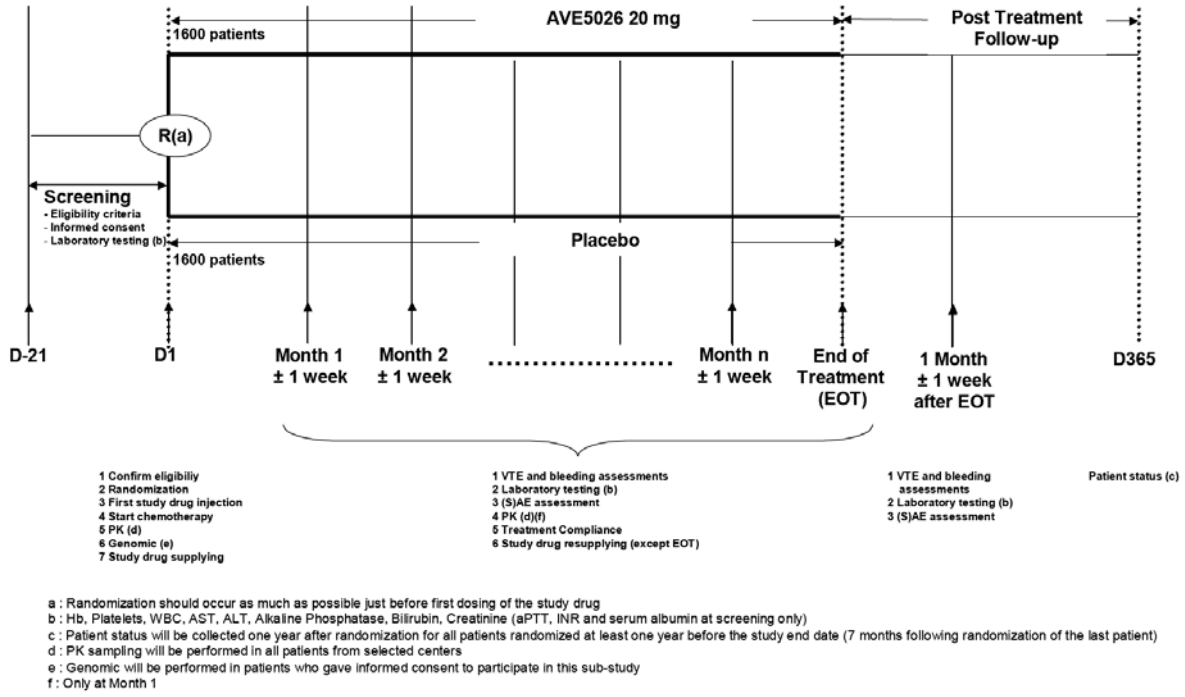
The Applicant has conducted 6 Phase 3 trials during development of semuloparin for VTE prophylaxis. A seventh trial, in acutely ill medical patients, was initiated but terminated early. By the sponsor's reports, overall, semuloparin was successful against placebo (SAVE-ONCO; SAVE-HIP3). Semuloparin failed to meet the primary efficacy endpoint of any VTE or all-cause death in 3 of the 4 completed enoxaparin-controlled trials, including in both superiority and noninferiority study designs. These were conducted in patients undergoing orthopedic surgery, including knee replacement (SAVE-KNEE) and hip fracture surgery (SAVE-HIP2), and in patients undergoing major abdominal surgery (SAVE-ABDO). One of the 4 enoxaparin-controlled trials (SAVE-HIP1) met the primary efficacy endpoint (any VTE or all-cause death), but did not meet the secondary efficacy endpoint (major VTE or all-cause death). The proportion of patients with under planned dosing was larger in the enoxaparin group (10.6%) than in the semuloparin group (4.5%) for the safety population in this study.

5. SAVE-ONCO Clinical Study

5.1 Study Design

SAVE-ONCO (EFC6521) was a multinational, randomized, double-blind, placebo-controlled trial of semuloparin vs. placebo (1:1 randomization) in patients with locally advanced or metastatic solid tumor of the lung, pancreas, stomach, colon/rectum, bladder, or ovary, who were initiating a new course of chemotherapy. The study was conducted between June 2008 and November 2010. The study schema is shown in the figure below.

Figure 1: SAVE-ONCO Study Schema



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

Applicant's figure

Randomization of patients in the study was stratified by the following factors:

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

5.2 Key Eligibility Criteria

The following were the key eligibility criteria for enrollment into SAVE-ONCO:

1) Adult (≥18 years) patients with metastatic or locally advanced solid tumor of the lung, pancreas, stomach, colon/rectum, bladder, or ovary
2) Initiating a new course of chemotherapy with a minimum intent of 3 months therapy with conventional cytotoxic agents
3) Life expectancy ≥3 months
4) ECOG performance status 0-2
5) Adequate organ function (creatinine clearance ≥30 mL/min)

6) No history of heparin-induced thrombocytopenia (HIT)
7) No clinical contraindications to anticoagulation, such as:
    a. Active or recent (<3 months) significant bleeding, including gastrointestinal bleeding or peptic ulcer
    b. History of bleeding disorder (congenital, acquired, or unexplained repeated bleeding episodes)
    c. Uncontrolled arterial hypertension (systolic blood pressure >180 mm Hg or diastolic blood pressure >110 mm Hg)
    d. Hemorrhagic stroke or recent (in the last 3 months) brain, spinal, or ophthalmic surgery
    e. Known cerebral hemorrhagic lesion
    f. Primary or metastatic tumor which is of high bleeding risk according to Investigator judgment
    g. Known structural damage or other pathologic process involving the central nervous system (e.g., brain metastases, vascular malformation)
    h. Thrombocytopenia with platelet count <100 $x10^9$/L
    i. Activated partial thromboplastin time (aPTT) >1.5x ULN or International Normalized Ratio (INR) >1.5
8) No treatment with other anti-thrombotic agents (except for chronic treatment with anti-platelet agents such as low dose aspirin [up to 325 mg/day] or clopidogrel or ticlopidine in patients with coronary artery disease) within 2 weeks prior to randomization or planned during the study such as:
    a. Parenteral anticoagulants (UFH, LMWH [e.g., enoxaparin, dalteparin, nadroparin], or other agents such as fondaparinux, bivalirudin, hirudin)
    b. Oral anticoagulants (vitamin K antagonists)
    c. Anti-GPIIb/IIIa (eptifibatide, tirofiban, abciximab)
    d. Thrombolytic agents
9) No patients requiring systemic venous thromboprophylaxis with anticoagulant or a curative anti-coagulant or thrombolytic treatment

5.3 Treatment

Patients were randomized 1:1 to receive either of the following treatments for a minimum of 3 months while receiving chemotherapy:

1) Semuloparin 20 mg SC, QD
2) Placebo SC, QD

Treatment was to continue for at least 3 months and until the change of antineoplastic regimen, unless chemotherapy was permanently discontinued earlier due to disease progression or toxicity. Treatment was to be self-administered, or administered by a caregiver or health care professional.

5.4 Efficacy Endpoints

The primary efficacy endpoint of Study SAVE-ONCO was the time-to-first occurrence of any component of a composite endpoint consisting of: symptomatic DVT (including CVC-related thrombosis), non-fatal PE, and VTE-related death (fatal PE and unexplained death), from randomization up to 3 days after the last study drug injection (on-treatment period). Efficacy events were reviewed and confirmed by a central independent adjudication committee (CIAC). Assessments were to be performed in the

presence of symptoms, and clinical diagnoses of VTE were to be confirmed within 72 hours by the modalities and criteria below:

- DVT of lower limbs:
    - Abnormal compression ultrasound (CUS); or
    - Intraluminal filling defect on venography
- DVT of upper limbs:
    - Abnormal ultrasound (US); or
    - Intraluminal filling defect on venography
      Note: Thrombosis of the central line was not considered as suspicion of DVT unless the patient presented with symptoms (e.g., swelling, erythema, pain, distal paresthesias, neck swelling, headache, congestion of subcutaneous collateral veins)
- Pulmonary Embolism (PE):
    - Intraluminal filling defect in (sub)segmental or more proximal branches on spiral CT scan; or
    - Intraluminal filling defect on pulmonary angiogram; or
    - 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 angiogram, or lung scintigram with demonstration of DVT in the lower extremities by CUS or venography
    - Fatal PE based on autopsy
- Death: All deaths were also adjudicated by the CIAC and classified as
    - VTE-related death (fatal PE or unexplained death)
    - fatal bleeding
    - other death not associated with VTE or bleeding

5.5 Monitoring

Patients in SAVE-ONCO were monitored for safety according to the schedule below:

- Routine laboratories: CBC and chemistries were collected at baseline and monthly during study treatment and at 1-month follow-up after study drug discontinuation. Platelet count was performed weekly during the 1st month of treatment.
- Adverse event (AE) data were collected through 30 days post treatment and AEs were classified by system organ class and preferred term using MedDRA version 13.1 terminology. AE severity was graded using the NCI CTCAE version 3.0.
- Vital signs, concomitant medications, transfusions, and ECOG status were also collected at monthly visits and through the 1-month follow-up visit

5.6 Safety Endpoints

All bleeding events were centrally reviewed by the CIAC. Bleeding safety analysis was performed for events occurring during the on-treatment period, from the first study drug injection up to 3 days after the last study drug injection. The criteria for clinically relevant bleeding event (CRBE) categories are listed below and are defined according to the International Society on Thrombosis and Hemostasis (ISTH) recommendation for clinical investigations of antihemostatic products in nonsurgical patients.

