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APPLICATION NUMBER:

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**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY REVIEW

Division of Clinical Pharmacology I

NDA 22138

Submission Date: November 17, 2006

Type: Efficacy Supplement, Priority

Brand Name: Lovenox®

Generic Name: Enoxaparin sodium injection

Dosage Strength: 100 mg/mL: Prefilled syringes 30 mg/0.3 mL, 40 mg/0.4 mL, graduated prefilled syringes: 60 mg/0.6 mL, 80 mg/0.80 mL and 100 mg/1 mL, multiple dose vials; 300 mg/3.0 mL, 150 mg/mL concentrations: Graduated prefilled syringes: 120 mg/0.8 mL, 150 mg/1 mL

Indication: Treatment of acute ST segment elevation myocardial infarction (STEMI)

Sponsor: Sanofi-Aventis, Bridgewater, NJ

Reviewing Division: Division of Cardiovascular and Renal Products, HFD-110

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1. Executive Summary

This is a priority efficacy supplement. The original NDA was approved in 1993. The sponsor seeks approval for the indication adjunct treatment of patients with acute ST-Segment Elevation Myocardial Infarction (STEMI) including patients to be managed medically or with subsequent Percutaneous Coronary Intervention (PCI). The sponsor seeks approval based on the results of a single pivotal study that showed a highly significantly improved outcome (death, reinfarction) for patients receiving enoxaparin compared to un-fractionated heparin (UFH) when used as an adjunct to fibrinolytic therapy.

UFH in the STEMI indication is not approved by the Agency, however UFH is recommended as adjunct treatment by the ACCP in their guidelines for the treatment of STEMI.

The submission contains 15 reports in the Clinical Pharmacology realm relating to assay validation (7), traditional PK (2), POPPK (5) and POPPK-PD (1) in healthy volunteers and patients with STEMI receiving enoxaparin by IV bolus and SC administration. All reports were reviewed.

In addition 7 clinical study reports including the report of the pivotal study EXTRACT were contained in the submission.

Enoxaparin is currently approved for:

- Prophylaxis of deep vein thrombosis, which may lead to pulmonary embolism in patients:
 - undergoing abdominal surgery at risk for thrombo-embolic complications
 - hip replacement surgery, during and following hospitalization
 - knee replacement
 - with severely restricted mobility during acute illness
- Treatment of acute deep vein thrombosis
- Prophylaxis of ischemic complications of unstable angina and non-Q-wave MI

Enoxaparin is a fractionated low molecular weight heparin (LMWH) comprised of multiple moieties with anti-Factor Xa (inhibition of thrombin generation) and anti-Factor IIa (inhibition of thrombin) activities. A physico-chemical assay for enoxaparin (and other LMWH) has not been developed. The potential anti-Factor Xa- and anti-Factor IIa activities of enoxaparin are being used as surrogates to measure the concentrations of the drug in plasma and urine. Activated partial thromboplastin time (aPTT) was employed as a pharmacodynamic biomarker of enoxaparin in selected studies. But as stated by the sponsor none of the classical hematologic tests including aPTT, thrombin time, prothrombin time and anti-Xa and anti-IIa activities of enoxaparin bring the full spectrum of enoxaparin's activities to bear. Because the incidence of bleeding events was found to depend on exposure in terms of anti-Xa activity, the sponsor considers the anti-Xa activity the most relevant of the 3 assays measuring the pharmacological activity of enoxaparin.

Pharmacokinetics

The Clinical Pharmacology database submitted in sNDA 20164 included the results from 6 clinical studies with PK information and 7 assay related reports. Two of the clinical studies RP54563Q-142 and RP54563Q-266 PEPCI used a data rich, traditional 2-stage approach and four sub-studies of RP54563Q-312 AMI-SK, XRP4563B-267 ENTIRE TIMI-23, XRP4563B/3001 BAY001 EXTRACT and DMPK/FR/2249 TIMI11A used POPPK analyses. The relationship between exposure and efficacy was tested in AMI SK. The exposure-safety relationship was examined in AMI-SK and TIMI11A. The 4 clinical studies with PK or PK-PD analyses used the dose regimens of enoxaparin shown in the below table:

Study	Population	Regimen		
		IV Loading Dose mg	SC Maintenance Dose mg/kg	Adjustment
AMI SK	Acute MI	30	1.0 q 12	No
TIMI 11A	NON-STEMI ^a	30	1.25 q 12 ^f	Yes ^b
	NON-STEMI ^a	30	1.0 q 12 ^{c,d}	Yes ^b
ENTIRE TIMI-23	STEMI	30	1.0 q 12 ^e	No
	STEMI	No	1.0 q 12 ^e	No
	STEMI	No	0.3 q 12	No
	STEMI	30	0.3 q 12	No
	STEMI	No	1.0 q 12 ^c	No
RP54563Q-142	Healthy	30	None	No
	Healthy	30	1.0 q 12	No
PEPCI	STEMI	30	1.0 q 12 ^f	No
EXTRACT	STEMI	30	1.0 q 12 ^d	Yes ^{f,g}

^a Unstable angina or Non-Q-wave MI ^b CLcr ≤ 30 mL/min: 1.0 mg/kg SC q 24 h ^c First 2 SC injections maximum 100 mg ^d Initially 1.5 mg/kg SC for second cohort, because of an excessive incidence of major hemorrhage (LL 90% CI ≥ 4.0%) in first cohort receiving 1.25 mg/kg q 12 h dose of second cohort reduced to 1.0 mg/kg q 12 h ^e First two injections 0.75 mg/kg SC ^f PCI > 8 h after last SC maintenance dose ^g CLcr ≤ 30 mL/min: 1.0 mg/kg SC q 24, age ≥ 75 y: no loading IV bolus, maintenance dose 0.75mg/kg SC

The studies were conducted in patient and healthy subject groups of comparable age. The treatments in the different studies included regimens with only maintenance doses given SC q 12 h for 2-8 days and regimens with a loading dose (IV bolus) preceding the SC maintenance doses. The SC maintenance doses ranged between 0.3 mg/kg and 1.25 mg/kg. The regimen with the highest total exposure to enoxaparin included a loading dose of 30 mg by IV bolus followed immediately by SC 1.25 mg/kg q 12. It was used in TIMI 11A and resulted in an unacceptable high incidence of major hemorrhages which exceeded the upper limit pre-specified by the sponsor in the first of the two cohorts to be investigated. Consequently, the sponsor reduced the originally planned regimen with SC maintenance doses of 1.5 mg/kg q 12 h for the second cohort in TIMI 11A to 1 mg/kg q 12 h. The regimen with the lowest total exposure to enoxaparin consisted of a treatment without a loading IV bolus and SC maintenance doses of 0.3 mg/kg and was used in ENTIRE-TIMI. The sponsored defined the therapeutic range for enoxaparin (0.5-1.1 IU anti-Xa/mL) as the span between mean peak and trough levels in TIMI 11A that provided

effective prophylaxis of unstable angina and non-Q-wave MI with a regimen of 1 mg/kg SC q 12 h.

That unadjusted doses increased exposure in patients with compromised renal function had been established previously for enoxaparin. The label for all currently approved indications stipulates reductions of the SC maintenance doses ranging between 25% and 50%. The POPPK analysis of the 4 clinical studies by the sponsor indicated that the parameters of enoxaparin in patients with STEMI, unstable angina (UA) or non-Q-wave MI were comparable. The analysis confirmed creatinine clearance (CLcr) as the only relevant covariate for exposure to enoxaparin.

The POPPK-PD analysis of AMI-SK and TIMI 11A by the sponsor indicated that severe renal impairment increases the risk for minor and major hemorrhages (clinically overt hemorrhage with a decrease of Hb ≥ 3 g/dL or a retroperitoneal, intracranial, or intraocular hemorrhage) more than expected from the increased exposure alone pointing to the known increased bleeding disposition of patients with compromised renal function.

The Agency's POPPK-PD analysis used a multivariate logistic model to define the impact of exposure and patient covariates. The findings showed that only CLcr and exposure have a significant impact on the risk to incur a major hemorrhage. Thus, risk for major bleeding is determined by kidney function as quantitated by CLcr and by exposure. The same increase in exposure to enoxaparin caused by compromised renal function results in an importantly greater risk for hemorrhage than by an increase in dose.

The Agency's analysis could not verify that age ≥ 75 y constitutes a separate and relevant covariate. Since the patients with reduced CLcr tended to be elderly (≥ 65 y) or older (≥ 75 y) it may be difficult to differentiate between the possibly separate effects of the two covariates on exposure and bleeding.

A relationship between exposure and efficacy for enoxaparin (combination of death/recurrent ischemia/reinfarction, change in TIMI flow grade, or ST segment resolution within 3 h) could not be demonstrated. This is not surprising given that study AMI-SK investigated a single dose level resulting in a limited concentration range.

Based on the findings of TIMI 11A, AMI-SK and ENTIRE TIMI-23 the sponsor selected for the pivotal EXTRACT study in STEMI patients a dose regimen of enoxaparin which included a loading dose of 30 mg IV followed immediately by SC maintenance doses of 1.0 mg/kg q 12 h. The first 2 maintenance doses were limited to 100 mg. Patients with a CLcr < 30 mL/min received a reduced maintenance dose of 1 mg/kg q 24 h (=50% dose reduction) and patients ≥ 75 y of age did not receive an IV bolus and the SC maintenance doses were reduced to 0.75 mg/kg q 12 h. Patients ≥ 75 y with CLcr ≤ 30 mL/min received no IV bolus and the SC maintenance doses were reduced to 1 mg/kg q 24.

The sponsor's rationale for the regimen used in EXTRACT appeared to be that 1 mg/kg SC q 12, the highest maintenance dose perceived to be safe by the sponsor in TIMI 11A, must be preceded

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by a proportionate IV loading dose to achieve quasi-instantaneously effective enoxaparin levels for an acute event such as STEMI. An IV bolus of 30 mg was shown to achieve enoxaparin concentrations that are slightly smaller (12-21%) than those obtained with a SC maintenance dose of 1 mg/kg SC in study RP54563Q-142 in healthy subjects of age 50-70 y.

The sponsor postulates that enoxaparin levels should remain in the target range of 0.6-1.8 IU anti-Xa/mL in patients during PCI. The upper value of 1.8 IU/mL corresponds to the 75th percentile of the peak concentrations in patients treated with 1.25 mg/kg enoxaparin q 12 h who did not experience a major hemorrhage in TIMI11A. The rationale of the sponsor appears to be that transiently greater enoxaparin concentrations are required in patients during the intervention. The lower value represents the median trough concentration observed in healthy subjects in the age between 50 and 68 y after SC administration of 1 mg/kg q 12 maintenance doses in study RP54563Q-142. An IV bolus of 0.3 mg/kg administered > 8 h after the last SC maintenance dose resulted in plasma concentrations in the target range in PEPCI. Based on these findings patients undergoing PCI > 8 h after the last SC maintenance dose received an IV bolus of 0.3 mg/kg in EXTRACT. However, this "booster dose" was not adjusted in patients with severe renal impairment or in patients $\geq$ 75 y old.

Assay

The 7 assays related reports describe the validation procedures and results for the anti-Xa- and anti-IIa activities of enoxaparin in plasma and urine and the performance of the aPTT assay.

The review of the assay reports showed that the amidolytic assays measuring the anti-Xa and anti-IIa activities of enoxaparin in plasma can be considered validated. However, short and long term stability of the amidolytic assays in urine was not adequately determined and/or described. Thus, the reported values of renal clearance and urinary excreted amounts of enoxaparin in healthy middle aged subjects in Study RP54563Q-142 cannot be considered reliable.

