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Sponsor / Company: Sanofi	**Study Identifiers:** NCT00714597, 2008-000228-13
Drug substance(s): Semuloparin sodium (AVE5026)	**Study code:** EFC10572

Title of the study:

A multinational, multicenter, randomized, double-blind study comparing the efficacy and safety of AVE5026 with Enoxaparin for the primary prevention of venous thromboembolism in acutely ill medical patients with restricted mobility (SAVE-VEMED)

Study center(s):

87 active centers in 22 countries/regions (Canada, United States of America, Mexico, Austria, France, Germany, Italy, Netherlands, Spain, United Kingdom, Czech Republic, Estonia, Hungary, Latvia, Lithuania, Romania, Russian Federation, Ukraine, India, Republic of Korea, Australia, New Zealand)

Study period:

Date first patient enrolled: 08 July 2008

Date last /patient completed: 16 March 2009

Phase of development: Phase 3

Objectives:

Primary: to compare the efficacy of once daily (QD), subcutaneous (SC) injections of 20 mg semuloparin (AVE5026) (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 10-14 days for the primary prevention of venous thromboembolic events (VTE) in patients hospitalized for acute medical illness.

Secondary: to evaluate the safety of semuloparin in patients hospitalized for acute medical illness, and to document semuloparin exposures in this population.

Methodology:

Multinational, multicenter, randomized, double-blind study, with 2 parallel groups (semuloparin and, enoxaparin used as an active comparator), in acutely ill medical patients with restricted mobility. The randomization was stratified by center and estimated creatinine clearance (< or ≥30 mL/min).

Number of patients**:** Planned: Approximately 12 300, i.e, about 6 150 per treatment group

Randomized: 421

Treated: 416

Evaluated: Efficacy: 340 Safety: 416 Pharmacokinetics: 26

During a portfolio prioritization review performed in January 2009, the Sponsor has decided to discontinue the EFC10572 study for strategic business reasons; 421 patients were randomized instead of approximately 12300 patients initially planned in the study protocol

Diagnosis and criteria for inclusion:

Patients with acute medical condition requiring bed rest for at least 3 days, age ≥40 years, and hospitalized for at least 1 of the following medical conditions: congestive heart failure (New York Heart Association [NYHA] class III/IV), acute respiratory failure (not requiring mechanical ventilation), acute infection (without septic shock)*, acute rheumatic disorder*, active episode of inflammatory bowel disease*.

*Patients with these conditions should have at least 1 additional risk factor for venous thromboembolism (VTE): age ≥75 years, active cancer or myeloproliferative disorders (having received treatment for cancer within the last 6 months), previous VTE, obesity (body mass index [BMI] ≥30 kg/m2), oral hormone therapy (antiandrogen or estrogen), chronic heart failure, chronic respiratory failure.

Study treatments

Investigational medicinal product(s): semuloparin sodium (AVE5026) or enoxaparin sodium

Formulation: Ready to use 0.5 mL prefilled syringes containing either 0.4 mL or 0.2 mL

Route(s) of administration: Subcutaneous injection

Dose regimen:

Semuloparin sodium: 20 mg QD (patients with no sever renal impairment (SRI)), or 10 mg QD (patients with SRI)

Enoxaparin: 40 mg QD (patients with no SRI), or 20 mg QD (patients with SRI)

SRI was defined as creatinine clearance <30 mL/min at randomization

Duration of treatment: Up to 10-14 days of treatment

Duration of observation: Maximum of 42 days, including a treatment period up to Day 10-14, and a follow-up period with a visit at Day 35-42 after randomization**.**

Criteria for evaluation:

Efficacy:

Primary endpoint: composite of the following VTE outcome results recorded during the efficacy analysis period, and confirmed by blinded independent adjudication Committees: asymptomatic proximal deep vein thrombosis (DVT) detected by CUS, symptomatic DVT in case of symptoms earlier than the date of the mandatory CUS, nonfatal pulmonary embolism (PE) in case of symptoms earlier than the date of the mandatory CUS, VTE-related deaths (fatal PE or unexplained deaths).

Secondary endpoints:

• Each component of the primary efficacy endpoint recorded during the efficacy analysis period: asymptomatic proximal DVT, any symptomatic VTE and VTE-related death.

• Initiation of curative treatment by Investigator following VTE assessment.

The efficacy analysis period was defined as the period from the randomization up to Day 15 or up to the day of the mandatory compression ultrasound (CUS) (Day 10 – Day 15), whichever came first

Safety:

• Bleeding events: clinically relevant, major, clinically relevant non-major bleeding events (adjudicated by the blinded CIAC), transfusions requirement.

• Adverse events (AE).

• Laboratory tests: hemoglobin, platelets count, liver and renal laboratory data.

The safety analysis period was defined as the period from the first investigational product (IP) injection, up to the last IP injection plus 3 calendar days.

Pharmacokinetics:

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

Pharmacokinetic sampling times and bioanalytical methods:

Blood samples were 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 IP; on the last treatment day (Day 10-14), or the day of discharge, whichever came first, just prior the last injection.

Plasma concentrations were classified as Ctrough if time interval between last IP injection before sampling and sampling time was between 22-26 h. Samples with missing date and/or time of the previous IP injection were discarded.

Semuloparin concentrations were quantified from anti-Xa activity using an automated chromogenic enzyme assay, with a lower limit of quantification (LLOQ) of 0.348 µgEq/mL.

