CENTER FOR DRUG EVALUATION AND RESEARCH

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STATISTICAL REVIEW(S)

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STATISTICAL REVIEW AND EVALUATION

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NDA #: 20-164/SE1 - 010

Drug: Lovenox (Enoxaparin Sodium) Injection

Drug Classification: S

Indication: Long Term Prevention of Deep Venous Thrombosis After Hip Replacement Surgery

Sponsor: Rhone Poulene-Rorer (RPR)

Clinical Reviewer: The issues addressed in this review have been discussed with the medical reviewer (Dr. Nenad Markovic, M.D.).

Statistical Reviewer: M. Mushfiqur Rashid, Ph.D.

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INTRODUCTION

Enoxaparin is a low molecular weight heparin obtained by partial and controlled depolymerization of a benzyl ester of porcine unfractionated heparin. Enoxaparin is approved for use in Europe for the prophylaxis of venous thromboembolic complications in high risk orthopedic surgery and moderate risk general surgery patients, for the treatment of acute deep vein thrombosis and for the prevention of thrombus formation in the extracoporeal circulation during hemodialysis. In the United States, enoxaparin has been approved for the prevention of deep vein thrombosis in total hip and knee replacement surgery.

This supplemental submission addresses the use of Lovenox (enoxaparin sodium) in the long term prevention of venous thromboembolic events (VTEs) after hospital discharge following hip replacement surgery. Lovenox (NDA #20-164, approved on March 29, 1993) was originally used for the prevention of deep vein thrombosis (DVT) which usually leads to pulmonary embolism (PE) following replacement surgery. In this submission the sponsor has

indicated the use of prefilled syringe with a volume of 0.4 ml, representing 40 mg of enoxaparin (0.4 ml of 100 mg/ml enoxaparin solution). Note that the selection of 40 mg subcutaneous once daily regimen for the clinical trials included in this application was based upon prior extensive European experience in clinical trials, primarily those supporting safety and efficacy of enoxaparin 40 mg once daily regimen in the prevention of venous thromboembolic complications in patients undergoing hip replacement surgery (extracted from sponsor's Volume 2, page 8-1-21).

The sponsor has studied the safety and efficacy of the product in the prevention of venous thrombolic complications after hip replacement surgery. Two (phase III) 2-phase single center studies (PK537 and ENX491001) have been conducted in support of the indication for the dosing regimen modifications proposed in this supplemental submission. The first phase is an open label study where patients who had undergone total hip replacement surgery and were treated with enoxaparin 40 mg. This is followed by a double blind placebo controlled phase. The study ENX 491001 was conducted in France from 1991 to 1994 whereas the study PK537 was conducted in Sweden from 1991 to 1995.

The primary efficacy parameter was the incidence of venous thromboembolic disease. Evidence of venous thromboembolic disease (treatment failure) was based on the incidence of deep venous thrombosis, pulmonary embolism or both. Patients were assessed for deep vein thrombosis on the evidence of venography results. Each venogram was assessed as positive, negative or inadequate for diagnosis of deep vein proximal or distal thrombosis in one of both extremities and in the operated or nonoperated extremity. Patients were considered positive for pulmonary embolus only if a pulmonary embolus was reported as the results of a ventilation-perfusion lung scan and /or pulmonary angiogram. Patients without such a result were considered positive if they had an adverse experience report listing a pulmonary embolus as either an incidental finding or as the cause of a patient's death.

I. STUDY PROTOCOL PK 537

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1.1 *Study Design*

This study is described in the protocol as an open label, inpatient lead-in to a randomly assigned double blind, placebo controlled, two parallel group, outpatient, single center clinical study. The purpose of this study was to compare the safety and the efficacy of enoxaparin 40 mg injection in the prevention of VTE in patients with hip replacement after hospital discharge.

In the first phase (open label phase) 288 patients underwent elective total hip replacement. The patients were initially treated with enoxaparin (40 mg) once daily for 9 ± 2 days with the first dose of open-label medication being administered preoperatively 12 ± 2 hours before surgery. This study was conducted at Malmo General Hospital, Lund University, Sweden. Patients (of

either sex) who qualified for this study were at least 40 years old (weighing at least 40 kg) and had undergone primary, elective hip replacement. Any anticoagulant drugs were to be discontinued five days before surgical operation and were not to be allowed during the trial. All patients are to receive the first sc dose of enoxaparin 40 mg 12 ± 2 hours before surgery. Subsequent doses were to be given every 24 ± 2 hours. Patients who required administration of high molecular weight plasma expanders such as Dextran were to be excluded from the studies. However, Tranexamic acid were to be included.