Clinically Relevant Bleeding Events (CRBE)

- Major bleeding (MB):

  - Fatal bleeding
  - Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, pericardial, intramuscular with compartment syndrome
  - Bleeding causing a fall of hemoglobin level of ≥2 g/dL, or leading to transfusion of 2 or more units of whole blood or red cells
- Clinically relevant non-major bleeding (CRNMB): All overt bleeding events requiring a medical intervention and not meeting any of the criteria for MB. Medical intervention was defined as any unscheduled contact with the physician due to bleeding or any specific treatment indicated for management of a bleeding episode.

All other bleeding events not meeting the criteria for the above 2 categories (MB, CRNMB) were classified as non-clinically relevant bleeding.

5.7 Statistical Analysis Plan

The primary efficacy analysis was a time-to-event analysis consisting of the time-to-first occurrence of any component of the composite primary endpoint (symptomatic DVT of the lower or upper limbs (including CVC-related thrombosis), non-fatal PE, and VTE-related death), from randomization up to 3 days after the last study drug dose. The primary efficacy analysis utilized CIAC-determined VTE events in the ITT population. Patients alive and not having experienced the primary efficacy endpoint were right censored at 3 days after the last study drug administration, regardless of whether an assessment was performed. The primary analysis was Gray's test. This analysis treated non-VTE related deaths while still being followed for VTE as competing risks. A competing risk is an event whose occurrence precludes the occurrence of a main event under investigation or greatly alters the probability of occurrence of the main event.

The trial was designed to enroll approximately 3200 patients (1600 per treatment arm) in order to have 90% power, at alpha level of 0.05, to detect a hypothesized 50% relative risk reduction (RRR) for semuloparin compared to the assumed placebo event rate of 4% for the primary efficacy measure. The primary efficacy analysis was the comparison of Cumulative Incidence Functions (CIF) between treatment groups, considering death due to other causes than VTE as a competing risk. Hazard ratio and 95% 2-sided confidence interval (CI) was calculated using the Fine and Gray regression model for CIF. The secondary endpoint of overall survival at 1 year after randomization or study end date (7 months after randomization of last patient) was to be sequentially tested at an alpha of 0.05 if the primary endpoint was significant.

5.8 Study Results

5.8.1 Patient Enrollment and Disposition

The first patient was randomized on June 6, 2008 and the last patient was randomized on May 3, 2010. The data cutoff date for efficacy was November 16, 2010.

Patient disposition in SAVE-ONCO is shown in the table below. There was an overall high rate (36%) of study treatment discontinuation. More than one third of patients in the study did not complete the study treatment period (minimum of 3 months on study drug). Reasons provided for study treatment discontinuation are shown in the table below.

Table 3: Patient Disposition in Study SAVE-ONCO (ITT)

	Semuloparin N=1608	**Placebo N=1604**
Randomized and not treated	19 (1.2)	21 (1.3)
Treated (safety population)	1589 (98.8)	1583 (98.7)
Completed study treatment period	1029 (64.0)	988 (61.6)
Did not complete study treatment period	560 (34.8)	595 (37.1)
Reason for study treatment discontinuation		
Adverse event	255 (15.9)	280 (17.5)
Lack of efficacy	20 (1.2)	48 (3.0)
Poor compliance to protocol	36 (2.2)	41 (2.6)
Lost to follow-up	5 (0.3)	2 (0.1)
Other reason	244 (15.2)	224 (14.0)
Investigator's decision	49 (3.0)	39 (2.4)
Subject's request	195 (12.1)	185 (11.5)

Reviewer's table based on data from Applicant's tables

Overall, a large number of patients requested discontinuation of study drug prior to completing the protocol treatment period. As queried in a separate question on the case report form, 291 (18.1%) patients in the semuloparin arm and 279 (17.4%) in the placebo arm were recorded as "subject's decision to permanently discontinue the treatment." Patient request for chemotherapy discontinuation for the same period was approximately 5% in each arm.

Patient enrollment by region is displayed in the table below. Patients in North America comprised approximately 6% of the total study enrollment in SAVE-ONCO.

Table 4: SAVE-ONCO Enrollment by Region

	Semuloparin N=1608 (%)	**Placebo N=1604 (%)**
North America	102 (6.3)	99 (6.2)
South America	194 (12.1)	192 (12.0)
Western Europe	402 (25.0)	407 (25.4)
Eastern Europe	620 (38.6)	618 (38.5)
Asia	264 (16.4)	263 (16.4)
Rest of the world	26 (1.6)	25 (1.6)

Reviewer's table based on information in Applicant's tables

5.8.2 Patient Demographics and Baseline Characteristics

The demographics and baseline characteristics of patients enrolled in SAVE-ONCO, including age, gender, race, and renal status were generally well-balanced between treatment arms. Demographics and baseline characteristics of patients in Study SAVE-ONCO are shown below.

Table 5: Demographics and Baseline Characteristics of Patients in SAVE-ONCO (ITT)

	Semuloparin N=1608 (%)	**Placebo N=1604 (%)**
Age, median (range), years	60 (20-89)	60 (18-87)
Age Group, n (%)		
<65 years	1049 (65.2)	1068 (66.6)
65 to <75 years	448 (27.9)	430 (26.8)
≥75 years	111 (6.9)	106 (6.6)
Sex, n (%)		
Male	974 (60.6)	956 (59.6)
Female	634 (39.4)	648 (40.4)
Race, n (%)		
Caucasian/white	1227 (76.3)	1237 (77.1)
Asian/Oriental	280 (17.4)	279 (17.4)
Other	80 (5.0)	59 (3.7)
Black	21 (1.3)	29 (1.8)
Renal status, n (%)		
Normal	857 (53.3)	833 (51.9)
Mild RI	617 (38.4)	646 (40.3)
Moderate RI	133 (8.3)	119 (7.4)
Severe RI	0	0
Missing	1 (0.1)	6 (0.4)

Reviewer's table based on data in Applicant's tables

Patient primary tumor types and other disease characteristics are listed in the table below. The majority of patients enrolled in SAVE-ONCO had lung (37%) or colorectal (29%) cancer, with a smaller proportion of patients having cancer of the stomach (13%), ovary (12%), pancreas (8%), or bladder (2%). More than 90% of patients in this trial had an ECOG performance status of either 0 or 1.

Table 6: Disease Characteristics of Patients in Study SAVE-ONCO (ITT)

	Semuloparin N=1608 (%)	**Placebo N=1604 (%)**
Location of primary tumor		
Lung	590 (36.7)	587 (36.6)
Pancreas	127 (7.9)	128 (8.0)
Stomach	203 (12.6)	207 (12.9)
Colon/rectum	465 (28.9)	462 (28.8)
Bladder	32 (2.0)	32 (2.0)
Ovary	190 (11.8)	187 (11.7)
Uterus	0	1 (<0.1)
Paratubal	1 (<0.1)	0
Stage of cancer at study entry		
Metastatic	1105 (68.7)	1104 (68.8)
Locally advanced	500 (31.1)	499 (31.1)
Other	3 (0.2)	1 (<0.1)
Time from initial diagnosis to randomization	N=1567	N=1563
Median time (range), months	2.0 (0, 450)	1.9 (0, 291)
ECOG performance status	N=1606 (%)	N=1602 (%)
0	645 (40.2)	650 (40.6)
1	820 (51.1)	828 (51.7)
2	140 (8.7)	124 (7.7)
3	1 (<0.1)	0

Reviewer's table based on data in Applicant's tables

More than half of the patients in the trial had no additional risk factors for VTE other than cancer. Among the 43% of patients in the semuloparin arm and 42% in the placebo arm patients with additional risk factors, the distribution of these risk factors between the treatment arms was fairly well-balanced, as listed in the table below.

Table 7: Additional VTE Risk Factors of Patients in Study SAVE-ONCO (ITT)

	Semuloparin N=1608 (%)	**Placebo N=1604 (%)**
Additional risk factors for VTE[a]	685 (42.6)	672 (41.9)
Presence of central venous catheter at baseline	316 (19.7)	302 (18.8)
Obesity (BMI ≥30 kg/m²)	208 (12.9)	206 (12.8)
Age ≥75 years	111 (6.9)	106 (6.6)
Chronic respiratory failure	78 (4.9)	91 (5.7)
Venous insufficiency/varicose veins	92 (5.7)	76 (4.7)
Chronic heart failure	56 (3.5)	57 (3.6)
History of DVT	26 (1.6)	32 (2.0)
Use of oral hormone therapy	21 (1.3)	27 (1.7)
History of PE	6 (0.4)	5 (0.3)

[a]Patients may have had more than one additional risk factor

Reviewer's table based on data in Applicant's tables

Among patients having more than one additional risk factor, most had only one additional risk factor as is shown in the following table.

