Other Adverse Events

The analysis of adverse events was restricted to events other than thromboembolism and hemorrhage that appeared during the 21 day treatment with enoxaparin or placebo. However, all patients had been previously treated 14 days with enoxaparin, and patients in enoxaparin group have received this drug for 5 weeks continuing treatment. Adverse events were classified according to intensity, outcome, and imputability to the study drug. The results are presented on table 6-12.

Table 6-12

DISTRIBUTION OF CLINICAL CHARACTERISTICS OF ADVERSE EVENTS

ADVERSE EVENT CHARACTERISTICS		ENOXAPARIN N	%	PLACEBO N	%	OVERALL N	%
Sample Size		6	100	9	100	15	100
INTENSITY							
AE	Mild	2	33.33	3	33.3	5	33.3
	Moderate	3	50.0	5	55.6	8	53.3
	Severe	1	16.7	1	11.1	2	13.3
OUTCOME							
AE	Persistence	2	33.3	3	33.3	5	33.3
	Recovery	4	66.7	6	66.7	10	66.7
IMPUTABILITY TO STUDY MEDICATION							
AE	None	4	66.7	7	77.8	11	73.3
	Possible	1	16.7	2	22.2	3	20.0
	Probable	1	16.7	0	0.0	1	6.7

From Statistical Appendix (Vol.3, p.8-2-161). AE= adverse event

Patient #207 presented a transitory thrombocytopenia, that was considered as "probably" related to enoxaparin.

Patient #13 was considered by the Investigator as having a "severe" adverse event, "possibly" related to enoxaparin. The event was a radiating nocturnal pain in both legs immediately after each sc injection from _____ (discontinuation). The pain resolved completely within the 24 hours following discontinuation of injections.
Patient # 13 was previously described.

Patient #286 in the placebo group presented with itching of the shoulder and of the back developing after 2 doses of placebo. No action was taken. The effect resolved within the two days following the end of treatment period. The event is classified as "possibly" related to study medication (in this case saline solution?). No comment is given.

Serious Adverse Events

Three patients (2 in the enoxaparin group and 1 in the placebo group) have been described as having serious adverse events. Patients #53 (enoxaparin) and #63 (placebo) have been described previously. Patient #55 in the enoxaparin group presented with edema of the right leg after 10 days of study and with bilateral edema after 11 days. This edema was not attributed to study medication, the study continued, and after 21 day, venography did not reveal venous thromboembolism.

Laboratory Parameters

Overall, there were no statistical differences between the two treatment groups with respect to the absolute and relative changes in red blood cell, white blood cell, and platelet counts, or in hematocrit and hemoglobin values, from randomization to Day 21±2.

However, within-group changes were significant. Mean platelet count at randomization was "above normal" to become "normal" at the end of the study. At the same time, mean hemoglobin values were "below normal" to become "normal". Although change of hemoglobin can be attributed to post-operative recovery, there is no explanation for "above normal" values of platelet count at randomization. These changes are summarized on table 6-13.

Table 6-13

CHANGES IN MEAN VALUES OF PLATELET COUNT AND HEMOGLOBIN LEVEL DURING THE 21 DAYS OF THE STUDY

STUDY PHASE	PARAMETER	ENOXAPARIN	PLACEBO	OVERALL	P=VALUE
PLATELET COUNT					
Pre-study	N	90	89	179	
	Mean±SD	475 ± 141	484 ± 127	480 ± 134	
	Range				
End of study	N	86	83	169	
	Mean±SD	281 ± 73	288 ± 77	285 ± 75	
	Range				
Absolute difference	N	86	83	169	.891
	Mean±SD (10^6/mL)	-197 ± 124	-199 ± 98	-198 ± 112	
	Range				
Relative difference	N	86	83	169	.696
	Mean±SD (10^6/mL)	-38 ± 17	-39 ± 14	-39 ± 15	
	Range				
HEMOGLOBIN LEVEL					
Pre-study	N	90	89	179	
	Mean±SD (g/dL)	10.45 ± 1	10.42 ± 1	10.44 ± 1	
	Range				
End of study	N	83	76	159	
	Mean±SD (g/dL)	11.83 ± 1	11.72 ± 1	11.78 ± 1	
	Range				
Absolute difference	N	83	76	159	.947
	Mean±SD (g/dL)	1.32 ± 1	1.31 ± 1	1.32 ± 1	
	Range				
Relative difference	N	83	76	159	.970
	Mean±SD (g/dL)	13.08 ± 9.6	13.02 ± 10.12	13.05 ± 9.8	
	Range				

From Table 43 (8-1-121) and Table 47 (8-1-123), both Vol. 2

In discussion, the sponsor believes that the observed thrombocytosis is reactive, and is probably due to an inflammatory process related to the surgical procedure. The sponsor does not believe that it may be a direct heparin effect as described for thrombocytopenic patients and in animal models.