At the end of the hospital period, just before discharge, patients who qualified for the double blind phase were assigned a number in a sequential ascending fashion, beginning with the lowest number. To enter into the double blind phase of the study the patient must satisfy the following criteria:

(1) Had undergone either primary elective or primary hip replacement (THP) surgery;

(2) Had no prior operation;

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(3) Was discharged at the $7th \pm 2$ post operative day;

(4) Did not exhibit objectively verified DVT (clinical method) and/or PE during hospitalization period;

(5) Did not exhibit major bleeding during this hospitalization period; received enoxaparin prevention with the first dose administered between 10 and 14 hours before surgery, and with a once daily sc injection of 40 mg enoxaparin during the hospitalization period, and the preventive medication was not discontinued for any reason.

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Sample Size Estimation/Randomization Schemes:

The patient population size estimate was based on a VTE incidence of 30% for placebo-treated patients and 13% for Enoxaparin treated patients with a two sided statistical test at a significance level of 5% and a power of 90%. Assuming 15% of patients with venography classified as inadequate and/or not done, the postulated sample size was found to be 260 patients to assure 220 evaluable patients.

Note that 288 entered the initial phase of the study. Of these, 262 patients who did not develop symptomatic venous thromboembolism and/ or did not discontinue the open-label enoxaparin therapy were eligible for randomization into the double blind phase.

Thus, 262 patients were randomly assigned to receive either Enoxaparin (131) or placebo (131) in the double blind phase. Note that patients were randomly allocated to receive either enoxaparin or placebo according to a predetermined randomization list within each of three strata:

(1) Unilateral not previously operated;

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(2) Bilateral;

(3) Unilateral previously operated.

The protocol indicated that randomization was performed on more than two occasions (March 8, 1994 and February 1994, other times were not specified). Each stratum patients were randomized in blocks of size four (4) in a 1:1 ratio to receive either Enoxaparin or placebo.

There were 113 male (43%) and 149 female (56.9%) patients who underwent elective primary total hip replacement surgery. Out of the 113 males, 56 went into the enoxaparin treated group and 57 went into the placebo treated group. Out of 149 female patients, 75 went into the enoxaparin treated group and 74 went into the placebo treated group. The mean age of the participants was 68.5 years

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Study Objectives and Primary Endpoints:

The objective of this study is to evaluate the efficacy and safety of 40 mg enoxaparin (Lovenox) for the prevention of venous thromboembolism (VTE) in patients who have undergone hip replacement surgery and have not developed venous thromboembolic complications during the postoperative, inpatient hospitalization period of recovery.

The primary efficacy variable (endpoint) was: Objectively documented venous thromboembolic disease, including both deep vein thrombosis (DVT) and pulmonary embolus (PE), occurring during or immediately following the double-blind outpatient phase. Deep vein thrombosis was diagnosed by adequate lower extremity contrast venography, ultrasonography, or other clinical evidence of deep vein thrombosis. Adequate bilateral lower extremity venography was required for evaluable subset analysis. Pulmonary embolus, documented by ventilation-perfusion lung scan or pulmonary angiography, as indicated, was also considered evidence of venous thromboembolic complications.

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1.2 *Sponsor's Analysis Method And Analysis Plan*

1.2.1 Data Set Analyzed and Statistical Analysis Plan

The protocol indicated that all treated patients were to be included in the primary efficacy analysis regardless of compliance. The primary efficacy parameter was the incidence of venous thromboembolism disease. Endpoint evaluations were classified as failures if

(I) positive DVTs were proven by bilateral phlebography and positively evaluated by a panel of experts,

(ii) positive pulmonary embolisms (PEs) were proven by perfusion/ventilation lung scan and/or by pulmonary angiogram, or by autopsy,

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or nonfailures if

iii) bilateral phlebography readings on non-positive DVTs were normal and PEs were not proven.

The primary efficacy parameter, the occurrence of venous thromboembolism (VTE), was also analyzed based on the evaluable patient population. This patient population excluded all randomized patients who meet at least one of the following criteria presented in descending hierarchical order:

1- Endpoint not available or inadequately established
2- Insufficient study therapy
3a- Inappropriate surgical procedure
3b- Inappropriate conventional prophylaxis period or outcome
4- Prohibited prior/concomitant medications
5- Randomized twice.