Table 8: Number of Additional VTE Risk Factors by Patient (ITT)

	Semuloparin N=1608 (%)	Placebo N=1604 (%)
No risk factor	923 (57.4)	932 (58.1)
1 risk factor	499 (31.0)	490 (30.5)
2 risk factors	153 (9.5)	142 (8.9)
≥3 risk factors	33 (2.1)	40 (2.5)

Reviewer's table based on data in Applicant's tables

The presence of other relevant medical conditions, such as hypertension, diabetes mellitus, coronary artery disease, myocardial infarction, peripheral arterial disease, and stroke was generally well-balanced between treatment arms, as displayed in the table below. There was a slight excess of patients with coronary artery disease other than MI and patients with diabetes mellitus in the semuloparin arm compared to the placebo arm.

Table 9: Other Medical Conditions in Patients from Study SAVE-ONCO (ITT)

	Semuloparin N=1608 (%)	Placebo N=1604 (%)
Any other medical conditions[a]	623 (38.7)	609 (38.0)
Arterial hypertension	479 (29.8)	494 (30.8)
Diabetes mellitus	215 (13.4)	181 (11.3)
Coronary artery disease (except MI)	146 (9.1)	103 (6.4)
Myocardial infarction	41 (2.5)	39 (2.4)
Peripheral arterial disease	26 (1.6)	26 (1.6)
Stroke	24 (1.5)	12 (0.7)

[a]Patients may have had more than one other medical condition

Reviewer's table based on data in Applicant's tables

For both treatment arms, the median duration of 1st chemotherapy exposure and total duration of chemotherapy exposure was 2.9 months and 3.1 months, respectively. Ninety-three percent (93%) of patients in each arm received 1 regimen, while 7% received 2 or more regimens.

Table 10: Concomitant Chemotherapy Regimens in Study SAVE-ONCO (ITT)

	Semuloparin N=1608 (%)	**Placebo N=1604 (%)**
Median total duration of chemotherapy, months (range)	3.1 (0, 20)	3.1 (0, 17)
Median duration of 1st chemotherapy, months (range)	2.9 (0, 15)	2.9 (0, 17)
Number of chemotherapy regimens	N=1587 (%)	N=1581 (%)
1 regimen	1472 (92.8)	1471 (93.0)
2 regimens	108 (6.8)	100 (6.3)
≥3 regimens	7 (0.4)	10 (0.6)
Reasons for discontinuation or change of chemotherapy	N=1580 (%)	N=1581 (%)
Completed treatment	737 (45.8)	722 (45.0)
Adverse event	236 (14.7)	237 (14.8)
Patient lost to follow-up	6 (0.4)	7 (0.4)
Patient's request	82 (5.1)	85 (5.3)
Investigator's request	49 (3.0)	50 (3.1)
Disease progression	333 (20.7)	310 (19.3)
Other reason	57 (3.5)	54 (3.4)
Ongoing	158 (9.8)	178 (11.1)

Reviewer's table based on data in Applicant's tables

Concomitant chemotherapies received by patients during the study were balanced between the treatment arms. The most common agents included platinum compounds and pyrimidine analogues.

Table 11: Concomitant Anticancer Therapies — Number of Patients (≥1% in Either Treatment Arm) by Standardized Medication Name (ITT)

Standardized Medication Name	Semuloparin N=1608 (%)	Placebo N=1604 (%)
Any concomitant anti-cancer therapy	1587 (98.7)	1581 (98.6)
Fluorouracil	444 (27.6)	453 (28.2)
Cisplatin	421 (26.2)	442 (27.6)
Carboplatin	391 (24.3)	377 (23.5)
Oxaliplatin	262 (16.3)	291 (18.1)
Paclitaxel	247 (15.4)	219 (13.7)
Folinic acid	190 (11.8)	184 (11.5)
Etoposide	189 (11.8)	216 (13.5)
Capecitabine	180 (11.2)	190 (11.8)
Gemcitabine	168 (10.4)	185 (11.5)
Irinotecan	141 (8.8)	110 (6.9)
Calcium folinate	129 (8.0)	142 (8.9)
Bevacizumab	116 (7.2)	114 (7.1)
Docetaxel	100 (6.2)	99 (6.2)
Gemcitabine hydrochloride	85 (5.3)	87 (5.4)
Vinorelbine tartrate	48 (3.0)	34 (2.1)
Doxorubicin	39 (2.4)	28 (1.7)
Epirubicin	38 (2.4)	35 (2.2)
Cyclophosphamide	36 (2.2)	40 (2.5)
Vinorelbine	36 (2.2)	43 (2.7)
Pemetrexed disodium	31 (1.9)	19 (1.2)
Mitomycin	29 (1.8)	26 (1.6)
Doxorubicin hydrochloride	28 (1.7)	28 (1.7)
Cetuximab	27 (1.7)	15 (0.9)
Pemetrexed	25 (1.6)	23 (1.4)
Irinotecan hydrochloride	22 (1.4)	21 (1.3)
Topotecan	17 (1.1)	11 (0.7)
Calcium levofolinate	13 (0.8)	20 (1.2)

Reviewer's table based on data in Applicant's tables

5.8.3 Efficacy

5.8.3.1 Primary Endpoint

Assessments were performed for VTE in the presence of symptoms. There were no assessments or adjudication beyond three days after the last dose. Patients without documented VTE had their times censored at three days after the last dose, regardless of whether an assessment was performed.

The following table shows the Applicant's primary efficacy analysis, which was confirmed by FDA analysis. The primary efficacy analysis was conducted on the intent-to-treat (ITT) population, defined as all randomized patients.

Table 12: Any VTE or VTE-related Death During the Efficacy Analysis Period per CIAC Review

	Semuloparin N=1608 (%)	**Placebo N=1604 (%)**
VTE or VTE-related death	20 (1.2%)	55 (3.4%)
Number of competing events of death	78 (4.9%)	74 (4.6%)
Hazard ratio (95% CI)	0.36 (0.21, 0.60)	
p-value*	<0.0001	

*Based on Gray's test
FDA Analysis table

The proportion of patients with primary endpoint events (any VTE or VTE-related death) was 1.2% in the semuloparin arm and 3.4% in the placebo arm. The hazard ratio for the comparison between arms was statistically significant (HR 0.36; p-value <0.0001). The number of patients with events (20 and 55 patients in the semuloparin and placebo arms, respectively) was small relative to the ITT population of 3,212 patients, with an absolute risk difference of 2.2%. All but three events were within the first 4 months. Therefore, the analysis of time to VTE or VTE-related death is essentially a comparison over the first four months. There were 28 patients (14 patients in each arm) who died during Month 1 whose times were censored in the analysis of time to VTE or VTE-related death. Additionally, there was a large amount of early censoring for time to VTE or VTE-related deaths; 33.4% and 31.5% of patient times in the semuloparin and placebo arms, respectively,(32.5% overall) were censored in the first three months; 51.2% and 49.5%, respectively, were censored in the first four months. The analysis treats the early censoring as non-informative censoring. Further details on the censored and event times are shown in the table below.

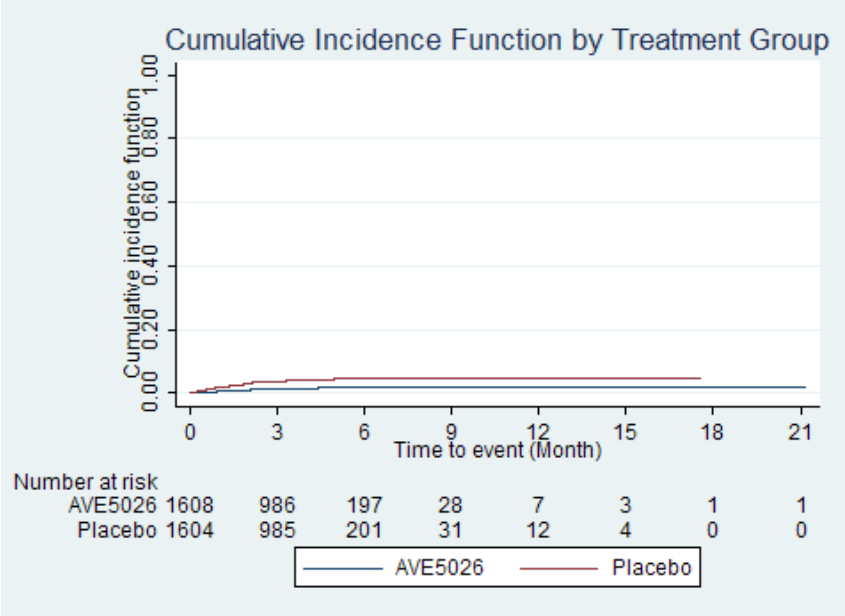
Table 13: Number of Events, Competing Risks of Death, and Censored Times by Month

Months	**Events**		**Competing Risk**		**Censored**	
	Semuloparin (N=20)	Placebo (N=55)	Semuloparin (N=78)	Placebo (N=74)	Semuloparin (N=1510)	Placebo (N=1475)
1	7	26	29	22	162	181
2	6	16	15	24	162	123
3	3	7	16	11	212	202
4	3	4	9	5	287	288
5	1	1	3	7	294	266
6	0	1	3	4	189	203
7	0	0	1	1	125	113
>7	0	0	2	0	79	99

Numbers are within the respective month.
FDA analysis table

The graph of the cumulative incidence function by treatment group is depicted below.

Figure 2: Any VTE or VTE-related Death During the Efficacy Analysis Period per CIAC Review



Note: "Number at risk" in the figure above accounts only for the number at risk among patients who are followed.