The sponsor did not evaluate the performance of their aPTT test relative to today's standards or cross-validated their assay with a comparable assay of a certified laboratory. Factors affecting the sample stability were not examined. Therefore, the aPTT assay cannot be considered fully validated.

Clinical Pharmacology Issues

Clinical Studies

1. Therapeutic Range and Optimum Dose Regimen

of 0.3 mg/kg enoxaparin prior to the intervention irrespective of renal function or age. A patient with CLcr < 30 mL/min undergoing PCI is expected to exhibit greater enoxaparin levels > 8 h after the last SC maintenance dose than a patient with normal renal function. 7

b(4)

Body Weight

b(4)

Severe Renal Impairment

The proposed label in accordance with the protocol of EXTRACT states that the interval between subsequent SC maintenance doses in STEMI patients with CLcr < 30 mL/min should be increased from q 12 to q 24 h (50% dose reduction). A comparison of the dose reductions across the different indications for enoxaparin shows an inconsistency in the adjustment. The recommended reduction in dose for the indications prophylaxis in abdominal surgery and prophylaxis in medical patients is only 25 %, whereas the dose reduction for the indications prophylaxis in hip replacement, prophylaxis of ischemic complications of UA and non-Q-wave MI, treatment of deep vein thrombosis, and treatment of STEMI is 50%. The rationale for this difference is not obvious and a uniform dose reduction of enoxaparin in patients with < 30mL/min is suggested.

Assays

1. The antiXa and anti-IIa based enoxaparin assays in urine cannot be considered fully validated.
2. The sponsor did not evaluate the performance of the aPTT test relative to today standards. Therefore, the aPTT assay cannot be considered fully validated.

The expectation is that in future submissions fully validated amidolytic (urine) and aPTT methods are used.

1.1 Recommendation

From a Clinical Pharmacology point of view the efficacy supplement of NDA 20164 is acceptable. Provided that an agreement can be obtained with the sponsor on the revised labeling there are no remaining issues.

2. Question Based Review

2.1 General attributes of the drug

Lovenox® (enoxaparin sodium) is a low molecular weight heparin exhibiting anti-thrombotic effects.

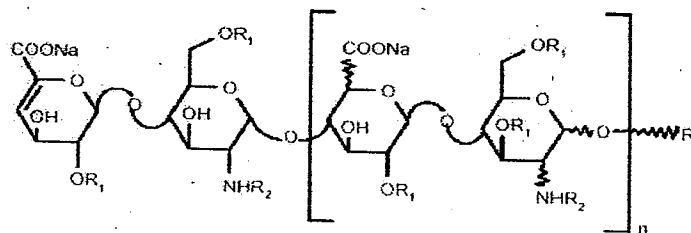
Reference is made to NDA 20-164 for enoxaparin approved by the Division of Medical Imaging and Hematology Products for the following indications (original NDA was approved in 1993):

- Prophylaxis of deep vein thrombosis, which may lead to pulmonary embolism in patients:
 - undergoing abdominal surgery at risk for thrombo-embolic complications
 - hip replacement surgery, during and following hospitalization
 - knee replacement
 - with severely restricted mobility during acute illness
- Treatment of acute deep vein thrombosis
- Prophylaxis of ischemic complications of unstable angina and non-Q-wave MI

2.1.1 What are the highlights of the chemistry and physico-chemical properties of the drug substance and the formulation of the drug product as they relate to the clinical pharmacology and biopharmaceutics review?

Lovenox injection is a sterile aqueous solution of pH 5.5- 7.5 containing enoxaparin sodium. Enoxaparin sodium is obtained by alkaline depolymerization of heparin benzyl ester derived from porcine intestinal mucosa. Enoxaparin's structure is shown below:

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$R_1 = \text{H or SO}_3\text{Na}$ and $R_2 = \text{SO}_3\text{Na or COCH}_3$

R	$X^* = 15 \text{ to } 25\%$		$n = 0 \text{ to } 20$
	$100 - X$	H	$n = 1 \text{ to } 21$

*X = Percent of polysaccharide chain containing 1,6 anhydro derivative on the reducing end.

The average molecular weight of enoxaparin is 4500 daltons with the following distribution:

Quantity, %	MW, daltons
≤ 20	< 2000
≥ 68	2000-8000
≤ 18	> 8000

2.1.2 What are the proposed mechanism(s) of action and therapeutic indication(s)?

Enoxaparin has anti-thrombotic anti-Factor Xa- (inhibition of thrombin formation) and anti-Factor IIa (inhibition of thrombin) activities. Due to the larger content of low molecular fragments in enoxaparin compared to UFH the anti-Xa activity is several times larger than the anti-IIa activity. Enoxaparin increases thrombin time and aPTT. However, as the sponsor states, there is no single biologic assay that could serve as an indicator for enoxaparin's pharmacological activity.

2.2 General clinical pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

Pivotal Clinical Study

The pivotal EXTRACT study used a multi-center, double-blind, double dummy, parallel group study with STEMI patients randomized in a 1:1 ratio to receive enoxaparin or UFH. A total of 20506 patients were enrolled. All patients were also treated with aspirin for a minimum of 30 days. Study medication was administered between 15 min before and 30 min after initiation of fibrinolytic therapy. UFH was administered beginning with an IV bolus of 60 U/kg and followed by a 48 h infusion of 12 U/kg/h that was adjusted to maintain an aPTT of 1.5 to 2.0 times the control value. The enoxaparin dosing strategy was adjusted for age and renal function. For patients < 75 y old enoxaparin was given as a single 30 mg IV bolus plus a 1mg/kg SC dose followed by an SC injection of 1.0 mg/kg every 12 h. For patients > 75 y old the IV bolus was not given and the SC dose was reduced to 0.75 mg/kg every 12 h. For patients with CLcr < 30 mL/min, the dose of enoxaparin was reduced to 1 mg/kg every 24 h. The SC injections were given until hospital discharge or for a maximum of 8 days. When PCI was to be performed during the study medication period patients were to receive anti-thrombotic support with blinded study drug. Therefore, for patients with enoxaparin the PCI was to be performed on enoxaparin using the regimen established in previous studies (study TIMI 11A, study RP54563Q-266), i.e. no additional dosing if the last SC dose was given < 8 h before balloon inflation, but an IV bolus of 0.3 mg/kg enoxaparin if the last SC administration was given > 8 h before balloon inflation. The primary efficacy endpoint was the composite of death from any cause or myocardial re-infarction in the first 30 days after randomization.

Clinical Pharmacology Studies

Two-Stage Approach PK Studies

Study RP54563Q-142 was an open label PK study in healthy volunteers of age 50-70 y who received in a first treatment period 30 mg enoxaparin by IV bolus and in the second treatment period a 30 mg enoxaparin IV bolus followed by 1 mg/kg SC enoxaparin every 12 h for 3.5 days. The goal of the study was to confirm that with the tested treatment a therapeutic quasi steady-state was attained instantaneously as desirable in patients with acute MI.

Study RP54563Q-266 was an open-label, parallel group study in 4 groups of patients undergoing PCI 8-12 h after the last of multiple SC administrations of enoxaparin given every 12 h. Prior to cardiac catheterization the subjects received a 30 mg IV bolus of enoxaparin followed by a SC dose of 1 mg/kg or at least five SC doses (1mg/kg) every 12 h to attain steady-state prior to the PCI procedure. Subsequently, the patients received an IV bolus of 0.3mg/kg enoxaparin at the start of the PCI or at the end of the diagnostic characterization if PCI was not performed. The goal of the study was to confirm that the tested dose regimens provide therapeutically effective anti-Xa levels. The target range for enoxaparin was 0.6-1.8 IU anti-Xa/mL, even though the therapeutic range was postulated to range between 0.5 and 1.1 IU anti-Xa/mL as determined in Study TIMI 11A and the PK parameters established from earlier submitted studies.

The goals of studies RP54563Q-142 and-266 was to test and establish a dose regimen that would attain quasi-instantaneous effective anti-Xa activity peak and trough concentrations within the postulated therapeutic window in patients with STEMI including patients to be managed medically or with subsequent PCI.

Population PK and PK/PD Studies

A total of 6 POPPK and POPPK-PD related reports are in this application and include:

DMPK/FR/2249 is a population PK study that analyzed the sparse PK samples from TIMI 11A trial in patients with unstable angina or non-Q wave myocardial infarction. TIMI 11A was a multicenter trial of the safety and tolerability of 2 doses of enoxaparin in patients. In this study, during the in-hospital phase, patients received a 30 mg IV bolus followed by either 1 mg/kg or 1.25 mg/kg sc q 12 hours. After hospital discharge, the patients were administered a fixed dose (40 mg for weight < 65 kg, or 60 mg for weight > 65 kg) SC q 12. The dosing regimen in the in-hospital phase was similar to the proposed dosing regimen for the treatment of STEMI. Blood samples taken from 300 patients were used in model build-up and a population PK base model and covariate model were established. PK data from 148 patients were used for model validation.

DMPK/FR 2409 is a POPPK-PD study from TIMI 11A trial that linked the exposure of enoxaparin to the incidence of major and/or all hemorrhage, based on the individual PK fitting from DMPK/FR/ 2249 study. Anti-Xa AUC is treated as exposure measure. Major bleeding is defined as a clinically overt hemorrhage resulting in a fall of ≥ 3 gm/dL in hemoglobin or a retroperitoneal, intracranial, or intraocular hemorrhage. All other episodes of bleeding were considered minor hemorrhages. The patients were assigned a binary variable (1, 0) according to whether or not they experienced hemorrhagic events while on treatment. Patients experiencing several events were assigned to the most severe one. A logistic regression was conducted to relate the probability of experiencing hemorrhage to drug exposure and other covariates.

BAY001 is a POPPK study from EXTRACT (XRP4563B/3001) trial in patients with acute STEMI receiving fibrinolytic therapy. Over 10166 patients were randomized into the enoxaparin treatment group. Only 76 patients had blood samples taken on Day 1 for PK analysis. Among them, 13 patients received 0.75 mg/kg enoxaparin SC without IV bolus (≥ 75 years group), 60 patients received a 30 mg IV bolus immediately followed by 1.0 mg/kg SC (<75 years group) and 3 patients received 1.0 mg/kg SC without IV bolus. All the patients received concomitant administration of thrombolytics such as streptokinase in 24 patients, tenecteplase in 14 patients and alteplase in 38 patients. Among the patients 2, 10 and 25 were severely, moderately and mildly renally impaired. Individual pharmacokinetic parameters were obtained by Bayesian estimation using anti-Xa-time data from each subject and the population model previously reported in TIMI 11A study.

RP54563Q – 312 is a safety and efficacy study of SC enoxaparin and streptokinase in patients with acute MI. An IV bolus of 30 mg enoxaparin followed by 1.0 mg/kg enoxaparin was administered SC q 12 h for 3 to 8 days. Study drug started within 1 h of streptokinase. Among

the 253 patients randomized to enoxaparin, 244 patients had blood samples drawn (about 2 per visit). Individual PK parameters of the patients were obtained by Bayesian approach using the population PK model established in TIMI 11A study. A Logistic regression was conducted to explore the enoxaparin exposure-safety (major hemorrhage, all hemorrhage) relationship and the exposure-efficacy (TIMI Grade 3 at Day 8, incidence of ST-segment resolution of at least 70% at 180 min post-streptokinase infusion, and the incidence of combined triple-endpoint (death, recurrent ischemia or reinfarction at Day 30) relationship.