Comment: In conclusion on the safety, the only significant difference between two treatment groups, was found in the category "minor hemorrhage". Majority of these events, 81%, were "injection site hemorrhage" and this difference is probably drug related. Other hemorrhages, one epistaxis, hematemesis and three wound hematoma, could not been related either because of the small number, or lack of statistical significance. There were no significant differences between treatment groups regarding the other adverse events.

One case of mild thrombocytopenia occurred during this study. This episode was not associated with thrombosis, and platelet count spontaneously returned to normal after the end of the study-treatment period.

7.0 STUDY PK-537

(NDA Volumes: M43.9-13)

7.1 Study Protocol
7.2 Statistical Analysis
7.3 Study Report

Compound Number: Enoxaparin RP 54563q

TITLE: *A double-blind, placebo-controlled, two-parallel group, randomized trial to evaluate the efficacy and safety of prolonged administration of enoxaparin 40 mg sc qd during the first three post-discharge weeks in the prevention of deep venous thrombosis in 260 patients undergoing elective total hip replacement*

Study Start Date:		04/28/91	
Study Completion Date:		03/20/95	
Study Report Date:		01/26/96	
Amendments:	1.	08/27/92,	sample size, additional hospital
	2.	11/12/92,	pre-operative administration
	3.	11/23/92,	added project physician: Dr. S. Combe
	4.	02/02/93,	administrative changes
	5.	02/18/94,	packaging changes

Authors: Eff J., Nicolas S., Pisapia G., Spiro T.

INVESTIGATORS AND CENTERS

David Berquist, M.D., Ph.D.
Lund University
Malmo General Hospital
Malmo 21401, Sweden

SPONSOR:

Rhone-Poulenc Rorer Pharmaceuticals Inc.

Identity of Test Material

Open-label phase: No information.
Double-blind phase of the study.

Enoxaparin,	Injectable solution 100 mg/mL, 40 mg/0.4 mL sc, qd. Lots CB 4733, 05369, 05668.
Placebo,	Injectable solution saline, 0.4 mL,sc, qd. Lots: CB 4863P, 4905P, 05822P.

7.1 STUDY PROTOCOL

7.1.1 Objective

The objective of this study was to evaluate the efficacy and safety of 21 days post-hospital treatment with enoxaparin 40 mg, sq,qd, versus similarly administered placebo (saline), in the prevention of late-occurring (week 2 to week 5) thromboembolism in 260 patients undergoing elective, primary, total hip replacement

7.1.2 Study Design

According to the submission, this was an open-label, inpatient lead-in to a randomly-assigned, double-blind, placebo-controlled, two parallel group, outpatient treatment, single-center clinical trial.

During the inpatient period, eligible patients who underwent THR surgery, were to receive enoxaparin 40 mg,sc, 12±2 hours before surgery, than 40 mg, sc, the day of surgery, and 40 mg,sc,qd, for 7±2 days.

Comment: In the Study Procedures section, day of discharge is another (9±2), and in the Results, duration of the open-label period was 9.9 days (range 6-12).

At hospital discharge, qualified patients (w/o clinical symptoms of DVT or PE) were randomly assigned either to continue enoxaparin 40 mg or start a matching placebo injection, each administered sc, qd for 21±2 days of the double-blind period. Patients who had been randomized on enoxaparin after hospital discharge, received enoxaparin 40 mg, in total of 30±4 consecutive days. Evaluations were performed at baseline (before beginning of in-hospital enoxaparin treatment), at discharge, 21 days after discharge (end of study period) and three months after discharge (end of follow-up period).

Two hundred eighty-eight (288) eligible patients both sexes entered the study. Two hundred sixty-two (262) qualified were randomly assigned to enoxaparin or placebo group, each including 131 patients.

The study efficacy endpoint was represented by development of VTE (venous thromboembolic event, DVT and PE) during, or immediately after the double-blind outpatient period. Surveillance for DVT was performed with bilateral ascending contrast venography on day 21±2 of the double-blind period. A symptomatic PE was to be confirmed by lung scan or arteriography.

