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Sponsor/company:	sanofi-aventis	**ClinialTrials.gov Identifier:**	NCT00043784
		Study Code:	ENO_GMA_301
Generic drug name:	enoxaparin	**Date:**	26 November 2007

Title

A Prospective, Randomized, Open-Label, Multicenter Study in Patients Presenting With Acute Coronary Syndromes (ACS).

Investigators and study sites

A multicenter study with 500 multinational, investigative centers in Argentina, Australia/New Zealand, Belgium, Brazil, Canada, Germany, Italy, Poland, Spain, Turkey, and the United States. Sponsor's responsible medical officer: Dr. Peter Wildgoose, PhD, Bridgewater N.J., USA.

Study duration and dates	The first subject was enrolled on 09 August 2001. The last subject exited the study on 03January 2004.	**Phase**	III

Objectives

Primary: To evaluate the efficacy and safety of enoxaparin vs. unfractionated heparin (UFH) in high-risk subjects with ACS who were treated with an aggressive, invasive strategy. The primary outcome measures were the composite endpoint of all-cause mortality or the first clinical events committee (CEC)-adjudicated nonfatal myocardial infarction (MI) within 30 days after randomization and the incidence of major bleeding during the index hospitalization.

Secondary: To evaluate the efficacy, safety, and health economics of enoxaparin vs. UFH in high-risk subjects with ACS who were treated with an aggressive, invasive strategy. Secondary outcome measures included the following endpoints:

- Combined and individual incidence of all-cause mortality, clinical events committee (CEC)-adjudicated nonfatal MI, stroke, or recurrent ischemia that required revascularization within 14 and 30 days after randomization
- Combined incidence of all-cause mortality or CEC-adjudicated nonfatal MI within 14 days and all-cause mortality or nonfatal MI within 6 months after randomization
- Incidence of all-cause mortality within 6 months and 1 year after randomization
- Incidence of minor and all bleeding during the index hospitalization

Health Economics:

- To evaluate total medical costs as derived from resource consumption

Study design

This was a prospective, randomized, open-label, multicenter study to evaluate the efficacy and safety of enoxaparin versus UFH used with established therapy, including glycoprotein (GP) IIb/IIIa inhibitors and aspirin, in high-risk subjects who presented with unstable angina or non-ST segment elevation MI (NSTEMI) managed with early, invasive treatment. The planned duration of the entire study (enrollment through 1-year

follow-up) was approximately 30 months. The study consisted of the following periods: Screening (Pre-Enrollment), Open-Label Treatment (Enrollment and Post Enrollment), 30-Day Follow-Up (Day 30), 6-Month Follow-Up (Day 180), and 1-Year Follow-Up (Day 365). Eligible subjects were randomized (1:1) to receive either enoxaparin or UFH, regardless of having already received or not received either or both drugs prior to enrollment and assigned therapy may have been the same or different from that which the subject may have received (enoxaparin and/or UFH) prior to enrollment. During the index hospitalization, subjects were not to receive the opposing therapy. Assigned therapy was to be continued through angiography and PCI (if performed) until further anticoagulation was no longer required. Assigned therapy may have been discontinued for reasons inclusive of hospital discharge, following PCI (if assigned therapy was no longer indicated), or bypass surgery. In addition to assigned therapy, all subjects were to receive daily, concomitant aspirin orally (or oral clopidogrel if aspirin was contraindicated). GPIIb/IIIa inhibitors were to be used after randomization and during PCI (if performed) for high-risk subjects with unstable angina and/or NSTEMI in accordance with guidelines for the management of subjects with such conditions. Study committees/boards utilized included the following: the Executive, Steering, Clinical Events, and Publications Committees as well as a Data and Safety Monitoring Board.

Number of subjects planned

The study population was to include approximately 10,000 adult male and female subjects (5000 subjects in each treatment arm) and was to be conducted at approximately 500 international, investigative centers.