XRP4563B-267 (ENTIRE – TIMI 23) study is a Phase II stratified, randomized, open-label, angiographic trial to assess the safety and efficacy of enoxaparin as an adjunct to thrombolytic therapy with or without GPIIb/IIIa antagonists, in subjects with STEMI (ENTIRE study). At selected study centers, a pharmacokinetic study (population approach) was implemented in subjects from different dose groups either starting with a 30 mg IV bolus or without an IV bolus dose, then followed by 0.3, 0.75, 1 mg/kg SC administration q 12 h in the first two days. The subsequent maintenance dose was 1mg/kg q 12 h. A total of 4 blood samples were to be collected on 2 occasions: 2 samples after the first SC injection (first occasion, Day 1) and 2 samples after the third, fourth, or fifth sc injection (second occasion, any day from Day 2 to Day 3). The population PK study was carried out in 209 subjects.

POH137 is population PK analysis that is based on the PK data from the combined Phase I, Phase II, and Phase III studies of enoxaparin. Totally 768 (69.3% male) subjects corresponding to 262 subjects from Phase I studies, including 24 obese, 39 elderly and 87 with different degrees of renal impairment and to 506 subjects from Phase II and III studies with acute MI were included in the analysis. Enoxaparin was administered either as an IV bolus (fixed (i.e. 30 mg) or weight adjusted (i.e. 0.30 mg/kg)) or as a SC dose 1 mg/kg q 12 or 1.5 mg/kg q 24. Data analysis was performed using a stepwise approach. Once a basic pharmacokinetic model was obtained, an initial exploratory analysis for covariate effects on individual pharmacokinetic parameters was performed.

2.2.2 What is the basis for selecting the response endpoints (i.e. clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics PD)) and how are they measured in clinical pharmacology and clinical studies?

The clinical efficacy endpoints are all-cause mortality and occurrence of myocardial re-infarction, and the safety endpoint is hemorrhage (major and minor). Both efficacy and safety endpoints and their incidence can be assessed reliably, and if the events occur sufficiently often a good risk-benefit assessment for the proposed new indication should be possible.

Prolongation of aPTT was measured in Study RP54563Q-142 as a biomarker of the anti-thrombotic activity of enoxaparin sodium. There exist linear relationships between prolongation of aPTT and extent of anti-IIa activity or anti-Xa activity of enoxaparin.

2.2.3 Are the active moieties in the plasma (or other biological fluids) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

To date no assay has been developed that measures the active moieties of enoxaparin in biological fluids by a physico-chemical method. Therefore, the anti-thrombotic activity of enoxaparin in terms of anti-Xa and anti-IIa activities is measured using amidolytic assay methodology. Since the anti-Xa activity of enoxaparin is significantly larger than the anti-IIa activity and because a dependency of bleeding events on exposure (AUC of anti-Xa activity) was found, the sponsor defined the therapeutic range based on enoxaparin's anti-Xa activity only. The amidolytic assay in plasma measuring the anti-Xa activity of all active moieties of enoxaparin is acceptable. However, the amidolytic assays measuring the anti-Xa and anti-IIa activities in urine cannot be considered validated.

2.2.4 Exposure-response

2.2.4.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy? What is time of onset and offset of the desirable pharmacological response or clinical endpoint?

There is insufficient information regarding the exposure and efficacy relationship in STEMI patients in the pivotal EXTRACT and in other trials with patients with unstable angina and non-Q-wave MI.

2.2.4.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?

The exposure-safety relationship was explored in patients with unstable angina and non-Q wave myocardial infarction from TIMI 11A on the assumption that the mechanism for hemorrhage is similar between this population and the STEMI population. Following enoxaparin administration, a logistic regression analysis was applied to explore the enoxaparin exposure-major/ all hemorrhage relationship. A significant enoxaparin exposure effect was demonstrated for the incidence of either major hemorrhagic events or all hemorrhagic events ($P < 0.05$). Logistic regression results also showed that a higher exposure value of enoxaparin yields a higher incidence of all hemorrhagic and major hemorrhagic events (Fig 1 and 2):

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Fig 1. Logistic Regression for All Bleeding Events vs. Enoxaparin AUC

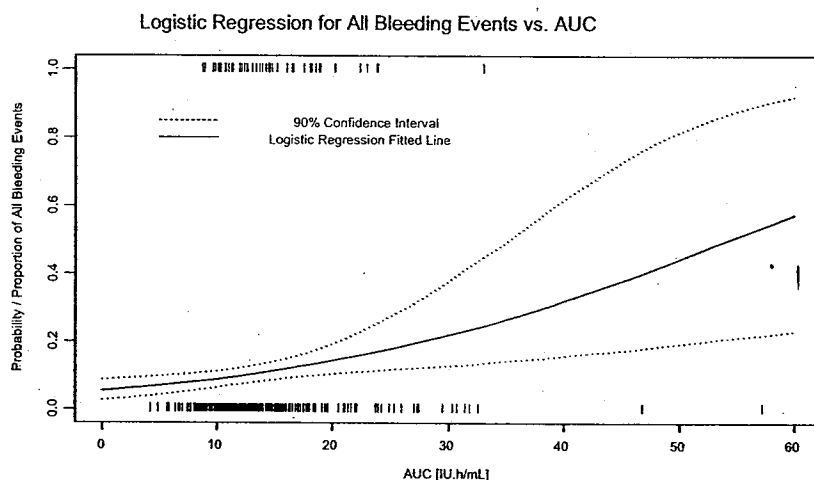
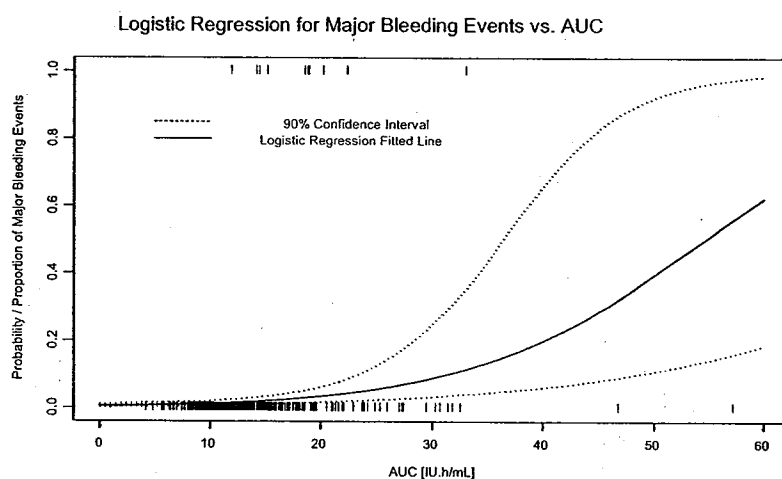


Fig 2. Logistic Regression for Major Bleeding Events vs. Enoxaparin AUC



2.2.4.4 Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

The regimen (including dose adjustments) for the indication adjunct treatment of STEMI patients in the proposed label is the same as that used in EXTRACT. The sponsor's exposure-efficacy analysis did not include the results from the ENTIRE TIMI-23 study which would have widened the concentration range available for a correlation analysis. The exposure-efficacy relationship for enoxaparin has not been optimally studied by the sponsor. Therefore, the therapeutic range of enoxaparin for the STEMI indication is not well defined and chances are that the enoxaparin treatment used in EXTRACT does not constitute the

optimum regimen for patients with STEMI even though the results of the pivotal study indicate a beneficial response in STEMI patients to enoxaparin compared to UFH. The EXTRACT study was overpowered and an additional dose level of enoxaparin could have aided in defining the therapeutic range of the drug in STEMI patients better.

The exposure-safety relationship for major hemorrhagic events is more adequately defined.

2.2.5 What are the PK characteristics of the drug and its major metabolite(s)

The interpretability of the PK of enoxaparin are limited for the following reasons:

Enoxaparin consists of multiple moieties with anti-Xa- and anti-IIa -activities. The amidolytic assays used measure all moieties that exhibit either anti-Xa- or anti-IIa-activities activities. Thus, the admidolytic assays cannot be considered specific. Even if the PK of the different moieties were truly linear, log linear terminal disposition phases for the moieties displaying anti-Xa- and anti-IIa activities could not be expected.

The dose refers to the anti-Xa activity of enoxaparin. The dose for the anti-IIa activity is not provided and it is unclear how meaningful values for oral clearance and volume of distribution could be obtained for the moieties contained in enoxaparin that exhibit anti-IIa-activities.

2.2.5.1 What are the single and multiple dose PK parameters?

According to the current enoxaparin label the PK of enoxaparin based on anti-Xa activity appear to be linear over the recommended dosage range. After IV bolus administration mean CL and V presumably in healthy subjects are indicated as 26 mL/min and 4.3 L, respectively, in the label. A value for the terminal $t_{1/2}$ after IV administration is not provided. The absolute bioavailability of enoxaparin administered SC is approximately 1.0 and peak anti-Xa activity occurs 3 h to 5 h after SC administration. Mean C_{max} for the anti-Xa activity after single SC administration of 20 mg and 40 mg enoxaparin is 0.16 IU/mL and 0.38 IU/mL, respectively. The respective apparent terminal $t_{1/2}$ after single and repeated SC administration is 4.5 h and 7 h, respectively. After repeated SC administrations q 24 h and q 12 h the respective accumulation factor is 1.15 and 1.65. The current label indicates that renal function (< 30 mL/min), body weight and age are clinically relevant covariates for exposure.

In the submitted study RP54563Q-142 healthy subjects between 50 and 70 y of age the mean $t_{1/2}$ based on anti-Xa activity is 3.65 h after a single IV bolus. After an IV bolus of 30 mg followed by a SC administration of 1 mg/kg bid the respective C_{max} on Day 1 and Day 4 is 1.164 IU/mL and 1.320 IU/mL. The peak concentration on both days occurs 3 h after administration. The mean $t_{1/2}$ of enoxaparin on Days 1 and 4 are 6.6 h and 7.0 h, respectively. The accumulation factor is 1.19.

In the submitted study RP54563Q-266 in STEMI patients undergoing PCI the sponsor attempted to fit a one compartment model to the data. However, the parameter estimates must be

considered biased. The sponsor did not provide pertinent parameters for enoxaparin with the compartment model independent approach.

The POPPK analysis of the patients in TIMI 11A yielded mean typical values of 11.5 mL/min, 6.54 L and 2.5 h for CL/F, V and t1/2ka, respectively. The corresponding values in EXTRACT were 12.1 mL/min, 6.01 L and 2.2 h. These results indicate-not surprisingly- that the PK of enoxaparin in UA/Non-Q-wave and STEMI populations are comparable. It should be noted that because of the flip-flop of the absorption- and elimination rate constants following SC administration of enoxaparin t1/2 ka is reported instead of t1/2ke.

2.2.5.2 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

The two tables below summarize the PK parameters for enoxaparin (anti-Xa activity) in healthy subjects and in patients receiving SC administrations and in healthy subjects after an IV bolus administration. The values of the parameters provided in the current label are also listed for comparison:

Mean Pharmacokinetic Parameters of Enoxaparin after repeated SC Administration in Patients with STEMI or UA/Non-Q-wave MI and Healthy Subjects

Study	Population		CL/F, mL/min	V/F, L	t1/2ka, h	F
	Healthy	Patients				
TIMI 11A		UA, NON-STEMI	11.5	6.54	2.5	
EXTRACT		STEMI	12.1	6.01	2.2	
RP54563Q-142	Middle Aged		ND	ND	6.6,7.0	
LABEL	Young ^a		15	NR	NR	1.0

ND=Not determined ^a Not defined NR=Not reported

Values for the apparent terminal disposition phase have been reported in healthy subjects and patients with STEMI or UA/non-Q-wave MI. The values for t1/2ka appear to differ significantly, but it should be noted that the PK parameters in the patient populations were obtained at steady-state using a sparse sampling approach. The estimates for t1/2ka in the healthy subjects in the age between 50 and 70 y were obtained post-steady state using a data rich two-stage approach.

