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Sponsor/company:	Sanofi-Aventis	**ClinicalTrials.gov Identifier:**	NCT00077753
		Study Code:	XRP4563C_3501
Generic drug name:	Enoxaparin Sodium	**Date:**	21/01/2008

Title of the study:	A double-blind, placebo-controlled, parallel, multicenter study on extended VTE prophylaxis in acutely ill medical patients with prolonged immobilization (EXCLAIM)
Coordinating Investigator(s):	Russel D. Hull, Thrombosis Research Unit, University of Calgary, Foothills Hospital, Room 601 South Tower, 1403 29th Street NW, Calgary T2N 2T9, Alberta, Canada
Study center(s):	370 study centers (354 in amendment 8 population) located in 20 countries were involved in this multicenter study.
Publications (reference):	Hull RD, Schellong SM, Tapson VF, Monreal M, Samama MM, Turpie AG, Wildgoose P, Yusen RD. Extended-duration thromboprophylaxis in acutely ill medical patients with recent reduced mobility: methodology for the EXCLAIM study. J Thromb Thrombolysis. 2006; 22:31-8.
Study period: Date first patient enrolled: 26 February 2002 Date last patient completed: 06 October 2006	**Phase of development:** IV
Objectives:	Primary Objective - To demonstrate the superiority of extended Venous Thrombo-embolism (VTE) prophylaxis using enoxaparin 40 mg sc qd for 28 ± 4 Days, compared with placebo, both following 10 ± 4 days of initial treatment with enoxaparin 40 mg sc qd. Secondary Objectives - To assess the reduction in mortality rate at the end of the double-blind (DB) treatment period, at 3 (90 ± 10 days) and at 6 (180 ± 10 days) months from the time of entry to the study, in patients on extended prophylaxis. - To assess the incidence of VTE at 3 months (90 ± 10 days) from the time of randomization to the study. - To evaluate the safety of extended enoxaparin VTE prophylaxis in acutely ill medical patients with prolonged immobilization. Safety evaluation involved: major and minor hemorrhage, heparin induced thrombocytopenia (HIT) and Serious Adverse Events (SAEs).
Methodology:	This was a phase-IV randomized, double-blind, placebo-controlled two-parallel group, multicenter study.

Number of patients:	Planned	Enrolled	Treated in OL	Randomized	Treated in DB (safety)	Efficacy population
Total population	7000	7500	7415	6085	5963	4995
Amendment 8 population	4726	5105	5049	4114	4040	3347
Diagnosis and criteria for inclusion:	Acutely ill medical patients, male or female = 40 years, with a recent immobilization = 3 days and predisposing factors of developing VTE, were considered for enrollment in the study. The anticipated survival time of the patient had to be at least 6 months and all enrolled patients were required to give written informed consent.					
Investigational product: Dose: Administration:	Enoxaparin sodium injection (Lovenox®/ Clexane®). Single doses of enoxaparin sodium in pre-filled syringes of 40 mg/0.4 mL. 40 mg subcutaneously (sc) once daily (qd).					
Duration of treatment: 38 ± 4 Days	**Duration of observation:** 180 ± 10 Days.					
Reference therapy: Dose: Administration:	Open label enoxaparin 40 mg sc qd for 10 ± 4 days, followed by placebo saline. 0.4 mL placebo. Sc qd.					
Criteria for evaluation: Efficacy	<u>Primary:</u> • Occurrence of documented VTE (DVT and/or PE) during the DB Treatment Period as assessed by ultrasound for all patients at 28 ± 4 days after randomization (or earlier if symptomatic VTE) and/or verifiable tests for symptomatic patients, respectively. <u>Secondary:</u> • Occurrence of VTE (DVT and/or PE) between Day 1 from randomization and Day 90 ± 10. • Mortality at the end of the DB Treatment Period, at 3 (90 ± 10 days) and at 6 (180 ± 10 days) months.					
Safety	<u>Primary:</u> • Adjudicated major hemorrhagic complications during the DB treatment period. <u>Secondary:</u> • Major and minor hemorrhagic complications during the DB treatment period. • Serious adverse events.					