Inclusion criteria

2. Male or non-pregnant female = 18 years old.
3. Ischemic pain originating or persisting at rest, or its clinical equivalent, lasting = 10 minutes, and occurring within the 24 hours before enrollment.
4. Have at least 2 of the following:
    - ECG changes: New or presumably new ST-segment depression = 0.1 mV (= 1 mm), or transient (< 30 minutes) ST-segment elevation = 0.1 mV (= 1 mm) in at least 2 contiguous leads.
    - Abnormal cardiac enzymes within the 24 hours before enrollment, which were defined as elevated troponin 1 or T > the established criteria at each site OR creatinine kinase myocardial band (CK-MB) level > the site's upper limit of normal.
    - Age = 60 years.

Treatments

Enoxaparin treatment arm

Enoxaparin, 1 mg/kg every 12 hours was administered subcutaneously to randomized subjects. Enoxaparin was given immediately after enrollment and dosage was based on actual body weight. Enoxaparin was continued at least through angiography and any PCI, and continued until the subject required no further anticoagulation. If the last enoxaparin dose was received = 8 hours before balloon inflation during a PCI, the subject was to receive enoxaparin 0.3 mg/kg IV prior to proceeding with such PCI. Enoxaparin may have been discontinued upon hospital discharge, after PCI (if post-PCI enoxaparin therapy was not indicated), bypass surgery, physician discretion, or subject withdrawal.

Unfractionated Heparin (UFH) treatment arm

Treatment of randomized subjects was initiated with a recommended bolus of 60 U/kg (5000 units maximum) and an initial infusion of 12 U/kg/hr (not to exceed 1000 U/hr). UFH was given according to a weight-adjusted nomogram based on recent guidelines for management of patients with unstable angina or NSTEMI. The clinical study protocol contained a suggested method to achieve a therapeutic partial Thromboplastin time (aPTT) of 50 to 70 seconds. UFH was to be given immediately after enrollment and

continued until the subject required no further anticoagulation. UFH was to continue at least through angiography and any PCI. UFH may have been discontinued for the following reasons: hospital discharge, after PCI (if post-PCI UFH therapy was not indicated), bypass surgery, physician discretion, and subject withdrawal.

Aspirin or Clopidogrel (concomitant medication)

In addition to study drug, all randomized subjects were to receive aspirin, 162 to 325 mg orally at enrollment and then daily. Subjects who had an aspirin allergy or for whom aspirin was contraindicated were to instead receive clopidogrel, 75 mg at enrollment and then daily.

Glycoprotein IIb/IIIa Inhibitors (potential concomitant medication)

High-risk subjects were to be treated with glycoprotein IIb/IIIa inhibitors after randomization and during PCI according to guidelines for the management of subjects with unstable angina and NSTEMI.

Efficacy data

Efficacy was primarily based on the clinical endpoints of death (all causes) or the first CEC-adjudicated nonfatal MI within 30 days after randomization. Efficacy was secondarily based on the following clinical endpoints at various additional time points: death (all causes), first nonfatal MI, stroke, and recurrent ischemia that required revascularization. Endpoints were recorded on the Clinical Event Assessment page of the CRF.

Safety data

Safety was evaluated via the following:

- **Adverse events, anticipated, disease-related events, and alert terms**

The monitoring of adverse events, anticipated, disease-related events, and adverse events predefined as alert terms extended from informed consent through Day 30. Adverse events were recorded on the Adverse Event page of the CRF.

- **Hemorrhage assessments**

Hemorrhage assessments of minor and major bleeding were performed during the index hospitalization, upon subject complaint, upon hospital discharge, and at Day 30. Hemorrhages were recorded on the Hemorrhage Assessment page of the CRF. Serious hemorrhages were also considered to be adverse events and were required to be documented as such.