Mean Pharmacokinetic Parameters of Enoxaparin after Single Dose IV Bolus Administration in Healthy Subjects

	CL, mL/min	V, L	t _{1/2ke} , h
RP54563Q-142	19.2	4.25	2.6
Label	26 ^a	4.3	NR

^a Not defined NR=Not reported

The current label indicates F=1 for enoxaparin after SC administration so that the respective estimates for V and CL for enoxaparin (anti-XXa activities) after IV and SC administration can be compared. It is interesting to note that the estimates for CL after SC administration are smaller and the estimates for V greater than after IV administration. This finding points to a possible bias in the parameter estimates and limits the interpretability of the results.

Enoxaparin consists of multiple active moieties that may display different PK characteristics. This is an additional reason why the estimated parameters should be interpreted with caution.

2.2.5.9 How do the PK parameters change with time following chronic dosing? (circadian rhythm, self induction, time to steady-state, single dose prediction of multiple dose PK, accumulation ratio)

In Studies RP54563Q 142 and- 266 there is no overt evidence for the presence of circadian rhythm. There is also no evidence for self-induction of enoxaparin. The multiple dose PK of enoxaparin (anti-Xa activity) are reasonably well predicted from single dose PK.

2.2.5.10 What is the intra- and inter-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

The respective inter-subject variability of CL/F in STEMI -and UA/Non-Q-wave MI patients was 39.4% and 40.9 %. Intra-subject variability was not reported. Inter-subject variation in CL/F after SC administration was not reported in healthy subjects in study RP54563Q-142.

2.3. Intrinsic factors

2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

CLcr (<30 mL/min) is the most important covariate for exposure and in addition is an indicator for risk for major hemorrhage in patients with Non-Q-wave MI. Weight is another identified covariate for exposure. The current label identifies old age as a minor covariate for exposure. The risk for major hemorrhage increases with increasing exposure. Gender and race are not important impact factors for exposure to enoxaparin. The impact of hepatic impairment or genetic polymorphism on exposure to enoxaparin has not been defined.

2.3.2 Based on what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations (examples shown below), what dosage adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

In EXTRACT the dose regimen of enoxaparin was adjusted for CLcr, weight, and old age. Patients with CLcr < 30 mL/min did receive an IV bolus of 30 mg. The weight adjusted SC maintenance dose was administered q 24 h instead of q 12 h. Older patients did not receive the 30 mg IV bolus loading dose and received SC maintenance doses reduced to 75% q 12 h.

2.3.2.1 Elderly

The current label describes old age as a covariate for increased exposure. The EXTRACT study used an age adjusted dose regimen. Old age cannot be ruled out as contributing to an increased risk for major hemorrhage.

2.3.2.3 Gender

Gender is not a significant covariate for the exposure to enoxaparin

2.3.2.4 Race, in particular differences in exposure and or response in Caucasians, African Americans, and/or Asians should be discussed

Race appears not to be a significant covariate for exposure to enoxaparin.

2.3.2.5 Renal Impairment

Severe renal impairment (CLcr < 30 mL/min) is the most important covariate for exposure and risk for major hemorrhage.

2.3.2.6 Hepatic Impairment

Neither the newly submitted material nor the current label provides information on the impact of hepatic impairment on exposure to enoxaparin or its antithrombotic effect. The label should reflect this situation.

2.3.2.7 What pharmacogenetic information is there in the application and is it important or not

There is no pharmacogenetic information in the current label or the newly submitted material.

2.4. Extrinsic Factors

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or- response and what is the impact of any differences in exposure on response?

There is no pharmacokinetic interaction between enoxaparin and thrombolytics such as streptokinase, tenecteplase, alteplase.

There is no information on the possible impact of herbal drugs, diet, smoking and alcohol use.

2.4.2 Based on what is known about the exposure-response relationships and their variability, what dosage regimen adjustments, if any, do you recommend for each of these factors? If dosage regimen adjustments across factors are not based on the exposure-response relationships, describe the basis for the recommendation.

There is no information on the impact of these extrinsic factors on the PK and PD of enoxaparin.

2.4.3 Drug-drug interactions. Some typical questions include:

2.4.2.6 Does the label specify co-administration of another drug (e.g. combination therapy in oncology) and, if so, has the interaction potential between these drugs been evaluated?

Co-administration of thrombolytics (streptokinase, tenecteplase, alteplase), acetylsalicylic acid and GP IIB/IIIA inhibitors and enoxaparin inpatients with STEMI is routine.

Only the possible pharmacokinetic interaction between thrombolytics (streptokinase, tenecteplase, alteplase) and enoxaparin was investigated in humans. No interaction was found.

2.4.2.7 What other co-medications are likely to be administered to the target population?

Antihypertensives, antilipidemics.

2.4.2.8 Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

See 2.4.2.9

2.4.2.9 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions, if any?

The label names the following drugs that may enhance the risk of hemorrhage: anticoagulants, platelet aggregation inhibitors including acetylsalicylic acid, NSAIDs, dipyridamole or

sulfinpyrazone. In addition direct thrombin inhibitors including argatroban, and lepirudin could interact with enoxaparin.

2.4.2.10 Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions, or protein binding?

NA

2.4.3 What issues related to dose, dose regimens, or administration are unresolved and represent significant omissions?

The therapeutic range in patients with STEMI and UA or non-Q-wave MI has not been well defined for enoxaparin. It is not known whether the dose regimen used in EXTRACT and proposed in the label is optimal.

2.4 General biopharmaceutics

NA

2.5 Analytical section

This section should address issues related to the analytical and bioanalytical methods used to support the clinical pharmacology and biopharmaceutics studies

2.6.1 How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

Enoxaparin comprises many molecules of different molecular weights. At present no physico-chemical method exists that can measure routinely the individual compounds or more importantly the active moieties of enoxaparin. Enoxaparin's antithrombotic potency is quantitated by measuring its anti-Xa- and anti-IIa activities.

2.6.2 Which metabolites have been selected for analysis and why?

Active metabolites of the moieties making up enoxaparin are being measured with the anti-Xa- and anti-IIa assays.

2.6.3 For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?

The average plasma protein binding of the individual compounds contained in enoxaparin has not been determined and even if known would not be helpful. The binding of the individual moieties comprising enoxaparin cannot be determined at present.

2.5.4 *What bioanalytical methods are used to assess concentrations? Refer to the guidance for industry on Bioanalytical Method Validation*

Amidolytic assays are used to measure the anti-Xa and anti-IIa activities of enoxaparin

2.5.4.1 *What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used*

Assay	Matrix	Calibration Curve		LLOQ IU/mL	Accuracy Range %	Precision %
		Range IU/mL	R2			
Anti-Xa	Plasma	0.000- 0.401	≥ 0.991	0.025 [#]	-12-10	≤ 12
Anti-Xa	Urine	0.000- 0.800	≥ 0.996*	0.80	-0.30- (-0.48)	≤ 3
Anti-IIa	Plasma	0.020- 0.150	≥ 0.994	0.020	-1- (-13)	≤ 17
Anti-IIa	Urine	0.000 - 0.200	≥ 0.995*	0.050	-7 -14	≤ 17

Precision and accuracy exceeded 20% in QCs of 0.025 IU/mL * Mean curves

The concentrations of the standards are proportional to the logarithm of the absorbance measured at 405 nm. Non-weighted linear regressions were fit to the calibration curves.

Enoxaparin is comprised of different moieties exhibiting antithrombotic activities. Thus, it may not be realistic to expect a log linear terminal phase. Thus, the usual sensitivity criterion, i.e. an assay must allow minimally a follow-up for a period $\geq 3 \bullet t_{1/2\lambda z}$, may not be applicable for enoxaparin. With the more sensitive anti-Xa assay log-linear terminal phases are not reached after either IV or SC administration with enoxaparin. With the less sensitive anti-IIa activity assay the plasma concentrations at steady-state can be measured over 12 h the dose interval in the majority of subjects.

2.5.4.2 *What are the lower and upper limits of quantification (LLOQ/ULOQ)?*

See above table

2.5.4.3 *What are the accuracy, precision, and selectivity at these limits?*

See above table

2.5.4.4 *What is the sample stability under the conditions used in the study (long-term, freeze-thaw, sample handling, sample transport, autosampler)?*

The stability of the samples during the analysis and the long term sample stability including freeze/thaw cycles for the anti-Xa- and anti-IIa assays of enoxaparin in plasma were confirmed. The stability of the samples during the analysis and the long term stability including freeze/thaw cycles for the anti-Xa and anti-IIa activity assays of enoxaparin in urine were not adequately

investigated. The anti-Xa and anti-IIa activity based assays of enoxaprin in urine cannot be considered validated.

2.5.4.5 What is the QC sample plan?

QC samples were co-analyzed with the plasma and urine samples to be measured.

3. Labeling Recommendations

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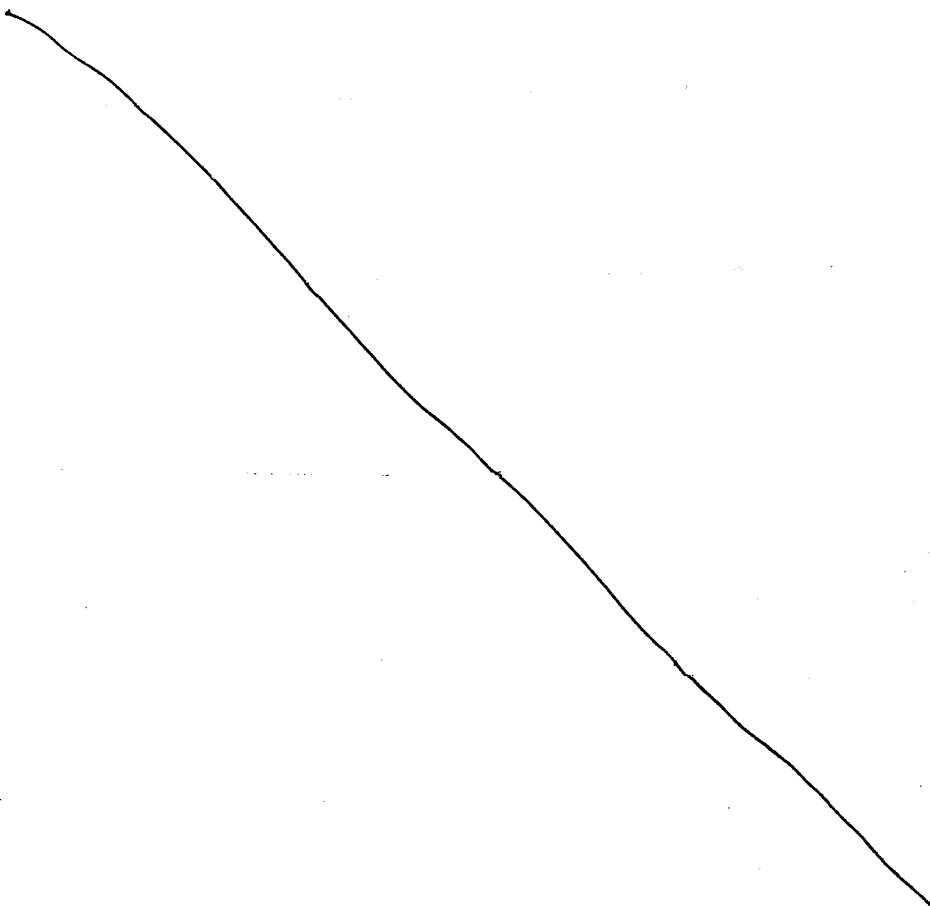
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_____ Draft Labeling (b5)

