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Sponsor / Company: sanofi **Drug substance(s):** semuloparin (AVE5026)	**Study Identifiers:** NCT00679588, EudraCT 2007-007942-36 **Study code:** EFC6520

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 Major Abdominal Surgery (EFC6520/SAVE-ABDO)

Study centers: This study was conducted at 268 sites in 39 countries.

Study period:

Date first patient enrolled: 30/Apr/2008

Date last patient completed: 12/Aug/2010

Phase of development: Phase 3

Objectives:

Primary objective:

To compare the efficacy and safety of once daily (QD) subcutaneous (SC) injections of 20 mg semuloparin (AVE5026) (10 mg in severe renal impairment [SRI] patients) with QD SC injections of 40 mg enoxaparin (20 mg in SRI patients) administered up to Day 7 to 10 for the prevention of venous thromboembolic events (VTEs) in patients undergoing major abdominal surgery.

Secondary objective:

To evaluate the safety of semuloparin in patients undergoing major abdominal surgery, and to document semuloparin exposures in this population.

Methodology: This was a multinational, multicenter, randomized, double-blind study to compare the efficacy and safety of QD SC injections of 20 mg semuloparin with QD SC injections of 40 mg enoxaparin for the prevention of VTE. The study was conducted in 2 parallel groups (semuloparin and enoxaparin) in patients who were scheduled to undergo major abdominal surgery.

Number of patients:

Planned: 4400 (2200 patients per treatment group)

Randomized: 4413

Treated: 4352

Evaluated:

Efficacy: 3030

Safety: 4352

Pharmacokinetics (PK): 656

Diagnosis and criteria for inclusion: Patients undergoing major surgery (open surgery under general anesthesia and expected to last >45 minutes) in the peritoneal and/or the retroperitoneal space and/or the pelvis minor (but not limited to the pelvis minor) for indications other than limited disease of the liver (including hepatobiliary system), the uterus, or the prostate. Patients <60 years of age having one of the following additional risk factors:

- history of VTE, obesity (body mass index of ≥30 kg/m^2), chronic heart failure, chronic respiratory failure, inflammatory bowel disease, cancer surgery

Study treatments

Investigational medicinal products: semuloparin (AVE5026)

Formulation: solution in ready-to-use prefilled syringe

Dose: 20 mg QD (10 mg QD for patients with SRI)

Route of administration: SC

Reference therapy: enoxaparin

Formulation: solution in ready-to-use prefilled syringe

Dose: 40 mg QD (20 mg QD for patients with SRI)

Routes of administration: SC

Duration of treatment: Enoxaparin was to be started preoperatively, semuloparin postoperatively. Both treatments were administered QD for 7 to 10 days postsurgery.

Duration of observation: The maximum duration of study participation was 42 days.

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 analysis period.

The efficacy analysis period lasted from the randomization up to the day of the mandatory bilateral venography of the lower limbs, or up to Day 11 (Day 1 was the day of surgery), whichever came first.

Secondary efficacy endpoints:

- Composite endpoint of any VTE confirmed by the CIAC and VTE-related deaths reported during the efficacy analysis period. (sensitivity analysis of the primary efficacy analysis)
- Composite endpoint of any proximal deep vein thrombosis (DVT), symptomatic distal DVT, nonfatal pulmonary embolism (PE), and all-cause deaths reported during the efficacy analysis period.
- Initiation of curative anticoagulant or thrombolytic treatment by the Investigator after local VTE assessment.

Safety:

Safety parameters assessed during the study included:

- Bleeding events
- Transfusions
- Adverse events (AEs) and serious adverse events (SAEs)
- Clinical laboratory tests (biochemistry, hematology)

Pharmacokinetics:

Plasma concentrations of semuloparin were assessed in all patients from selected centers using a chromogenic enzyme assay.

Pharmacokinetic sampling times and bioanalytical methods:

Blood samples were taken in all patients at selected centers. For each patient, 5 blood samples were drawn at the following time points:

- On Day 1: at 0.5 to 1 and 2 to 4 hours after the first postoperative intraperitoneal (IP) injection (if for any reason the PK sampling was not performed on Day 1, it had to be done on Day 2 with the same timing after the daily IP injection).
- On Day 4: 6 to 8 and 10 to 16 hours after the daily IP injection.
- On the last treatment day (Day 7 to 10) or the day of discharge, whichever came first, just before the last IP injection.

Semuloparin plasma concentrations were determined based on the 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 major abdominal surgery (open surgery under general anesthesia and lasting more than 45 minutes), and had a nonmissing primary efficacy assessment;
- Secondary efficacy population: all randomized patients who received at least one study treatment injection, underwent major abdominal surgery, and had a nonmissing secondary efficacy assessment;
- Efficacy evaluable population: all randomized patients who received at least one study treatment injection underwent major abdominal surgery, and had a nonmissing assessment for the parameter analyzed (ie, components of primary and secondary composite endpoints);
- Per-protocol populations : the per-protocol population for the analysis of the primary and secondary efficacy composite endpoints consisted of the primary and secondary efficacy composite endpoint population respectively, excluding:
  - Patients <60 years of age with no additional risk factor for VTE
  - Patients who took a prohibited medication during the efficacy analysis period and before a confirmed VTE event, if any
  - Patients with at least one day without active injection during the efficacy analysis period and before a confirmed VTE event, if any;
- Safety population: all randomized patients who received at least one study treatment injection;
- 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 a stratified common odds ratio. The noninferiority was reached if the upper limit of the confidence interval (CI) was lower than 1.25. The superiority was to be tested if the noninferiority was demonstrated on both the primary efficacy and the secondary efficacy composite endpoints. Stratification factors were the reason for surgery (cancer/noncancer), and patients with/without SRI at randomization (actual strata). The event rates and exact 2-sided 95% CIs per treatment group together with common odds ratio, 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 any clinically relevant bleeding, major bleeding and clinically relevant nonmajor bleeding only.