FDA Analysis figure

Sensitivity Analyses: Time-to-VTE or Any Cause Death

The Applicant performed an analysis of "VTE or any cause death" that treated the competing risks of deaths as events. This analysis uses the same follow-up as the analysis for the primary endpoint of time to VTE or VTE-related death. Patient times that were censored in the analysis of time to VTE or VTE-related deaths are also censored at the same time in this analysis of time to VTE or any cause death. The Applicant's analysis does not follow patients for any death. The numbers of patients with these events are shown below.

Table 14: Any VTE or All Cause Death During the On-Treatment Period

	Semuloparin N=1608 (%)	**Placebo N=1604 (%)**
VTE or all cause death during the on-treatment period, n (%)	98 (6.1%)	129 (8.0%)

Reviewer's table based on data in Applicant's tables

The Applicant's statistical analysis of time to VTE or all cause death (Kaplan Meier survival estimates) for semuloparin versus placebo showed an unstratified hazard ratio of 0.75 (95% CI, 0.58, 0.98) and unstratified log-rank test p-value of 0.0325.

These time-to-event analyses, treat censored times as non-informative censoring. For a patient whose time is censored, their remaining time to an event is represented equally by all patients on the same treatment arm still being followed for an event. The censoring is informative censoring when the prognosis of the patient at their censored

time is different from those patients on the same treatment arm still being followed for an event. The table below provides the Kaplan-Meier probabilities for Alive and VTE-free based on the Applicant's analysis and the Kaplan-Meier probabilities for Alive at months 1, 2, 3, and 4. The Kaplan-Meier probabilities for being alive at months 1, 2, 3, and 4 are provided in parentheses. If the patients whose times are censored in the Applicant's analysis of VTE or all cause death have similar prognosis as those patients on the same treatment arm whose follow-up continues for VTE or all cause death, then the proportion of patients at any given time who are alive and VTE-free should be less than or equal to the proportion of patients who are alive. However, as seen in Table 15, the Kaplan-Meier probabilities for alive and VTE-free, based on the Applicant's analysis, are greater than the Kaplan-Meier probabilities that a patient is alive for the semuloparin arm. For the placebo arm this is also the case except at one month. Therefore, patients who were censored in the analysis of VTE or any cause death had worse prognosis for survival than those in which follow-up continued. The same follow-up was used for VTE or VTE-related deaths as with the sponsor's analysis of VTE or any cause deaths. Therefore, the patients who were censored in the analysis of VTE or VTE-related death had worse prognosis for survival than those in which follow-up continued. This is suggestive of informative censoring in the analyses of VTE or VTE-related deaths and of VTE or any cause deaths.

Table 15: Kaplan-Meier Probabilities for Alive and VTE-free and for Alive Based on the Applicant's Analysis

	Semuloparin (N=1608)		**Placebo (N=1604)**	
	Kaplan-Meier probabilities for Alive and VTE-free	Kaplan-Meier probabilities for Alive	Kaplan-Meier probabilities for Alive and VTE-free	Kaplan-Meier probabilities for Alive
1 Month	0.976	0.973	0.968	0.974
2 Month	0.961	0.945	0.939	0.934
3 Month	0.943	0.904	0.924	0.892
4 Month	0.932	0.864	0.914	0.848

FDA Analysis table

5.8.3.2 Secondary Efficacy Endpoints

Event rates for the individual components of the primary endpoint are shown in the table below. The treatment effect was consistent across categories. However, the number of patients with events in each category was low. The percentage of patients experiencing pulmonary embolism during the efficacy analysis period was 0.6% in the semuloparin arm and 1.5% in the placebo arm. Fatal PE occurred in only 0.4% and 0.6% of patients in the semuloparin and placebo arm, respectively.

Table 16: Components of the Primary Efficacy Endpoint—VTE Type

	Semuloparin N=1608 (%)	Placebo N=1604 (%)	Odds Ratio (95% mid-p CI)
Any VTE or VTE-related Death	20 (1.2)	55 (3.4)	0.35 (0.21, 0.59)
Symptomatic DVT	11 (0.7)	34 (2.1)	0.32 (0.15, 0.62)
Upper limb	3 (0.2)	9 (0.6)	0.33 (0.07, 1.18)
Lower limb	8 (0.5)	25 (1.6)	0.32 (0.13, 0.69)
Proximal DVT	4 (0.2)	19 (1.2)	0.21 (0.06, 0.58)
Distal DVT	4 (0.2)	12 (0.7)	0.33 (0.09, 0.99)
Pulmonary Embolism (PE)	10 (0.6)	24 (1.5)	0.41 (0.19, 0.85)
Nonfatal PE	3 (0.2)	15 (0.9)	0.20 (0.05, 0.63)
Symptomatic Nonfatal PE	3 (0.2)	12 (0.7)	0.25 (0.06, 0.83)
PE detected by tumor evaluation	0	3 (0.2)	0.00 (0.00, 1.71)
Any VTE-related death	7 (0.4)	9 (0.6)	0.77 (0.27, 2.13)

FDA Analysis table

The following table and figure show 1-year survival. There was no difference in 1-year survival between the two treatment arms. The Kaplan-Meier curves are nearly superimposed upon each another (Hazard Ratio and 95% CI 0.95 (0.85 to 1.05); p= 0.31, unstratified log-rank test).

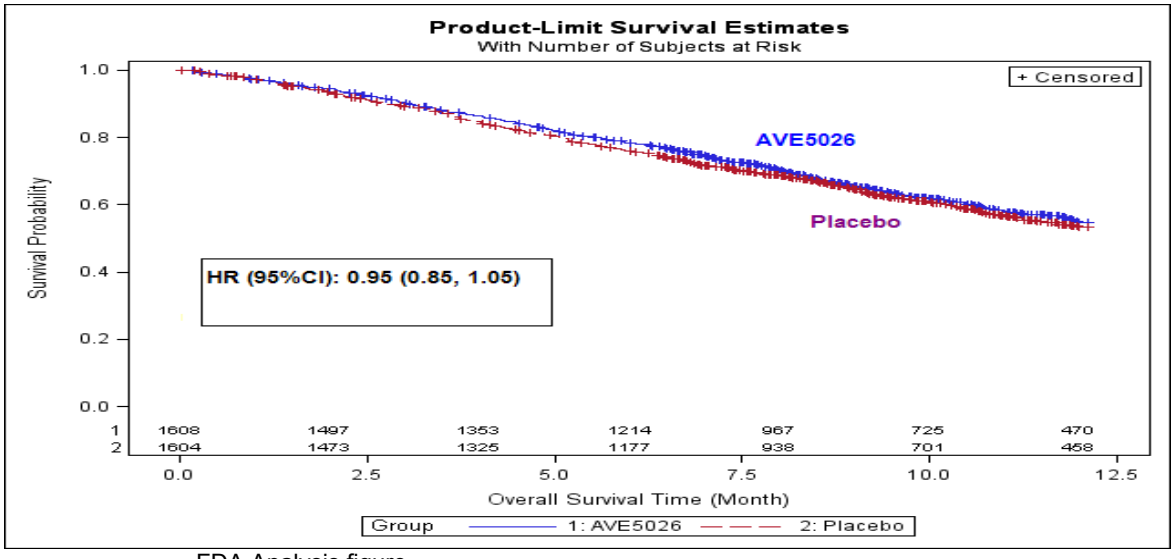
Table 17: Overall Survival ---Kaplan Meier Survival Estimates

	Semuloparin N=1608 (%)	Placebo N=1604 (%)
Number of Deaths	644 (40.0)	665 (41.5)
12 Month HR (95% CI); p-value*	0.95 (0.85, 1.05); p= 0.31	

*unstratified log-rank test

FDA Analysis table

Figure 3: Overall Survival (months)—Kaplan Meier Plots



FDA Analysis figure

5.8.3.3 Subgroup Analyses

After discussion with the Agency regarding an attempt to better identify a target population for the proposed indication, the Applicant proposed a revised treatment indication, based on post-hoc, exploratory analysis of subgroups in SAVE-ONCO who appeared to have greatest benefit. These included patients with locally advanced or metastatic pancreatic or lung cancer, and those with VTE risk score ≥3. Subgroup analyses of the primary efficacy endpoint by primary tumor type and VTE risk score are shown in the following table.

Table 18: Any VTE or VTE-related Death (Primary EP) During the Efficacy Analysis Period—Subgroup Analysis by Cancer Type and VTE Risk Score

Covariates	Semuloparin n/N (%)	Placebo n/N (%)	Hazard Ratio (95% CI)
All patients	20/1608 (1.2)	55/1604 (3.4)	0.36 (0.21, 0.60)
Location of primary tumor			
Lung	9/591 (1.5)	25/589 (4.2)	0.36 (0.17, 0.77)
Pancreas	3/126 (2.4)	14/128 (10.9)	0.22 (0.06, 0.76)
Stomach	1/204 (0.5)	4/207 (1.9)	0.25 (0.03, 2.20)
Colon/rectum	5/464 (1.1)	9/461 (2.0)	0.54 (0.18, 1.60)
Bladder	1/32 (3.1)	3/31 (9.7)	0.30 (0.03, 2.95)
Ovary	1/191 (0.5)	0/188 (0)	NA
VTE risk score			
0	3/313 (1.0)	4/301 (1.3)	0.71 (0.16, 3.15)
[1-2]	13/995 (1.3)	35/1003 (3.5)	0.37 (0.20, 0.70)
≥3	4/271 (1.5)	15/279 (5.4)	0.27 (0.09, 0.82)

FDA Analysis table

The subgroup analyses suggest that there may be sizable variation in baseline starting VTE risk between patients with different tumor types (as reflected by the proportion of patients with VTE events in the placebo group); however, the overall event rate is small and the number of patients enrolled for some tumor types is small. In SAVE-ONCO, patients in the subgroups stomach, colon/rectum, and ovary had much lower apparent baseline VTE risk, compared to patients with cancer of the pancreas, bladder, and lung.