_____ Deliberative Process (b5)



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4. Individual Study Reports

List of Reviewed Reports

Reports on Bioassays

1. Study DMPK/FR/2032: Complementary Validation of Anti-Xa Chromogenic Assay for the Determination of Enoxaparin in Human Plasma
2. Study DMPK/FR/2320: 6 Month Stability Data of the Enoxaparin Anti-Xa Activity in Human Plasma Stored at -20° C and - 80° C. Addendum #1 to
_____ “Complementary Validation of Anti-Xa Chromogenic Assay for the Determination of Enoxaparin in Human Plasma”

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3. Study II _____ Enoxaparin: An Amidolytic Anti-Xa Activity Assay for the Determination of Low Molecular Weight Heparin in Biological Components in Urine b(4)
4. Study _____ Anti-II Chromogenic Assay Supplemented with Antithrombin III for the Measurement of Enoxaparin in Human Plasma b(4)
5. Study DMPK/FR/2318: 6 Month Stability Data of the Enoxaparin Anti-IIa Activity in Human Plasma Stored at -20° C and -80° C. Addendum to J _____ "Anti-IIa Chromogenic Assay Supplemented with Antithrombin III for the Measurement of Enoxaparin in Human Plasma" b(4)
6. Study DMPK/FR/2396 RP54563 Chromogenic Anti-II assay with Antithrombin Supplementation: Adaptation of the Assay Consecutive to a Change of the Bovine Thrombin Manufacturing Process.
7. Study _____ Design and Evaluation of Analytical Methods Dedicated to the Pharmacokinetics of Enoxaparin in Man, Clotting Methods, Amidolytic Methods (Anti-Xa and Anti-IIa or Antithrombin Activity) b(4)

Reports on PK or PK-PD

8. Study RP54563Q-142: A Phase I, Open-Label Pharmacokinetic Study of Enoxaparin 30 mg Intravenous Bolus Injection and of Enoxaparin 30 mg Bolus Injection Followed by Subcutaneous 1mg/kg bid in Healthy Volunteers
9. Study RP54563Q-266: Pharmacokinetic Study in Patients undergoing Percutaneous Coronary Intervention (8-12 Hours after Subcutaneous Injection): The PEPCI Study
10. Study Bay 0001: Population Pharmacokinetic Analysis of Extract (XRP4563B/3001) Enoxaparin (ECF6147) PK Sub-study: A Randomized, Double-Blind, Double-Dummy, Parallel Group, Multinational, Clinical Study to Evaluate the Efficacy and Safety of Enoxaparin versus Unfractionated Heparin in Patients with Acute ST-Segment Elevation Myocardial Infarction Receiving Fibrinolytic Therapy
11. Study DMPK/FR/2249: Population Pharmacokinetics of Enoxaparin: Analysis of Data from the TIMI11A Study
12. Study DMPK/FR 2409: PK/PD Analysis of Enoxaparin TIMI-11A Data
13. Study POH0137: Population Pharmacokinetic Study: A Combined Analysis of Phase I, Phase II and Phase III Studies of Enoxaparin
14. Study RP54563-312 AMI-SK: The Safety and Efficacy of Subcutaneous Enoxaparin and Streptokinase in Patients Presenting with Acute Myocardial Infarction: An International, Double-Blind, Placebo Controlled Study, Randomized, Parallel Group, Multi-Center Study
15. Study XPR54563B-267 ENTIRE-TIMI-23: Enoxaparin and TNK-TPA with or without GPIIb/IIIa Inhibitor as Reperfusion Strategy in ST Elevation MI-Study 123

Study RP54563Q-142: A Phase 1, Open-Label Pharmacokinetic Study of Enoxaparin 30 mg Intravenous Bolus Injection and of Enoxaparin 30 mg Intravenous Bolus Injection Followed by Subcutaneous 1 mg/kg bid in Healthy Volunteers

Study Investigator and Study Site:

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Objectives

1. Characterization of the pharmacokinetic profile of the combination of enoxaparin 30 mg intravenous (IV) bolus injection followed by repeated subcutaneous (SC) 1 mg/kg enoxaparin q 12 h administrations
2. Characterization of the pharmacokinetic profile of enoxaparin after a 30 mg intravenous bolus injection

Formulations

One mL ampules containing 100 mg/mL enoxaparin (batch CB06420)

Design

This was an open-label study comprising two periods separated by a washout of at least 3 days. In the first period healthy subjects in the age range 50-70 years received an enoxaparin 30 mg intravenous bolus and in the second period a 30 mg enoxaparin intravenous bolus followed by 1 mg/kg sc enoxaparin q12 for 3.5 days. The study drug was to be administered at around 0800 h and 2000 h

The scheduled study activities are shown in the below scheme:

Table 1: Overall flowchart

	Screening	Period 1					Period 2					Follow-up
		Wash out (±3 D)										
Day of study	D-21- D-2	D-1	D1	D2		D-1	D1	D2	D3	D4	D5	D8- D12
Admitted to unit	X	X	---	X		X	---	---	---	---	X	
Review entry criteria	X	X				X						
Administration of study drug			X ¹				X ²	X ³	X ³	X ⁴		
Informed consent	X											
Medical history	X	X	X			X						
Height	X											
Weight	X	X										
Vital signs	X	X									X	
Physical examination	X											
12-lead ECG	X											
Full laboratory profile	X											
Limited laboratory profile		X		X ⁷			X ⁵				X	X
Template bleeding time	X											
Drug screening	X	X										
HIV, HBV, HCV tests	X											
PK plasma sample			X	X			X	X	X	X	X	
Urine collection for PK			X ⁶	X ⁶						X	X	
Adverse event recording			X	---	---	---	---	---	---	---	---	X
Prior and concomitant medication	X	---	---	---	---	---	---	---	---	---	---	X

- 1 : Intravenous bolus injection
- 2 : Intravenous bolus injection + subcutaneous injection *b.i.d*
- 3 : Subcutaneous injection *b.i.d*
- 4 : Subcutaneous injection morning only
- 5 : aPTT only
- 6 : urine collection for PK and creatinine
- 7 : serum creatinine only

The inclusion and exclusion criteria used to select the participants of the study are shown below:

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5.2.1 Inclusion criteria

Eligible subjects had to meet the following inclusion criteria:

Be healthy (aged 50 to 70 years) male or female subjects,

Have a Body Mass Index (BMI) ≤ 30 kg/m²

Accept and be able to give written informed consent,

Not be in the exclusion period of a preceding study,

Have no contraindications from the following: a detailed medical and surgical history, a complete physical examination including vital signs, 12-lead ECG, hematology, blood chemistry, urinalysis,

Have laboratory coagulation parameters within normal ranges,

Have a negative drug screen (barbiturates, benzodiazepines, amphetamines, opiates, cocaine, cannabinoids) at screening and on Day -1.

Be registered under a French social welfare system.

5.2.2 Exclusion criteria

Subjects having the following conditions were excluded from the study :

Past medical history

History of any hematological, hepatic, respiratory, cardiovascular, renal or CNS disease or other medical condition that is capable of altering the metabolism or elimination of drugs; or of constituting a risk factor when taking the study drug,

Evidence or history of blood dyscrasia and bleeding disorder including thrombocytopenia, thrombopathy, hypofibrinogenemia, hemophilia, vascular purpura, anemia or known - antithrombin III or protein S or protein C - deficiency,

Evidence or history of diseases associated with bleeding risk, including evolutive hemorrhagic vascular lesions, gastro-duodenal ulcer, ulcerative colitis, recent surgery (within the previous month), hypertension...,

History of thrombocytopenia related to enoxaparin or other LMWH or UH,

History of drug addiction or alcoholism,

History of allergy or hypersensitivity to any medication, particularly to aspirin, heparin or heparin-derived compound,

Any condition which could relapse during or immediately after the study,

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Current status

Positive serology to hepatitis B or hepatitis C or Human Immunodeficiency Viruses,
Significant acute or chronic disease,
Any other contra-indication to anticoagulant including any organ lesion susceptible to bleeding or uncontrolled high blood pressure (> 160/95 mm Hg),
Likely to need concomitant medication during the study period (including for dental conditions),
Blood donation during the month preceding study entry,
Regular smoker,
Alcohol consumption averaging > 40 g daily,
Coffee (or tea) consumption > 6 cups per day or xanthine containing drinks >1 liter/day,
Special diet (e.g. vegetarian or vegan),
Subject without the means of contacting the Investigator rapidly in case of emergency or not able to be contacted rapidly by the Investigator,
Adults protected by the french law and people with restriction of freedom by administrative or legal decisions,

Prior medication

Use of any drug which could induce or inhibit hepatic microsomal enzymes within one month of the start of the study (including general anesthetics),
Any treatment that may have the potential to interfere with the metabolism and / or biological activities of LMWHs within 2 weeks (or 5 elimination half-lives) of the study starting (i.e. aspirin, NSAIDs, antiplatelets, anticoagulants, blood-derived drugs...),
Use of any other experimental new drug within the previous month,
Consumption of any medicine whatsoever (including over-the-counter drugs) within 2 weeks of the scheduled administration of the study drug were to be reviewed and discussed for approval by the Sponsor.

Pharmacokinetic Profiling

Blood samples for the determination of enoxaparin activity were obtained at the following scheduled times:

Day 1 (Period 1): Pre-dose, 5, 15, 30 min, 1, 1.5, 2, 3, 4, 6, 9, and 12 h post-dose
Day 1 (Period 2): Pre-morning dose, 5, 15, 30 min, 1, 1.5, 2, 3, 4, 6, 9, and 12 h post-dose
Days 2 and 3 (Period 2): Pre-morning dose, 3, and 12 h post-dose
Day 4 (Period 2): Pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 12, 15, and 24 h post-dose

Total urine volumes for the determination of enoxaparin activity were collected during the following intervals:

Day 1 (Period 1): Pre-dose, 0-3, 3-6, 6-9, 9-12, 12-24, and 24-36 h post-dose
Day 4 (Period 2): 0-3, 3-6, 6-9, 9-12, and 12-24 h post-dose

Bioassay

Enoxaparin activity in plasma was determined by measuring the amidolytic anti-Xa- and anti-IIa activity and aPTT. Enoxaparin activity in urine was determined by measuring anti-Xa and anti- IIa activities.

Amidolytic assays in plasma

The anti-Xa assay calibration curve was linear over the concentration range 0.025 to 0.40 IU anti-Xa/mL range with r^2 values ≥ 0.991 . The LLOQ was 0.025 IU anti-Xa /mL. The accuracy ranged between -4.2 to 7.4%. A 1/6 dilution control was within 0.8% of the nominal value. The precision of the anti-Xa assay was $\leq 8.5\%$.

The anti-IIa assay calibration curve was linear over the range of 0.010 to 0.15 UI anti-IIa /mL with r^2 values of 0.991. The LLOQ was 0.020 IU anti-IIa/mL. The accuracy ranged from -8.7% to 7.5%. A ¼ dilution control (0.50 IU anti-IIa/mL) was within 5.1% of the nominal value. The precision of the anti-IIa assay was $\leq 8.0\%$.