Statistical methods:

Efficacy analyses:

Due to the premature termination of the study (and the low number of patients finally enrolled), no formal statistical analyses were performed.

Analyses of the primary efficacy endpoint were performed on the primary efficacy population (all randomized patients who received at least one IP injection, and with a non-missing primary efficacy endpoint). Event rate and exact 2-sided 95% confidence interval (CI) per treatment group and stratum (patients with SRI and patients with no SRI) were calculated. Odds ratio (OR) and exact 2-sided 95% CI were calculated based on the mid-p method.

Safety analyses:

All safety analyses were carried out on the safety population (all randomized patients who received at least one IP injection).

Event rates and exact 2-sided 95% CI per treatment group, as well as OR and exact 2-sided 95% CI (based on the mid-p method), were calculated for any clinically relevant bleeding, major, and clinically relevant non-major bleeding only.

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

For laboratory parameters, potentially clinically significant abnormality (PCSA) criteria were computed and summarized whatever 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 [CV], geometric mean, median, minimum and maximum) were presented for semuloparin Ctrough concentrations on pharmacokinetic (PK) population.

Summary:

Population characteristics:

Study population was consistent with the expected population in this indication, in regards to demographic characteristics and risk factors qualifying for VTE prophylaxis

Efficacy results:

The rate of any confirmed adjudicated VTE was 7/164 (4.3%) (95% mid p CI: [1.9 – 8.3]) in patients on semuloparin, and 5/176 (2.8%) (95% mid p CI: [1.0 – 6.2]) in patients on enoxaparin. One VTE-related death was observed in a patient receiving enoxaparin. Due to the small number of patients finally randomized in the study (3.4% of the initial planned sample size), the power of the primary efficacy analysis did not allow any reliable conclusion.

Safety results:

Seven out of 204 (3.4%) patients on semuloparin, and 7/212 (3.3%) patients on enoxaparin had treatment-emergent bleeding AE; among those, few had bleeding(s) considered as clinically-relevant by the CIAC: 3/204 (1.5%) patients on semuloparin, compared to none on enoxaparin had non-major bleeding(s), while 1/204 (0.5%] patient on semuloparin, compared to 2/212 (0.9%) on enoxaparin, had major bleeding(s). These discordant differences between treatment groups could have been due to the reduced number of patients enrolled (very large CIs). All major bleedings were nonfatal, gastrointestinal events.

The incidence of patients experiencing at least one TEAE other than treatment-emergent bleeding, was numerically lower in the semuloparin-treated patients (61/204, ie, 29.9%), compared to the incidence in the enoxaparin-treated patients (72/212, ie, 34.0%).

Among the patients receiving semuloparin, 3/204 (1.5%) experienced a TEAE leading to death (one post-treatment death), compared to 9/212 (4.2%) patients receiving enoxaparin (one post-treatment death).

A total of 9/204 (4.4%) semuloparin-treated patients and 19/212 (9.0%) enoxaparin-treated patients experienced a serious TEAE, including 1 (0.5%) patient in each treatment group with a serious treatment-emergent bleeding AE. The serious TEAE most frequently reported were consistent with the preexisting diseases of the patients at study entry.

A total of 10/204 (4.9%) semuloparin-treated patients and 12/212 (5.7%) enoxaparin-treated patients permanently discontinued the IP due to TEAE, including 2 (1.0%) semuloparin-treated patients and 1 (0.5%) enoxaparin-treated patient experiencing a treatment-emergent bleeding AE.

PCSA in hemoglobin values (decrease from baseline ≥20 g/L) were observed with a higher incidence in the enoxaparin-treated patients (26/204 [12.7%]), compared to the semuloparin-treated patients (19/199 [9.5%]). Low incidences of thrombocytopenia (platelet count <100 Giga/L) were observed across both treatment groups (3/202 [1.5%] patients on semuloparin, and 5/208 [2.4%] patients on enoxaparin). Among the 3 patients assessed for antiplatelet antibodies, there were no cases of documented drug-induced thrombocytopenia.

Increases of ALT value >3xULN were noted in 11/202 (5.4%) patients receiving semuloparin, and in 7/207 (3.4%) patients receiving enoxaparin. During the on-treatment period, 3/202 (1.5%) patients on semuloparin and 1/207 (0.5%) patient on enoxaparin had ALT value(s) >3xULN in association with total bilirubin value(s) >2xULN; all these increases in liver function parameters were related to the presence or the worsening of the patient's preexisting disease, and were adjudicated as "No Hy's Law" cases by the DILI independent adjudicator expert.

Pharmacokinetic results:

Out of the 204 patients under semuloparin treatment, 38 patients had blood samples drawn, and 26 Ctrough plasma concentrations were analyzed. Overall, the mean Ctrough value was 0.88 µgEq/mL (coefficient of variation of 42.6%).

Three Ctrough values were obtained in severe renally impaired patients after a 10 mg treatment, with a mean value of 0.65 µgEq/mL, a coefficient of variation of 32%, and 23 Ctrough values were obtained in normal or mild/moderate renally impaired patients after a 20 mg treatment with a mean value of 0.91 µgEq/mL and a coefficient of variation of 42.2%. Ctrough concentrations, measured after 10 mg of semuloparin in patients with SRI, were close to those obtained after 20 mg of semuloparin in patients with no SRI, which justified the dosage adjustment in patients with SRI.

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