The study safety endpoints included: deaths, hemorrhage (major and minor), and other adverse events.

Comment: There were 5 amendments to the Protocol. One of them increased the sample size, others were administrative changes. All occurred during the study, but had no impact on data.

Assignment

7.1.3 Study Population

Patients of either sex, older than 40 years of age, and weighing more than 60 kg were eligible for the 1st phase of the study.

Double-blind phase entered patients who had primary (no reoperation) elective hip surgery, received enoxaparin prophylaxis beginning 12±2 hours before surgery, and than daily (40 mg, sc) for the entire period of hospitalization (median 10 days), who did not experienced VTE or major hemorrhage during this period, did not received any forbidden concomitant treatment, and who maintained criteria for the first phase. Some patients had protocol deviations during the first phase: occasional use of NSAID (including aspirin), and major hemorrhage that was not considered to be a serious adverse event. They were identified, but also considered for the efficacy analysis.

Patients were discontinued from the study for any of the following reasons: Suspected adverse reaction, Intercurrent illness, Lost to follow-up, Test drug ineffective or patients clinical condition deteriorated during treatment, Death and Consent withdrawn. Administrative reasons, such as Violated inclusion criteria, and Violation of protocol specified procedures were also considered for discontinuation.

Treatment Assignment and Randomization

The investigator had to establish the eligibility of patients to enter the double-blind phase before hospital discharge. Qualified patients were assigned a patient number in an ascending sequential order obtained from a randomization list. Randomization was balanced in block of 4 patients. The randomization list was issued by the sponsor. Patients were given a treatment pack containing 23 syringes, each containing 0.4 mL 40 mg enoxaparin or saline. Packs were labeled with the corresponding randomization number.

7.1.4 Study Procedures

The planned duration of treatment for each patient was 21±2 days following randomization.

Study Medication and Blinding

The study medication was prepared by the sponsor as ready-for-use prefilled syringes containing 0.4 mL of enoxaparin (100 mg/mL injectable solution) or isotonic saline. Enoxaparin and placebo

lot numbers are given before. Lot numbers are not provided for enoxapaprin given during the open-label phase.

All test medication and packaging were visually identical for both treatment groups. Patients, nurses, attending physicians and investigators were blinded for their content until the completion of the study. Sealed envelopes containing the individual patient code were delivered to the Investigator. If the code had be broken, for such patients, study medication had to be discontinued, and case report form completed with full explanation.