- **Laboratory tests**

Hematology tests (hemoglobin, hematocrit, and platelet count), serum chemistries (creatinine, total cholesterol, low-density lipoprotein, high-density lipoprotein, and C-reactive protein), coagulation studies (prothrombin time and international normalization ratio [exclusionary purposes only and not collected in CRF] and activated, partial thromboplastin time [aPTT]), HbA1c (glycosolated hemoglobin), cardiac enzymes (troponin I or T, creatine kinase, and CK-MB), and a serum pregnancy test (women of childbearing potential) were performed at baseline. Post randomization daily hematology was performed while on study medication. For subjects randomized to UFH, an aPTT was performed every 6 to 8 hours after starting UFH and then daily thereafter. Cardiac enzymes were assessed at 8, 16, and 24 hours post randomization and in the case of suspected reinfarction or ischemic chest pain, during or as soon as possible after the episode and then every 8 hours for 24 hours thereafter. Cardiac enzymes were also assessed in the case of PCI or bypass surgery before the procedure and every 8 hours thereafter for 24 hours. Laboratory test results were recorded on the appropriate CRF pages during the index hospitalization.

- **Blood transfusions**

Blood transfusions were to be recorded on the Transfusions page of the CRF during the index hospitalization.

- **Interventions**

Coronary angiography, PCI, or coronary artery bypass graft (CABG) surgery was to be recorded on the Coronary Angiography/Intervention Information page of the CRF during the index hospitalization.

Health economic data

Total medical costs as derived from resource consumption were evaluated.

Statistical procedures

The primary efficacy variable was the composite incidence of all-cause mortality or first nonfatal MI (CEC-adjudicated) within 30 days after randomization. All efficacy analyses were based on a strict intent-to-treat (ITT) principle and utilized two approaches to hypothesis testing, one of superiority and one of noninferiority. The adjusted 95% confidence interval (CI) for the Cox Proportional Hazard Ratio was constructed and p values were provided for individual and composite endpoints, with the overall, 2-sided, Type I error maintained at 5%. Kaplan-Meier survival plots were generated and summaries were provided.

Interim analysis

Interim analyses performed for the DSMB included the monitoring of safety, efficacy, and futility. All-cause mortality and safety outcome variables (major bleeding, serious adverse events, adverse events that resulted in discontinuation, and any unforeseen, safety-related issues) were monitored with the unweighted log-rank test and the Haybittle-Peto monitoring boundary, with an overall, 2-sided Type I error rate of 5%. This boundary used a critical value of plus or minus 3 for the Z-score for the difference between treatment arms before the final analyses.

Efficacy outcome variables were monitored with the unweighted log-rank test. An interim monitoring boundary (using the upper critical value relevant to the superiority approach) based on the Lan-Demets implementation of the O'Brien-Fleming a-spending function, with an overall, 2-sided, Type I error rate of 5% was used. Four equally spaced analyses (3 interim, 1 final) were to be performed when 25, 50, 75, and 100% of 1100 events occurred for the primary endpoint.

Futility was monitored by the calculation of conditional power (the probability that the test of significance would reject the null hypothesis at the end of the study) via the Lan and Wittes method for noninferiority and superiority testing.

Results – Efficacy

Primary efficacy

There were 696/4992 subjects (14.0%) and 722/4982 subjects (14.5%) in the enoxaparin and UFH treatment arms, respectively, who experienced the composite primary efficacy endpoint of death or first CEC-adjudicated nonfatal MI within 30 days after randomization. Since the upper bound of the 95% CI of the hazard ratio was not <1.0, enoxaparin was not shown to be superior to UFH. However, since the upper bound of the 95% CI of the hazard ratio was <1.1 (1.063), enoxaparin was shown to be non-inferior to UFH with regard to the composite primary efficacy endpoint of death or first CEC-adjudicated nonfatal MI within 30 days of randomization in the ITT population. Similar results were observed in the Safety (Treated) population. In the CONS population, the upper bound of the 95% CI of the hazard ratio was <1.0 and <1.1 (0.940), therefore enoxaparin was shown to be both non-inferior and superior to UFH.

