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Sponsor/company:	sanofi-aventis	**Study Identifier:**	NCT00622648
Drug Substance:	Enoxaparin	**Study Code:**	ENOXA_C_01249

Title of the study:	International, multi-center, randomized, double-blind study to compare the overall mortality in acutely ill medical patients treated with enoxaparin versus placebo in addition to Graduated Elastic Stockings.			
Study center(s):	353 active centers located in 8 countries: China, Hong-Kong, Korea, India, Malaysia, Mexico, Philippines, and Tunisia.			
Study period: Date first patient enrolled: 30 January 2008 Date last patient completed: 10 December 2010			**Phase of development:** Phase 4	
Objectives:	Primary objective: - The primary objective was to demonstrate in patients hospitalized for an acute medical illness that enoxaparin 40 mg subcutaneous (SC) once daily for 10 ± 4 days with graduated elastic stockings was superior to enoxaparin-placebo with graduated elastic stockings on overall mortality at Day 30 after randomization. Secondary objectives: - The main secondary objective was to compare in patients hospitalized for an acute medical illness enoxaparin 40 mg SC once daily for 10 ± 4 days with graduated elastic stockings versus enoxaparin-placebo with graduated elastic stockings on overall mortality at Day 90 after randomization. - The other secondary objective was to evaluate the safety of enoxaparin venous thromboembolism (VTE) prophylaxis in patients hospitalized for an acute medical illness with respect to major hemorrhage, total bleedings, heparin-induced thrombocytopenia (HIT), adverse events (AEs), and serious adverse events (SAEs).			
Methodology:	International, prospective, multicenter, randomized, double-blind, placebo-controlled, comparative 2 parallel-group study with enoxaparin 40 mg or placebo administered subcutaneously once daily and graduated elastic stockings used in both groups.			
Number of patients/subjects:	Planned : 8300	Included : 8392	Randomized : 8323	Treated : 8307 (4145 placebo; 4178 enoxaparin)
Evaluated:	Efficacy : 8307 (intent-to treat population [ITT])		Safety : 8307	

Diagnosis and criteria for inclusion:	Hospitalized patients with an acute medical illness
Investigational product: **Dose:** **Administration:**	Enoxaparin sodium injection (Lovenox®/ Clexane®) in prefilled syringes of 40 mg/0.4 mL 40 mg single dose Subcutaneous injection once daily (every 24 ± 4 hours)
Duration of treatment: At least 6 days up to 14 days (10 ± 4 days)	**Duration of observation:** Approximately 90 days (including hospitalization and 2 follow-up visits at Day 30 and Day 90)
Reference therapy: **Dose:** **Administration:**	Placebo (0.9% normal saline) in matched prefilled syringes 0.4 mL placebo Subcutaneous injection once daily (every 24 ± 4 hours)
Other therapy:	Graduated elastic stockings were to be worn in both groups at least during the study treatment period (ie, at least during hospitalization).
Criteria for evaluation:	
Efficacy:	Primary: - All-cause mortality between randomization and Day 30. Secondary: - All-cause mortality between randomization and Day 14 and all-cause mortality between randomization and Day 90. - Composite of cardio-pulmonary deaths (sudden death, death due to acute myocardial infarction, heart failure, pulmonary failure, and pulmonary embolism) on Days 14, 30, and 90. - Composite of sudden death and pulmonary embolism on Days 14, 30, and 90.
Safety:	Primary: - Major hemorrhagic events during the study treatment period. Other safety criteria: - All hemorrhagic events (major and minor) during the study treatment period and up to Day 30; - Treatment-Emergent Adverse Events (TEAEs), Serious Adverse Events (SAEs), Heparin-Induced Thrombocytopenia (HIT) during the entire observation period up to Day 90; - Non-major bleedings clinically relevant (leading to hospitalization or study treatment discontinuation), composite of major and non-major bleedings clinically relevant during the study treatment period and up to Day 30.