The analysis of the plasma samples was performed as described in the reports DMPK/FR/2032 (anti-Xa assay) and (anti-IIa assay) and (aPTT assay). The samples from Period 1 and Period 2 were analyzed in the same run. Samples with concentrations expected to be larger than the calibration curve were diluted. A standard calibration curve and sets of 3 quality control samples (including a dilution control) were analyzed in each analysis group. An analysis run was accepted when 75% of all standards and controls were within 20 % of the nominal concentrations at the LLOQ, and within 15% of the nominal concentration for the rest of standards and controls, provided that at least 2/3 of standards and controls and at least one control at each concentration level was acceptable. Also, no significant bias was to be observed.

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aPTT assay

Three quality controls were also used with the aPTT assay. The precision ranged between 2.0% and 4.1%.

Amidolytic assays in urine

The assay range of the anti-Xa assay was 0.050 to 0.80 IU anti-Xa/mL and linear with $r^2 \geq 0.976$. The LLOQ was 0.050 IU anti-Xa/mL. A 1/6 dilution control (3.05 IU/mL) was within -2.7% of the nominal value. The accuracy of the assay ranged between -2.7% and 7.6%. The inter-day precision of the assay was $\leq 11\%$.

For the anti-IIa assay supplemented with anti-thrombin III, the assay range was from 0.026 to 1.00 IU anti-IIa/mL and linear with $r^2 \geq 0.981$. The LLOQ was 0.026 anti-

Ila/mL. The accuracy of the assay ranged between -1.9% and 2.0%. The precision was $\leq 10\%$.

PK Analysis

Non-compartmental and compartmental methods were used. The PK parameters maximum observed activity (anti-Xa, anti-IIa or aPTT) (Amax), activity at trough (Amin), Tmax, AUC0-tlast), AUC, AUC0- τ and/or AUCss, CL, MRT, Vss, t1/2 λ_z , Ae, fe (fraction of enoxaparin excreted in urine) and Clr of enoxaparin after intravenous administration (Period 1) and subcutaneous administration (Day 4, Period 2) were determined. The renal clearance after bolus administration on Day 1 was obtained from $CLr=fe \bullet CL$. The CLr on Day 4 (Period 2) was computed from $Ae(0-12)/AUC(0-12)$. The ratio of Amax and AUCss (Day1) to Amax and AUCss (Day 4) in Period 2 was also determined. The compartmental model dependent approach used a 1-compartment model with 1/y weighting.

Statistical Analysis

Attainment of steady-state for the activities measured at 3 h and 12 h after the morning doses on Days 1, 2, 3 and 4 and the pre-morning doses on Days 2, 3, and 4 was evaluated using the REGWQ multiple range test after a SAS GLNM procedure.

For the comparison of AUCss and Amax the SAS UNIVARIATE procedure (=paired t-test) on difference and calculation of 90% confidence intervals for mean ratios was used.

RESULTS

All of the 16 subjects enrolled completed the trial. The demographics of the participants are shown in Table 3:

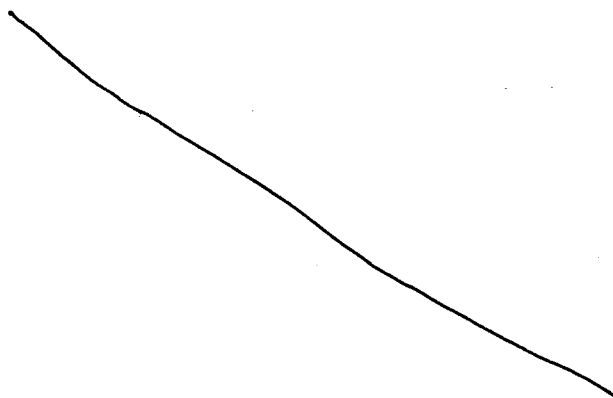
Table 3: Demographic parameters (N=16)	
No. of subjects entered:	16
Race: Caucasian	16
Other	0
Sex: Males	8
Females	8
Age (mean $\pm$ SEM)	57 $\pm$ 1.4
Min - Max (year)	50 - 68
Weight (mean $\pm$ SEM)	73.6 $\pm$ 2.80
Min - Max (kg)	57.9 - 102.0
Height (mean $\pm$ SEM)	167.4 $\pm$ 2.1
Min - Max (cm)	157 - 185
Data extracted from Appendix II.F, table 1.01	

The mean maximum anti-Xa activity was 0.787 IU/mL with a CV of 17 % after an IV bolus injection of 30 mg enoxaparin. This value is within the sponsor postulated therapeutic range of 0.5-1.1 IU anti-Xa/mL. The mean apparent terminal half life estimates by the sponsor measured by the anti-Xa- and anti-IIa activities were 3.65 h and 1.22 h, respectively. The sponsor did not compute derived parameters including CL, Vss or MRT for the data obtained with the compartment model independent approach.

The mean maximum anti-IIa activity was 0.187 IU anti-IIa/mL and the mean apparent terminal half-life was 1.22 h. The sponsor did not compute derived parameters including CL, Vss or MRT for the data obtained with the compartment model independent approach.

The ratio of the mean AUC0-t of the anti-Xa activity to the mean AUC0-t of the anti-IIa activity was 9.4.

Semi-logarithmic plots of the plasma concentration time profile in three of the subjects for the anti-Xa activity and anti-IIa activity, respectively, of enoxaparin are shown below:



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 Deliberative Process (b5)

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The plots are from the subjects in whom the profiles could be followed for the longest time, i.e. 12 h-24 h after administration. The anti-Xa data indicated a multi phase disposition of enoxaparin. The data also suggest that there exists a slower terminal phase which is not sufficiently characterized with the current sensitivity of the assay.

The anti-IIa activity data of enoxaparin could only be followed for 3 h to 4 h after injection. The activity time profile definable with the current assay sensitivity appeared to be monophasic.

It is unclear what criteria were used by the sponsor to determine the data points in the apparent terminal log linear disposition phase.

The urinary amounts of enoxaparin (as anti-Xa and anti-IIa activities) excreted in 36 h following the 30 mg enoxaparin bolus injection are shown in Tables 15 and 16, respectively:

Table 15

Study RP 54563Q-142

Urine anti-Xa activity (IU anti-Xa/mL) in healthy elderly volunteers on Day 1(Period 1) following 30 mg IV bolus dose of enoxaparin

Subject number	Urine excretion (IU)						Ae	Ae
	T 0h - 3h	T 3h - 6h	T 6h - 9h	T 9h - 12h	T 12h - 24h	T 24h - 36h	0-36 IU	0-36 mg
00001								
00002								
00003								
00004								
00005								
00006								
00007								
00008								
00009								
00010								
00011								
00012								
00013								
00014								
00015								
00016								
Mean	181.49	7.84	123.55	3.82	2.36	0.00	326.08	3.20
SD	43.92	16.33	62.67	7.00	9.44	0.00	68.34	0.67
CV%	24	208	51	183	400		21	21
Min								
Max								

* : not available

b(4)

Table 16

Study RP 54563Q-142

Urine anti-IIa activity (IU anti-IIa/mL) in healthy elderly volunteers on Day 1(Period 1) following 30 mg IV bolus dose of enoxaparin

Subject n°	Urine excretion (IU)						Ae	Ae
	T 0h - 3h	T 3h - 6h	T 6h - 9h	T 9h - 12h	T 12h - 24h	T 24h - 36h	IU	mg
00001								
00002								
00003								
00004								
00005								
00006								
00007								
00008								
00009								
00010								
00011								
00012								
00013								
00014								
00015								
00016								
Mean	74.93	4.23	0.64	0.00	0.00	0.00	83.52	3.30
SD	21.40	6.10	2.55	0.00	0.00	0.00	21.80	0.86
CV%	29	144	400				26	26
Min								
Max								

* : not available (extravascular administration of enoxaparine)

b(4)

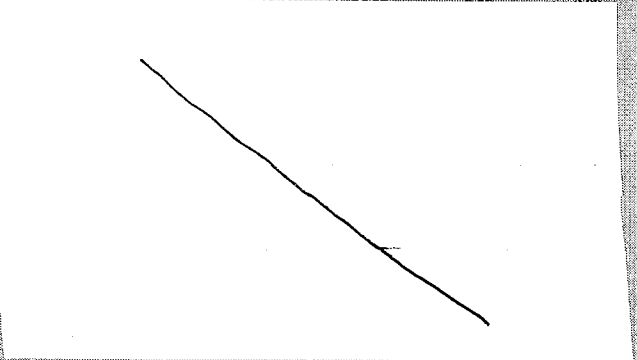
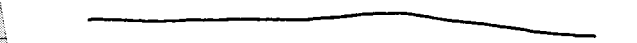
The mean and individual fractions of the dose excreted in urine, f_e , and the mean and individual renal clearances of enoxaparin, CL_r , as measured by the anti-Xa- and anti-IIa activities are shown in Tables 11 and 44, respectively:

Table 11: Renal clearance (Cl_r) of anti-Xa and anti-IIa activities after a 30 mg IV bolus. Mean (%CV), n = 14

	Ae mg	fe	Cl _r L.h ⁻¹
anti-Xa	3.20 (21)	0.11 (21)	0.12 (26)
anti-IIa	3.30 (26)	0.11 (26)	0.27 (41)

The respective mean percentage of the dose of enoxaparin excreted in urine was 11% whether measured by the anti-Xa activity assay or the anti-IIa activity assay. It appears that the active moieties of enoxaparin are excreted by the kidney within 12 hours after injection. The moiety responsible for the anti-IIa activity appeared to be excreted faster than the moiety responsible for the anti-Xa activity.

Table 44: Renal clearance (Cl_r or Cl_{rss}) of anti-Xa activity obtained after 30 mg IV bolus or at steady-state after 1 mg/kg SC q12h

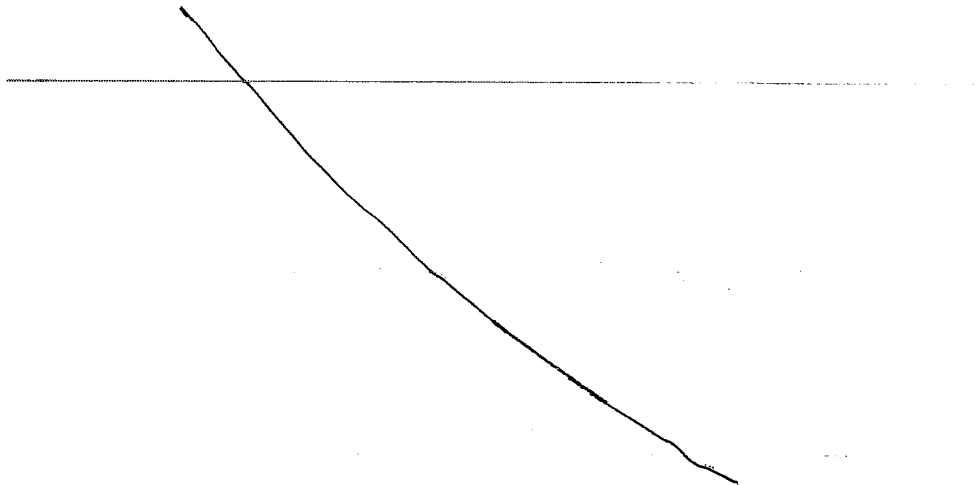
Subject number	30 mg IV bolus			1 mg/kg SC at steady-state		
	Ae mg	fe	Cl _r L.h ⁻¹	Ae (0-12) mg	fe	Cl _{rss} L.h ⁻¹
00001						
00002						
00003						
00004						
00005						
00006						
00007						
00008						
00009						
00010						
00011						
00012						
00013						
00014						
00015						
00016						
Mean	3.20	0.11	0.12	11.67	0.16	0.10
SD	0.67	0.02	0.03	1.96	0.02	0.03
%CV	21	21	26	17	13	32
Min						
Max						

* : not available

b(4)

The mean CL_r derived from the anti-Xa activity was 2.0 mL/min indicating glomerular filtration and reabsorption of the measured entity. The mean CL_r based on the anti-IIa activity was 4.5 mL/min implying the same renal handling of the moieties responsible for the anti-IIa and anti-Xa activities.