Secondary and exploratory efficacy

- In both treatment arms, the combined (<18%) and individual incidences of death (<4%), first CEC-adjudicated nonfatal MI (<13%), recurrent ischemia that required revascularization (<5%), or stroke (≈1%) within 14 and 30 days after randomization were similar between treatment arms in the ITT and Safety populations and significantly lower ($p<0.05$) in the enoxaparin treatment arm in the cases of first CEC-adjudicated nonfatal MI and the composite of all of these endpoints in the CONS population within 14 and 30 days after randomization.
- In both treatment arms, the combined incidence (<14%) of death or first CEC-adjudicated nonfatal MI within 14 days after randomization was similar between treatment arms in the ITT and Safety populations and significantly lower ($p=0.004$) in the enoxaparin treatment arm in the CONS population.

- In both treatment arms, the combined incidence (<12%) of death or first CEC-adjudicated nonfatal MI within 6 months after randomization was similar between treatment arms in the ITT, Safety (Treated), and CONS populations.
- In both treatment arms, the incidence of death within 6 months and 1 year after randomization (<6% and <8% respectively), was similar between treatment arms in the ITT, Safety (Treated), and CONS populations within 6 months after randomization and in the ITT and Safety (Treated) populations within 1 year after randomization.
- In both treatment arms, the incidences of death (=0.5%), first CEC-adjudicated nonfatal MI (=6.1%), and the composite of both endpoints (=6.5%) within 48 hours after randomization were similar between treatment arms in the ITT and Safety (Treated) populations and significantly lower ($p<0.05$) in the enoxaparin treatment arm in the cases of first CEC-adjudicated nonfatal MI ($p=0.038$) and the composite of both endpoints ($p=0.031$) in the CONS population.
- In the ITT population, concomitant CABG surgery and smoking were associated with a significantly lower composite rate of death or first CEC-adjudicated nonfatal MI within 30 days of randomization in subjects in the enoxaparin treatment arm ($p=0.032$ and 0.009, respectively).

Results – Safety

Adverse Events

During the period of observation in the Safety (Treated) population and in both treatment arms, ~50% of subjects experienced an adverse event. The most frequently reported (incidence >5%) adverse events included chest pain and headache (~7%). Approximately 12 to 13% of subjects experienced a serious adverse event and the most frequently reported (incidence =1%) serious adverse events were myocardial infarction and chest pain. Drug-related adverse events occurred in <3% of subjects. Drug-related adverse events were considered by the investigator to have been serious in <1% of subjects. Adverse events resulted in discontinuation in <2% of subjects. Anticipated, disease-related events that were most frequently reported (incidence >2%) included congestive heart failure and atrial fibrillation/flutter (~8 to 9%). Adverse events that represented alert terms (significant overdose of study drug or thrombocytopenia <50,000/mm^3) occurred in 0.1% and <1.2% of subjects, respectively. The incidence of all such adverse events appeared similar between treatment arms upon inspection of the data. Similar results were observed in the ITT population.

Laboratory Safety Tests

Overall, in both treatment arms in the Safety (Treated) population, the mean Hgb, Hct, and platelet count was ~12 g/dL, 36-40%, and 198,000/mL and mean changes from baseline to the last recorded value for each analyte were similar to baseline. In the UFH treatment arm and Safety (Treated) population, aPTT results <50 seconds were observed in 33% of subjects within 6 to 12 hours, 23 to 25% within 12 to 36 hours, and 11-18% within 36 to 96 hours post randomization. An aPTT 50 to 70 seconds was observed in 32 to 33% of subjects within 6 to 24 hours, 10 to 17% of subjects within 24 to 48 hours, and 4 to 8% of subjects within 48 to 96 hours post randomization. An aPTT >70 seconds was observed in 37% of subjects within 6 to 12 hours, 17% of subjects within 12 to 24 hours, and 4 to 8% of subjects within 24 to 96 hours post randomization. Similar results were observed for the UFH treatment arm in the ITT population.

Overall, in both treatment arms in the Safety (Treated) population, CK and CK-MB results > 5 times ULN were observed in ~22-23% of subjects at baseline, ~17% at 8 hours post randomization, ~12 to 13% at 16 hours post randomization, and 8% at 24 hours post randomization. Of subjects who underwent PCI, ~28-29% experienced such elevations prior to PCI. Upon hospital discharge, such elevation was observed in ~1% of subjects. Similar results were observed in the ITT population. Troponin I and T elevations >5 times ULN were reported in 51% and 15% of subjects, respectively, at any time post randomization.

