SYNOPSIS

Title of the study: A Multinational, Multicenter, Randomized, Double-Blind study Comparing the Efficacy and Safety of AVE5026 with enoxaparin for the Prevention of Venous Thromboembolism in Patients Undergoing Hip Fracture Surgery (EFC10343, SAVE-HIP2).

Investigator(s): [redacted]

Study center(s): 118 active centers in 25 countries

Publications (reference): None.

Study period:

Date first patient enrolled: 19-Jul-2008

Date last patient completed: 28-Oct-2009

Phase of development: Confirmatory Phase 3 study

Objectives:

Primary: To compare the efficacy of once daily (QD) subcutaneous (SC) injections of 20 mg AVE5026/semuloparin (10 mg in patients with severe renal insufficiency [SRI]) with QD SC injections of 40 mg enoxaparin (20 mg in patients with SRI) administered during 7-10 days after surgery for the prevention of venous thromboembolic events (VTE) in patients undergoing hip fracture surgery.

Secondary: To evaluate the safety of semuloparin in patients undergoing elective hip fracture surgery, and to document semuloparin exposure in this population.

Methodology: This was a multinational, multicenter, randomized, double-blind, double-dummy study with 2 parallel groups: semuloparin and enoxaparin (active comparator). Semuloparin treatment was started 8 hours post-surgery. Enoxaparin treatment was started 12 hours before surgery or 12 hours after surgery in accordance with local standard. Study treatment was to be administered for 7 to 10 days after surgery (surgery being performed on Day 1). Mandatory bilateral venography was to be performed 7 to 11 days after surgery. Randomization was stratified by region (North America, South America, Western Europe, Eastern Europe, Asia, and Rest of the World), timing of the first study treatment injection (pre or postoperatively), and patient renal function status (SRI/no SRI) based on the estimated creatinine clearance (CLcr) at screening (< or ≥30 mL/min).

Number of patients:

Planned: approximately 1000 randomized patients (500 in each treatment group)

	AVE5026	enoxaparin	All
Randomized population	500 (100%)	503 (100%)	1003 (100%)
Primary efficacy population	384 (76.8%)	369 (73.4%)	753 (75.1%)
Pharmacokinetic population	222	0	222
Safety population	488	499	987

Diagnosis and criteria for inclusion: Patients with standard surgery for fracture of the upper third of the femur, including femoral head and neck.

Investigational product: AVE5026 (semuloparin sodium): ready-to-use 0.5 mL prefilled syringes containing 0.4 mL (patients without SRI) or 0.2 mL (patients with SRI) of AVE5026 50 mg/mL.

Dose: 20 mg QD (patients without SRI) or 10 mg QD (patients with SRI, ie, with CLcr <30 mL/min at screening)

Administration: SC route

Batch numbers: [redacted]

Duration of treatment: 7 to 10 days after surgery

Duration of observation: Maximum of 42 days from surgery, including a treatment period of 7 to 10 days, and a follow-up period with a visit at Day 35-42 after surgery.

Reference therapy: Enoxaparin: ready-to-use prefilled syringes containing 0.4 mL (patients without SRI) or 0.2 mL (patients with SRI) of enoxaparin 100 mg/mL

Dose: 40 mg QD (patients without SRI) or 20 mg QD (patients with SRI)

Administration: SC route

Batch numbers: [redacted]

Placebo (used as a dummy treatment): ready-to-use prefilled syringes containing 0.4 mL (patients without SRI) or 0.2 mL (patients with SRI) of sterile isotonic solution with 0.9% sodium chloride and water for injection

Dose: 0 mg

Administration: SC route

Batch numbers: [redacted]

Criteria for evaluation:

Efficacy: The primary efficacy endpoint was a composite of any VTE confirmed by a blinded Central Independent Adjudication Committee (CIAC) and deaths from any cause reported during the efficacy evaluation period, ie, from the day of randomization up to Day 11 or up to the day of the mandatory bilateral venography (Day 7-Day 11), whichever came first.

Secondary endpoints:

- Composite of the following endpoints recorded during the efficacy evaluation period: any proximal deep vein thrombosis (DVT), symptomatic distal DVT, nonfatal pulmonary embolism (PE), and all cause deaths
- Initiation of curative anticoagulant or thrombolytic treatment by the Investigator after local VTE assessment.

Safety: Major bleedings and clinically relevant nonmajor bleedings as confirmed by the CIAC, transfusion requirement, hemoglobin, platelet count, liver and renal laboratory data, serious and nonserious adverse events (AEs), and deaths up to 3 calendar days after last study treatment injection as well as up to Day 42.