Adverse event data were summarized by system organ class (SOC) and preferred term (PT). 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.

Pharmacokinetics

Plasma concentrations of semuloparin were summarized using descriptive statistics (number of observation, arithmetic mean, standard deviation (SD), coefficient of variation (CV), geometric mean, median, minimum and maximum) and were presented for semuloparin C_{trough} concentrations on the PK population, overall and by dose. Plasma concentrations were classified as C_{trough} if

- the time interval between last IP injection before sampling and sampling time was between 22 to 26 hours;
- the number of active injections up to the sampling was at least:
  - 4 for patients with normal or mild renal status,
  - 6 for patients with moderate or not very severe renal status at baseline (creatinine clearance >15 mL/min),
  - 7 for patients with very severe renal status at baseline (creatinine clearance ≤15 mL/min)

Samples with missing date and/or time of the previous IP injection were discarded. Concentrations below the LLOQ were replaced by the value of the LLOQ/2. If the median, the minimum, and/or a calculated mean were below the LLOQ, then the result was provided as "<LLOQ".

Summary:

Efficacy results:

The primary efficacy outcome occurred in 97/1531 (6.3%) patients in the semuloparin group and in 82/1499 (5.5 %) patients in the enoxaparin group. Based on the prespecified, conservative noninferiority margin of 1.25 on common odds ratio, noninferiority of semuloparin started postoperatively versus enoxaparin started preoperatively could not be demonstrated (common odds ratio: 1.16 [95% exact CI: 0.84 to 1.59]). The slightly higher incidence of VTE in the semuloparin group was mainly driven by distal DVT.

The 5.5% primary endpoint event rate observed with enoxaparin was in line with the statistical hypothesis of the protocol (6.0%). Similar conclusions were obtained from the per-protocol population.

The secondary efficacy composite outcome occurred in 2.2% patients in the semuloparin group and in 2.3% patients in the enoxaparin group. The odds ratio for the comparison of semuloparin versus enoxaparin was 0.95 [95% exact CI: 0.61 to 1.49].

The slightly higher incidence in the primary efficacy outcome observed in the semuloparin group compared to enoxaparin was no longer seen when asymptomatic distal DVT events were excluded. Nevertheless, noninferiority could not be demonstrated (ie, the 95% upper limit of the CI was greater than 1.25).

Safety results:

Overall, 90/2175 (4.1%) patients in the semuloparin group and 125/2177 (5.7%) patients in the enoxaparin group experienced a bleeding event that was adjudicated as clinically relevant (odds ratio and 95% mid-p CI: 0.71 [0.54 to 0.93]).

The number of patients with major bleeding events was lower in the semuloparin group that was started postoperatively (63 [2.9%]) than in the enoxaparin group that was started preoperatively (98 [4.5%]) (odds ratio and 95% mid-p CI: 0.63 [0.46 to 0.87]). The incidence of TEAEs, serious TEAEs and permanent treatment discontinuations due to TEAEs were similar between the treatment groups.

The incidence of on-treatment deaths was comparable in both treatment groups with 17 (0.8%) patients in the semuloparin group and 16 (0.7%) patients in the enoxaparin group. However, there were more fatal bleedings in the enoxaparin group and more cardiovascular deaths in the semuloparin group. The percentage of patients with post-treatment deaths was higher in the semuloparin group (1.9%) compared with the enoxaparin group (1.2%). Except for the fatal bleedings in the enoxaparin group, the deaths in both treatment groups appeared to be linked to the patients' underlying conditions, based on the time of onset of fatal AEs and the medical history of these patients. Since the randomization was not stratified according to stage of cancer or life expectancy, it is possible that the higher incidence of post-treatment deaths in the semuloparin group reflects a play of chance.

The frequency of major off-treatment thrombotic events was slightly lower in the semuloparin group (0.6%) than in the enoxaparin group (1.0%). The incidence of patients who experienced platelet count of <100 Giga/L was similar in both treatment groups, with 2.6% for the semuloparin group and 2.8% for the enoxaparin group. Of these patients, 52 (21 in the semuloparin group and 31 in the enoxaparin group) were tested for antiplatelet antibodies. One patient in the enoxaparin group had a positive result, but the subsequent platelet aggregation test was negative, therefore the suspected heparin-induced thrombocytopenia was not confirmed.

The percentage of patients with alanine aminotransferase (ALT) of >3 ULN in the semuloparin group (6.4%) was similar to that in the enoxaparin group (6.2%); as well as the percentage of patients with total bilirubin of >2 ULN, with 5.0% in the semuloparin group and 5.6% in the enoxaparin group. A total of 32 patients, 15 in the semuloparin group and 17 in the enoxaparin group, experienced ALT >3 ULN associated with total bilirubin of >2 ULN during the on-treatment period. None of these cases were adjudicated as Hy's law cases.

Pharmacokinetic results:

Semuloparin was detected in most of the 656 patients analyzed. In the 20 mg treatment group (n=649), the mean semuloparin C_{trough} plasma concentration was 0.600 µgEq/mL and showed a coefficient of variation of 103%.

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