Additional subgroup analyses of the primary endpoint, including by age, gender, race, weight, and renal function, showed generally consistency of the observed treatment effect favoring semuloparin over placebo across subgroups.

5.8.4 Safety (SAVE-ONCO)

The safety population of the SAVE-ONCO trial in patients with cancer, defined as all randomized patients who received at least one dose of study drug, consisted of 98.8% (1589) of randomized patients in the semuloparin arm and 98.7% (1583) patients in the placebo arm.

5.8.4.1 Exposure

The median durations of study treatment were 3.6 and 3.5 months in the semuloparin and placebo arms, respectively. After adjustment for periods of temporary treatment interruption for any reason, the exposure durations remained similar between groups. Durations of exposure to study drug for various categories of duration are shown in the table below.

Table 19: Exposure to Study Treatment in Study SAVE-ONCO (Safety Population)

	Semuloparin N=1589 (%)	Placebo N=1583 (%)
Median duration of study treatment, months (range)	3.6 (0, 21)	3.5 (1, 17)
Duration of study treatment, n(%)		
< 1 month	207 (13.0)	228 (14.4)
1 to <3 months	430 (27.1)	401 (25.3)
3 to <6 months	776 (48.8)	765 (48.3)
6 to <8 months	136 (8.6)	145 (9.2)
8 to <10 months	23 (1.4)	23 (1.5)
10 to <12 months	12 (0.8)	10 (0.6)
≥ 12 months	5 (0.3)	11 (0.7)

Reviewer's table based on data in Applicant's tables

5.8.4.2 Safety Overview

An overview of the treatment-emergent adverse events (TEAEs) in SAVE-ONCO is shown in the summary table below.

Table 20: Treatment-emergent Adverse Events in Study SAVE-ONCO (Safety Population)

Number of Patients with:	Semuloparin N=1589 (%)	Placebo N=1583 (%)
TEAE	1350 (85.0)	1339 (84.6)
Serious TEAE	418 (26.3)	403 (25.5)
TEAE leading to death	193 (12.1)	185 (11.7)
TEAE leading to permanent treatment discontinuation	241 (15.2)	260 (16.4)
Bleeding TEAE	320 (20.1)	254 (16.0)
Serious Bleeding TEAE	30 (1.9)	23 (1.5)
Bleeding TEAE leading to death	3 (0.2)	4 (0.3)
Bleeding TEAE leading to permanent treatment discontinuation	37 (2.3)	26 (1.6)

TE= treatment-emergent; TEAE treatment-emergent adverse event

Reviewer's table based on data in Applicant's tables

The incidence of overall treatment-emergent adverse events (TEAEs; 85% in each arm) and serious TEAEs (26% in each arm) in Trial SAVE-ONCO were similar between treatment arms. However, there were more patients with treatment-emergent bleeding AEs overall in the semuloparin group (20%) compared to the placebo group (16%), and a slightly higher incidence of serious TE bleeding AEs in the semuloparin arm (1.9%) compared to the placebo arm (1.5%). The incidences and types of adjudicated bleeding events are discussed in further detail in section 5.8.4.6. The majority of TEAEs and SAEs reflected adverse events expected from concurrent chemotherapy treatment and were balanced between treatment arms.

5.8.4.3 Deaths

The following table summarizes total deaths over the course of the study.

Figure 4: Number (%) of Patients Who Died by Study Period (Safety Population)

	AVE5026 (N=1589)	Placebo (N=1583)
Death on-study[a]	250 (15.7%)	252 (15.9%)
Death on-treatment[b]	85 (5.3%)	83 (5.2%)
Fatal PE	7 (0.4%)	9 (0.6%)
Fatal bleeding	2 (0.1%)	3 (0.2%)
Cardiovascular death	5 (0.3%)	3 (0.2%)
Other	71 (4.5%)	68 (4.3%)
Death post-treatment	165 (10.4%)	169 (10.7%)
Fatal PE	4 (0.3%)	5 (0.3%)
Fatal bleeding	0	6 (0.4%)
Cardiovascular death	2 (0.1%)	6 (0.4%)
Other	123 (7.7%)	117 (7.4%)
Not adjudicated[d]	36 (2.3%)	35 (2.2%)
Death post-study[c]	443 (27.9%)	455 (28.7%)
Other	9 (0.6%)	12 (0.8%)
Not adjudicated[d]	434 (27.3%)	443 (28.0%)

[a] includes all deaths occurring from the start of treatment up to end of study (defined as the latest between end of treatment + 3 days (TEAE period), the last planned protocol visit and the resolution of all serious TEAE)
[b] On-treatment is TEAE period
[c] Includes deaths occurring after the end of the study (as defined in footnote a) and reported in the database
[d] Deaths not adjudicated correspond to deaths occurring after the follow-up visit
PGM=PRODOPS/AVE5026/EFC6521/CSR/REPORT/PGM/ae_deathcsr_t_s.sas OUT=REPORT/OUTPUT/ae_deathcsr_t_s_i.rtf (01JUN2011 - 23:35)

Copy of Applicants's table

Patient deaths on-study were similar between treatment arms (about 16% in each arm). On-study was defined as the on-treatment period and follow-up through the last planned protocol visit and resolution of all SAEs. , The observed deaths by one year of follow-up or end-of-study were 40.0% and 41.5% in the semuloparin and placebo arms, respectively (See section 5.8.3.2). The overall high mortality reflects the advanced stage disease in the studied population.

Deaths adjudicated as VTE-related (fatal PE) during the treatment period were observed in 0.4% and 0.6% of patients in the semuloparin and placebo arms, respectively (see section 5.8.3.2).

"TEAEs leading to death" were balanced between treatment arms and are shown in the table below. Consistent with the advanced disease state of the enrolled population, the majority of these "TEAEs" could be attributed to underlying disease progression (combined Preferred Terms of "malignant disease progression" and Preferred Terms related to metastases to various sites). These were similar between treatment arms (approximately 9% in each arm).

Table 21: TEAEs Leading to Death by Primary SOC[a], Including Preferred Term ≥0.5% (Safety Population)

Primary SOC[a]/ PT[b] (MedDRA v13.1)	Semuloparin N=1589 (%)	Placebo N=1583 (%)
Any class	193 (12.1)	185 (11.7)
Neoplasms benign, malignant & unspecified (including cysts & polyps)	148 (9.3)	136 (8.6)
Malignant neoplasm progression	145 (9.1)	129 (8.1)
Infections & infestations	16 (1.0)	19 (1.2)
Respiratory, thoracic & mediastinal disorders	11 (0.7)	14 (0.9)
General disorders & administration site conditions	11 (0.7)	10 (0.6)
Cardiac disorders	6 (0.4)	8 (0.5)
Hepatobiliary disorders	6 (0.4)	5 (0.3)
Gastrointestinal disorders	5 (0.3)	7 (0.4)
Nervous system disorders	3 (0.2)	4 (0.3)
Metabolism & nutrition disorders	3 (0.2)	3 (0.2)
Blood & lymphatic system disorders	2 (0.1)	2 (0.1)
Renal & urinary disorders	1 (<0.1)	2 (0.1)
Vascular disorders	1 (<0.1)	1 (<0.1)
Injury, poisoning & procedural complications	1 (<0.1)	1 (<0.1)

[a]SOC= system organ class; [b]PT= preferred term
Reviewer's table based on data in Applicant's tables

5.8.4.4 Serious Adverse Events

Approximately 26% of patients in both treatment arms experienced serious TEAEs. Types of SAEs, as categorized by Preferred Term, were balanced between arms. The observed SAEs most commonly paralleled those events experienced in patients with cancer receiving chemotherapy (infection, cytopenias, malignancy progression, gastrointestinal disorders). SAEs by primary system organ class or preferred term that occurred in ≥1% of patients are listed in the table below. Bleeding events are discussed separately under Section 5.8.4.6.

