SYNOPSIS

Title of the study: A multinational, randomized, double blind, placebo-controlled study to evaluate the efficacy and safety of AVE5026 in the prevention of venous thromboembolism (VTE) in cancer patients at high risk for VTE and who are undergoing chemotherapy (EFC6521, SAVE-ONCO)
Investigator(s): [redacted]
Study center(s): 395 active centers in 47 countries (North America, South America, Western Europe, Eastern Europe, Asia and Rest of the world)
Publications (reference): Not applicable.
Study period: Date first patient enrolled: 05 June 2008 Date last patient completed: 16 November 2010
Phase of development: Phase 3 study
Objectives: Primary: To compare the efficacy of semuloparin 20 mg subcutaneous (SC), once daily (QD) with placebo SC QD for the prevention of venous thromboembolism (VTE) in cancer patients at high VTE risk and undergoing chemotherapy. Secondary: To evaluate the safety of semuloparin in cancer patients undergoing chemotherapy, to document semuloparin exposures, to try identifying a metagene predictor of VTE, and to assess the survival status at one year in this population.
Methodology: This was a multinational, multicenter, randomized, double-blind, 2 parallel-group study comparing the efficacy of semuloparin versus placebo, in cancer patients at high VTE risk.
Number of subjects/patients: Planned: approximately 3200 (ie, approximately 1600 patients per treatment group) Randomized: 3212 Treated: 3172 **Evaluated:** Efficacy: 3212 Safety: 3172
Diagnosis and criteria for inclusion: Cancer patients, with metastatic or locally advanced solid tumor (lung, pancreas, stomach, colon/rectum, bladder or ovary), initiating a (new) course of chemotherapy with a minimum intent of 3 months therapy.
Investigational product (IP): semuloparin sodium (AVE5026) – ready-to-use 0.5 mL prefilled syringes containing 0.4 mL of semuloparin 20 mg Dose: 20 mg QD Administration: SC route Batch number(s): [redacted]

Duration of treatment: The study treatment was administered for the duration of the initial chemotherapy, which was expected to last a minimum of 3 months. During the first 3 months, the IP was to be discontinued only if the initial chemotherapy regimen was stopped and was not replaced by a new chemotherapy regimen. After the initial 3 months, the study treatment was discontinued when chemotherapy was stopped, or when at least one antineoplastic drug was changed (ie, addition or removal) due to disease progression or toxicity; however, in case of antineoplastic dose adjustment only, the study treatment was continued as planned. Therefore, the study treatment duration was variable, depending on the duration of chemotherapy.

Duration of observation: Duration of the study treatment, followed by a 1-month follow-up period after the end-of-treatment visit. In addition, survival status was to be collected for all patients, either one year after randomization or at the end of the study (ie, 7 months following randomization of the last patient), whichever came first.

Reference therapy: Placebo - ready-to-use 0.5 mL prefilled syringes, identical in appearance to semuloparin syringes

Dose: not applicable

Administration: SC, QD injection

Batch number(s): [redacted]

Criteria for evaluation:

Efficacy:

Primary efficacy endpoint: Time-to-first occurrence of any component of the composite endpoint of the following documented outcome results, confirmed by the Central Independent adjudication Committee (CIAC), occurring from randomization up to 3 calendar days after last IP injection: any symptomatic deep vein thrombosis (DVT) of the lower limbs, any symptomatic DVT of the upper limbs (including Central venous catheter [CVC]-related thrombosis), any nonfatal pilmonary embolism (PE), or any VTE-related deaths (fatal PE or unexplained deaths)

Secondary efficacy endpoints

- Initiation of curative anticoagulant or thrombolytic treatment by the Investigator after local VTE assessment, during the efficacy evaluation period
- Overall survival (OS) based on the patient survival status that was to be reported either 1 year after randomization, or at study end date (7 months following randomization of the last patient), whichever came first.

