SYNOPSIS

Title of the study: A Multinational, Multicenter, Randomized, Double-Blind study Comparing the Efficacy and Safety of AVE5026 with placebo for the Extended Prevention of Venous Thromboembolism in Patients Having Undergone Hip Fracture Surgery (EFC10636/SAVE-HIP3)

Investigators: [redacted]

Study centers: 77 active centers in 16 countries

Publications (reference): Not applicable

Study period:

Date first patient enrolled: 30-Jun-2008

Date last patient completed: 22-Jan-2010

Phase of development: Phase 3 study

Objectives:

Primary objective: To compare the efficacy of once daily (QD) subcutaneous (SC) injections of 20 mg semuloparin (10 mg in patients with severe renal insufficiency [SRI]) with placebo during 3 additional weeks following an initial 7 to 10 days of open-label venous thromboprophylaxis with QD SC injections of 20 mg semuloparin (10 mg in patients with SRI) for the prevention of venous thromboembolic events (VTE), in patients having undergone hip fracture surgery (HFS).

Secondary objectives: To evaluate the safety of extended semuloparin prevention in patients having undergone HFS.

Methodology: This was a multinational, multicenter, randomized, double-blind study, with two parallel groups (semuloparin and placebo) after an initial open-label run-in phase with semuloparin for 7 to 10 days.

All eligible patients were enrolled in the run-in phase and were to be treated with QD, SC injections of semuloparin 20 mg (10 mg for patients with chronic SRI) for 7 to 10 days after surgery. At Day 7-10 of the run-in phase, patients were randomly assigned in a double-blind manner to receive subcutaneously either semuloparin 20 mg QD (10 mg for patients with SRI), or placebo for 19 to 23 additional days. Randomization was stratified by region (North America, South America, Western Europe, Eastern Europe, Asia, and Rest of the World), and patient renal function status (SRI/no SRI) based on the estimated creatinine clearance (CL_{CR}) at randomization (CL_{CR} <30 or ≥30 mL/min).

Number of patients:

Planned: Approximately 505 patients were planned to be included in the run-in phase, in order to randomize at least 454 patients in the double-blind treatment phase in a 2:1 randomization ratio (2 patients with semuloparin for 1 with placebo).

Treated during the run-in phase: 506

Randomized in the double-blind treatment phase: 469 (see table below)

	semuloparin	placebo	All
Randomized population	312 (100%)	157 (100%)	469 (100%)
Primary efficacy population	230 (73.7%)	102 (65.0%)	332 (70.8%)
Safety population*	312	157	469

*all randomized and treated population during the double-blind treatment phase

Diagnosis and criteria for inclusion:

Patients with standard surgery for fracture of the upper third of the femur, including femoral head and neck, who had completed the run-in phase, and were still complying with the selection criteria.

Investigational product: semuloparin sodium (AVE5026) – ready-to-use 0.5 mL pre-filled syringes containing 0.4 mL (semuloparin 20 mg QD) or 0.2 mL (semuloparin 10 mg QD)

Doses: In the open run-in phase and in the double-blind treatment phase: 20 mg QD for patients without SRI or 10 mg QD for patients with SRI (ie, with an estimated CL_{CR} <30 mL/min)

Administration: SC injection QD

Batch numbers: semuloparin 20 mg/0.4 mL: [redacted]

semuloparin 10 mg/0.2 mL: [redacted]

Duration of treatment: Open-label semuloparin treatment for 7 to 10 days during the run-in phase followed by a double-blind treatment phase with semuloparin or placebo for additional 19 to 23 days

Duration of observation: Maximum of 64 days from surgery including a run-in phase of 7 to 10 days, a double-blind treatment phase of 19 to 23 days, and a follow-up period of 28 $\pm$ 3 days after study medication discontinuation

Reference therapy: Placebo during the double-blind treatment phase - ready-to-use 0.5 mL prefilled syringes, identical in appearance to semuloparin syringes

Dose: not applicable

Administration: SC injection QD

Batch numbers: placebo 0.4 mL: [redacted]; placebo 0.2 mL: [redacted]

Criteria for evaluation:

Efficacy:

Primary efficacy endpoint: 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. The efficacy evaluation period lasted from the day of randomization, up to Day 24, or up to the day of the mandatory bilateral venography (Day 19 - Day 24), whichever came first.