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A secondary efficacy analysis using venography results based on the anatomic distribution of thrombi was to be presented as well. Thrombi was classified as proximal, distal or absent. A patient with proximal and distal thrombi was considered as having proximal thrombi. These subgroup of patients were analyzed for all the treated patients and the evaluable patient population. The incidence of venous thromboembolism was also analyzed by other subgroups, for example age, sex, anatomic location, etc. These subgroup analysis were performed for the all treated patient population only.

As mentioned earlier, a total of 288 patients entered the initial phase of the study, and 262 continued into the double blind phase of the study. The reasons for not randomizing the remaining 26 patients into the second phase were consent withdrawals (8), drug ineffectiveness (5), violation of protocol (4), intercurrent/adverse events (2), administrative (1), deaths (1),

and other reasons (5). Thus only 5 (1.87%) out of 267 patients (intend to treat) were diagnosed as having VTE after the initial phase of the study. It is worth mentioning that all the patients are of the same race (Caucasian).

About 85.1% (223 out of 262) of all the randomized patients were evalauble. Out of the 39 nonevaluable patients, 20 belonged to the Enoxaparin group and 19 belonged to the placebo group. Twenty nine(14 in Enoxaparin group and 15 in the placebo group) of the nonevaluable patients had as inadequate/not done final endpoint; six were randomized twice (4 in Enoxaparin group and 2 in placebo group): 4 (2 in enoxaparin and 2 in placebo) had insufficient study therapy.

This reviewer does not disagree with the sponsor's claim that the two treatment groups (randomized as well as evaluable) were comparable (see Table in the Appendix for some demographic characteristics comparisons) with regard to demographic characteristics (age, sex, height, body mass index, body surface area, supine pulse, obesity, vital signs and risk factors). One hundred eighteen (52.9%) of the evaluable patients were described as obese according to Lorenz formula, but only 94 (42.2%) were described as obese according to the body mass index. Among these 94 patients 41 were randomized to the enoxaparin group and 53 to the placebo group. The two treatment groups were comparable with regard to surgical parameters (rheumatoid arthritis, surgical approaches, anesthesia, etc.).

The sponsor noted that the two treatment groups were also comparable with regard to drug exposure variables as well as to the usage of concomitant medication. See Table A.1 in the Appendix for details.

1.2.2 Sponsor's Analysis Results/Reviewer's Analysis and Comments

The following table summarizes the efficacy data (extracted from sponsor's Table B.11.1, page 8-9-129, Vol 10) for all treated patients at the end of the second phase (double blind).

Table 1.1 / Failure Rates of Randomized Patients by Treatment Group

	Overall N(%)	Enoxaparin N(%)	Placebo N (%)
Number of patients	262 (100%)	131 (50%)	131 (50%)
No VTE	196 (74.8%)	110 (84%)	86 (65.6%)
DVT	64 (24.4%)	21 (16.0%)	43 (32.8%)
PE	2 (.8%)	0 (0.0%)	2 (1.5%)
Total: VTE=DVT+PE	66 (25.2%)	21 (16.0%)	45 (34.4%)

It is clear from the above table that there were numerically more VTEs in the placebo group

than in the enoxaparin group. Among the patients randomized to placebo treatment, 45 (34.4%) were diagnosed as having venous thromboembolism compared to 21 (16.0%) enoxaparin treated patients diagnosed with venous thromboembolism. Pulmonary emboli were diagnosed in two patients both in the placebo group. The venous thromboembolism incidence for the treatment group (16%) was significantly lower (asymptotic chi-square p-value 0.001) than that of the placebo group. The resulting estimated odds ratios was 2.74 indicating that the odds of developing venous thromboembolism was 2.74 times greater among the placebo patients than the enoxaparin patients. A 95% confidence interval of the odds ratio is (1.52, 4.94). Thus the two treatment groups are different in terms of enoxaparin. Note that all the 64 positive VTE diagnosed patients were reviewed by the expert panel.

The following table summarizes the efficacy data (extracted from sponsor's Table B.11.2, Vol 10, page 8-9-131) for the evaluable patients.

Table 1.2/ Failure Rates for Evaluable Patients

	Overall N(%)	Enoxaparin N(%)	Placebo N (%)
Number of Patients	223 (100%)	111 (49.8%)	112 (50.2%)
No VTE	158 (70.9%)	91 (82%)	67 (59.8%)
DVT	63 (28.3%)	20 (18.0%)	43 (38.4%)
PE	2 (.9%)	0 (0.0%)	2 (1.8%)
VTE=DVT+PE	65 (29.1%)	20 (18.0%)	45 (40.2%)

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The incidence VTE rate for the enoxaparin (18.0%) was significantly lower (asymptotic chi-square p-value= 0.00027) than that of the placebo group (40.2%). The resulting estimated odds ratio was 3.06 indicating that the odds of developing a venous thromboembolism was 3.06 times greater for placebo patients than for enoxaparin patients. Note that a 95% confidence interval of the odds ratio is (1.65, 5.65) suggesting that the two treatment groups are different in favor of enoxaparin.

