These results are supplied for informational purposes only.

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

Sponsor/company:	sanofi-aventis	Clinicaltrials.gov Identifier:	NCT00077818
		Study Code:	XRP4563B_4001
Generic drug name:	Enoxaparin	Date:	9 November 2009

Title of the study:	A prospective, open-label, randomized, parallel-group investigation to evaluate the efficacy and safety of enoxaparin versus unfractionated heparin in subjects who present to the emergency department with acute coronary syndrome.		
Investigator (s):	Multicenter study		
Study center (s):	Approximately 200 investigative centers located in the United States and Canada.		
Publications (reference):	Not Applicable		
Study period: Date first subject enrolled: Date last subject completed:	26-Jun-2002 24-Mar-2005	Phase of development: Phase IV	
Objectives:	The primary objective of the study was to determine the efficacy of enoxaparin compared to unfractionated heparin (UFH) for subjects diagnosed with ACS in the emergency department (ED). Efficacy was to be assessed using a composite score that considered the occurrence of all-cause mortality, non-fatal myocardial infarction (MI), or recurrent angina requiring the need for revascularization up to 30 days (± 2 days) following randomization. The secondary endpoints included the following: the incidence of major hemorrhage during the index hospitalization, the incidence of minor hemorrhage during the index hospitalization, the combined incidence of 30-day all-cause mortality and nonfatal MI, the incidence of 30-day all-cause mortality by itself, and total health care utilization from baseline (initial hospitalization) through the Day 30 follow-up visit.		
Methodology:	This was a prospective, open-label, randomized (1:1 ratio), parallel-group investigation designed to evaluate the efficacy and safety of enoxaparin compared to UFH.		
Number of subjects:	Planned: 3000	Randomized: 1131	Treated: 1096
Evaluated:	ITT: 1131	Safety: 1096	Pharmacokinetics: N/A
	Approximately 3000 intent-to-treat (ITT) subjects were planned for enrollment with 1500 in each group. One thousand one hundred and thirty-one subjects were randomized to the ITT population (560 subjects in the enoxaparin group and 571 subjects in the UFH group), 35 subjects were not treated (16 subjects in the enoxaparin group and 19 subjects in the UFH group), and 1096 subjects were included in the safety population (544 subjects in the enoxaparin group and 552 subjects in the UFH group).		

Diagnosis and criteria for inclusion:	Subjects who presented to the ED with acute coronary syndrome (ACS) and who met all of the following inclusion criteria were considered for enrollment into the study: male or non-pregnant female (negative serum pregnancy test required for females of childbearing potential), ≥18 years of age who were capable of signing the informed consent; resting angina lasting at least 10 minutes that was highly suggestive of myocardial ischemia and it was not explained by trauma or obvious abnormalities on chest x-ray, occurring within 24 hours of randomization; and a TIMI risk score ≥4.	
Investigational product: Dose: Administration:	Enoxaparin 1 mg/kg Subcutaneous injection	
Duration of treatment Minimum of 48 hours or until a diagnostic/therapeutic procedure was performed or at the discretion of the investigator.		Duration of observation: 180 days
Reference therapy: Dose: Administration:	Unfractionated Heparin 60 U/kg Intravenous	
Criteria for evaluation:	The study was terminated early due to lower than initially anticipated event rates and slow recruitment. Although 3,000 patients were planned for the study, 1,131 patients were randomized. Thus the statistical power for the planned analyses was inadequate to evaluate the comparison of enoxaparin with unfractionated heparin. This current clinical study report is an abbreviated report, and as such, only the safety results are being presented. The following safety criteria were evaluated, and analyzed using descriptive statistics: adverse events, bleeding events (major and minor), laboratory tests, blood transfusions, and electrocardiograms.	
Statistical methods:	The primary safety endpoints included the incidence of major hemorrhage during the index hospitalization and the incidence of minor hemorrhage during the index hospitalization. Safety variables include the incidence of bleeding (major and minor), serious adverse events, and non-serious adverse events. A clinical events committee (CEC) was formed to review clinical data and to adjudicate safety and efficacy endpoints while blinded to the assigned study drug. An independent data safety and monitoring board (DSMB) was appointed to monitor the progress of the trial and to ensure that the safety of patients enrolled in the trial was not compromised in any way. Bleeding was classified according to the TIMI criteria during the index hospitalization. In addition to the TIMI criteria for major hemorrhage, the Aventis criterion for major hemorrhage was utilized to allow for cross comparison among other Aventis enoxaparin studies. TIMI Criteria: Bleeding was classified as major or minor. Bleeding was classified as major if associated with a ≥5-g/dL decrease in hemoglobin (each unit of packed red blood cells or whole blood transfused counted as 1 g of hemoglobin) or a ≥15% absolute decrease in hematocrit (each unit of packed red blood cells or whole blood transfused counted as 3% points) or it was intracranial (confirmed by magnetic resonance imaging or computed tomography). Bleeding was classified as minor if associated with gastrointestinal or genitourinary bleeding, observed bleeding with an absolute decrease in hemoglobin ≥3 g/dL but <5 g/dL or in	