Statistical methods:	Primary efficacy analysis: The primary efficacy analysis was to compare the incidence of all-cause mortality within 30 days after randomization between the 2 treatment groups (enoxaparin versus placebo) using a chi-square test. To check for robustness of the study results, the time-to-event analysis was also performed by using a log-rank test. Kaplan-Meier curves were used to graphically present calculated event probabilities over time. Secondary efficacy analysis: - The incidence of all-cause mortality on Day 14 was compared between the 2 treatment groups by chi-square test (main test); hazard rates and hazard ratio were also calculated, and survival curves were compared by log-rank test. Risk ratio and hazard ratios with their associated confidence intervals (CIs) were provided. - The hazard rate for all-cause mortality on Day 90 was compared between the 2 treatment groups using a log-rank test. The hazard ratio and its associated CI were provided. - The same analyses were done on the composite of cardio-pulmonary deaths and on the composite of sudden death and pulmonary embolism on Days 14, 30, and 90. The primary and secondary efficacy analyses were performed in the Intent To Treat population (all patients randomized) and Per-Protocol (PP) population (as supportive analyses for the primary efficacy analysis). Safety analyses: Safety variables included major and minor hemorrhages during the treatment period and up to Day 30, TEAEs, SAEs, HIT during the entire observation period up to Day 90, laboratory evaluations (platelets, hemoglobin, hematocrit) and vital signs (heart rate, systolic and diastolic blood pressure) during the treatment period. Adverse events (including hemorrhages) were coded using MedDRA (version 11.0) and presented by system-organ class and preferred term in incidence tables. Reasons for death (as adjudicated) were described and compared by chi-square test. For laboratory variables and vital signs, changes from baseline were tabulated by treatment group. The frequency of major hemorrhages, minor hemorrhages, major or minor hemorrhages, nonmajor hemorrhages clinically relevant, and major and nonmajor hemorrhages clinically relevant (composite) at 48 hours post-treatment and on Day 30 were compared between the 2 treatment groups by chi-square tests. All the safety analyses were performed on the treated population.

Summary:	
Efficacy results:	The difference between the 2 treatment groups for the incidence of all-cause mortality on Day 30 (primary endpoint) in the ITT population was not statistically significant (4.9% in the enoxaparin group versus 4.8% in the placebo group, p=0.826). No statistical and numerical differences were observed on any of the secondary endpoints in the ITT population: - All-cause mortality on Day 14 (2.9% in both treatment groups, p=0.948) and Day 90 (8.4% in the enoxaparin group versus 8.6% in the placebo group, p=0.709). - Cardio-pulmonary death on Day 30 (3.4% in the enoxaparin group versus 3.3% in the placebo group, p=0.767). - Composite of sudden-death and PE on Day 30 (0.7% in both treatment groups, p=0.974); only 1 PE occurred in each group up to Day 30. - In any subgroups of patients. Similar results were observed in the PP population.
Safety results:	No significant differences were observed between enoxaparin and placebo in the percentage of patients who experienced major bleedings during the on-treatment period (primary safety endpoint) (0.4% for enoxaparin versus 0.3% for placebo, p=0.346) or in the percentage of patients who experienced clinically relevant nonmajor bleedings (0.4% for enoxaparin versus 0.3% for placebo, p=0.494). Two major bleedings with a fatal outcome were observed in the enoxaparin group versus none in the placebo group. A significantly higher percentage of patients with minor bleedings was observed in the enoxaparin group compared to placebo (1.8% versus 1.1%, p=0.019) and the composite of minor and/or major bleedings was higher in the enoxaparin group compared to placebo (2.2% versus 1.5%, p=0.013). The overall rate of TEAEs was similar in the enoxaparin and placebo groups (37.8% versus 36.9%, respectively). The most frequent TEAEs were gastrointestinal disorders (mainly constipation, diarrhea, and vomiting) and pyrexia, without differences between treatment groups. The percentage of patients who experienced serious TEAEs was similar in the 2 treatment groups (5.8% for enoxaparin versus 5.3% for placebo). The percentages of patients who experienced TEAEs with a fatal outcome during the treatment period (2.2% in each treatment group) and the post treatment period (7.0% for enoxaparin versus 7.1% for placebo) were similar in the 2 treatment groups. The percentage of patients with thrombocytopenia was similar in the 2 treatment groups (0.2% for enoxaparin versus 0.3% for placebo). No HIT was reported in either treatment group.
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