Statistical methods	Primary efficacy analysis: The primary efficacy endpoint was the occurrence of a documented VTE (DVT and PE) event during the DB period. The primary efficacy analysis was performed using chi-square test. The corresponding confidence intervals (CI) for the relative risk were constructed; the nominal alpha being two-tailed 0.047. The VTE analysis was based on Efficacy and Per Protocol (PP) Populations. Secondary efficacy analyses: Secondary efficacy variables were defined as follows: - incidence of VTE at day 90 (Day 1 was first day of treatment in DB period); - mortality rate at Day 30 (from Day 1 to Day 32), Day 90 and Day 180. All secondary efficacy parameters including VTE were analyzed similarly to the efficacy primary analysis. Time to death was analyzed using Cox proportional hazard model. Hazard ratio and 2-sided 95%CI was calculated on the Safety population and presented. Safety analyses: Safety analyses were performed on the Safety Population. Safety variables included major and minor hemorrhages during the treatment period, thrombocytopenia, adverse events (AEs), serious adverse events (SAEs) and laboratory evaluations (hemoglobin, hematocrit, platelets) during DB period. Other safety variables included activated Partial Thromboplastin Time (aPTT), Thromboplastin Time (PTT), creatinine, calculated creatinine clearance at baseline, physical examination, vital signs and transfusion, by visit (if applicable).
Summary:	Out of 7 500 patients enrolled, 5105 were fulfilling amendment 8 population, 5049 patients were exposed to enoxaparin during the open period. At the end of the initial open period, 4114 subjects originating from 20 countries were randomized to receive either placebo or enoxaparin 40 mg qd sc for a period of 28 ± 4 days. The efficacy population included 3347 patients who received either enoxaparin (1666 patients) or placebo (1681 patients). The PP population included 2969 patients who received either enoxaparin (1459 patients) or placebo (1510 patients). The safety population involved 4040 patients who received either enoxaparin (2013 patients) or placebo (2027 patients). The majority of patients were female (52.6%) and Caucasian (73.8%). The mean patients'age was 70.6 ± 12.4 years and the mean BMI was 27.8 ± 7.4 kg/m². Most of patients were hospitalized at time of enrollment (93.0%). Main enrollment diagnoses were acute infection without septic shock (30.8%), followed by acute respiratory insufficiency (27.1%), heart failure (NYHA III or IV) (21.3%) or were post-ischemic stroke (8.1%). Overall, 63.7% had level 1 immobilization while 36.3% had level 2 immobilization. The majority of patients had risk factors other than immobilization (88.5%); the most frequent risk factors for VTE other than immobilization being age over 75 years (44.0%), chronic respiratory failure (39.3%), chronic heart failure (29.2%) and obesity (29.1%). There were no clinically relevant differences between groups in respect of demographic or other baseline characteristics during the OL and DB periods.

Efficacy results:	Following the DB period, the overall incidence of VTE was 2.8% in the enoxaparin group and 4.9% in the placebo group, which means that a statistically significant difference equivalent to a 44% relative risk reduction, was observed in favor of enoxaparin (relative risk; 0.56; 95.3% IC: 0.39-0.80; p=0.0011). Similarly, the incidence of symptomatic VTE events was 0.3% in the enoxaparin group versus 1.1% in the placebo group corresponding to a 73% relative risk reduction (relative risk: 0.27, 95.3% CI: 0.10-0.72; p=0.0044). Enoxaparin was found to be more effective than placebo in reducing all VTE events except PE. The benefit was maintained at 3-month VTE follow-up assessment as a significant treatment effect was observed with enoxaparin (3.0%) in comparison with placebo (5.2%) during the DB period (relative risk: 0.58, 95.3% CI: 0.41-0.82; p=0.0015). Similar results were obtained in the PP population. No significant reduction in all causes mortality was observed with enoxaparin when compared with placebo in both treatment groups at Days 30, 90 and 180.
Safety results:	Total (major and/or minor) bleeding was observed in 5.7% of patients receiving enoxaparin compared with 3.8% receiving placebo (relative risk, 1.47; 95% CI: 1.11-1.95; p=0.0067). The rate of adjudicated major bleeding was 12 patients (0.6%) in the enoxaparin group vs. 3 patients (0.1%) in the placebo group (relative risk, 4.03; 95% CI: 1.14-14.25; p=0.0192). No noticeable differences were observed between the two treatment groups in terms of TEAEs, i.e. possibly related TEAEs, serious TEAEs, TEAEs leading to permanent study medication discontinuation and TEAEs leading to death. Of the 4040 patients exposed to the study drug, 174 (4.3%) dropped out of the study due to TEAEs (3.9% in the enoxaparin group vs. 4.7% in the placebo group), 322 (8.0%) experienced at least one SAE (7.8% in the enoxaparin group vs. 8.1% in the placebo group); 70 patients died due to SAE and 1011 patients (25.0%) experienced at least one TEAE (25.4% in the enoxaparin group vs. 24.7% in the placebo group). Moreover, one heparin-induced thrombocytopenia was reported in the enoxaparin group.
Date of report:	13 December 2007.