Other Safety Data

Hemorrhage events
Overall, in both treatment arms in the Safety (Treated) population, the incidence of thrombolysis in MI (TIMI) major hemorrhage events during index hospitalization was <10% and appeared similar between treatment arms upon data inspection. Similar results were observed in the ITT and CONS populations.

Overall, in both treatment arms in the Safety (Treated) population, the incidences of TIMI minor (<13%), Aventis major (<20%), GUSTO severe (<3%), CABG-related (<7%), and non-CABG-related (<3%) hemorrhage events during the index hospitalization and the incidences of hemorrhage events (serious [=8%] and nonserious [<42%]) during the period of observation (through Day 30) were numerically higher in the enoxaparin treatment arm. Similar results were observed in the ITT population.

Overall, in both treatment arms, there were small numerical differences in the incidence of hemorrhage events (TIMI major and GUSTO severe) and blood transfusions (PRBC or whole blood) in subjects who received neither prior enoxaparin or UFH, either prior enoxaparin or UFH, or both enoxaparin and UFH during the period of observation. Similar results were observed in the ITT population.

Overall, in both treatment arms in the Safety (Treated) population, the incidences of TIMI major hemorrhage events during index hospitalization with regard to PCI, CABG surgery, and actual use of a GPIIb/IIIa inhibitor were 3.7% and 2.5%, 36.5% and 34.2%, and 7.7% and 6.6% in the enoxaparin and UFH treatment arms, respectively, and the between-group difference in the former factor (PCI) was significant (p=0.026). A statistically significant (p<0.05) increase in TIMI major hemorrhage events during index hospitalization was observed in the enoxaparin treatment arm for the presence or absence of the following risk/prognostic factors: heart rate, Killip class, biomarkers, ST depression, diabetes, prior PCI, PCI, and CABG surgery. The treatment groups were similar with regard to age and clopidogrel usage. Similar results were observed in the ITT population. In the CONS population, a statistically significant (p<0.05) increase in TIMI major hemorrhage events during index hospitalization was observed in the enoxaparin treatment arm for the following risk/prognostic factors: heart rate, Killip class (II), and the presence of ST depression and diabetes.

Interventions
Overall, in both treatment arms in the ITT population, approximately 92% of subjects received a diagnostic cardiac catheterization, 47% received a PCI, and 18 to 19% of subjects received CABG surgery during the index hospitalization and the mean times to diagnostic cardiac catheterization, PCI, and CABG surgery were approximately 37 to 40 hours, 42 to 43 hours, and 129 to 134 hours, respectively. Regardless of GPIIb/IIIa inhibitor use or non-use, the incidences of and mean times to diagnostic cardiac catheterization, PCI, and CABG surgery were similar between treatment arms upon data inspection. However, in both treatment arms, subjects with GPIIb/IIIa inhibitor use received all such procedures earlier (between approximately 10 to 19 hours earlier) in the study with respect to randomization.

Blood transfusions
Overall, in both treatment arms regardless of CABG, the incidence of subjects who required transfusion of PRBC, whole blood, or platelets was <19%, the mean quantity transfused was <1 unit, and the number of subjects who required the transfusion of PRBC/whole blood =5 units was <5%. Similar results were observed in the ITT population. When comparing the incidence of blood transfusions during the index hospitalization with regard to CABG surgery, between 76 and 77% and between 21 and 26% of subjects who underwent CABG surgery received 1 or more PRBC/whole blood and platelet transfusions, respectively, during the index hospitalization, whereas the incidence of PRBC/whole blood and platelet transfusions were relatively low (~5% and <1%, respectively) for subjects without CABG surgery during the index hospitalization. Similar results were observed in the ITT population.

Results - Health economics

Total medical costs as derived from resource consumption were evaluated and the analysis is provided in a separate document.

Report Date: 4 Apr 06