Secondary efficacy endpoint

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

Safety:

Safety parameters included major bleedings, clinically-relevant nonmajor bleedings as confirmed by the CIAC, transfusions requirements, hemoglobin, platelet count, liver and renal laboratory data, serious and nonserious adverse events (AEs), and deaths up to 3 days after last investigational product (IP) injection and up to 28 $\pm$ 3 days after study medication discontinuation, as per Protocol Amendment No. 1.

Deaths and bleedings occurring from randomization to the end of study were adjudicated by the CIAC.

Pharmacokinetic sampling times and bioanalytical methods:

Not applicable.

Statistical methods:

Populations analyzed:

Efficacy populations: All randomized patients who received at least one IP injection during the double-blind treatment phase, underwent HFS, and with a nonmissing efficacy assessment for the parameter analyzed.

Main safety population: All randomized patients who received at least one IP injection during the double-blind treatment phase.

Second safety population: All patients who received at least one open-label semuloparin treatment injection during the run-in phase.

Efficacy analyses:

Primary efficacy endpoint: 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 as well as common odds ratio and exact 2-sided 95% CIs, stratified on renal function status (SRI/Non SRI), were calculated. In addition, risk reduction and absolute difference were presented with 2-sided 95% CIs.

Safety analyses:

Safety analyses were carried out on the main safety population for the double-blind treatment phase and on the secondary safety population for the run-in phase. Event rates and exact 2-sided 95% CIs per treatment group as well as odds ratio and exact 2-sided 95%CIs (based on the mid-p method) were calculated for any clinically-relevant bleeding, major and clinically-relevant nonmajor bleeding only, for the main safety population. Adverse event data were summarized by study period, system organ class and preferred term, numbers and percentages of patients with treatment-emergent adverse events (TEAEs), serious TEAEs, TEAEs leading to permanent treatment discontinuation, and deaths, and numbers and percentages of patients with run-in AEs, serious run-in AEs, and run-in AEs leading to permanent run-in treatment discontinuation. For laboratory parameters, potentially clinically significant abnormalities criteria (including liver toxicity criteria) were computed and summarized irrespective of baseline status and/or according to the baseline status categories.

Summary:

Study population:

Population characteristics: Patients' demographic and baseline characteristics were similar in the 2 treatment groups. In the main safety population, patients had a mean age of 69.0 years with 41.4% of patients older than 75 years. Approximately 42% of the patients had a normal renal function, 40% had mild renal impairment, 16% had moderate renal impairment, and 3% had severe renal impairment.

Efficacy results:

Primary efficacy outcome:

After HFS, treatment with semuloparin 20 mg QD (10 mg QD in patients with SRI) for 19 to 23 additional days, following 7 to 10 days of open-label treatment with semuloparin 20 mg QD (10 mg QD in patients with SRI), significantly reduced the rate of any confirmed VTE or all cause death, compared with placebo (odds ratio and 95% exact CI: 0.18 [0.07 to 0.45], p<0.0001; relative risk and 95% CI: 0.21 [0.10 to 0.45]).

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

	AVE5026 (N=230)	Placebo (N=102)
Any VTE or death		
n (%)	9 (3.9)	19 (18.6)
95% exact CI	(1.8 to 7.3)	(11.6 to 27.6)
Comparison vs. placebo		
Common Odds ratio (95% exact CI)		0.18 (0.07 to 0.45)
p-value		<0.0001
Relative risk (95% CI)		0.21 (0.10 to 0.45)
Absolute risk difference (95% CI)		-14.71 (-22.67 to -6.75)

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

All sensitivity analyses confirmed the robustness of the primary efficacy result. The superiority of semuloparin compared to placebo demonstrated in the primary efficacy population for all patients was observed in the most important subgroups analyzed (stratification factors and demographic characteristics).

