SYNOPSIS

Title of the study:	SAVE-KNEE - A multinational, multicenter, randomized, double-blind study comparing the efficacy and safety of semuloparin (AVE5026) with enoxaparin for the prevention of venous thromboembolism in patients undergoing elective knee replacement surgery
Investigator(s):	[redacted]
Study center(s):	97 active investigational sites in 17 countries
Publications (reference):	None.
Study period:	
Date first patient enrolled:	02-Jul-2008
Date last patient completed:	26-May-2009
Phase of development:	Confirmatory phase 3 study
Objectives:	
Primary:	To compare, in patients undergoing elective knee replacement surgery, or revision of component(s) of a knee replacement, the efficacy of once daily (OD) subcutaneous (SC) injections of 20 mg semuloparin (AVE5026) (10 mg in patients with severe renal insufficiency [SRI]) and twice daily (BID) SC injections of 30 mg enoxaparin (20 mg OD in patients with SRI) administered for 7 to 10 days after surgery, for the prevention of venous thromboembolic events (VTE), ie, deep vein thrombosis (DVT) and/or pulmonary embolism (PE).
Secondary:	To evaluate the safety of semuloparin in patients undergoing elective knee replacement surgery, and to document exposures of semuloparin in this population.
Methodology:	
	This was a multinational, multicenter, randomized, double-blind study with two parallel groups (semuloparin and enoxaparin). Patients were randomly assigned to treatment with either semuloparin 20 mg SC OD (10 mg for patients with SRI), or enoxaparin 30 mg SC BID (20 mg OD for patients with SRI) for 7 to 10 days after surgery. A mandatory bilateral venography was to be performed between Day 7 and 11. The randomization was stratified by region (North America, South America, Western Europe, Eastern Europe, Asia, and Rest of the World) and by the estimated creatinine clearance at screening (< or ≥ 30 mL/min).
Number of patients:	Planned: 1060 (530 in each of the two treatment groups)
	Randomized: 1150 Treated: 1141
Evaluated:	Efficacy: 855 Safety: 1141 Pharmacokinetics: 212
Diagnosis and criteria for inclusion:	
	Patients with a signed informed consent were included if they had undergone an elective knee replacement surgery or a revision of at least one component of a knee prosthesis implanted ≥ 6 months prior to study entry.

Investigational product: Semuloparin (AVE5026)

Dose: 20 mg SC OD (or 10 mg SC OD for patients with SRI, defined as estimated creatinine clearance < 30 mL/min)

Administration: Subcutaneous injection using prefilled syringes containing 20 mg (or 10 mg for patients with SRI)

Patients with normal renal function or mild/moderate renal impairment (estimated creatinine clearance ≥ 30 mL/min) were to receive:

- the first injection (semuloparin 20 mg SC) 8 ± 1 hours after incision closure,
- the second injection (placebo) 12 ± 1 hours after incision closure,
- the third injection (placebo) 12 ± 1 hours after the second injection,
- then, two injections per day: one using semuloparin 20 mg SC and one using placebo.

Patients with SRI (estimated creatinine clearance < 30 mL/min) were to receive:

- the first injection (semuloparin 10 mg SC) 8 ± 1 hours after incision closure,
- the second injection (placebo) 12 ± 1 hours after incision closure,
- then, one injection per day of semuloparin 10 mg SC.

Batch number(s): placebo / semuloparin

- placebo / 20 mg semuloparin, for patients with no SRI: [redacted]
- placebo / 10 mg semuloparin, for patients with SRI: [redacted]

Duration of treatment: 7 to 10 days after surgery (Day 1 is the day of randomization).

Duration of observation: up to 42 days, ie, from surgery (Day 1) to the follow-up visit at Day 35-42 after surgery.

Reference therapy: Enoxaparin

Dose: 30 mg SC BID (20 mg OD for patients with SRI, defined as estimated creatinine clearance < 30 mL/min)

Administration: Subcutaneous injection using prefilled syringes containing 30 mg (or 20 mg for patients with SRI)

Patients with normal or mild/moderate renal impairment renal function (estimated creatinine clearance ≥ 30 mL/min) were to receive:

- the first injection (placebo) 8 ±1 hours after incision closure,
- the second injection (enoxaparin 30 mg SC) 12 ±1 hours after incision closure,
- the third injection (enoxaparin 30 mg SC) 12 ±1 hours after the second injection,
- then,,two injections per day of enoxaparin 30 mg SC.