	hematocrit ≥10% but <15%, or any absolute decrease in hemoglobin ≥4 g/dL but <5 g/dL or in hematocrit of ≥12% but <15%. Aventis Criteria: Major bleeding was defined as bleeding that was clinically overt and associated with at least one of the following features: death, transfusion of at least two units of packed red blood cells or whole blood (of any source, donor, directed or autologous), 30 g/L (3 g/dL) or greater fall in hemoglobin (transfusion of any unit of red blood cells or whole blood was counted as 1 g/dL in decreased hemoglobin calculation), not associated with coronary artery bypass surgery, required surgical intervention or decompression of a closed space to stop or control the event, (e.g. cardiac tamponade, compartment syndrome), it was: • retroperitoneal (confirmed by magnetic resonance imaging, computed tomography, surgery, or autopsy), • intracranial (confirmed by magnetic resonance imaging, computed tomography, or autopsy), or intraocular Adverse events were summarized by presenting, for each treatment group, the number and percentage of subjects having any adverse event, an adverse event in each body system, and each individual adverse event. Any other information collected (e.g., severity or relatedness to study medication) was listed, as appropriate. Descriptive statistics for the relation of safety variables with prognostic factors, included age, race, sex, TIMI score, and baseline characteristics were generated. In this clinical study report, no efficacy analyses are being reported. However, the primary efficacy endpoint was the composite of all-cause mortality, nonfatal MI, or recurrent angina requiring revascularization, whichever occur first within 30 days after randomization. The blinded adjudicated data on MI was used. In the presence of possible censored data, the cumulative 30-day primary endpoint event rate was estimated with the Kaplan-Meier method, stratified by the baseline TIMI-score for each treatment group, based on the ITT population of subjects. Two strata were employed for TIMI score, ≤ 4 and > 4. Statistical tests to assess hypotheses relating to non-inferiority and superiority were planned to be conducted by constructing 95% confidence interval (adjusted for TIMI score ≤4 and >4) for the hazard ratio of the primary endpoint for enoxaparin versus UFH. Stratified Kaplan-Meier parameter estimates were calculated with TIMI score (≤4 and >4) as the stratification variable. Enoxaparin was declared superior to or non-inferior to UFH if the upper bound of the confidence interval was less than 1.0 or less than 1.1, respectively. SAS PROC LIFETEST and PROC PHREG were employed for the foregoing calculations.

Summary:	This clinical study synopsis is an updated version of the one dated 13 April 2007. Approximately 3000 ITT subjects were planned for enrollment with 1500 in each group. The study was terminated early by the sponsor due to slow enrollment and lower than initially anticipated event rates. One thousand one hundred and thirty-one subjects were randomized to the ITT population (560 subjects in the enoxaparin group and 571 subjects in the UFH group), 35 subjects were not treated (16 subjects in the enoxaparin group and 19 subjects in the UFH group). One thousand ninety-six subjects were included in the safety population (544 in the enoxaparin group and 552 in the UFH group). Of these, 395 (36.0%) subjects (210 in the enoxaparin group and 185 in the UFH group) completed 48 hours of study medication, 3 (0.6%) subjects (02810, 14407, and 14411) in the enoxaparin group were randomized but did not receive study medication, and 698 (63.7%) subjects (331 in the enoxaparin group and 367 in the UFH group) prematurely discontinued study medication. The most reported primary reason for discontinuation included the need for coronary artery bypass graft (CABG)/percutaneous intervention ([PCI] 200 subjects, 28.5%), hospital discharge (181 subjects, 25.8%), and physician preference (143 subjects, 20.4%). The most commonly reported adverse event was chest pain (179 subjects, 16.33%), headache (97 subjects, 8.85%), nausea (51 subjects, 4.65%), anxiety (41 subjects, 3.74%), and back pain (33 subjects, 3.01%). The incidence of adverse events by body system was similar between the two treatment groups. Twenty-five subjects (2.3%) discontinued from the study due to an adverse event. Of these, 14 were considered related to study medication. The most commonly reported treatment emergent adverse event (TEAE) was chest pain (176 subjects, 16.06%), headache (92 subjects, 8.39%), nausea (44 subjects, 4.01%), anxiety (37 subjects, 3.38%), and back pain (32 subjects, 2.92%). Twenty-four subjects (2.2%) discontinued from the study due to a TEAE. Bleeding events with 95% confidence intervals were summarized for the safety population with TIMI major bleeding having a relative risk of 0.76 (0.27, 2.18), Aventis major bleeding with a relative risk of 1.22 (0.79, 1.90), and any bleeding with a relative risk of 1.76 (1.30, 2.39). Forty-five (45) subjects reported TIMI major bleeding during the study. The most frequently reported TIMI major bleeding locations overall included CABG related (16 subjects, 35.6%), other (13 subjects, 28.9%), gastrointestinal (4 subjects, 8.9%), and hematoma (4 subjects, 8.9%). The most reported serious adverse event was angina pectoris (19 subjects, 1.73%), myocardial infarction (18 subjects, 1.64%), and chest pain (18 subjects, 1.64%). The incidence of serious adverse events by body system was similar between the two treatment groups. There were 35 deaths reported during the study; • At discharge, 6 (0.5%) subjects died (5 [0.9%] subjects in the enoxaparin group and 1 [0.2%] subject in the UFH group). • At discharge to Day 30 follow-up visit, 8 (0.8%) subjects died (6 [1.2%] subjects in the enoxaparin group and 2 [0.4%] subjects in the UFH group). • At Day 30 to 6 month follow-up visit, 21 (2.1%) subjects died (8 [1.7%] subjects in the enoxaparin group and 13 [2.6%] subjects in the UFH group). Eight subjects died during the follow-up visit and outside of the safety reporting observation period. One death was not adjudicated by clinical events committee (CEC).
Date of report:	1-Oct-2009