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Sponsor / Company: sanofi-aventis **Drug substance:** Enoxaparin (XRP4563)	**Study Identifier:** NCT00723216 **Study code:** EFC10094

Title of the study:
Multicenter, randomized, open-label study to evaluate the efficacy and safety of enoxaparin sodium (RP54563) 20 mg bid for 14 days for prevention of venous thromboembolism in patients with curative abdominal cancer surgery. Physical prophylaxis only arm (IPC) will be used as an indicator of event rates in presence of IPC.

Study center(s): 36 centers in Japan

Study period:

Date first patient enrolled: 28 March 2007

Date last patient completed: 17 December 2007

Phase of development: Phase 3

Objectives:

The primary objective of this study was to evaluate the effect of enoxaparin 20 mg bid for 14 days (28 times) on venous thromboembolism (VTE) incidence and bleeding rate (major and minor bleeding) in patients with curative abdominal cancer surgery.

The secondary objective of this study was to evaluate the incidence of adverse events of enoxaparin 20 mg bid for 14 days (28 injections) in patients with curative abdominal cancer surgery.

Methodology: Multicenter, randomized, open-label

Number of patients:

Planned: 125 patients; Randomized: 151 Patients

Treated: 147 Patients; assessed for efficacy: 114 patients with adequate VTE measurements (intent-to-treat) and 109 patients (per protocol, excluded patients with major protocol violations); assessed for safety: 147 patients

Diagnosis and criteria for inclusion:

1) Malignant tumor patients undergoing laparotomy which is expected to take 45 minutes or more

2) Male or female patients, ≥40 years of age at the time of giving informed consent.

Investigational product: enoxaparin sodium (XRP4563)

Dose: 20 mg bid (morning and evening).

Administration: Medication was started 24 to 36 hours after surgery, and given subcutaneously in anterolateral or posterolateral abdominal wall.

Duration of treatment: 14 days or until hospital discharge

Duration of observation: 28 days (treatment period of 14 days and follow-up period of 14 days)

Criteria for evaluation:

Efficacy:
Efficacy was evaluated by deep vein thrombosis (DVT) incidence using venography or by pulmonary thromboembolism (PTE) incidence using lung ventilation/blood flow scintigraphy, pulmonary angiography or computed tomography (CT). Thrombosis incidence was evaluated by an independent panel of experts based on the previous exams performed.

Safety:
Safety was evaluated by bleeding events observed from Day 1 up to the completion of the follow-up period (through Day 28 or discontinuation on follow-up period).
Bleeding events were classified as major if it was associated with at least one of the following items: it resulted in death, it was clinically overt and resulted in a transfusion of at least 2 units of packed red blood cells or whole blood, it was clinically overt and resulted in decrease of 2 g/dL or greater in hemoglobin, compared to the baseline value, it was a retroperitoneal, intracranial or intraocular bleeding, it resulted in serious or life threatening clinical events, or surgical or medical intervention to control the events.

Adverse events reported by the patient or noted by the investigator included standard hematology, blood chemistry and coagulation.

Statistical methods:

Primary efficacy analyses were based on the intent-to-treat (ITT) population defined as all randomized and exposed patients with appropriate VTE measurements. The primary efficacy variable was the VTE incidence (DVT/PTE) observed during the treatment period. Count of VTE incidence and calculate point estimates and 95% 2-sided confidence intervals (CIs) for the enoxaparin group were based on Clopper-Pearson method. No covariates and center effects are considered.

Safety analyses were based on the total treated population. The primary safety analysis was the listing of the major bleeding. The secondary analyses of bleeding were the rates of major or minor bleedings out of total treated population, respectively. The 95% 2-sided CI was also calculated.

Summary:

Efficacy results:
In the primary efficacy analysis, the point estimates of the VTE incidence was 1.2% (1/83 patients) with the 95% CI of 0.03 to 6.53 in the enoxaparin group and 19.4% (6/31 patients) with 95% CI of 7.45 to 37.47 in the intermittent pneumonic compression (IPC) group. The VTE incidence was very much lower in the enoxaparin group than in the IPC group. All DVTs observed in this study were distal. No PTE was reported the both groups. The result of the per protocol population as a sensitivity analysis was similar to that of the ITT population.

Safety results:
The rate of major bleeding was 4.6 %(5/109) in the enoxaparin group with 95%CI of 1.51 to 10.38 and 2.6 % (1/38) the IPC group with 95%CI of 0.07 to 13.81. Major bleeding was observed in 5 patients in the enoxaparin group with bleedings at the incision (5 patients) and insertion site (1 patient). There were no bleedings in clinically significant regions such as retroperitoneal, intracranial, and intraocular.

The rate of bleeding events (major bleeding and minor bleeding) after administration of enoxaparin 20mg bid was 9.2 % with 95%CI of 4.49 to 16.23.

Issue date: 13-Aug-2008