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 elective total hip replacement surgery (EFC10342, SAVE-HIP1).

Investigator(s): [redacted]

Study center(s): 146 active centers in 30 countries

Publications (reference): None

Study period:

Date first patient enrolled: 04-Jun-2008

Date last patient completed: 30-Jun-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 for 7 to 10 days after surgery for the prevention of venous thromboembolic events (VTE) in patients undergoing elective total hip replacement (THR) surgery.

Secondary: To evaluate the safety of semuloparin in patients undergoing elective THR 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 (CL_{cr}) at screening (< or ≥30 mL/min).

Number of patients:

Planned: Approximately 2320 randomized patients (1160 per treatment group)

	AVE5026	enoxaparin	All
Randomized population	1161 (100%)	1165 (100%)	2326 (100%)
Primary efficacy population	916 (78.9%)	933 (80.1%)	1849 (79.5%)
Pharmacokinetic population	537	0	537
Safety population	1153	1155	2308

Diagnosis and criteria for inclusion:

Patients with elective total hip replacement surgery or revision of at least 1 component of a previously implanted total hip prosthesis performed ≥6 months prior to study entry.

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 CL_{cr} <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: 40 mg/0.4 mL and 20 mg/0.2 mL: [redacted]

Placebo (used as 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: 0.4 mL and 0.2 mL: [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, serum potassium, 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 taken in all patients at selected centers. For each patient, 4 blood samples were 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 elective THR, and had a nonmissing primary efficacy assessment;
- Efficacy evaluable patients: all randomized patients who received at least one study treatment injection, underwent elective THR, 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 population (considered for descriptive statistics): all randomized patients treated with semuloparin and for whom at least one plasma trough concentration (C_{trough}: predose concentration) 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. 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.

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 all clinically relevant bleedings, major bleedings and clinically relevant nonmajor bleedings only.

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 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 [SD], coefficient of variation [CV], geometric mean, median, minimum, and maximum) were presented for semuloparin C_{trough} concentrations (predose 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 value of 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 20 mg QD (10 mg in patients with SRI) for 7 to 10 days after THR surgery was more effective in preventing VTE and death than enoxaparin 40 mg QD (20 mg in patients with SRI). The rate of any confirmed VTE or all cause death (primary efficacy endpoint) was significantly lower in the semuloparin group than in the enoxaparin group (6.3% versus 11.1%, odds ratio and 95% exact CI: 0.54 [0.38-0.76], p = 0.0003), see table below.

Any VTE or death during the efficacy analysis period – Primary efficacy analysis

	AVE5026 (N=916)	**enoxaparin (N=933)**
Any VTE or death		
n (%)	58 (6.3)	104 (11.1)
95% exact CI	(4.8 to 8.1)	(9.2 to 13.3)
Comparison vs. enoxaparin		
Common Odds ratio (95% exact CI)		0.54 (0.38 to 0.76)
p-value		0.0003
Relative risk (95% CI)		0.57 (0.42 to 0.77)
Absolute risk difference (95% CI)		-4.81 (-7.38 to -2.25)

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.

The rate of any proximal DVT, symptomatic distal DVT, nonfatal PE, and all cause death (secondary composite endpoint) was lower in the semuloparin group compared to the enoxaparin group but the difference did not reach statistical significance (1.5% versus 2.2%, odds ratio 0.68 [95% CI 0.35-1.33]).

Safety results:

Overall, in patients undergoing elective hip replacement surgery, semuloparin produced less clinically relevant major or nonmajor bleedings than enoxaparin. No other differences were observed between the safety profiles of the 2 drugs.

Treatment-emergent bleeding events were reported by 11.4% of patients in the semuloparin group and 13.2% of patients in the enoxaparin group. Of these, 4 (0.3%) patients in the semuloparin group and 5 (0.4%) patients in the enoxaparin group reported serious bleedings, none of them being associated with a fatal outcome.

