SYNOPSIS

Title of the study: A Multicenter, Randomized, Double-Blind, Double-Dummy, Parallel group, Dose Response Study of subcutaneous AVE5026 with an Enoxaparin Calibrator Arm in the Prevention of Venous Thromboembolism in Patients Undergoing Elective Total Knee Replacement Surgery (Study DRI6243)

Investigator(s): Multicenter/Multinational

Study center(s): 71 active sites in 19 countries (Argentina, Bulgaria, Chile, Colombia, Denmark, Finland, Greece, Mexico, Malaysia, Norway, Philippines, Poland, Portugal, Romania, Russian Federation, Sweden, Taiwan, Thailand, Turkey).

Publications (reference): Lassen MR, Dahl OE, Mismetti P, Destr°e D, Turpie AGG. AVE5026, a new hemisynthetic ultra-low-molecular-weight heparin for the prevention of venous thromboembolism in patients after total knee replacement surgery - TREK: A dose ranging study. J Thromb Haemost 2009; 7: 566-72.

Study period:

Date first patient enrolled: 09 May 2006

Date last patient completed: 18 June 2007

Phase of development: Phase 2

Objectives:

Primary Objective:

To demonstrate the efficacy of AVE5026 for prophylaxis of venous thromboembolism (VTE) via demonstration of a dose-response in patients at risk of VTE (eg, undergoing total knee replacement [TKR] surgery) and consequently to identify an appropriate dose for evaluation in other VTE prophylaxis patient populations.

Secondary Objectives:

- To evaluate the safety (incidence of major bleeding events) of AVE5026 in the prevention of VTE after elective TKR surgery
- To document the efficacy and safety of AVE5026 postoperative regimens in the prevention of VTE after elective TKR surgery
- To assess AVE5026 pharmacokinetic (PK) parameters in patients

Methodology: Multicenter, multinational, randomized, stratified, double blind, double dummy, parallel group, dose-response study, with enoxaparin used as a positive calibrator.

Number of patients: Planned: 600 to 800 Randomized: 705 Treated: 693

Evaluated: Efficacy: 464 patients (primary efficacy population), 449 (per-protocol population)

Safety: 693 patients (all randomized and treated population)

Pharmacokinetics: 308 patients (all randomized and treated population sampled for AVE5026 antihuman blood coagulation factor Xa [anti-Xa] assessment)

Diagnosis and criteria for inclusion: Patients ≥18 years undergoing TKR surgery or a revision of a primary procedure performed ≥6 months prior to study entry.

Study drug: 0.8 mL of single-use vials containing 1.15 mL of AVE5026-placebo, AVE5026 6.25 mg/mL, AVE5026 12.5 mg/mL, AVE5026 25 mg/mL, AVE5026 50 mg/mL, or AVE5026 75 mg/mL.

Dose: 5 mg, 10 mg, 20 mg, 40 mg or 60 mg once daily.

Administration: subcutaneous (SC) route.

Batch numbers: [redacted]

Duration of treatment: From Day –1 (stratum 1) or from Day 1 (stratum 2), up to Day 10 (Day 1 was the day of surgery).

Duration of observation: 34 to 61 days (including screening, treatment period, and follow up).

Reference therapy (calibrator): Prefilled syringes containing 0.4 mL of enoxaparin-placebo or enoxaparin 100 mg/mL.

Dose: 40 mg once daily.

Administration: SC route.

Batch numbers: enoxaparin-placebo: [redacted]; enoxaparin: [redacted].

Criteria for evaluation:

Efficacy:

Primary endpoint*:* composite endpoint of the following VTE outcome results recorded from surgery up to Day 11 or up to the day of mandatory venography, whichever came first: any Deep Vein Thrombosis (DVT) identified on mandatory venography of the lower limbs performed between Day 5 and Day 11; symptomatic documented DVT and/or nonfatal pulmonary embolism (PE) before the mandatory examination; VTE-related deaths, (ie, fatal PE and deaths which could not be attributed to a documented cause and for which DVT/PE could not be ruled out).