Table 7-1

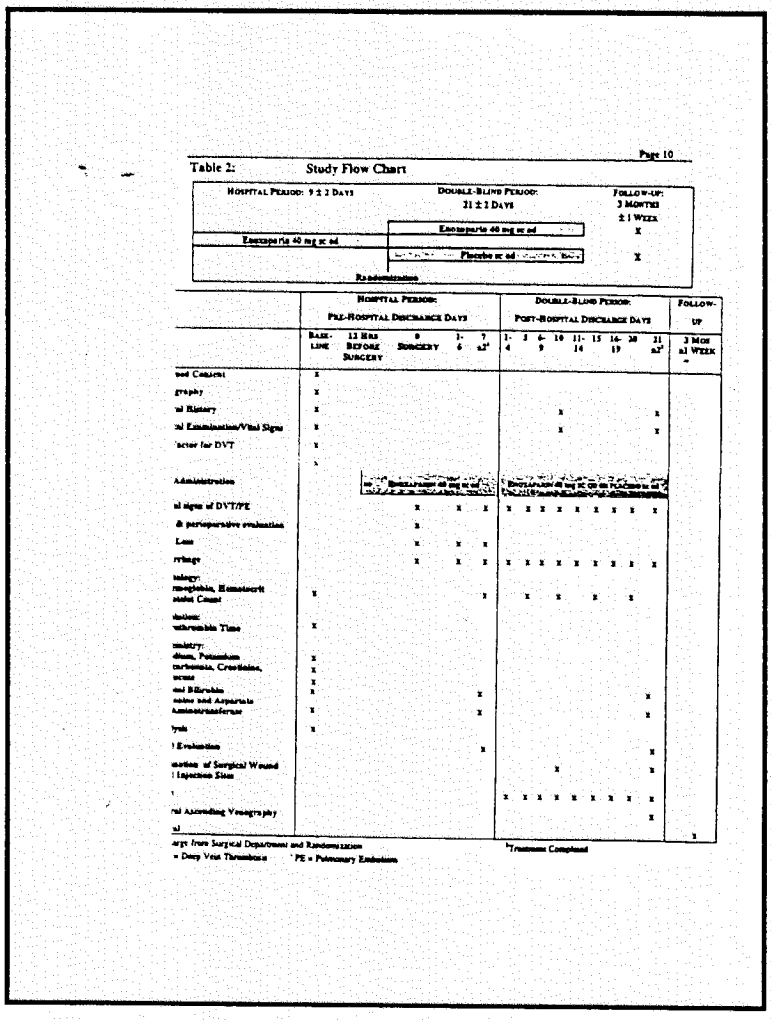

Table 2: Study Flow Chart

Page 10

	Hospital Period: Pre-Hospital Discharge Days				Double-Blind Period: Post-Hospital Discharge Days								Follow-up
	Base-line	12 Hrs Before Surgery	0 Surgery	1-6	7 ±2*	1-4	5-9	6-10	11-14	15-19	20	21 ±2*	3 Mos ±1 Week
Informed Consent	x												
Demography	x												
Medical History	x												
Physical Examination/Vital Signs	x												
Risk Factor for DVT	x												
Randomization	x												
Administration													
Clinical signs of DVT/PE			x	x	x	x	x	x	x	x	x	x	
Intra & perioperative evaluation			x										
Blood Loss			x	x	x								
Bleeding			x	x	x	x	x	x	x	x	x	x	
Hematology: Hemoglobin, Hematocrit, Platelet Count	x				x		x		x		x		
Biochemistry: Prothrombin Time	x												
Biochemistry: Albumin, Potassium, Carbamide, Creatinine, Glucose	x												
Biochemistry: Total Bilirubin, Alkaline and Aspartate Aminotransferase	x				x							x	
Urinalysis	x												
Clinical Evaluation					x							x	
Observations of Surgical Wound & Injection Sites							x					x	
Clinical Assessment						x	x	x	x	x	x	x	
Bilateral Ascending Venography												x	
Withdrawal													x

*Discharge from Surgical Department and Randomization
DVT = Deep Vein Thrombosis
PE = Pulmonary Embolism
†Treatment Completed

Evaluations and Scheduling

The study procedures are summarized on table 7-1: Study Flow Chart. The text provides description of procedures on daily basis, and criteria for assessment of safety and efficacy. There were three phases of this study:

- Pre-study evaluation, including screening period, and open-label period (surgery and 9±1 days of enoxaparin prophylaxis),
- Study, 21±2 days from the day of discharge, period of late-prophylaxis, and

- Post-study, three months±1 week follow-up period. At the end of this period only information dead/alive or lost to follow-up were required.

The following parameters were considered:

APPEARS THIS WAY ON ORIGINAL

- Medical history
- Physical examination
- ECG and Laboratory (hematology, coagulation /PT, biochemistry, urinalysis).
- Details of surgery (side, cemented prosthesis, type of anesthesia, the amount of intraoperative and perioperative blood loss, nature and volume of infusions and transfusions give perioperatively)
- Amount of blood loss via drain, amount of transfusions, observation in the region of the wound - hematoma, clinical signs for hemorrhage, DVT and PE.

Hemorrhage was classified as major(clinically overt, with either a fall of the hemoglobin level of at least 20 g/L, required at least 2 units of transfused blood, was retroperitoneal, or intracranial, or required reoperation to be controlled. Any hemorrhage that did not meet criteria for major, but was considered excessive by the investigator, was classified as minor hemorrhage.

Clinical signs of thromboembolic event were thoroughly searched for. In case of suspicion for DVT an unilateral or bilateral venography was performed and assessed by an independent panel of experts to confirm the diagnosis.

- Bilateral, lower extremity ascending contrast venography was performed to all patients at the end of the study period (day 21 post discharge). Venograms were read by the investigators and a panel of exprienced radiologists who were blinded for patient treatment assignment. In case of discrepancy between investigator and panel reading, the sponsor has filed the panel reading.
- Investigator's global evaluation of the double-blind period included: hemorrhage (minor or major), local tolerance at the operative site classified as Grade 0 for absence of complication, or Grade 1 for unusual operative site complications; local tolerance at injection site classified as Grade 0 for hematoma smaller than 5 cm, or Grade 1 for

larger than 5 cm hematoma; clinical signs of VTE and evaluation by appropriate expert panel; record of any other postoperative adverse event.

Comment: Binomial classification 0/1 as applied, is convenient for computerized statistical analysis, but may be misleading in clinical evaluation. Conventional classification in this case uses 0 for absence, 1-3 for grading of a clinical event.