Pharmacokinetics: Plasma concentrations of semuloparin were assessed in all patients at selected centers.

Pharmacokinetic sampling times and bioanalytical methods:

Blood samples were to be taken from all patients at selected centers. For each patient, 4 blood samples were to be drawn at the following times: on Day 1 between 0.5-1h, 2-4h, and 10-16h after the first postoperative study drug injection, and on the last treatment day (Day 7-10) or the day of discharge whichever came first, just prior to last dosing.

Semuloparin concentrations were determined based on their anti-Xa activity using an automated chromogenic assay, with a lower limit of quantification (LLOQ) of 0.348 µgEq/mL.

Statistical methods:

Populations analyzed

- Primary efficacy population: all randomized patients who received at least one study treatment injection, underwent hip fracture surgery, and had a nonmissing primary efficacy assessment;
- Efficacy evaluable patients: all randomized patients who received at least one study treatment injection, underwent hip fracture surgery, and had a nonmissing assessment for the parameter analyzed (ie, components of primary and secondary composite endpoints);
- Safety population: all randomized patients who received at least one study treatment injection;
- Pharmacokinetic (PK) population (considered for descriptive statistics): all randomized patients treated with semuloparin and for whom at least one plasma trough concentration (C_{trough}: predose concentration) at steady-state was available.

Efficacy analysis

Primary efficacy endpoint: analyses were performed on the primary efficacy population. The primary analysis consisted in the comparison of the 2 treatment groups using an exact 2-sided stratified test at the alpha level of 0.05 (Gart 1970). Event rates and exact 2-sided 95% confidence intervals (CI) per treatment group together with common odds ratio, stratified on renal status (SRI/Non SRI) and timing of first study treatment injection (preoperative/postoperative), and exact 2-sided 95% CI were calculated. In addition, risk reduction and absolute difference were 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.

Safety analyses

All safety analyses were performed on the safety population.

Event rates and exact 2-sided 95% CI per treatment group together with odds ratio and exact 2-sided 95%CI (based on the mid-p method) were calculated for any clinically relevant bleeding, major and clinically relevant nonmajor bleeding only.

Adverse event data were summarized by system organ class and preferred term. The number and percentage of patients with treatment-emergent adverse events (TEAEs), serious TEAEs, TEAEs leading to permanent treatment discontinuation, and deaths, were provided.

For laboratory parameters, potentially clinically significant abnormality (PCSA) criteria were computed and summarized regardless of baseline status and/or according to baseline status categories.

Pharmacokinetic analyses

Descriptive statistics (number of observations, arithmetic mean, standard deviation, coefficient of variation, geometric mean, median, minimum and maximum) were presented for semuloparin C_{trough} concentrations in the PK population, overall and by dose. Samples with missing date and/or time for the previous investigational product injection were discarded. Concentrations below the LLOQ were replaced by the LLOQ/2 (0.348 µgEq/mL/2 = 0.174 µgEq/mL). If the median, the minimum, and/or the calculated mean were below the LLOQ, then the result was provided as “<LLOQ”.

Summary of results:

Population characteristics: Patient demographic and baseline characteristics were similar in the 2 treatment groups.

Efficacy results:

Semuloparin produced a nonsignificant reduction in the rate of any confirmed VTE or all cause death (primary efficacy endpoint) compared to enoxaparin. The odds-ratio was 0.77 (0.53 to 1.12), 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.

Any VTE or death during the efficacy analysis period - Primary efficacy analysis - Primary efficacy population

	AVE5026 (N=384)	**enoxaparin (N=369)**
Any VTE or death		
n (%)	68 (17.7)	81 (22.0)
95% exact CI	(14.0 to 21.9)	(17.8 to 26.5)
Comparison vs. enoxaparin		
Common Odds ratio (95% exact CI)		0.77 (0.53 to 1.12)
p-value		0.1699
Relative risk (95% CI)		0.81 (0.60 to 1.08)
Absolute risk difference (95% CI)		-4.24 (-9.94 to 1.45)

Note: Stratification factors are SRI/non-SRI (based on the actual estimated creatinine clearance at randomization) and timing of first study treatment injection.
Note: Common odds ratio and p-value from exact two-sided stratified test (Gart 1970)

The rate of any proximal DVT, symptomatic distal DVT, nonfatal PE, and all cause death (secondary composite endpoint) was lower in the semuloparin group than in the enoxaparin group but the difference was not significant (5.6% versus 7.7%, respectively, odds ratio 0.71 [95% mid-p CI: 0.41 to 1.24]).