Secondary endpoints*:*

- Each of the above listed adjudicated events taken separately up to Day 11 or to the day of mandatory venography (Day 5 to Day 11), whichever came first, ie, any DVT, any proximal DVT, distal DVT only, symptomatic VTE (any and by type: fatal PE, nonfatal PE and DVT)
- Initiation of curative treatment by Investigator following VTE assessment

Safety:

Primary parameter: major bleeding, from the first study treatment injection, up to 3 calendar days after the last study treatment injection.

Other parameters: any bleeding/bleeding-related event, AEs spontaneously reported by the patients or observed by the Investigator, laboratory tests (biochemistry, hematology), vital signs (blood pressure, heart rate).

Pharmacokinetics:

Plasma concentrations of AVE5026 (anti-Xa activity) were assessed at trough, ie, just before dosing (C_{trough}), in a subset of patients. AVE5026 plasma concentrations obtained were classified as C_{trough} if time interval between last study drug injection before sampling and sampling time was 24h ± 2h.

Pharmacokinetic sampling times and bioanalytical methods:

Sampling times (selected sites): on Day 1: 1h30 to 2h30 postdose; on Day 2: predose, 2h to 4h postdose, 6h to10h postdose, 24h postdose; last day of administration: predose, 2h to 4h postdose.

Bioanalytical methods: Plasma concentrations of AVE5026 were determined via the anti-Xa activity, using an automated chromogenic assay. Concentrations below the lower limit of quantification (LLOQ) of 0.3125 µg Eq/mL were replaced by half of the LLOQ.

Statistical methods:

Populations analyzed:

- All randomized patients who received at least one dose of study drug, underwent elective TKR surgery and were not missing a primary efficacy endpoint assessment were included in the primary efficacy analyses (primary efficacy population)
- A per-protocol population was defined for supportive analyses on the primary efficacy endpoint
- All randomized patients who received at least one dose of study drug were included in the safety analyses (all randomized and treated population)

Efficacy analyses:

- Primary efficacy endpoint: Dose-response relationship between the five AVE5026 doses (each dose includes AVE5026 preoperative regimen arm for the preoperative stratum and AVE5026 postoperative regimen arm for the no preoperative stratum) was tested using a two-sided stratified trend test on proportions at the 0.05 significant level (Cochran-Armitage test using the values of the logarithm of the doses as score). Point estimates and exact two-sided 95% confidence intervals (CIs) were calculated. Univariate logistic regression model using the logit link function and incorporating term for the logarithm of the dose was investigated
- Secondary efficacy endpoints: Dose-response relationship was tested for any DVT, any proximal DVT and any symptomatic VTE using the same statistical method as for the primary efficacy endpoint. Point estimates and exact two-sided 95% CIs (when appropriate) were calculated for all the secondary efficacy parameters.

Safety analyses:

- Main safety parameter: Dose-response relationship was tested using the same statistical method as for the primary efficacy endpoint. Point estimates and exact two-sided 95% CIs were calculated,
- Other safety parameters: Dose-response relationship was tested for any bleeding event using the same statistical method as for the primary efficacy endpoint. Point estimates and exact two-sided 95% CIs were calculated for any bleeding event and minor bleeding event only. Univariate logistic regression model using the logit link function and incorporating term for the logarithm of the dose was investigated for any bleeding event. Point estimates were computed for the number of patients with transfusions, serious adverse events, and deaths. Shift tables using safety ranges were computed for laboratory parameters as well as summaries on differences between baseline and measurements after starting study drug injection up to last study drug injection plus 3 days.

Pharmacokinetic analyses:

- Descriptive statistics (number of observation, arithmetic and geometric mean, standard deviation, coefficient of variation, minimum and maximum) were presented for AVE5026 C_{trough} at prespecified time-points,
- A Bayesian estimation was also performed on 308 patients using the individual AVE5026 plasma concentrations obtained during the study (results given in a separate report).

Summary:

Efficacy results:

The incidence of patients with confirmed adjudicated VTE decreased from 28/70 (40.0%) patients in the 5 mg group, to 4/76 (5.3%) patients, in the 60 mg AVE5026 group, demonstrating a highly significant dose response across the 5 treatment groups (p-value=8.9×10^{-11}).

There was also evidence of a statistically significant dose-response across the 5 AVE5026 groups, in the incidence of patients with confirmed adjudicated DVT (p-value=8.9×10^{-11}), as well as in the incidence of patients with confirmed adjudicated proximal DVT (p-value=0.0002).