7.1.5 Assessment of Efficacy and Safety

Efficacy

The primary efficacy parameter was the incidence of VTE (venous thromboembolic event) including DVT (proximal, distal, both) and PE. All clinically suspected DVT or PE needed objective confirmation (venography, lung scan, or pulmonary arteriography). All venograms were evaluated by the investigator and an independent panel of experts who were blinded for treatment assignments.

Two study populations were determined for assessment of efficacy:

- All-treated patients - all randomly assigned patients who received at least one dose of study medication, and
- Evaluable patients - all patients who completed the study and did not show any of the following: endpoint not available or inadequate, insufficient study therapy, inappropriate surgical procedure, inappropriate prophylactic treatment or outcome during the open-label period, prohibited prior or concomitant medication (heparins and coumarins), randomized twice.

The primary efficacy analysis was the incidence of VTE in all-treated patient. Patients who developed VTE were considered as "treatment failure". All others were "treatment successes".

Secondary Efficacy Analysis included the incidence of VTE on placebo *vs.* enoxaparin for evaluable patients. Venographic analysis were based on anatomic distribution of thrombi: proximal, distal, absent, and both (classified as proximal).

Subgroup Analysis

The subgroup analyses were performed on both all-treated and evaluable patient populations. They included the effect of gender, age (<65>), obesity (BMI >27.2 men, or >26.9 women), surgical procedure and anesthesia.

Safety

All safety analyses included both all-treated randomized patients and the enrolled patients into the open-label period of the study.

Safety parameters included: hemorrhagic episodes, adverse events and laboratory analyses.

Hemorrhagic episodes

They were classified as major or minor, total blood loss via drains. Overt hemorrhages were analyzed by site (non-operative sites were classified as GI, retroperitoneal, intracranial, etc.).

Adverse events

The number of patients with at least one adverse experience (including VTE and hemorrhage) were presented using COSTART system (globally, by body system and preferred term) and were displayed by severity (mild, moderate, severe), and with the investigator's assessment of the event relation to the study medication (none, possible, probable).

Laboratory test analyses

Laboratory analyses are presented in tables that summarize the count and percent of patients with laboratory values categorized as missing, low, or high relative to normal ranges at the end of the open-label period and the end of the open-label period *vs.* the end of the double-blind period.

Criteria of clinical concern were determined as:

Hemoglobin: <80 g/L, or ⇓≥20 g/L

Platelet, thrombocytosis

Moderate: >600 *10^9/L - 1,000 *10^9/L

Platelet, thrombocytopenia

Moderate: 50*10^9/L - 100*10^9/L

Aspartate and alanine aminotransferase:	≥2.1	μkat/L
Total bilirubin:	>35	μmol/L
Potassium:	>4.2	mmol/L

Shifts of laboratory parameters from "normal" to outside normal range (beyond, below) were analyzed separately.

7.2 Statistical Analysis

Sample Size

Planning this study, the sponsor has assumed that patients treated with enoxaparin in the double-blind phase would have VTE incidence rate of 13% in comparison with 30% VTE incidence in the placebo treated group. To provide 90% power to detect this treatment difference (α=0.05/ two-sided) a sample size of 110 evaluable patients per group was calculated. Assuming that 15% will have no adequate venography, a total of 260 patients were considered for enrollment.

Statistical Analyses

Statistical tests were only performed for primary efficacy and safety parameters. Most analyses were performed using descriptive statistics or confidence interval approach. Missing data were not included in the analyses, and the total number of observations was appropriately reduced.

Open-label Period (Perioperative Prophylaxis)

The following parameters were analyzed for patients enrolled in this phase of the study: patient outcome (reasons for non-randomization), demographics, medical history, prior and concomitant medications, surgery (diagnosis, surgical approach, operated extremity, duration of surgery etc.), study drug exposure (number of doses administered versus number of days exposed).

Safety was considered separately. It was assessed by the incidence of hemorrhagic episodes, other adverse events and laboratory tests.

Double-Blind period (Extension of Prophylaxis)

The same parameters as above were used, but this time they were summarized by treatment groups to demonstrate inter-group balance.

In addition a completion status and evaluability status were summarized by treatment groups. Efficacy endpoints, incidence of VTE were compared by using either a Chi-Square or a Fisher's exact test. VTE was also analyzed by subgroups. Similar approach was used for safety analysis endpoints.

All of the data from case report forms were entered into an INGRESS database. Using this database, SAS®(statistical analysis system), version 6.08, datasets used for all analyses were generated (See Appendix V, Part A).