Table 22: Serious TEAEs, Including Primary SOC[a] or Preferred Term[b] ≥1% (Safety Population)

Primary SOC[a]/ PT[b]/ Other (MedDRA v13.1)	Semuloparin N=1589 (%)	Placebo N=1583 (%)
Any class	418 (26.3)	403 (25.5)
Neoplasms benign, malignant & unspecified (including cysts & polyps)	125 (7.9)	106 (6.7)
Malignant neoplasm progression	117 (7.4)	87 (5.5)
Metastases to central nervous system	3 (0.2)	11 (0.7)
Gastrointestinal disorders	101 (6.4)	97 (6.1)
Vomiting	18 (1.1)	21 (1.3)
Diarrhea	14 (0.9)	14 (0.9)
Blood & lymphatic system disorders	82 (5.2)	70 (4.4)
Anemia	28 (1.8)	20 (1.3)
Neutropenia	21 (1.3)	17 (1.1)
Thrombocytopenia	16 (1.0)	26 (1.6)
Febrile neutropenia	18 (1.1)	14 (0.9)
Infections & infestations	81 (5.1)	82 (5.2)
Pneumonia	23 (1.4)	31 (2.0)
General disorders & administration site conditions	44 (2.8)	38 (2.4)
Respiratory, thoracic & mediastinal disorders	38 (2.4)	37 (2.3)
Metabolism & nutrition disorders	29 (1.8)	19 (1.2)
Cardiac disorders	19 (1.2)	21 (1.3)
Nervous system disorders	19 (1.2)	16 (1.0)
Hepatobiliary disorders	16 (1.0)	19 (1.2)
Renal & urinary disorders	12 (0.8)	20 (1.3)

[a]SOC= system organ class; [b]PT= preferred term
Reviewer's table based on data in Applicant's tables

5.8.4.5 Discontinuations

Similar overall rates of treatment discontinuation were observed in both groups (15% and 16% in the semuloparin and placebo arms, respectively). TEAEs leading to treatment discontinuation were balanced between the 2 groups, by both SOC and Preferred Term. The most common "TEAE" leading to treatment discontinuation was related to progression of underlying disease (malignant neoplasm progression in 5% of patients in each arm). The remaining types of TEAEs leading to discontinuation were less frequent and did not differ between treatment arms, as shown in the table below.

Table 23: TEAEs Leading to Permanent Treatment Discontinuation in Study SAVE-ONCO, Including Primary SOC[a] or Preferred Term[b] ≥1% (Safety Population)

Primary SOC[a]/ PT[b]/ Other (MedDRA v13.1)	Semuloparin N=1589 (%)	Placebo N=1583 (%)
Any class	241 (15.2)	260 (16.4)
Neoplasms benign, malignant & unspecified (including cysts & polyps)	88 (5.5)	90 (5.7)
Malignant neoplasm progression	86 (5.4)	75 (4.7)
Gastrointestinal disorders	38 (2.4)	42 (2.7)
Infections & infestations	23 (1.4)	21 (1.3)
Respiratory, thoracic & mediastinal disorders	23 (1.4)	19 (1.2)
General disorders & administration site conditions	23 (1.4)	17 (1.1)
Blood & lymphatic system disorders	19 (1.2)	23 (1.5)
Thrombocytopenia	11 (0.7)	14 (0.9)
Cardiac disorders	11 (0.7)	15 (0.9)
Nervous system disorders	11 (0.7)	13 (0.8)

[a]SOC= system organ class; [b]PT= preferred term
Reviewer's table based on data in Applicant's tables

5.8.4.6 Significant Adverse Events: Bleeding

More patients experienced treatment-emergent clinically relevant bleeding AEs in the Semuloparin arm (2.8%) compared to the Placebo arm (2.0%). Approximately half of the clinically relevant bleeding events were adjudicated as major bleeding, and the other half as CRNMB. The difference between treatment arms was primarily driven by a larger number of CRNMB in the Semuloparin arm.

Table 24: Clinically Relevant Bleeding Events in Study SAVE-ONCO (Safety Population)

Number (%) Patients With:	Semuloparin N=1589 (%)	Placebo N=1583 (%)	Odds Ratio (95% mid-p CI)
Clinically Relevant Bleeding Events (CRBE)	45 (2.8)	32 (2.0)	1.41 (0.89, 2.25)
Major Bleeding (MB)	19 (1.2)	18 (1.1)	1.05 (0.55, 2.04)
Clinically Relevant Nonmajor Bleeding (CRNMB)	26 (1.6)	14 (0.9)	1.86 (0.98, 3.68)

Note: Patients with both MB and CRNMB are counted in the MB category
Note: CRBE = MB + CRNMB
FDA Analysis

Occurrence of major bleeding was similar in the two treatment arms (1.2% of patients in the semuloparin arm and 1.1% of patients in the placebo arm). However, major bleeding into a critical area or organ, as adjudicated by central review, was observed in six patients in the semuloparin group and no patients in the placebo group. These cases included 2 pericardial, 1 intraocular (resulting in retinal detachment), and 3 intracranial bleeds, of which one case was fatal. FDA analysis considers an additional patient, who experienced life-threatening splenic hemorrhage, to meet the criteria of symptomatic bleeding into a critical area or organ. This patient was also in the semuloparin treatment arm.

Table 25: Major Bleeding by Adjudication Criterion (Safety Population)

	Semuloparin N=1589		Placebo N=1583
Any treatment-emergent major bleeding (MB)	19*		18
Fatal bleeding	2*		4
Symptomatic bleeding into a critical area or organ	6	FDA Analysis 7	0
Intracranial	3	3	0
Intraocular	1	1	0
Pericardial	2	2	0
Splenic		1	0
Retroperitoneal	0		0
Intraarticular	0		0
Intramuscular/compartment syndrome	0		0
Intraspinal	0		0
Fall of hemoglobin ≥ 2 g/dL or transfusion of ≥ 2 units of whole blood or RBC	13		15

*An additional death in the Semuloparin arm (not tabulated) was reported by the Investigator as "fatal bleeding," but adjudicated by the CIAC as non-clinically relevant bleeding and noncardiovascular death. The patient was a 55-year old male with metastatic lung cancer who on Day 25, per family, choked at home, experienced respiratory tract hemorrhage, and soon afterwards died. No autopsy was performed.

Reviewer's table based on data in Applicant's tables, patient narratives, and case report forms

The patients in the semuloparin arm who experienced major bleeding into a critical area or organ are briefly described below.

- Patient #1 (pericardial bleed): 59-year old male with metastatic gastric cancer who experienced pericardial hemorrhage on Day 32 of Semuloparin treatment. The patient was receiving acetylsalicylic acid 1500 mg daily for pericarditis 20 days prior to the bleeding event. The last dose of study treatment was received on Day 31.
- Patient #2 (pericardial bleed): 69-year old male with metastatic lung cancer who experienced pericardial hemorrhage on Day 6 of Semuloparin treatment. The patient underwent pericardiocentesis and continued to receive study treatment for another 3 months. The last dose of study treatment was received on Day 97.
- Patient #3 (intraocular bleed): 63-year old female with locally advanced pancreatic cancer who experienced retinal detachment and vitreous hemorrhage on Day 16 of Semuloparin treatment. After recovery reported on Day 27, the recorded reason for study drug discontinuation on Day 28 was "poor compliance." The last dose of study treatment was received on Day 28.
- Patient #4 (intracranial bleed): 46-year old male with metastatic lung cancer who experienced convulsions on Day 37 of Semuloparin treatment. The patient was thought to have had brain metastases. Imaging studies demonstrated a new 4 mm hyperdense lesion in the lenticular nucleus, interpreted to be a possible hemorrhagic focus triggering the convulsions. The last dose of study treatment was received on Day 37.
- Patient #5 (intracranial bleed): 71-year old male with metastatic lung cancer moderate renal insufficiency who developed a cerebral hematoma on Day 43 of

Semuloparin treatment, suspected to be due to a cavernoma rupture. The patient had residual lower extremity paresis at the time of discharge. The last dose of study treatment was received on Day 42.

- Patient #6 (intracranial bleed-- fatal): 54-year old male with locally advanced colorectal cancer who experienced a fatal intracranial bleed presenting with convulsions on Day 58 of Semuloparin treatment. The patient was reported to have suspected bleeding from brain metastasis. No imaging was conducted due to the patient's poor condition. The last dose of study treatment was received on Day 56.
- Patient #7 (splenic hematoma—life-threatening): 53-year old female with metastatic ovarian cancer who developed abdominal pain on Day 63 and was diagnosed with a subcapsular splenic hematoma (10 x 10 x 5.5 cm on abdominal ultrasound), requiring hospitalization on Day 72. On Day 73 the splenic hematoma worsened and was assessed as life-threatening. The patient underwent splenectomy for bleeding and received 3 units of blood perioperatively, with recovery from the event by Day 86. The last dose of study treatment was received on Day 71.

Major bleeding by primary system organ class and preferred term are listed in the table below.