There were no patients with confirmed adjudicated symptomatic VTE in any of the 5 AVE5026 groups.

None of the covariates tested (eg, gender, race, age, weight, body mass index, creatinine clearance,…) appeared to affect the occurrence of confirmed adjudicated VTE across the 5 AVE5026 doses.

Safety results:

The incidence of patients with confirmed adjudicated major treatment-emergent bleeding events was very low, and there was a statistically significant dose-response across the AVE5026 groups (p-value=0.0231) (none on AVE5026 5 mg or 10 mg, 1 [0.8%] patient each on AVE5026 20 mg and AVE5026 40 mg, and 4/117 [3.4%] patients on AVE5026 60 mg); no major treatment-emergent bleeding event occurred in the enoxaparin arm. The incidence of patients with confirmed "any treatment-emergent bleeding event" increased from 5/92 (5.4%) patients in the group on AVE5026 5 mg, to 24/117 (20.5%) patients in the group on AVE5026 60 mg (6/119 [5%] patients on enoxaparin) with a statistically significant dose-response (p-value=0.0003).

The incidence of patients experiencing at least 1 TEAE, was in the same range across the AVE5026 5 mg, 10 mg, 20 mg and 40 mg treatment groups (respectively 42/92 [45.7%] patients, 37/87 [42.5%] patients, 50/130 [38.5%] patients and 63/133 [47.4%] patients), and higher in the AVE5026 60 mg group (65/117 [55.6%] patients). Similarly, the incidence of patients with at least 1 treatment-emergent bleeding, was higher in the patients receiving AVE5026 60 mg (12/92 [13.0%] patients on 5 mg, 9/87 [10.3%] patients on 10 mg, 12/130 [9.2%] patients on 20 mg, 15/133 [11.3%] patients on 40 mg, 31/117 [26.5%] patients on 60 mg, and in 10/119 [8.4%)] patients on enoxaparin).

Three deaths occurred during the course of the study, including one, in the AVE5026 10 mg (myocardial infarction), during the treatment period. The 2 other deaths occurred in 1 patient on AVE5026 40 mg and in 1 patient on 60 mg; they died respectively from acute myocardial infarction on Day 20, and from "Burkitt lymphoma" on Day 39.

A total of 20/559 (3.8%) AVE5026-treated patients, and 3/119 (2.5%) enoxaparin-treated patients, experienced serious TEAE(s). The highest incidences of serious TEAE were observed in the AVE5026 40 mg (7/133 [5.3%] patients) and 60 mg (6/117 [5.1%] patients) groups. In the AVE5026 60 mg group, the most frequently reported serious TEAEs were bleeding events.

A total of 18/559 (3.2%) AVE5026-treated patients, and 2/119 (1.7%) enoxaparin-treated patients permanently discontinued the study drug due to TEAEs. In the AVE5026 60 mg group, the most frequently reported TEAEs leading to discontinuation were the serious bleeding events.

The incidence of liver enzymes increase on AVE5026 (mainly alanine aminotransferase [ALT increase ≥3 ULN) was as expected in this class of drug, and was similar to that observed with enoxaparin. No increases of ALT ≥3 ULN in association with a total bilirubin ≥34 µmol/L were observed. No clinical signs of liver toxicity were observed. Low PCSAs in platelet count (<100 Giga/L), were observed across all treatment groups, and were as expected in this surgical setting. Overall, there was no clinically significant difference between the treatment groups for laboratory-related parameters.

Pharmacokinetic results:

The AVE5026 plasma C_{trough} concentrations measured as anti-Xa activities on Day 3 and on Day 9, or on the last day of study drug administration (prior to the daily administration) roughly increased in proportion with the administered dose from 20 to 60 mg. At 5 and 10 mg, these concentrations were below the LLOQ on both Day 3 and Day 9. On Day 9, plasma AVE5026 C_{trough} concentrations were similar to those obtained on Day 3.

Total subject variability was high, ranging from 43.7% to 92.1%, when the 5 and 10 mg doses were not taken into account, since, at these doses, C_{trough} concentrations were below the LLOQ.

Conclusions:

[redacted]

Date of report: 16-Jul-2010