In both the all treated and evaluable patient populations, the venous thromboembolism incidence rate of the enoxaparin-treated patents was significantly lower than that of the placebo-treated patients. In each of these populations, the estimated odds of venous thromboembolism in placebo patients was more than two and half time greater than that of the enoxaparin patients.

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1.3 *Other Subsets Analysis and Reviewer's Comments*

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Venous Thromboembolism Summary by Subgroup:

The following table gives the summary of the efficacy information by sex and age for all treated patients (extracted from sponsor's Table B.12.1, Vol 10, page 8-9-145).

Table 1.3/ Failure Rates by Subgroup (All Treated Patients)

	Overall	Enoxaparin	Placebo	P-value (asymptotic)
Number of Patients	262	131	131	
Patients with VTE	66 (25.2%)	21 (16%)	45 (34.4%)	
Age Group				
<65	16/88 (18.2%)	3/38 (7.9%)	13/50(26%)	.025
≥65	50/174(28.7%)	18/93(19.4%)	32/81(39.5%)	.003
Sex				
Male	20/113(17.7%)	6/56 (10.7%)	14/57(24.6%)	.054
Female	46/149(30.9%)	15/75 (20%)	31/74(41.9%)	.004

It is clear from the above table that for the all treated patients, the venous thromboembolism incidence rates for enoxaparin patients was less than the incidence rate for placebo patients for each subset listed above. Also in patients with VTE, no significant age group by treatment interaction effect is found (asymptotic chi-square p-value=.197). Similarly in patients with VTE, sex is independent of the treatment groups (asymptotic chi-square p-value=.834). Similar conclusions are valid for patients with no VTE.

The following table (extracted from sponsor's Table B12.2, Vol 10, page 8-9-148) summarizes VTE rates among all evaluable patients by subgroups (age and sex).

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Table 1.4/ Failure Rates by Subgroup (Evaluable Patients)

	Overall	Enoxaparin	Placebo	P-value (asymptotic)
Number of Patients	223	111	112	
Patients with VTE	65 (29.1%)	20 (18%)	45 (40.2%)	
Age				
<65	16/80 (20%)	3/33 (9.1%)	13/47 (27.7%)	.041
≥65	49/143 (34.3%)	17/78 (21.8%)	32/65 (49.2%)	.001
Sex				
Male	20/100 (20%)	6/50 (12%)	14/50 (28%)	.046
Female	45/123 (36.6%)	14/61 (23%)	31/62 (50.0%)	.002

It is clear that VTE rate for enoxaparin patients was significantly less than the incidence rates for placebo patients for the subsets listed above (in Tables 1.3 and 1.4). Further, in patients with VTEs, the age factor is independent of the treatment groups (asymptotic chi-square p-value=.230). However, in patients with no VTE, the age factor is not independent of the treatment groups (asymptotic chi-square p-value= .024). The factor sex is independent of the treatment group in both VTE (asymptotic chi-square p-value 0.929) and non-VTE (asymptotic chi-square p-value =0.594) patient groups.

In addition, in other subgroups (obesity and predetermined risk factors, primary diagnosis, operated-extremity, surgical approach, surgical procedure, type of anesthesia and type of prosthesis) except for one group (patients who underwent unilateral primary total hip replacement of the contralateral extremity) the venous thromboembolism incidence rate for enoxaparin patients was less than the incidence rate for placebo patients for the subgroups listed (extracted from sponsor's Table B.12.1, page 8-9-148 of Volume 10).

Deep Vein Thrombosis Anatomic Location:

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The following Table summarizes treatment failures for the all treated randomized patients by location(extracted from sponsor's Table B.11.2, Vol 10, page 8-9-131).