Figure 6 shows a statistically significant dependence of CL_r measured by the anti-Xa activity on creatinine clearance (

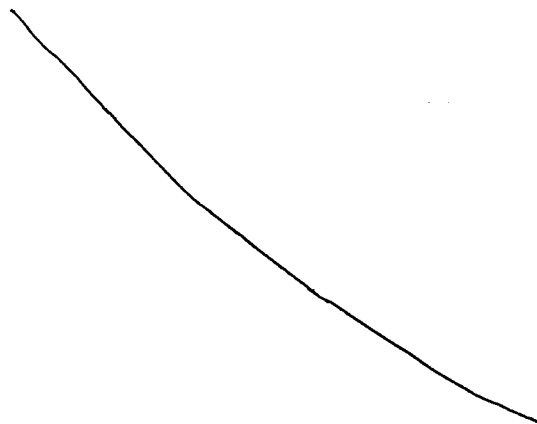


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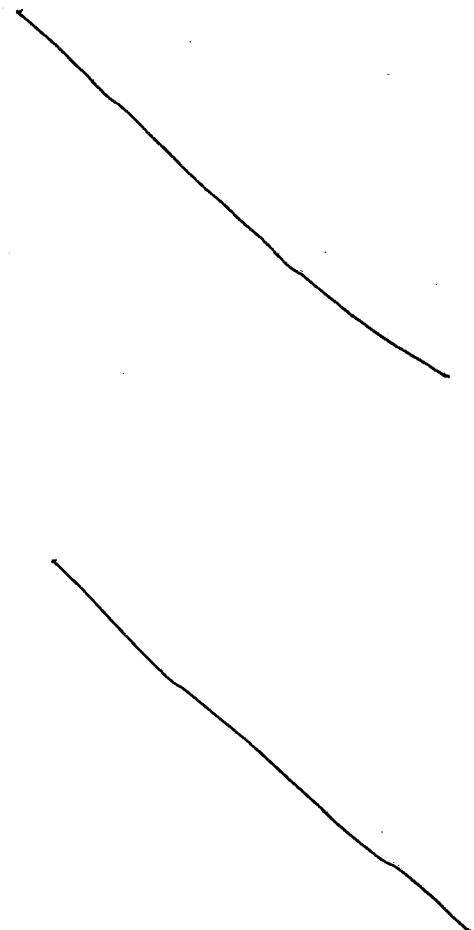
The CL_r of the 13 subjects considered were in a narrow range of 60 to 90 mL/min. In contrast to CL_r, CL did not depend on creatinine clearance.

Compartment Model Dependent Approach

The sponsor fitted a 1-compartment model to the anti-Xa activities of enoxaparin, despite the multi-phasic time profile shown above in the semi-logarithmic plots. The model fits to the individual data of subjects 1, 2 and 3 are shown in the Figures below:



b(4)



b(4)

b(4)

It can be seen that the fits to the data of subjects 2 and 3 tend to under-predict the anti-Xa activity in the apparent terminal disposition phase.

The mean parameters obtained from fitting the anti-Xa activities to a 1- compartment model are shown in Table 42:

Table 42: Pharmacokinetic parameters for anti-Xa activity after a single 30 mg IV bolus (one compartment weighted 1/Y model)

Subject n°	Amax IU.mL ⁻¹	AUC IU.h.mL ⁻¹	K10 h ⁻¹	t1/2λz h	Vss L	Cl L.h ⁻¹	MRT h
00001	0.911	3.42	0.266	2.60	3.36	0.89	3.76
00002	0.718	3.17	0.227	3.05	4.26	0.97	4.41
00003	0.922	4.44	0.208	3.34	3.32	0.69	4.82
00004	0.769	3.48	0.221	3.14	3.98	0.88	4.53
00005	0.831	2.53	0.328	2.11	3.68	1.21	3.05
00006	0.726	2.59	0.281	2.47	4.21	1.18	3.56
00007	0.590	2.26	0.261	2.66	5.18	1.35	3.83
00009	0.674	2.44	0.276	2.52	4.54	1.25	3.63
00010	0.556	1.56	0.356	1.95	5.50	1.96	2.81
00011	0.650	2.31	0.282	2.46	4.71	1.33	3.55
00012	0.715	2.93	0.244	2.84	4.28	1.04	4.10
00014	0.677	3.06	0.221	3.14	4.52	1.00	4.52
00015	0.763	2.64	0.289	2.40	4.01	1.16	3.46
00016	0.787	2.60	0.302	2.29	3.89	1.18	3.31
Mean	0.735	2.82	0.269	2.64	4.25	1.15	3.81
SD	0.107	0.69	0.043	0.41	0.62	0.30	0.60
%CV	15	24	16	16	15	26	16
Min	0.556	1.56	0.208	1.95	3.32	0.69	2.81
Max	0.922	4.44	0.356	3.34	5.50	1.96	4.82

The compartment model dependent mean Amax value was 0.735 IU anti-Xa /mL and comparable to the value obtained with the compartment model independent value. The mean t1/2λz estimate was smaller (2.64 h) than that observed with the non-compartment model approach (3.65 h). The AUC values obtained by the two approaches were similar. With the compartment model dependent approach the mean CL was 19 mL/min indicating low extraction of the measured moiety by the eliminating organs. The mean estimate for Vss of 4.25 L indicates that the measured moieties are sequestered intra-vascularly, i.e. in the intended biophase.

A 1-compartment model was also fitted to the enoxaparin data measured by the anti-IIa activity and the fits to the individual data of subjects 1, 2 and 3 are shown in the figures below:

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 X Trade Secret / Confidential (b4)

 Draft Labeling (b4)

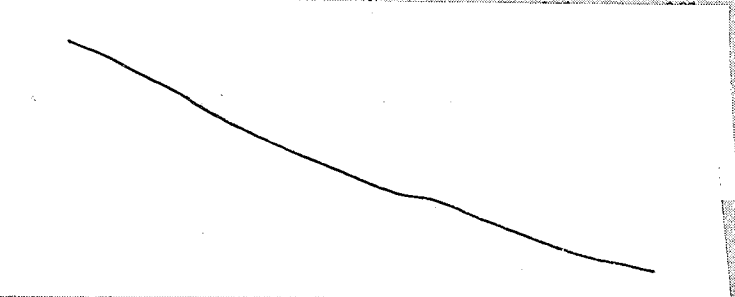
 Draft Labeling (b5)

 Deliberative Process (b5)

The ratio of the mean AUC of the anti-Xa activity to the mean AUC of the anti-IIa activity after a single IV bolus of 30 mg enoxaparin was 8.1.

The apparent fraction of the dose of enoxaparin excreted in urine, f_e , and for CL_r, as measured by the anti-IIa activity, are shown in Table 45:

Table 45: Renal clearance (CL_r or CL_{rss}) of anti-IIa activity obtained after 30 mg IV bolus or at steady-state after 1 mg/kg SC q12h

	30 mg IV bolus			1 mg/kg SC at steady-state		
Subject number	Ae mg	f_e	CL _r L.h ⁻¹	Ae(0-12) mg	f_e	CL _{rss} L.h ⁻¹
00001						
00002						
00003						
00004						
00005						
00006						
00007						
00008						
00009						
00010						
00011						
00012						
00013						
00014						
00015						
Mean	3.30	0.11	0.27	7.76	0.11	0.20
SD	0.86	0.03	0.11	1.54	0.03	0.05
%CV	26	26	41	20	25	25
Min						
Max						

not available

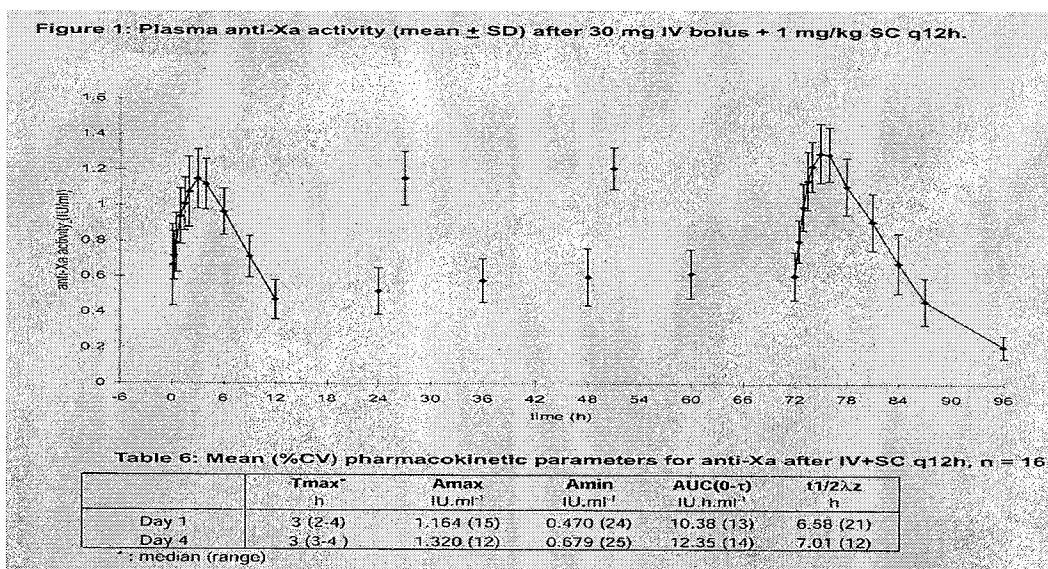
b(4)

The mean CL_r of 4.5 mL/min of the moieties responsible for the anti-IIa activity was the same as that for the moities responsible for the anti-Xa activity with the same implication for renal handling.

Data after bolus injection of 30 mg plus 1mg/kg sc q 12 h

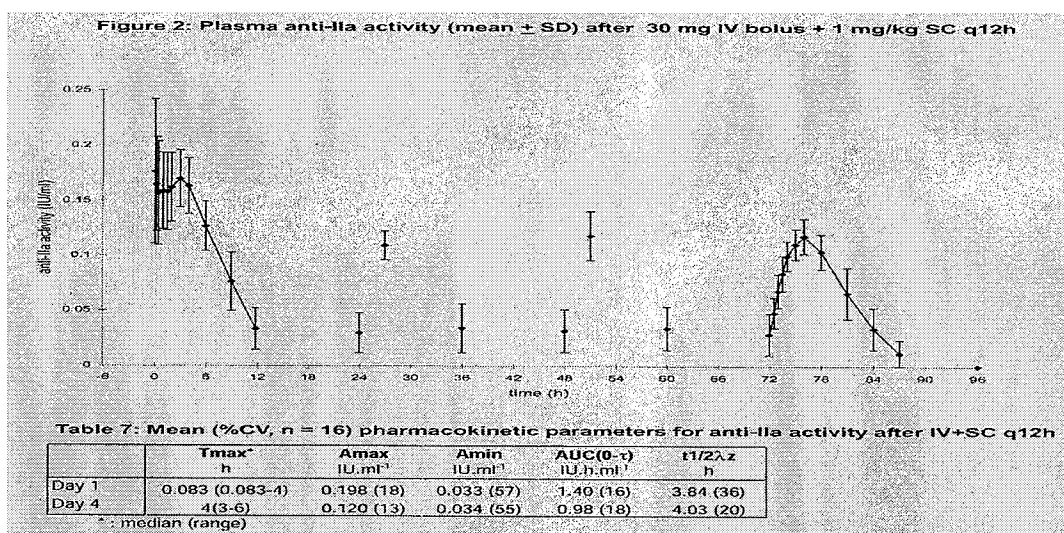
Linear plots of the time profiles of the mean anti-Xa activities of enoxaparin and derived mean parameters obtained by non-compartmental methods are shown in Figure 1 and Table 6, respectively:

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Maximum anti-Xa activity was reached on average 3 h after SC administration of enoxaparin on Days 1 and 4. Mean Amax was 1.164 and 1.320 IU anti-Xa/mL on Days 1 and 4, respectively. The corresponding Amin values were 0.470 and 0.679 IU anti-Xa/mL. Amin on Day 1 and Amax on Days 1 and 4 were outside of the postulated therapeutic range of 0.5-1.1 IU anti-Xa/mL. Mean AUC0-τ, Amax, Amin on Day 1 were 84%, 88% and 69% of the corresponding values on Day 4 indicating that the loading dose was slightly infra-proportional relative to the maintenance dose. The CV about the mean Amin values on Days 1 and 4 was 24% and 25%. The respective t1/2λz values on Day 1 and 4 of 6.58 h and 7.01 h were significantly greater than those observed after IV administration suggesting a flip-flop of the rate constants for absorption and elimination.

