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Sponsor / Company: sanofi-aventis **Drug substance(s):** enoxaparin sodium	**Study Identifier:** NCT00349180 **Study code:** EFC6770
Title of the study: Multicenter, randomized, double-blind study to evaluate the efficacy and safety of enoxaparin sodium (RP54563) 20 mg qd and 20 mg bid for 14 days in patients with total hip replacement	
Study center(s): 20 centers in Japan	
Study period: Date first patient enrolled: 14-Jun-2006 Date last patient completed: 26-Jan-2007	
Phase of development: Phase III	
Objectives: Primary: To evaluate effects on Venous Thromboembolism (VTE) (Deep Vein Thrombosis [DVT]/Pulmonary Thromboembolism [PTE]) incidence of RP54563 20 mg qd and 20 mg bid for 14 days in patients undergoing total hip replacement. Secondary: To evaluate bleeding events (major bleeding and minor bleeding) of RP54563 20 mg qd and 20 mg bid for 14 days in patients undergoing total hip replacement	
Methodology: Multicenter, randomized, double-blind	
Number of patients: Planned: 156 Randomized: 161 Treated: 161 Evaluated for efficacy: 141 (Intent To Treat) & 140 (Per Protocol Set) ; for safety: 161	
Diagnosis and criteria for inclusion: 1) Patients undergoing elective primary total hip replacement 2) Male or female ≥20 years old at the time of giving informed consent	
Investigational product: enoxaparin sodium (RP54563) Dose: For the 20 mg qd group, RP54563 20 mg in the morning and placebo in the evening, or placebo in the morning and RP54563 20 mg in the evening. For the 20 mg bid group, RP54563 20 mg in the 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 **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 DVT incidence using venography or by PTE incidence using lung ventilation/blood flow scintigraphy, pulmonary angiography or CT (computed tomography). The presence of thrombosis was judged by an Independent Panel.

Safety: Safety was evaluated by bleeding events observed from Day 1 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 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. Standard hematology, blood chemistry and coagulation were tested.

Statistical methods:

Primary efficacy analyses were based on ITT population (all randomized and treated patients with appropriate VTE measurements). The primary efficacy variable was VTE (DVT or PTE) incidence observed during the treatment period. The point estimates and 95% two-sided Confidence Interval (CI) of the VTE incidence for each group, and the difference of the incidences of two groups based on Clopper-Pearson method were calculated. No covariates and center effects are considered.

Safety analyses were based on the safety population (all treated patients). The primary safety analysis was the listing of the major bleeding. The secondary analyses of bleeding were the rates of major/minor bleedings out of safety population, respectively. The 95% two-sided CI was also calculated.

Summary:

Efficacy results:

In the primary efficacy analysis, the point estimates of the VTE incidence adjudicated by Independent Panel were 17.14% (12/70 patients) with the 95% CI of (9.18 to 28.03) in the 20 mg qd group and 2.82% (2/71 patients) with 95% CI of (0.34 to 9.81) in the 20 mg bid group. The treatment difference of VTE incidence was −14.33%. Thus, in terms of VTE incidence, the VTE incidence in the 20 mg bid group was lower than that in the 20 mg qd group. The result of the PPS population (ITT population without major protocol deviation) as a sensitivity analysis was similar to that of the ITT population.

Safety results:

Two major bleedings in the 20 mg bid group were observed, but no major bleedings in the 20 mg qd group were observed. Two major bleedings in the 20mg bid group were reported as adverse event possibly related with the study medication. Ecchymosis/haematoma that severity was judged mild was shown in one patient and the treatment with the study medication was continued. In another patient, there was haematoma at incision-site that severity was judged moderate and the treatment was discontinued. The rate of all bleeding event was 7.4% (6/81 patients) with 95% CI of (2.77 to 15.43) in the 20 mg qd group and 6.3% (5/80 patients) with 95% CI of (2.06 to 13.99) in the 20 mg bid group. The rate of major bleeding was 0.0% (0/81 patients) with 95% CI of (0.00 to 4.45) in the 20 mg qd group and 2.5% (2/80 patients) with 95% CI of (0.30 to 8.74) in the 20 mg bid group.

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