Patients with SRI (estimated creatinine clearance < 30 mL/min) were to receive:

- the first injection (placebo) 8 ±1 hours after incision closure,
- the second injection (enoxaparin 20 mg SC) 12 ±1 hours after incision closure,
- then, one injection per day of enoxaparin 20 mg SC.

Batch number(s): placebo / enoxaparin

- 30 mg enoxaparin, for patients with no SRI: [redacted]
- 20 mg enoxaparin, for patients with SRI: [redacted]

Criteria for evaluation:

Efficacy:

The efficacy evaluation period lasted from the day of randomization (Day 1) up to Day 11 or up to the day of the mandatory bilateral venography (between Day 7 and Day 11), whichever came first.

The primary efficacy endpoint was a composite of any VTE, confirmed by the blinded Central Independent Adjudication Committee (CIAC), and deaths from any cause reported during the efficacy evaluation period.

Secondary endpoints:

- Composite endpoint of the following events reported during the efficacy evaluation period: any proximal DVT, symptomatic distal DVT, nonfatal PE, and all cause deaths.
- Initiation of curative anticoagulant or thrombolytic treatment by the Investigator after VTE assessment.

Safety:

The safety evaluation period was defined as the period from the first up to the last injection of investigational product plus 3 calendar days.

Safety parameters included:

- clinically relevant bleeding events (as adjudicated by the CIAC)
- transfusions
- hemoglobin, platelet count, liver and renal laboratory data
- adverse events

Pharmacokinetics:

Blood samples (4 per patient) were to be drawn in all patients from selected centers to document the exposures of semuloparin in this population.

Pharmacokinetic sampling times and bioanalytical methods:

The pharmacokinetics of semuloparin was to be evaluated in all patients of selected centers. Blood samples were to be collected at the following time-points or during the following time-windows:

- On Day 1: at 0.5-1 h, 2-4 h, and 10-16 h after the first injection of investigational product
- On the last treatment day (Day 7-10) or the day of discharge (whichever came first), just before the last injection of active investigational product.

C_{trough} plasma concentrations were defined as concentrations obtained in the time-window 22-26 hours after the last injection preceding blood sampling.

Semuloparin concentrations were determined by the anti-Xa activity using an automated chromogenic enzyme assay:

- Analyte: semuloparin
- Biological fluid: plasma
- Lower limit of quantification: 0.348 µgEq/mL

Statistical methods:

Populations analyzed:

- Efficacy populations: All randomized patients who underwent elective knee replacement surgery, who received at least one injection of investigational product, and who had a nonmissing assessment for the efficacy parameter analyzed
- Safety population: All randomized patients who received at least one injection of investigational product
- Pharmacokinetic population (considered for descriptive statistics): All randomized patients treated with semuloparin and having at least one plasma trough concentration (C_{trough}).

Efficacy analyses:

Primary efficacy endpoint: The primary analysis consisted in the comparison of the two treatment groups using an exact 2-sided stratified test at the alpha level of 0.05. Event rates and exact 2-sided 95% confidence interval (CI) per treatment group as well as common odds ratio and exact 2-sided 95% CI were calculated. In addition, risk reduction and absolute difference are presented with 2-sided 95% CI. A post-hoc non-inferiority analysis was also performed using a conservative but not pre-specified margin of 1.15.

Secondary efficacy endpoints: Event rates and exact 2-sided 95% CI per treatment group were calculated as well as 2-sided exact 95% CI (based on the mid-p method) on the odds ratio for each secondary efficacy endpoint. Risk reduction and absolute difference were also presented with 2-sided 95% CI for the secondary efficacy composite endpoint.

Safety analyses:

All safety analyses were carried out using data from the safety population.

Event rates and exact 2-sided 95% CI per treatment group as well as odds ratio and exact 2-sided 95% CI (based on the mid-p method) were calculated for all clinically relevant bleedings, major bleedings, and clinically relevant nonmajor bleedings

Adverse event data were summarized by system organ class and preferred term. Number and percentages of patients with treatment emergent adverse events (TEAEs), serious TEAEs, TEAEs leading to permanent treatment discontinuation, and deaths were calculated.

For laboratory parameters, criteria for potentially clinically significant abnormalities, including liver toxicity criteria, were computed and summarized irrespective of the baseline status and/or according to the baseline status categories.