7.3 Study Report

7.3.1 *Selected patients*

Two hundred eighty-eight (288) consecutive patients of both sexes, aged more than 45 years, body weight between having undergone total hip replacement [THR] or prosthetic replacement in the preceding 15 days, having received from surgery to randomization a prophylactic treatment for

postoperative VTE with enoxaparin 40 mg sc, od, and being without VTE as assessed by clinical investigation, were screened for inclusion/exclusion criteria. Twenty six (26) were found ineligible because 8 patients withdraw their consent (30.8%), 5 had a deteriorating outcome (19.2%), 6 were protocol violators (15.4%), 2 died (3.8%) and 5 did not qualify for other reasons.

Two hundred sixty-two (262) were randomized into enoxaparin (131) and placebo (131) group.

Comment: Seven patients including two deaths who were on prophylactic treatment during the open-label phase showed "study efficacy failure" that was not encountered by the sponsor.

Thirty-nine randomized patients (19, 14.5% placebo, and 20,15.3% enoxaparin) were found to be unevaluable because of

- Twenty-nine (E=14/P=15) either did not have the required venography, or had inadequate final assessment;
- six (E=4/P=2) were randomized twice and found evaluable twice;
- four (E=2/P=2) had an insufficient study therapy performed.

Thirty-seven patients, (E=15/P=22) were prematurely discontinued because of consent withdrawal (15, E=10/P=5), ineffectiveness/ deterioration (13, E=3/P=10), intercurrent adverse event, illness, administrative reasons (1, E=1/P=0), etc.

Table 7-2

DISPOSITION OF PATIENTS

EVALUABILITY STATUS	ENOXAPARIN		PLACEBO		OVERALL	
	N	%	N	%	N	%
ALL-ASSIGNED	131	100	131	100	262	100
ALL-TREATED	131	100	131	100	262	100
EVALUABLE	111	84.7	112	85.5	223	85.1
UNEVALUABLE	20	15.3	19	14.5	39	14.9
DISCONTINUED	15	11.4	22	16.8	37	14.1
COMPLETED	116	88.5	109	83.2	225	85.8
COMPLETED EVALUABLE	108	82.4	103	78.6	211	80.5

From table 3,4 and 5 (Vol.9, pp. 8-8-39/40)

Population description

Demographics

1. All treated patients

Table 7-3

PATIENTS DEMOGRAPHIC CHARACTERISTICS. INTENT-TO-TREAT POPULATION

	PARAMETER	ENOXAPARIN		PLACEBO		OVERALL		P= VALUE not available
TOTAL	N/%	131	100	131	100	262	100	
MALE	N/%	56	42.7	57	43.5	113	43.1	
FEMALE	N/%	75	57.3	74	56.5	149	56.9	
AGE	Mean±SD	69.0		68.1		68.5		
	≥65 years	93	71.0	81	61.8	174	66.4	
	<65 years	38	29.0	50	38.2	88	33.6	
	Range							
HEIGHT (cm)	Mean±SD	169.5		170.1		169.8		
	Range							
WEIGHT (kg)	Mean±SD	76.4		78.5		77.5		
	Range							
BMI	Mean±SD	26.6		27.2		26.9		
	Range							
BSA*	Mean±SD	1.91		1.95		1.92		
	Range							

From Table 6, 7,8 (Vol. 9, pp8-8-42/48)

* BSA= Body Surface Area; BMI= Body Mass Index (weight/kg:height/meters squared)

Vital signs measured as pulse, blood pressure (systolic and diastolic) have shown no difference between treatment groups at baseline.

Same characteristics were analyzed for Enrolled Patients (288) who started open-label phase of the study, and for Evaluable Patients (223, E=111/P=112) who completed the study according to the protocol. In both populations, distribution of demographic characteristics between treatment group was not significantly

different, and they differed slightly from the Intent-To-Treat population. Results are presented on Table 7, and 8 (Vol. 9, pp. 8-8-44/48).

Concomitant Medications

Concomitant medications were used by 253 of 262 randomized patients (96.6%). Most frequently used medications were acetaminophen (89%), dextropropoxyphene (75%) and ferrous fumarate (51%). NSAIDS were used by 14 patients on placebo (10.7%) and 9 patients in the enoxaparin group (6.9%). All other medications, including anticoagulants (2, E=1/P=1), estrogen containing (6,E=4/P=2) and transfusion products (3,E=2/P=1) were distributed equally between treatment groups.