There were significantly fewer patients with confirmed major or nonmajor clinically relevant bleedings in the semuloparin group than in the enoxaparin group (1.0% versus 2.2%, odds ratio and 95% mid-p CI: 0.48 [0.23-0.94]). There were also significantly fewer patients with major bleedings in the semuloparin group than in the enoxaparin group (4 [0.3%] versus 14 [1.2%]), see table below. No fatal bleedings and no symptomatic bleedings into critical areas or organs were reported in any treatment group.

Safety results (Cont'd):

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

	AVE5026 (N=1153)	enoxaparin (N=1155)	Odds Ratio (95% mid-p CI)
Any clinically relevant bleeding			
n (%)	12 (1.0%)	25 (2.2%)	0.48
95% mid-p CI	(0.6 to 1.8)	(1.4 to 3.1)	(0.23 to 0.94)
Any major bleeding			
n (%)	4 (0.3%)	14 (1.2%)	0.28
95% mid-p CI	(0.1 to 0.8)	(0.7 to 2.0)	(0.08 to 0.83)
Any clinically relevant non major bleeding only			
n (%)	8 (0.7%)	11 (1.0%)	0.73
95% mid-p CI	(0.3 to 1.3)	(0.5 to 1.6)	(0.28 to 1.83)

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. Slightly less patients in the semuloparin group had at least one postbaseline hemoglobin value <70 g/L compared to the enoxaparin group.

Overall, TEAEs were reported in approximately half of the patients (semuloparin: 48.0%; enoxaparin: 49.4%) and led to permanent treatment discontinuation in a small number of patients (2.0% in the semuloparin group versus 2.9% in the enoxaparin group) in the 2 treatment groups (see table below).

The percentage of patients who experienced serious TEAEs was low and comparable in the semuloparin group and the enoxaparin group (2.8% and 3.7%, respectively). Three patients experienced serious TEAEs leading to death, one patient in the semuloparin group, who actually only received the preoperative placebo injection, and 2 patients in the enoxaparin group.

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

n(%)	AVE5026 (N=1153)	enoxaparin (N=1155)
Patients with any TEAE	554 (48.0%)	571 (49.4%)
Patients with any treatment-emergent bleeding AE	131 (11.4%)	152 (13.2%)
Patients with any TEAE other than bleeding AE	508 (44.1%)	513 (44.4%)
Patients with any serious TEAE	32 (2.8%)	43 (3.7%)
Patients with any serious treatment-emergent bleeding AE	4 (0.3%)	5 (0.4%)
Patients with any TEAE leading to death	1 (<0.1%)	2 (0.2%)
Patients with any treatment-emergent bleeding AE leading to death	0	0
Patients with any TEAE leading to permanent treatment discontinuation	23 (2.0%)	34 (2.9%)
Patients with any treatment-emergent bleeding AE leading to permanent treatment discontinuation	3 (0.3%)	4 (0.3%)

Safety results (Cont'd):

The incidence of thrombocytopenia was low in both treatment groups (1.5% and 1.3% for semuloparin and enoxaparin, respectively). A total of 14 patients (6 in the semuloparin group and 8 in the enoxaparin group) were tested for antiplatelet antibodies and all of them gave negative results.

Alanine aminotransferase (ALT) values >3 x the upper limit of normal (ULN) were observed in 4.2% of patients in the semuloparin group and 5.8% of patients in the enoxaparin group. Total bilirubin values >2 ULN were observed in 3.2% of patients in the semuloparin group and 1.8% of patients in the enoxaparin group. Six patients in the semuloparin group and 1 patient in the enoxaparin group had ALT values >3 ULN combined with total bilirubin values >2 ULN during the on-treatment period. None of the cases was adjudicated as "Hy's law cases" by a blinded independent adjudicator expert.

Serum potassium values $\geq$5.5 mmol/L were observed in 14/562 (2.5%) of patients in the semuloparin group and 11/557 (2.0%) of patients in the enoxaparin group. None of these patients had associated cardiac disorders.

Pharmacokinetic results: The PK population consisted of 537 patients (all non SRI patients). $C_{through}$ values ranged from <LLOQ to 5.0 µgEq/mL with a mean value of 0.56 µgEq/mL and a coefficient of variation of 76.6%.

Conclusions: [redacted]

Date of report: 03-May-2011