Pharmacokinetic analyses:

Descriptive statistics (number of observation, arithmetic mean, standard deviation (SD), coefficient of variation, geometric mean, median, minimum and maximum) were presented for semuloparin C_{trough} concentrations using data from the pharmacokinetic population, by dose (10 mg in patients with SRI and 20 mg in patients with no SRI).

Summary of Results:

In this study comparing semuloparin 20 mg OD versus enoxaparin 30 mg BID for the prevention of VTE after knee replacement surgery, 1150 patients were randomized.

Efficacy results:

- The superiority test did not reach statistical significance but the primary efficacy endpoint of any VTE or all cause death occurred in fewer patients (105 of 428; 24.5%) in the semuloparin 20 mg OD group (10 mg OD in patients with SRI) than in the enoxaparin 30 mg BID group (20 mg OD in subjects with SRI) (120 of 427 patients; 28.1%) with a common odds ratio (95% CI) of 0.83 (0.60 to 1.14) (p = 0.2440). The relative risk was 0.87 (0.70 to 1.09), and a post-hoc non-inferiority analysis of the primary endpoint based on a conservative non-inferiority margin of 1.15, suggested that treatment with semuloparin is non-inferior to treatment with enoxaparin.
- The rates of the secondary efficacy composite endpoint (including symptomatic distal DVT, any proximal DVT, nonfatal PE and all-cause death) were similar in the semuloparin (5.9%) and the enoxaparin group (5.1%).

Safety results:

The safety profile of the two treatment groups was overall similar:

- Treatment-emergent bleeding AEs were reported by 16.1% of the patients in the semuloparin group and 18.1% of the patients in the enoxaparin group, with 0.9% of the patients in both groups experiencing serious treatment-emergent bleeding AEs.
- Fifteen patients (2.6%) in the semuloparin group and 10 patients (1.8%) in the enoxaparin group experienced a bleeding event that was confirmed to be clinically relevant by the CIAC. The number of patients with major bleeding events was similar in the semuloparin group (3 [0.5%]) and in the enoxaparin (4 [0.7%]) group. The number of patients with nonmajor bleeding events, however, was slightly higher in the semuloparin group (12 [2.1%]) than in the enoxaparin group (6 [1.1%]). This difference did not reach statistical significance as the lower bound of the 95% mid-p CI of the odds ratio is lower than 1. In addition, this imbalance was primarily due to a higher number of patients with excessive wound bleeding or drainage not requiring invasive intervention in the semuloparin group (n = 4) compared with the enoxaparin group (n = 0).
- No differences were observed between the two treatment groups with regard to the number of blood transfusions or the extent of hemoglobin decreases from baseline.
- The incidence of alanine aminotransferase (ALT) increase > 3 x the upper limit of normal (ULN) was similar in the semuloparin (2.6%) and enoxaparin group (2.8%).
- One patient experienced an increase in ALT > 3 x ULN and total bilirubin > 2 x ULN. This event occurred in the enoxaparin group and was considered as not related to investigational product.
- Nineteen patients had platelet counts < 100 Giga/L. The frequency was similar in the AVE5026 (11 [1.9%]) and enoxaparin treatment group (8 [1.4%]). Seven of these 19 patients (3 in semuloparin group, 4 in enoxaparin group) were tested for antiplatelet antibodies but none of the test results was positive. An additional patient in the semuloparin group was also tested for antiplatelet antibodies due to a decrease of platelets from the baseline value; the test result was negative.
- TEAEs were reported in about half of the patients (semuloparin: 52.5%; enoxaparin: 54.9%) and led to permanent treatment discontinuation in slightly more patients in the semuloparin group (2.8%) than the enoxaparin group (1.8%).
- The number of patients with SAEs was low and comparable between the two groups (semuloparin: 2.3%; enoxaparin: 3.0%).
- Two deaths were reported during the study. Both events occurred in the enoxaparin group post-treatment, ie, during the follow-up period. Both events were assessed as not related to investigational product and were adjudicated by the CIAC as cardiovascular deaths not associated with VTE or bleeding.

Pharmacokinetic results:

Semuloparin was detected in most of the 212 patients analyzed; only for 7 patients concentrations were below the lower limit of quantification (LLOQ) in all samples taken at various time points.

C_{trough} plasma values ranged from <LLOQ to 1.9 µgEq/mL, with a mean value (SD) of 0.51 µgEq/mL (0.37 µgEq/mL).
The rather high between-subject variability (coefficient of variation: 73%) may be due to the variability in the sampling times.

Conclusions: [redacted]

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