Medical History

Informations are summarized below (Table 7-4).

Table 7-4

DISTRIBUTION OF PATIENTS WITH CONDITIONS KNOWN TO BE ASSOCIATED WITH INCREASED RISK FOR VTE.
ALL-TREATED PATIENT POPULATION

CATEGORY	DIAGNOSIS	ENOXAPARIN		PLACEBO		OVERALL		P=VALUE
ITT PATIENTS	NUMBER/ % ⇒	131	100%	131	100%	262	100%	Not available
VTE	History of DVT	7	5.3	8	6.1	15	5.7	
	Varicose Veins	27	20.6	31	23.7	58	22.1	
	PE	1	0.8	4	3.1	5	1.9	
	Phlebitis	2	1.5	3	2.3	5	1.9	
CARDIO-VASCULAR	Congestive Heart Failure	5	3.8	3	2.3	8	3.1	
OBESITY	Lorenz' Formula	63	48.1	76	58	139	53.1	
	BMI	49	37.4	62	47.3	111	42.4	
DRUGS	Estrogen containing medications	5	3.8	2	1.5	7	2.7	

From table 10 (Vol.9, p.8-8-50)

Although patients on placebo seems to be more obese than patients on enoxaparin, this difference was not significant.

Surgery

Surgery was assessed as Type of Hip Disease, Operated Extremity (one or both), Surgical Procedure (Approach), Cement Use, Type of Anesthesia, Duration of Operation and Blood Loss. Results are summartized on Table 7-5.

Table 7-5

DISTRIBUTION OF PATIENTS WITH REGARD TO SURGERY. INTENT-TO-TREAT PATIENTS

CATEGORY	SUBCATEGORY	ENOXAPARIN N	ENOXAPARIN %	PLACEBO N	PLACEBO %	OVERALL N	OVERALL %	P=VALUE
HIP DISEASE	PATIENTS	131	100	131	100	262	100	Not available
	Osteoarthtritis	123	94	119	91	242	92	
	Rheumatiod arthritis	2	1.5	0	0.0	2	0.8	
	Avascular Necrosis	4	3.1	3	2.3	7	2.7	
	Other	2	1.5	9	6.9	11	4.2	
SURGICAL INTERVENTION	Bilateral	16	12.2	15	11.5	31	11.8	
	Unilateral	115	88	116	88	231	88	
	Hardinge	85	65	83	63	168	64	
	Charnley	45	34	48	37	93	35	
	Cement +	113	86	112	85	225	86	
ANESTHESIA	General	5	3.8	8	6.1	13	5	
	General and Local	126	96	123	94	249	95	
DURATION OF SURGERY (hours)	Mean/Median	1.97	1.68	2.08	1.85	2.02	1.75	
	Range							
INTRA-OPERATIVE BLOOD LOSS (mL)	Mean/Median	818	700	848	700	833	700	
	Range							

From Table 11 (Vol.9, pp.8-8-51/52)

There was no statistical difference between group for any one of these categories and subcategories.

Transfusion data

During the open label period of the study patients in both treatment groups received blood transfusion. The combined mL of donor and autologous blood transfused peri-operatively was 710±36 (E=707±51/P=652±48) mL. During the double-blind period two enoxaparin treated patients and one in placebo group received three units of blood. Distribution of patients between treatment groups was comparable. Data are summarized in Tables B.15, Appendix IV, Part B. No significant difference was found.

Comment: According to data presented, the two treatment groups did not differ significantly in baseline characteristics (demographics, medical and surgical history, vital signs, surgical procedure, and concomitant medications), and the results of efficacy and safety assessment should not be influenced by baseline confounding variables (at least those discussed).

7.3.2 *Efficacy Results*

The primary criterion for analysis of efficacy was the occurrence of a venous thromboembolic event (VTE) that was referred as "treatment failure". VTE was a composite endpoint includung a venography confirmed DVT, a lung scan confirmed PE, and autopsy confirmed death by thromboembolism.

Two patients died during the open-label period. One (patient #1225) developed atrial arrhythmia, and was found dead three days after surgery. Autopsy was not perfomed, MI was suspected. Other (patient #1231), two days after the operation developed a cerebral infarction and MI was also suspected. Study drug was discontinued. The patient died 17 days later due to MI (confirmed by autopsy). In both cases the investigator concluded that deaths were not related to the study drug.