Safety: Major bleeding and clinically relevant nonmajor bleeding (as classified by the CIAC), vital signs, transfusions requirement, hemoglobin, platelet count, liver and renal laboratory data, (serious)adverse events ([S]AEs) and deaths up to the follow up visit.

Pharmacokinetics: Pharmacokinetic data were included in a population PK analysis, which is presented in a separate report.

Genomics: Demographics and efficacy outcomes were associated with genomic profiles for analyses, which are to be presented in a separate report.

Pharmacokinetic sampling times: 4 blood samples per patient, ie, 2 samples on Day 1 (0.5-1h after the first IP injection, and 2-4h after the first IP injection) and 2 samples at the following visit (upon patient's arrival, just before IP injection if done on site, and upon patient's discharge, as late as possible).

Genomics sampling time: 1 blood sample per patient on Day 1; mRNA was isolated from the peripheral mononuclear cells, and submitted for microarray analysis.

Statistical methods:

Main populations analyzed:

- Intent-to-treat (ITT) population: population that included all randomized patients, irrespective of the treatment actually received, and which was used for the analysis of the primary and the secondary efficacy endpoints
- Safety population: all randomized patients who received at least one study treatment injection

Efficacy analyses (ITT population):

Primary efficacy endpoint analyses:

The primary analysis consisted in the comparison of the 2 treatment groups, using the 2-sample test of Gray for comparing Cumulative Incidence Functions (CIF), at a significant level of 0.05 (2-sided). Competing events were deaths from cause other than VTE. An estimation of the treatment effect (hazard ratio [HR] and 95% confidence interval [CI]) was given using Fine and Gray regression model for CIFs.

Secondary efficacy endpoint analyses:

- For curative antithrombotic treatment initiated based on the Investigator's assessment of VTE, the event rates and exact 2-sided 95% CI (based on the mid-p method) were calculated per treatment group, as were the exact 95% CI (also based on the mid-p method) on the odds ratio.
- For the OS, comparison between the 2 treatment groups was performed, using a 2-sided log-rank test, at a significant level of 0.05. To handle multiplicity of testing, the test for OS was to be performed if the test on the primary endpoint was significant. An estimation of the treatment effect (HR with corresponding 2-sided 95% CI) was provided using Cox regression model with treatment group as the only term.

Safety analyses (safety population):

For clinically relevant bleeding events (ie, major bleedings, or clinically relevant nonmajor bleedings) and for major bleeding events, the same methodology as for the primary efficacy endpoint was used, but without formal test. Competing events were deaths from cause other than bleedings. For any clinically relevant bleeding, any major bleeding, and any clinically relevant nonmajor bleeding only, event rates and exact 95% CI per treatment group based on the mid-p method were also calculated, as was the exact 95% CI (also based on the mid-p method) on the odds ratio.

Adverse event data (including bleeding events as reported by the Investigator) were summarized by system organ class (SOC) and preferred term (PT). The number and percentage of patients with treatment-emergent AEs (TEAEs), serious TEAEs, TEAEs leading to permanent treatment discontinuation, and deaths, were provided.

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

Summary:

Population characteristics:

Demographic characteristics, cancer diagnosis characteristics, and stages of cancer at baseline, as well as the number and type of VTE risk factors, and the VTE risk score were well balanced between the semuloparin and placebo groups.

Efficacy results:

The patient population consisted of patients receiving chemotherapy for locally-advanced or metastatic solid tumor. More than 40% of the patients had at least 1 VTE risk factor in addition to the risk imposed by the cancer and chemotherapy, and approximately 80% of the patients had a VTE risk score ≥1. In these patients, the treatment with semuloparin 20 mg QD, significantly reduced the rate of any confirmed VTE or VTE-related death, compared with placebo (HR and 95% CI: 0.36 [0.21 - 0.60]; p-value<0.0001). The treatment effect was consistent for DVT and PE with a significant difference with placebo for any symptomatic DVT (odds ratio and 95% mid-p CI: 0.32 [0.15 - 0.62]), as well as for PE (odds ratio and 95% mid-p CI: 0.41 [0.19 - 0.85]).