Linear plots of the time course of the mean anti-IIa activity of enoxaparin and derived mean parameters obtained by non-compartment model methods are shown in Figure 2 and Table 7, respectively.

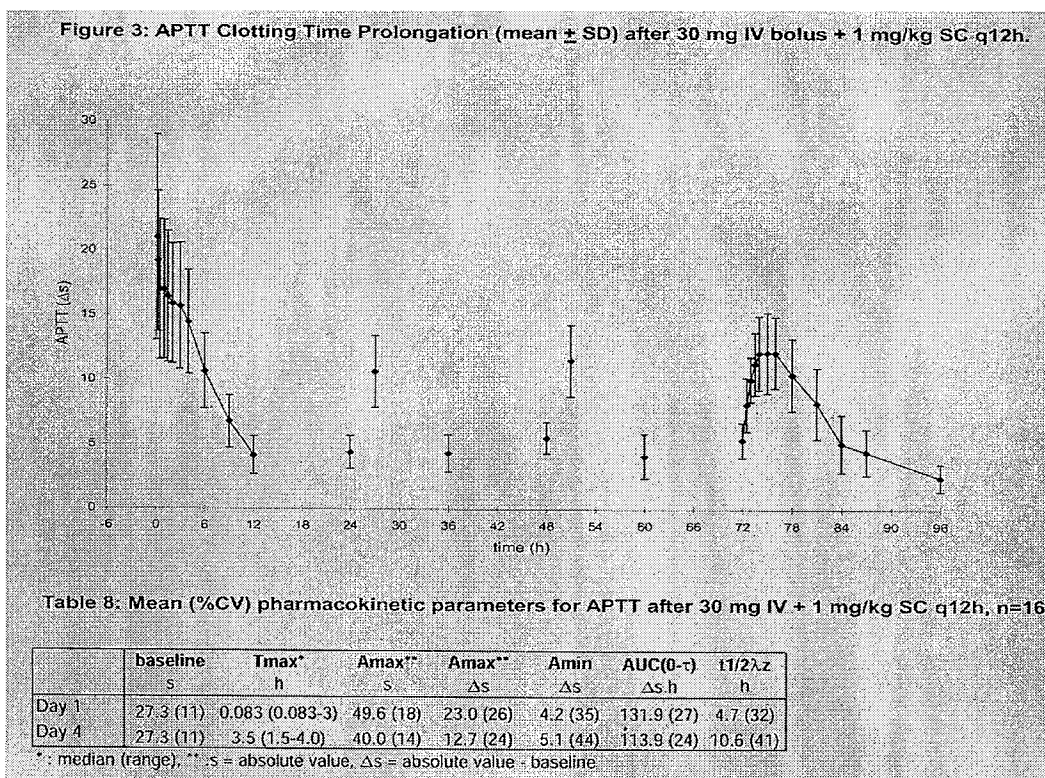


Maximum anti-IIa activity was observed after administration of the IV bolus on Day 1. On Day 4 maximum anti-IIa activity was observed 4 h after SC administration of enoxaparin.

The mean AUC_{0- τ} , Amax and Amin values on Day 1 were 143%, 165% and 97% of the corresponding values on Day 4 suggesting that the loading dose was supra-proportional relative to the SC maintenance dose. The respective CV about Amin on Day 1 and Day 4 were 57% and 55%, and considerable. The respective apparent terminal t_{1/2 λ_z} values on Days 1 and 4 (Period 2) were 3.84 and 4.03 h, indicating a significant increase of t_{1/2 λ_z} for the anti-IIa activity after single or repeat SC administration of enoxaparin compared to after IV administration. This finding was indicative for a flip-flop of absorption and elimination rate constants of the moiety measured by the anti-IIa activity after SC administration.

The respective ratios of the mean AUC_{0- τ} of the anti-Xa activity to the mean AUC_{0- τ} of the anti-IIa activity on Days 1 and 4 are 7.4 and 12.6.

Linear plots of the mean time profiles of the effect of enoxaparin on aPTT and mean parameters using compartment model- independent methods are shown in Figure 3 and Table 8, respectively:



The maximum observed effect of enoxaparin on aPTT on Days 1 and 4 of the treatment occurred immediately after the bolus IV injection on Day 1 and 3.5 h after the SC administration on Day 4. The increase in aPTT was larger on Day 1 than on Day 4. Mean AUC_{0-τ}, Amax and Amin of aPTT (normalized for baseline) on Day 1 were 116%, 181% and 82% of the corresponding values on Day 4. The respective CV about the mean Amin values on Days 1 and Day 4 were 35% and 44%. The apparent t_{1/2λz} values on Days 1 and 4 as assessed by aPTT were 4.7 h and 10.6 h, respectively.

The mean values of Amax and Amin on Day 1 through Day 4 as assessed from the anti-Xa activity, anti-IIa activity and effect on aPTT are shown in Tables 14 and 15, respectively:

Table 15: Amax of anti-Xa and anti-IIa activities and APTT prolongation from Day 1 to Day 4 (Period 2). Mean (%CV), n = 16

	time (h) after the first administration on Day 1 (Period 2)			
	3 h	27 h	51 h	75 h
anti-Xa (IU.mL ⁻¹)	1.148 (15)	1.154 (13)	1.213 (10)	1.301 (13)
anti-IIa (IU.mL ⁻¹)	0.170 (15)	0.109 (12)	0.119 (19)	0.111 (13)
APTT (Δs)	15.7 (31)	10.6 (26)	11.5 (24)	12.2 (26)

Table 14: Amin of anti-Xa and anti-IIa activities and APTT prolongation from Day 1 to Day 4 (Period 2). Mean (%CV), n = 16

	time (h) after the first administration on Day 1 (Period 2)						
	12 h	24 h	36 h	48 h	60 h	72 h	96 h
anti-Xa (IU.ml ⁻¹)	0.470 (24)	0.519 (25)	0.579 (21)	0.600 (27)	0.618 (23)	0.607 (22)	0.679 (25)
anti-IIa (IU.ml ⁻¹)	0.033 (57)	0.030 (61)	0.034 (65)	0.032 (60)	0.034 (58)	0.029 (65)	0.034 (55)
APTT (Δs)	4.2 (35)	4.4 (29)	4.3 (33)	5.5 (22)	4.1 (42)	5.4 (25)	5.1 (44)

The Amax and Amin values for the anti-Xa activity tended to increase slightly over time, whereas Amax for the anti-IIa activity tended to be initially larger than at later times. The Amin values of the anti-IIa activity appeared not to vary importantly with time. The Amax value for the effect on aPTT was initially greater than at subsequent times, whereas Amin tended to increase over time.

In Tables 16 and 17 the parameters derived from measuring the anti-Xa activity, the anti-IIa activity and effect on aPTT obtained on Days 1 and 4 of the combined IV and SC treatments are compared:

Table 16: Pharmacokinetic parameters ratios (Day 1/Day 4) for anti-Xa activity. Mean (%CV), n = 16

	Amax IU.ml ⁻¹	Amin [*] IU.ml ⁻¹	AUC(0-τ) IU.h.ml ⁻¹
D1	1.164 (15)	0.470 (24)	10.38 (13)
D4	1.320 (12)	0.679 (25)	12.35 (14)
ratio	0.88 (12)	0.70 (9)	0.84 (7)
90% CI	0.84 - 0.93	0.67 - 0.72	0.82 - 0.87
Pr> T	0.0002	0.0001	0.0001

Table 17: Pharmacokinetic parameters ratios (Day 1/Day 4) for anti-IIa activity. Mean (%CV), n = 16

	Amax IU.ml ⁻¹	Amin IU.ml ⁻¹	AUC(0-τ) IU.h.ml ⁻¹
D1	0.198 (18)	0.038 (39)	1.40 (16)
D4	0.120 (13)	0.039 (37)	0.98 (18)
ratio	1.67 (20)	0.99 (21)	1.49 (31)
90% CI	1.52 - 1.81	0.90 - 1.09	1.29 - 1.69
Pr> T	0.0001	0.6984	0.0001

Table 18: Pharmacokinetic parameters ratios (Day 1/Day 4) for APTT clotting time prolongation. Mean (%CV), n = 16

	Amax ΔS	Amin** ΔS	AUC(0- τ) $\Delta S.h$
D1	23.0 (26)	4.15 (35)	131.92 (27)
D4	12.7 (24)	5.12 (44)	113.90 (24)
ratio	1.84 (22)	0.83 (36)	1.17 (15)
90% CI r	1.67 - 2.02	0.70 - 0.96	1.09 - 1.25
Pr> T	0.0001	0.0514	0.0017

* : median, ** : Amin = A12h

The comparison of Amax, Amin and AUC0- τ obtained by the three methods reiterated that there were statistically significant differences between AUC0- τ , Amin and Amax on Days 1 and Day 4. An explanation for the different time dependencies of the anti-Xa activity, anti-IIa activity and effect on aPTT by enoxaparin seen with the dose regimen was not provided.

The respective amounts excreted in urine and the renal clearance values based on the anti-Xa- and anti-IIa activities of enoxaparin on Day 1 (Period 1) and Day 4 (Period 2) are shown in Tables 11 and 12:

Table 11: Renal clearance (Clr) of anti-Xa and anti-IIa activities after a 30 mg IV bolus. Mean (%CV), n = 14

	Ae mg	fe	Clr L.h ⁻¹
anti-Xa	3.20 (21)	0.11 (21)	0.12 (26)
anti-IIa	3.30 (26)	0.11 (26)	0.27 (41)

Table 12: Renal clearance (Clr_{ss}) of anti-Xa and anti-IIa activities at steady-state (Day 4 - Period 2). Mean (%CV°, n = 16 for anti-Xa activity and n = 15 for anti-IIa activity)

	Ae(0-12) mg	fe	Clr _{ss} L.h ⁻¹
anti-Xa	11.67 (17)	0.16 (13)	0.10 (32)
anti-IIa	7.76 (20)	0.11 (25)	0.20 (25)

The mean fraction of the dose excreted in urine on Day 4 (Period 2) derived from the anti-Xa- activity tended to be greater than the corresponding values after administration of 30 mg enoxaparin by the intravenous route on Day 1 (Period 1), whereas the respective