Comment. This conclusion is questionable. Both MI and cerebral thrombosis are thromboembolic events. Both occurred while the patient was on enoxaparin prophylaxis. Enoxaparin is more effective against venous than arterial thrombosis (more platelets are involved in arterial thrombosis). However, if antiplatelet aggregation agents were forbidden as concomitant medications, could an arterial thrombosis be considered as "treatment failure"?

Two PE occurred during the double-blind period. Both in placebo group. This incidence is indicative, but not sufficient for statistical analysis.

With these two exclusions, VTE was represented by DVT only (Table 7-6).

Table 7-6

INCIDENCE OF DVT AS TREATMENT FAILURE. INTENT-TO-TREAT POPULATION

CATEGORY		ENOXAPARIN N	%	PLACEBO N	%	OVERALL N	%	P=VALUE & ODDS RATIO
FAILURE[a]	Total	131	100	131	100	262	100	P=0.001
	No	110	84	86	65.6	196	74.8	OR: 2.74
	Yes	21	16*	43+2(PE)	34.3*	66#	25.2	95%CI:
DVT[b]	Total	131	100	131	100	262	100	
	Yes	21	16.0*	43	32.8*	64	24.2	
Proximal DVT	Yes	8	6.1*	28	21.4*	36	13.7	P<0.05
Distal DVT	Yes	13	9.9	15	11.5	28	10.7	P>0.05

From Table 12, and 15 (Vol.9, pp. 8-8-54 and 59)

Includes 2 PE. [a] Primary efficacy analysis. [b] Secondary efficacy analysis. * Significant difference

The majority of reported thrombi in both populations were located in the operated extremity (ed.: This is a surgical manipulation related risk!).

Significant difference (p=0.001, Odds ratio= 2.74) was found between two treatments in the incidence of DVT, due primarily to proximal DVT, indicating that the extended prophylaxis with enoxaparin prevented at least one half of DVT occurrence.

Comment: DVT or treatment failures in this study were confirmed by a single venography performed day 30±4 after surgery. All DVT were clinically asymptomatic (except for 2 PE when DVT was not confirmed). *They could not have been detected at the end of the open-label period.* Patients in placebo treatment group had received 9 days enoxaparin prophylaxis, prior to 21 day placebo. Therefore, this analysis is between short (9 days) and long (30 days) enoxaparin prophylaxis following hip surgery.

Secondary Efficacy Analysis

Three analysis were performed: VTE in evaluable patients, VTE analysis by subpopulations (age, sex, risk factors [obesity, varicose veins, congestive heart failure, estrogen containing

medications, history of PE and phlebitis], surgical diagnosis, and operated extremity), and Distribution by site and clinical significance of VTE (presented above).

There was no difference between distribution of VTE outcome by treatment group for evaluable patients in comparison with intent-to-treat population. Evaluable patient population values for placebo (N=112/VTE=45), and enoxaparin (N=111/VTE=20) group, were comparable to those obtained from ITT population analysis (placebo [N=131/VTE=45]; enoxaparin [N=131/VTE=21]. Data are summarized on Table 13 (Vol.9, p. 8-8-55) and Table 7-7.

Table 7-7

DISTRIBUTION OF VTE BY SUBPOPULATION. INTENT-TO-TREAT POPULATION

SUBSETS		ENOXAPARIN n/N	PLACEBO n/N	OVERALL n/N
AGE	<65 years	3/38	13/50	16/88
	≥65 years	18/93	32/81	50/174
SEX	male	6/56	14/57	20/113
	female	15/75	31/74	46/149
RISK FACTORS	Obesity (BMI)	11/49	24/62	35/111
	Varicose veins	5/27	11/31	16/58
	History of DVT	1/7	2/8	3/15
	CHF	3/5	2/3	5/8
	Estrogen containing drugs	0/5	1/2	1/7
	History of PE	0/1	2/4	2/5
	Post-phlebitic syndrome	0/2	2/3	2/5
SURGERY	Osteoarthritis	21/123	42/119	63/242
	Bilateral	4/16	9/15	13/31
	Unilateral	17/115	36/116	53/231
	Primary THR	16/105	36/111	52/216
	Bilateral THR	4/16	9/15	13/31
	Hardinge	11/85	28/83	39/168
	Charnley	9/45	17/48	26/93
	Cement use	20/113	39/112	59/225
ANESTHESIA	General	1/5	4/8	5/13
	General and Local	20/126	41/123	61/249
TRANSFUSION REQUIRED	Yes	21/131	45/131	66/262

From Table 14 (Vol.9, pp. 8-8-57/58)