The treatment effect of semuloparin on VTE-related deaths appeared to be lower: 7 (0.4%) patients in semuloparin, versus 9 (0.6%) patients in placebo; odds ratio and 95% mid-p CI: 0.77 [0.27 - 2.13]. However, it should be noted that VTE-related death included fatal PE and unexplained deaths, without confirmatory autopsy. As detailed in the CIAC adjudication manual, any sudden death could have been adjudicated as fatal PE unless “performed diagnostic test results strongly indicated an alternative diagnosis”. Of the 16 VTE-related deaths that occurred during the study, only one death in the placebo group was adjudicated as fatal PE, while the CIAC commented that all VTE-related deaths in the semuloparin group, and 8 of the 9 VTE-related deaths in the placebo group were cases for which fatal PE could not be excluded or sudden deaths. Of the 16 VTE-related deaths, none of the 7 deaths in the semuloparin group, and 4 of the 9 deaths in the placebo group were reported as fatal PE by the Investigator. Of all the deaths occurring during the study, the Investigator considered due to fatal PE 2 deaths in the semuloparin group (neither one adjudicated as VTE-related death) and 5 deaths in the placebo group (4 of which were adjudicated as VTE-related death). Considering that the adjudication of non fatal PE required objective radiographic evidence, it is likely that the apparently lower treatment effect of semuloparin on VTE-related deaths reflects the more subjective interpretation of the cause of death and the very conservative approach to the diagnosis of this endpoint that included fatal PE and “unexplained death", since an autopsy is almost never performed in patients with cancer.

All sensitivity analyses confirmed the robustness of the primary efficacy analysis. The treatment effect was consistent across the most important subgroups, including cancer type, cancer stage, number of additional risk factors and VTE risk score.

Semuloparin did not show superiority over placebo in OS (HR and 95% CI: 0.96 [0.86 - 1.06]; p-value = 0.4028). Lack of benefit on OS was not unexpected since the study was not designed as a survival study; hence it enrolled patients with heterogenous cancer types and stages. In addition, the vast majority of patients had metastatic cancer and life expectancy too short to be significantly prolonged. Indeed, the HR and 95% CI for OS in patients with locally-advanced cancer was 0.86 [0.70 - 1.05], while no favorable trend was observed in patients with metastatic cancer (HR and 95% CI: 1.00 [0.89 - 1.13]). In addition, a post-hoc analysis on patients with locally-advanced lung cancer, the only subgroup of adequate size (n= 491), suggested a benefit of semuloparin on OS, confirming previous findings that anticoagulants may improve survival in patients with better prognosis.

Safety results:

In cancer patients receiving chemotherapy for metastatic or locally advanced solid tumor, treatment with semuloparin 20 mg SC, QD resulted in a higher incidence of clinically relevant bleeding events as compared to placebo (45 [2.8%] patients in the semuloparin group compared with 32 [2.0%] patients in the placebo group; HR and 95% CI: 1.40 [0.89 - 2.21]). This was driven by the clinically relevant nonmajor bleeding events, (26 [1.6%] patients in the semuloparin group and 14 [0.9%] patients in the placebo group; odds ratio and 95% mid-p CI: 1.86 [0.98 - 3.68]), whereas the incidence of major bleeding events was similar between the treatment groups: (19 [1.2%] patients in the semuloparin group and 18 [1.1%] patients in the placebo group; odds ratio and 95% mid-p CI: 1.05 [0.55 to 2.04]). These included:

- 6 patients who experienced a fatal bleeding: 2 (0.1%) in the semuloparin group (1 patient who committed suicide by slashing his wrists, 1 patient who experienced convulsion suspected by the Investigator to be due to bleeding brain metastasis), and 4 (0.3%) in the placebo group, who all experienced a gastrointestinal hemorrhage
- 5 patients who experienced a nonfatal bleeding into a critical area or organ, all of them in the semuloparin group: 1 patient had a cerebral hematoma, suspected to be due to a cavernoma rupture, which recovered with sequelae (lower extremity paresis), and 4 patients (2 pericardial events, 1 intraocular event, and 1 intracranial event in a patient with known brain metastases [major protocol violator]) who recovered.

