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Prescribing decisions should be made based on the approved package insert in the country of prescription.

Sponsor / Company: Sanofi **Drug substance(s):** Semuloparin sodium (AVE5026)	**Study Identifiers:** NCT01567904, 2011-005155-14, U1111-1115-8281 **Study code**: PKM11204

Title of the study:

An open-label, pharmacokinetic/pharmacodynamic and tolerability study of AVE5026 administered at weight-adjusted doses to patients under 18 years of age with a Central Venous Line

Study center(s): One active center in Hungary

Study period:

Date first patient enrolled: 10-May-2012

Date last patient completed: 10-Jul-2012

Phase of development: 2a

Objectives:

Primary: To determine the pharmacokinetic [PK] and pharmacodynamic [PD] parameters of semuloparin (AVE5026) (assessed from the anti-Xa activity of the compound with and without addition of antithrombin [AT] in the reaction medium) in children, to identify the most significant covariates that may affect semuloparin PK in children in order to determine the dose needed to achieve a PD exposure in children similar to that obtained in adults at the therapeutic dose for thromboprophylaxis.

Secondary: To evaluate the tolerability of semuloparin when administered at a weight-adjusted, once daily dose for up to 30 days to patients less than 18 years of age with a Central Venous Line [CVL].

Methodology:

Multicentre, multinational, open-label, non-randomized study in patients <18 years (5 age groups: ≥12 to <18 years, ≥6 to <12 years, ≥2 to <6 years, ≥3 months to <2 years, and < 3months) and with a CVL. Patients received a subcutaneous single daily dose of semuloparin for a minimum of 6 days and a maximum of 30 days. The study employed a Steering Committee responsible for the good conduct of the study and an independent Data Monitoring Committee [DMC] responsible for monitoring the patients' safety and available PK and PD data before progression to the next age group dosing. Enrollment staggered by age group starting with the older children (≥12 years). In each younger age group, enrolment was planned to initiate only following a review by the DMC of the clinical safety data and available PK and PD data from the first 3 out of 7 children from the previous older age group. Enrollment of infants <3 months was planned to initiate after recruitment of all patients ≥3 months had been completed and all data analyzed by the DMC.

Number of patients**:** **Planned**: at least 35 patients to have 7 evaluable patients per age group (≥12 to <18 years [Group 1], ≥6 to <12 years [Group 2], ≥2 to <6 years [Group 3], ≥3 months to <2 years [Group 4], and <3 months [Group 5])

Treated: 2 in Group 1

Evaluated: **Pharmacokinetics/Pharmacodynamics: 2**

Safety: 2

The study has been early terminated. The decision to discontinue has been taken in keeping with the Company's decision to withdraw, on a worldwide basis, the marketing authorization applications [MAA] for semuloparin in adult indication (Prophylaxis of venous thromboembolism in cancer patients receiving chemotherapy for locally-advanced or metastatic solid tumors).

Diagnosis and criteria for inclusion:

- Patient aged between ≥38 gestational weeks and <18 years
- CVL implanted for an expected duration ≥6 days from study enrollment
- Hospitalized or able to receive daily injections for at least 6 days and provide plasma samples for 3 days (Day 4 to 6)
- Written informed consent signed by legal representative(s) in accordance with local regulation, and possibly assent form by the child (country/age specific)

Study treatments

Investigational medicinal product(s): Semuloparin sodium (AVE5026)

Formulation: Solution for injection in single dose vials (10 mg/mL and 20 mg/mL)

Route(s) of administration: Subcutaneous

Dose regimen: weight-adjusted dose once daily

Duration of treatment: minimum of 6 days and up to 30 days

Duration of observation: The maximum study duration was 68 days, including a screening up to 6 days, a treatment period of 6 days minimum and 30 days maximum, and an end-of-study visit performed 4 weeks (30 ± 2 days) after last dosing.

Criteria for evaluation:

Primary endpoints:

Pharmacokinetics/ Pharmacodynamics: Six plasma samples for each enrolled patient were assayed. A validated anti-Xa chromogenic enzyme assay, with addition of AT-III in excess, was used to assess plasma concentrations of semuloparin as well as PD activity of semuloparin. Individual PK parameters of semuloparin in children were to be derived from a full population PK model building (including covariates assessment). Individual PD parameters of semulparin in children were to be derived from a full population PK/PD model building (including covariates assessment).

Secondary endpoints:

Safety: Safety parameters included bleeding, transfusions requirement, hemoglobin, platelet count, liver and renal laboratory data, and serious or non-serious adverse events monitored by the DMC

Statistical methods:

Due to the early discontinuation of the study, no statistical analysis was performed

Summary:

Population characteristics: The two patients were enrolled in Group 1 (age group: ≥12 to <18 years) and completed the treatment period (6 days for both patients) when the study was early terminated. Indeed at the time of early termination, the first patient already completed the study as per protocol and the second patient already completed the treatment period and the follow up period was still ongoing.

Pharmacokinetic/pharmacodynamic results: Due to early termination of the study, no PK parameters were determined.

Safety results: Both patients experienced adverse events of specific interest [AESI] of severe thrombocytopenia. Both had a history of cancer (neuroblastoma and medulloblastoma, respectively) and thrombocytopenia was suspected to be related to chemotherapy according to the Investigator in both cases. The first patient experienced severe thrombocytopenia on the last dosing day (Day 6). After review, the DMC recommended to continue the study without amendment for Group 1 (DMC immediate review – May, 24th, 2012). The second patient experienced severe thrombocytopenia one month after the last dosing day. At that time, the first patient had already completed both the treatment and follow-up period.

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