Table 26: Major Bleeding by Primary SOC[a] and Preferred Term[b] (Safety Population)

Primary SOC[a]/ PT[b] (MedDRA v13.1)	**Semuloparin N=1589 (%)**	**Placebo N=1583 (%)**
Any class	19 (1.2)	18 (1.1)
Nervous system disorders	3 (0.2)	0
Cerebral hematoma	1 (<0.1)	0
Cerebral hemorrhage	1 (<0.1)	0
Hemorrhagic stroke	1 (<0.1)	0
Eye disorders	1 (<0.1)	0
Vitreous hemorrhage	1 (<0.1)	0
Cardiac disorders	2 (0.1)	0
Pericardial hemorrhage	2 (0.1)	0
Respiratory, thoracic & mediastinal disorders	2 (0.1)	2 (0.1)
Epistaxis	1 (<0.1)	0
Hemoptysis	1 (<0.1)	2 (0.1)
Gastrointestinal disorders	7 (0.4)	15 (0.9)
Gastrointestinal hemorrhage	5 (0.3)	3 (0.2)
Duodenal ulcer hemorrhage	1 (<0.1)	2 (0.1)
Gastrointestinal ulcer hemorrhage	1 (<0.1)	0
Diarrhea hemorrhagic	0	1 (<0.1)
Gastric hemorrhage	0	1 (<0.1)
Gastric ulcer hemorrhage	0	1 (<0.1)
Hematemesis	0	1 (<0.1)
Lower gastrointestinal hemorrhage	0	1 (<0.1)
Mallory-Weiss syndrome	0	1 (<0.1)
Esophageal ulcer hemorrhage	0	1 (<0.1)
Esophagitis hemorrhagic	0	1 (<0.1)
Small intestinal hemorrhage	0	1 (<0.1)
Upper gastrointestinal hemorrhage	0	1 (<0.1)
Reproductive system & breast disorders	1 (<0.1)	0
Postmenopausal hemorrhage	1 (<0.1)	0
Injury, poisoning & procedural complications	3 (0.2)	1 (<0.1)
Operative hemorrhage	1 (<0.1)	0
Splenic hematoma	1 (<0.1)	0
Traumatic hemorrhage	1 (<0.1)	0
Post procedural hemorrhage	0	1 (<0.1)

[a]SOC= system organ class; [b]PT= preferred term
Reviewer's table based on data in Applicant's tables

Clinically relevant nonmajor bleeding (CRNMB) AEs were slightly more common in the semuloparin arm than in the placebo arm. CRNMB AEs by primary system organ class and preferred term are listed in the table below.

Table 27: Clinically Relevant Non-major Bleeding (CRNMB) by Primary SOC[a] and Preferred Term[b] (Safety Population)

Primary SOC[a]/ PT[b] (MedDRA v13.1)	**Semuloparin N=1589 (%)**	**Placebo N=1583 (%)**
Any class	27 (1.7)	14 (0.9)
Respiratory, thoracic & mediastinal disorders	7 (0.4)	6 (0.4)
Epistaxis	5 (0.3)	2 (0.1)
Bronchial hemorrhage	1 (<0.1)	1 (<0.1)
Hemoptysis	1 (<0.1)	3 (0.2)
Gastrointestinal disorders	10 (0.6)	7 (0.4)
Rectal hemorrhage	3 (0.2)	3 (0.2)
Gastrointestinal hemorrhage	2 (0.1)	0
Hematochezia	2 (0.1)	0
Anal hemorrhage	1 (<0.1)	0
Duodenal ulcer hemorrhage	1 (<0.1)	0
Hematemesis	1 (<0.1)	2 (0.1)
Intestinal hemorrhage	0	1 (<0.1)
Melena	0	1 (<0.1)
Renal and urinary disorders	6 (0.4)	2 (0.1)
Hematuria	6 (0.4)	2 (0.1)
Reproductive system & breast disorders	1 (<0.1)	0
Vaginal hemorrhage	1 (<0.1)	0
Injury, poisoning & procedural complications	3 (0.2)	0
Post procedural hemorrhage	3 (0.2)	0

[a]SOC= system organ class; [b]PT= preferred term
Reviewer's table based on data in Applicant's tables

All treatment-emergent bleeding AEs by primary system organ class and preferred term are listed in the table below. Overall, there were more patients with treatment-emergent bleeding events in the semuloparin (20%) compared to the placebo (16%) arms.

Table 28: Treatment Emergent Bleeding AEs by Primary SOC[a] and Preferred Term[b] (Safety Population)

Primary SOC[a]/ PT[b] (MedDRA v13.1)	Semuloparin N=1589 (%)	Placebo N=1583 (%)
Any class	320 (20.1)	254 (16.0)
Neoplasms benign, malignant & unspecified (including cysts & polyps)	2 (0.1)	0
Hemorrhagic tumor necrosis	1 (<0.1)	0
Tumor hemorrhage	1 (<0.1)	0
Blood & lymphatic system disorders	0	1 (<0.1)
Purpura non-thrombocytopenic	0	1 (<0.1)
Nervous system disorders	3 (0.2)	1 (<0.1)
Cerebral hematoma	1 (<0.1)	0
Cerebral hemorrhage	1 (<0.1)	0
Hemorrhagic stroke	1 (<0.1)	0
Hemorrhage intracranial	0	1 (<0.1)
Eye disorders	2 (0.1)	0
Conjunctival hemorrhage	1 (<0.1)	0
Vitreous hemorrhage	1 (<0.1)	0
Ear & labyrinth disorders	1 (<0.1)	0
Ear hemorrhage	1 (<0.1)	0
Cardiac disorders	2 (0.1)	0
Pericardial hemorrhage	2 (0.1)	0
Vascular disorders	2 (0.1)	1 (<0.1)
Extravasation blood	1 (<0.1)	0
Hematoma	1 (<0.1)	0
Hemorrhage	0	1 (<0.1)
Respiratory, thoracic & mediastinal disorders	132 (8.3)	112 (7.1)
Epistaxis	102 (6.4)	86 (5.4)
Hemoptysis	33 (2.1)	28 (1.8)
Bronchial hemorrhage	1 (<0.1)	1 (<0.1)
Hemothorax	1 (<0.1)	0
Respiratory tract hemorrhage	1 (<0.1)	0
Pharyngeal hemorrhage	0	1 (<0.1)
Gastrointestinal disorders	61 (3.8)	72 (4.5)
Rectal hemorrhage	12 (0.8)	11 (0.7)
Hematochezia	10 (0.6)	12 (0.8)
Gastrointestinal hemorrhage	8 (0.5)	6 (0.4)
Hemorrhoidal hemorrhage	7 (0.4)	11 (0.7)
Gingival bleeding	6 (0.4)	8 (0.5)
Hematemesis	6 (0.4)	3 (0.2)
Mouth hemorrhage	4 (0.3)	3 (0.2)
Anal hemorrhage	3 (0.2)	3 (0.2)
Melena	3 (0.2)	2 (0.1)
Duodenal ulcer hemorrhage	2 (0.1)	2 (0.1)
Intestinal hemorrhage	2 (0.1)	1 (<0.1)
Diarrhea hemorrhagic	1 (<0.1)	2 (0.1)
Gastrointestinal ulcer hemorrhage	1 (<0.1)	0
Hemorrhagic erosive gastritis	1 (<0.1)	0

Feces discolored	0	1 (<0.1)
Gastric hemorrhage	0	1 (<0.1)
Gastric ulcer hemorrhage	0	1 (<0.1)
Hemorrhagic ascites	0	1 (<0.1)
Lower gastrointestinal hemorrhage	0	1 (<0.1)
Mallory-Weiss syndrome	0	1 (<0.1)
Esophageal ulcer hemorrhage	0	1 (<0.1)
Esophagitis hemorrhagic	0	1 (<0.1)
Small intestinal hemorrhage	0	1 (<0.1)
Stomatitis hemorrhagic	0	1 (<0.1)
Upper gastrointestinal hemorrhage	0	1 (<0.1)
Skin & subcutaneous tissue disorders	12 (0.8)	9 (0.6)
Ecchymosis	5 (0.3)	3 (0.2)
Petechiae	4 (0.3)	4 (0.3)
Skin hemorrhage	2 (0.1)	0
Blood blister	1 (<0.1)	0
Skin ulcer hemorrhage	1 (<0.1)	1 (<0.1)
Hemorrhage subcutaneous	0	1 (<0.1)
Increased tendency to bruise	0	1 (<0.1)
Renal & urinary disorders	10 (0.6)	11 (0.7)
Hematuria	10 (0.6)	11 (0.7)
Reproductive system & breast disorders	7 (0.4)	6 (0.4)
Vaginal hemorrhage	4 (0.3)	3 (0.2)
Genital hemorrhage	1 (<0.1)	0
Menorrhagia	1 (<0.1)	2 (0.1)
Postmenopausal hemorrhage	1 (<0.1)	0
Penile hemorrhage	0	1 (<0.1)
General disorders & administration site conditions	139 (8.7)	68 (4.3)
Injection site hematoma	97 (6.1)	43 (2.7)
Injection site hemorrhage	41 (2.6)	22 (1.4)
Catheter site hemorrhage	6 (0.4)	2 (0.1)
Catheter site hematoma	3 (0.2)	4 (0.3)
Vessel puncture site hematoma	1 (<0.1)	4 (0.3)
Vessel puncture site hemorrhage	1 (<0.1)	1 (<0.1)
Investigations	2 (0.1)	4 (0.3)
Blood urine present	2 (0.1)	4 (0.3)
Injury, poisoning & procedural complications	41 (2.6)	42 (2.7)
Contusion	13 (0.8)	12 (0.8)
Post procedural hemorrhage	7 (0.4)	8 (0.5)
Traumatic hemorrhage	5 (0.3)	6 (0.4)
Subcutaneous hematoma	4 (0.3)	5 (0.3)
Traumatic hematoma	4 (0.3)	4 (0.3)
Skin laceration	3 (0.2)	1 (<0.1)
Operative hemorrhage	2 (0.1)	1 (<0.1)
Periorbital hematoma	1 (<0.1)	1 (<0.1)
Scratch	1 (<0.1)	0
Splenic hematoma	1 (<0.1)	0
Wound hemorrhage	1 (<0.1)	3 (0.2)
Incision site hemorrhage	0	1 (<0.1)
Post procedural hematoma	0	1 (<0.1)
Post procedural hematuria	0	3 (0.2)

[a]SOC= system organ class; [b]PT= preferred term

Reviewer's table based on data in Applicant's tables

Transfusions
Eleven percent of patients in each treatment arm required two or more blood transfusions. Numbers of RBC units and other blood products transfused were similar between the treatment arms.