Semuloparin also reduced the rates of all the components of the primary efficacy endpoint. The difference was statistically significant for any DVT and any proximal DVT.

Secondary efficacy composite outcome:

The rate of any proximal DVT, symptomatic distal DVT, nonfatal PE, and all-cause deaths was significantly lower in the semuloparin group than in the placebo group (1.5% versus 10.3%, respectively, odds ratio 0.13 [95% mid-p CI: 0.04 to 0.40]).

Initiation of curative treatment, following VTE assessment at Investigators site:

The percentage of patients requiring the initiation of curative treatment following VTE assessment was significantly lower in the semuloparin group than in the placebo group (1.7% versus 7.9%, odds ratio: 0.21 [95% mid-p CI: 0.06 to 0.60]).

Safety results:

Overall, during the double-blind treatment phase, treatment-emergent bleeding events were reported in 7 patients: 5 in the semuloparin group and 2 in the placebo group. In the semuloparin group, 2 bleeding events were adjudicated as clinically-relevant bleeding events, including one major. In the placebo group, one intracranial hemorrhage not radiologically confirmed and one pulmonary hemorrhage secondary to pulmonary embolism (PE) were adjudicated as not clinically relevant.

Treatment-emergent AEs were reported in approximately one quarter of the patients (semuloparin: 23.1%; placebo: 25.5%), and led to permanent double-blind treatment discontinuation in a small number of patients in both treatment groups (semuloparin: 1.6%; placebo: 2.5%). The incidence of serious TEAEs was lower in the semuloparin group than in the placebo group (1.9% versus 4.5%).

Three patients, one in the semuloparin group and two in the placebo group, experienced a TEAE leading to death. In the semuloparin group, the death was adjudicated as not associated with VTE or bleeding and in the placebo group, one death was adjudicated as fatal PE and one as cardiovascular death.

The overview of AE profile in the double-blind treatment phase is presented in the table that follows.

Overview of adverse event profile: Treatment-emergent adverse events - All randomized and treated population during Double-blind phase

n(%)	AVE5026 (N=312)	Placebo (N=157)
Patients with any TEAE	72 (23.1%)	40 (25.5%)
Patients with any treatment-emergent bleeding AE	5 (1.6%)	2 (1.3%)
Patients with any TEAE other than bleeding AE	68 (21.8%)	40 (25.5%)
Patients with any serious TEAE	6 (1.9%)	7 (4.5%)
Patients with any serious treatment-emergent bleeding AE	1 (0.3%)	2 (1.3%)
Patients with any TEAE leading to death	1 (0.3 %)	2 (1.3%)
Patients with any treatment-emergent bleeding AE leading to death	0	1 (0.6%)
Patients with any TEAE leading to permanent treatment discontinuation	5 (1.6%)	4 (2.5%)
Patients with any treatment-emergent bleeding AE leading to permanent treatment discontinuation	1 (0.3%)	1 (0.6%)

n (%) = number and percentage of patients with at least one TEAE

Two out of 308 patients in the semuloparin group, and none in the placebo group, had a platelet count <100 Giga/L. Thrombocytopenia was not reported as AE, and antiplatelet antibodies were not assessed.

Alanine aminotransferase (ALT) values >3 ULN were observed in 7/307 (2.3%) semuloparin-treated patients versus none in the 151 placebo-treated patients. Total bilirubin values>2 ULN were observed in 7/308 (2.3%) semuloparin-treated patients versus 2/151 (1.3%) placebo-treated patients. Two patients in the semuloparin group, versus none in the placebo group, had ALT values >3 ULN combined with total bilirubin values >2 ULN during the double-blind treatment period (two additional patients had ALT >3 ULN and total bilirubin >2 ULN during the run-in period). All events were adjudicated as “No Hy’s law” by the blinded independent adjudicator expert.

Conclusions:

[redacted]

Date of report: 10-Jun-2011