Overall, 7 patients suffered a fatal or disabling bleeding: 3 in the semuloparin group and 4 in the placebo group.

A higher incidence of clinically relevant bleeding events in the semuloparin group compared to placebo was not observed in patients at increased risk of bleeding, such as the elderly (<65 years: HR and 95% CI of 1.64 [0.94 – 2.85]; 65-75 years: HR and 95% CI of 1.05 [0.45 – 2.48]; ≥75 years: HR and 95% CI of 0.97 [0.14 – 6.79]). Similarly, no pattern of increased bleeding risk with semuloparin was observed with worsening of renal impairment (RI) (normal renal function: HR and 95% CI of 1.79 [0.95 - 3.37]; mild RI: HR and 95% CI of 0.90 [0.43 - 1.89]; moderate RI: HR and 95% CI of 2.20 [0.43 - 11.22]).

Overall, the frequencies of TEAEs, on-treatment, post-treatment, and post-study deaths, serious TEAEs, permanent treatment discontinuations due to TEAEs, and off-treatment major thrombotic events in the semuloparin group, were similar to the corresponding frequencies in the placebo group.

A slightly higher incidence of TEAEs of neoplasm progression was noted in the semuloparin group versus placebo group (21.6%.versus 19.4%). In the study, there was no systematic evaluation of cancer progression. The investigators did not receive any specific guidance or criteria as to when report neoplasm progression as an AE, and, therefore, they may have reported neoplasm progression when new metastases were detected, or when patient's clinical status deteriorated due to his/her underlying cancer. The slightly different rates of neoplasm progression amongst the 2 treatment groups did not result in an imbalance in death, since the OS (deaths up to the survival status that had to be assessed one year after randomization or at the end of the study [ie, 7 months following randomization of the last patient]), was similar between both treatment groups (HR and 95% CI: 0.96 [0.86 – 1.06]). In addition, the Kaplan Meier curves for time to AEs of neoplasm progression or death (progression-free survival) up to the follow-up visit by treatment group were also similar (HR and 95% CI: 1.03 [0.91 - 1.18]). Therefore, the likelihood that the administration of semuloparin promotes neoplasm progression does not appear plausible.

A higher frequency of patients with serious TEAEs in the SOC "Immune system disorder" was observed in the semuloparin group (7 [0.4%] patients) compared to placebo (2 [0.1%] patients). A review of the cases revealed they were generally secondary to chemotherapy or platelet transfusion, with the exception of one event assessed as related to semuloparin. This event (pruritic papules at injection site) led to permanent discontinuation of semuloparin on Day 15 and resolved on Day 30. Furthermore, a review of the SOC "Immune system disorder" or "Skin and subcutaneous tissue disorder" did not reveal any association between generalized hypersensitivity/allergic-type reactions and semuloparin administration.

The rates of patients with a platelet count <50 Giga/L and between the range [50 -100[Giga/L, were similar in both treatment groups, and no cases of study drug-induced thrombocytopenia were evidenced in the 25 patients (10 in the semuloparin group and 15 in the placebo group) assessed for antiplatelet antibody.

The rates of patients with alanine aminotransferase (ALT) >3 ULN during the on-treatment period was 69 (4.8%) in the semuloparin group and 54 (3.8%) in the placebo group among patients with baseline ALT ≤3 or missing (HR and 95% CI: 1.29 [0.90 - 1.84]); 15 [1.0%] patients on semuloparin and 22 [1.5%] patients on placebo presented both ALT >3 ULN and total bilirubin >2 ULN (not necessarily concomitantly) during the treatment period: none were adjudicated as Hy's law case.

The rates of patients with PCSA in vital signs during the on-treatment period were similar in the 2 treatment groups.

Conclusions:

[redacted]

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