5.8.4.7 Common Adverse Events

Treatment-emergent adverse events occurring in ≥5% of patients in trial SAVE-ONCO are listed in the table below. Overall, 85% of patients in each treatment arm experienced treatment-emergent adverse events. The majority of TEAEs reflected adverse events expected from concurrent chemotherapy treatment and were balanced between treatment arms. TEAEs occurring in >10% of patients included: nausea, malignant neoplasm progression, anemia, diarrhea, vomiting, neutropenia, asthenia, fatigue, decreased appetite, abdominal pain, and constipation.

TEAEs occurring at a frequency ≥5% in any treatment group are listed in the table below.

Table 29: TEAEs at a Frequency ≥5% in Any Treatment Group by Primary SOC[a] and Preferred Term[b] (Safety Population)

Primary SOC[a]/ PT[b] (MedDRA v13.1)	Semuloparin N=1589 (%)	Placebo N=1583 (%)
Any class	1350 (85.0)	1339 (84.6)
Gastrointestinal disorders	802 (50.5)	805 (50.9)
Nausea	383 (24.1)	424 (26.8)
Diarrhea	250 (15.7)	249 (15.7)
Vomiting	246 (15.5)	229 (14.5)
Abdominal pain	164 (10.3)	135 (8.5)
Constipation	153 (9.6)	166 (10.5)
General disorders & administration site conditions	643 (40.5)	576 (36.4)
Asthenia	207 (13.0)	203 (12.8)
Fatigue	194 (12.2)	178 (11.2)
Pyrexia	115 (7.2)	103 (6.5)
Injection site hematoma	97 (6.1)	43 (2.7)
Blood & lymphatic system disorders	516 (32.5)	508 (32.1)
Anemia	256 (16.1)	254 (16.0)
Neutropenia	223 (14.0)	200 (12.6)
Leukopenia	115 (7.2)	101 (6.4)
Thrombocytopenia	111 (7.0)	120 (7.6)
Respiratory, thoracic & mediastinal disorders	349 (22.0)	300 (19.0)
Epistaxis	102 (6.4)	86 (5.4)
Dyspnea	94 (5.9)	68 (4.3)
Cough	86 (5.4)	92 (5.8)
Neoplasms benign, malignant & unspecified (including cysts & polyps)	344 (21.6)	307 (19.4)
Malignant neoplasm progression	291 (18.3)	248 (15.7)
Nervous system disorders	336 (21.1)	313 (19.8)
Dizziness	78 (4.9)	69 (4.4)
Metabolism & nutrition disorders	276 (17.4)	243 (15.4)
Decreased appetite	192 (12.1)	174 (11.0)
Skin & subcutaneous tissue disorders	268 (16.9)	285 (18.0)
Alopecia	110 (6.9)	122 (7.7)
Infections & infestations	261 (16.4)	250 (15.8)
Musculoskeletal & connective tissue disorders	246 (15.5)	263 (16.6)
Back pain	66 (4.2)	77 (4.9)
Investigations	191 (12.0)	156 (9.9)
Psychiatric disorders	99 (6.2)	98 (6.2)

[a]SOC= system organ class; [b]PT= preferred term

Reviewer's table based on data in Applicant's tables

5.8.4.8 Laboratories

Hepatic TEAEs were observed more frequently in patients receiving semuloparin than placebo. The most common hepatic adverse events were reversible transaminase elevations. Hepatic TEAEs ≥0.5% in each arm by preferred term are shown in the table below.

Table 30: Hepatic TEAEs ≥0.5% in Study SAVE-ONCO by Preferred Term (Safety Population)

Hepatic Disorders Preferred Term (MedDRA v13.1)	Semuloparin N=1589 (%)	Placebo N=1583 (%)
Any treatment-emergent hepatic disorders	145 (9.1)	102 (6.4)
Ascites	48 (3.0)	35 (2.2)
Alanine aminotransferase increased	29 (1.8)	17 (1.1)
Aspartate aminotransferase increased	23 (1.4)	17 (1.1)
Transaminases increased	13 (0.8)	5 (0.3)
Blood bilirubin increased	12 (0.8)	8 (0.5)
Blood alkaline phosphatase increased	10 (0.6)	4 (0.3)

Reviewer's table based on data in Applicant's tables

No significant differences between treatment groups were observed for other laboratory measurements, including creatinine and hematologic parameters (hemoglobin, platelet count, white blood cell count, and neutrophil count).

5.8.4.9 Immunogenicity

No cases of HIT were observed in Trial SAVE-ONCO. No formal immunogenicity studies have been performed.

6. Safety (Overall Clinical Database)

A total of 7,616 patients have been exposed to semuloparin across 21 clinical trials. This includes one Phase 2 dose-finding study and six Phase 3 efficacy/safety studies of semuloparin for VTEp in other patient populations (6,826 patients) and thirteen Phase 1 clinical pharmacology studies (354 exposed to semuloparin, including 255 healthy subjects). The totality of safety data from these studies suggest that the safety profile of semuloparin, including bleeding AEs, was similar to that of enoxaparin in these studies.

7. Other Studies

Regarding other experience with semuloparin for VTE prophylaxis in patients with cancer, in the study SAVE-ABDO, 81% (2,451) of the primary efficacy population were patients with cancer undergoing oncologic surgery. SAVE-ABDO was a randomized active-controlled trial in patients undergoing major abdominal surgery. A total of 4,413 patients were randomized 1:1 to receive either semuloparin 20 mg SC QD or enoxaparin 40 mg SC QD for a duration of 7-10 days after surgery. An FDA exploratory analysis in the subgroup of patients with cancer showed a numerically higher proportion of subjects with VTE events in the semuloparin compared to the enoxaparin arm (7.1% vs. 5.9%, respectively; Odds Ratio 1.23 (0.89, 1.69). This trial failed to meet its primary efficacy endpoint of any VTE or all-cause death in a noninferiority comparison of semuloparin versus enoxaparin (Odds Ratio 1.16, with the upper bound of the 95% confidence interval (1.59) failing to meet the pre-specified noninferiority margin of 1.25).

8. Discussion

Semuloparin is a low molecular weight heparin (LMWH) that has been investigated in 6 completed Phase 3 trials for VTE prophylaxis in several clinical settings. The current application is submitted for semuloparin prophylaxis of VTE in patients with cancer receiving chemotherapy for locally advanced or metastatic solid tumors. A single trial (SAVE-ONCO) was conducted to demonstrate efficacy and safety of semuloparin for the indication in the target population. In the trial, the primary efficacy outcome of symptomatic VTE or VTE-related death occurred in 1.2% of patients receiving semuloparin compared to 3.4% receiving placebo, giving an absolute risk reduction of 2.2%. The observed small treatment effect consisted predominantly of nonfatal VTE events. The percentage of patients experiencing a fatal VTE event was only 0.4% and 0.6% in the semuloparin and placebo arm, respectively. The statistical analysis of the primary efficacy endpoint was complicated by a high rate of premature censoring (32.5%). The censoring appears to be informative as patients who were censored in the primary analysis had shorter survival than did those patients who continued to be followed for VTE or VTE-related death. The early censoring undermines confidence in the analysis results. There was no difference between groups in the secondary endpoint, overall survival at 1 year (40.0% deaths in the semuloparin arm and 41.5% deaths in the placebo arm). There are no available other sources of support for efficacy of semuloparin for the indication being sought.

Interpretation of the efficacy findings of the SAVE-ONCO study raises two concerns. First, event rate for the primary efficacy outcome was very low (3.4%) in the placebo arm suggesting that only a very small percentage of patients in the study stood to gain from the potential benefit of thromboprophylaxis even if semuloparin was maximally effective. Thus, it is not clear that the population studied is an appropriate target population for thromboprophylaxis. Second, total deaths during the treatment period were 5.3% in the semuloparin arm and 5.2% in the placebo arm overshadowing the VTE-related deaths. These findings call into question the clinical value of semuloparin in the proposed clinical setting.

Safety analysis of Trial SAVE-ONCO showed an overall higher incidence of bleeding adverse events occurring in patients receiving semuloparin (20%) compared to those receiving placebo (16%). Major bleeding into a critical area or organ occurred in 7 patients receiving semuloparin (2 pericardial, 1 intraocular, 1 splenic, and 3 intracranial), with one case of intracranial bleeding being fatal. No patients in the placebo arm experienced bleeding into a critical area or organ. Likewise, clinically relevant nonmajor bleeding events requiring medical attention were also higher in the semuloparin arm, contributing to the overall higher incidence of bleeding events adjudicated as clinically relevant (2.8% semuloparin, 2.0% placebo).

This single placebo-controlled trial is presented by the Applicant for approval of a new treatment indication. Although the Applicant has proposed to narrow the labeled population to include only patients receiving chemotherapy for locally advanced or metastatic pancreatic or lung cancer or for locally advanced or metastatic solid tumors with a VTE risk score ≥3 based on subset analyses of SAVE-ONCO, it is unclear whether an appropriate target population/subpopulation has been identified for the proposed new treatment indication.