Safety results:

Overall, in patients undergoing hip fracture surgery, semuloparin and enoxaparin showed similar safety profiles.

Treatment-emergent bleeding events were reported by 10.7% of patients in the semuloparin group and 8.4% of patients in the enoxaparin group. Of these, 4 (0.8%) patients in the semuloparin group and 2 (0.4%) patients in the enoxaparin group reported serious bleedings, none of them associated with a fatal outcome.

The proportions of patients with any confirmed clinically relevant bleedings (major or nonmajor) were 2.0% and 0.8% in the semuloparin and enoxaparin groups, respectively.

Safety results (Cont'd):

Number (%) of patients with treatment-emergent clinically relevant bleeding(s) - Safety population

	AVE5026 (N=488)	enoxaparin (N=499)	Odds Ratio (95% mid-p CI)
Any clinically relevant bleeding			
n (%)	10 (2.0%)	4 (0.8%)	2.59
95% mid-p CI	(1.0 to 3.6)	(0.3 to 1.9)	(0.83 to 9.57)
Any major bleeding			
n (%)	5 (1.0%)	3 (0.6%)	1.71
95% mid-p CI	(0.4 to 2.3)	(0.2 to 1.6)	(0.39 to 8.73)
Any clinically relevant non major bleeding only			
n (%)	5 (1.0%)	1 (0.2%)	5.16
95% mid-p CI	(0.4 to 2.3)	(0.0 to 1.0)	(0.71 to 122.89)

No fatal bleedings and no symptomatic bleedings into a critical area or organ were reported in either treatment group. No differences were observed between the 2 treatment groups with regard to the number of blood transfusions or the extent of hemoglobin decreases from baseline.

Overall, TEAEs were reported at a similar frequency (approximately 36%) in the 2 treatment groups and led to permanent treatment discontinuation in a small number of patients (3.3% in the semuloparin group versus 3.2% in the enoxaparin group) (see table below).

The percentage of patients who experienced serious TEAEs was low and similar in the semuloparin and enoxaparin groups (5.7% and 5.4%, respectively). Eleven patients experienced TEAEs leading to death, 8 of them in the semuloparin group (5 deaths unrelated to VTE or bleeding and 3 deaths related to PE: 2 during the on-treatment period and 1 during the post-treatment period) and 3 in the enoxaparin group (all unrelated to VTE or bleeding).

Overview of adverse event profile: Treatment emergent adverse events - Safety population

n(%)	AVE5026 (N=488)	enoxaparin (N=499)
Patients with any TEAE	174 (35.7%)	180 (36.1%)
Patients with any treatment-emergent bleeding AE	52 (10.7%)	42 (8.4%)
Patients with any TEAE other than bleeding AE	160 (32.8%)	165 (33.1%)
Patients with any serious TEAE	28 (5.7%)	27 (5.4%)
Patients with any serious treatment-emergent bleeding AE	4 (0.8%)	2 (0.4%)
Patients with any TEAE leading to death	8 (1.6%)	3 (0.6%)
Patients with any treatment-emergent bleeding AE leading to death	0	0
Patients with any TEAE leading to permanent treatment discontinuation	16 (3.3%)	16 (3.2%)
Patients with any treatment-emergent bleeding AE leading to permanent treatment discontinuation	5 (1.0%)	1 (0.2%)

Safety results (Cont'd):

Low incidences of patients with thrombocytopenia were observed in the 2 treatment groups (0.8% and 1.0% for semuloparin and enoxaparin, rexpectively). A total of 7 patients (4 in the semuloparin group and 3 in the enoxaparin group) were tested for antiplatelet antibodies and all of them had negative results.

Alanine aminotransferase (ALT) values >3 x the upper limit of normal (ULN) were observed in 3.5% patients of the semuloparin group and 1.4% patients of the enoxaparin group. Total bilirubin values >2 ULN were observed in 1.9% patients of the semuloparin group and 2.8% patients of the enoxaparin group. No cases of ALT >3 ULN associated with total bilirubin >2 ULN during the on-treatment period were observed.

Pharmacokinetic results:

The PK population consisted of 222 patients. The mean semuloparin C_{trough} plasma concentration was 0.78 µgEq/mL with a coefficient of variation of 90.0%, following treatment with semuloparin 20 mg QD in non SRI patients (n = 209). In patients with SRI receiving SC administration of 10 mg of semuloparin (n = 13), the mean semuloparin C_{trough} plasma concentration was 0.56 µgEq/mL with a coefficient of variation of 119%.

Conclusions: [redacted]

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