Table 1.5/ Failure Rates of All Treated Patients by Location

Site of Thrombi	Overall N(%)	Enoxaparin N(%)	Placebo N(%)
Number of Patients	262	131	131
All Proximal	36 (13.7%)	8(6.1%)	28 (21.4%)
Proximal	16 (6.1%)	4(3.1%)	12 (9.2%)
Proximal and Distal	20 (7.6%)	4(3.1%)	16 (12.2%)
Distal	28 (10.7%)	13 (9.9%)	15 (11.5%)
Indeterminate	2 (0.8%)	0 (0.0%)	2 (1.5%)
No Thrombus	196 (74.8%)	110 (84.0%)	86 (65.6%)

The all proximal deep vein thrombosis incidence rate of the enoxaparin group (6.11%) was significantly lower (asymptotic chi-square p-value=0.00033) than that of the placebo group (21.37%). The resulting estimated odds ratio was 4.8 indicating that the odds of developing at least a proximal deep vein thrombosis was 4.18 times greater among placebo patients than enoxaparin patients. A 95% confidence interval of the odds ratio is (1.83 , 9.57) which does not contain 1.

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Efficacy Conclusions:

In both, the all treated and evaluable patient populations, the venous thromboembolism incidence rate of the enoxaparin treated patients was significantly lower than that of the placebo treated patients. In each of these populations, the estimated odds of venous thromboembolism in placebo patients was more than two and a half greater than that of enoxaparin group. Furthermore the estimated odds of at least a proximal deep vein thrombosis in placebo patients was more than four times greater than that of enoxaparin patients.

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1.4 *Sponsor's Safety Event Summary Results and Reviewer's Comments:*

The following Table summarizes all hemorrhage episodes (HE) by treatment group (extracted from sponsor's Table B.16.2, Vol 10, page 8-9-165).

Table 1.6/Hemorrhage Episodes (HE) By Treatment Group

	Overall N (%)	Enoxaparin N(%)	Placebo N(%)	P-value
Number of patients	262	131	131	
patients with HE: At Least One	11(4.2%)	8 (6.1%)	3 (2.3%)	0.217 (Fisher's exact)
No episode	251(95.8%)	123 (93.9%)	128 (97.7%)	
Patients with any major HE:				
No major HE	262 (100%)	131 (100%)	131(100%)	

There is no significant difference in the incidence rates of minor hemorrhagic episodes between the two treatment group (Fisher's exact p-value 0.217). No major hemorrhagic episodes were reported.

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III STUDY PROTOCOL ENX491001(Double Blind, Placebo Controlled)

2.1 *Study Design*

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Like PK537, this study also consisted of two treatment phases (open label treatment phase followed by a double blind phase). The study is described in the protocol as a two-phase randomized double blind placebo controlled, parallel group, single center study. The purpose of the study is to demonstrate that the continuation of the anticoagulation treatment (enoxaparin 40 mg) two days after the release from the hospital prevents the formation of late venous thrombosis of the lower limbs. In this study the 40 mg once daily dosing regimen was administered to patients who had undergone hip replacement surgery for 14 ± 1 days during the open label treatment phase (hospitalization phase). The first dose of enoxaparin 40 mg was administered 12 ± 2 hours preoperatively. At the end of the hospital period, patients who did not develop VT D (diagnosed by venography) were randomized into the control group and the enoxaparin group. The patients in the enoxaparin group were administered 40 mg once daily treatment regimen for 19 to 23 days (21 ± 2 days) of therapy. The control patient group

received matching placebo injections.

Patients qualified for this trial if they satisfied the following inclusion criteria:

(1) Age 45 years and above;

(2) weight between _____ kg;

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(3) had total hip replacement surgery at most 15 days prior to study initiation and were still receiving prophylaxis for VTE;

(4) had absence of deep venous thrombosis verified by echography, confirmed by bilateral phlebography in case of doubt;

(5) capable of walking alone with total support.

(6) could be seen within 21 ± 3 days.

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It should be noted that patients with total hip replacement (THR) or repeated surgery for prosthesis could be included provided the patient resumed total support during prior clinical examination for inclusion.

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Sample Size Estimation/Randomization Schemes

A sample of 160 patients (80 in each group) was planned. In the absence of clinical data, the estimation of the number of patients was based on the following hypotheses:

Estimated percentage of VTE:
In the placebo group: 13%;
In the enoxaparin group: 2%;
with a significance (two-sided) level of 5% and 80% power.

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The protocol indicated that patients who qualified for the second phase of the study were to be randomized in blocks of size 4 in a 1:1 ratio to receive either the placebo treatment or enoxaparin 40 mg in a double blind fashion.

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Study Objectives and Primary Endpoints:

The objective of this study was also to determine efficacy and safety of enoxaparin in the prevention of late occurring deep venous thrombosis in patients who had recently undergone elective total hip replacement and had received conventional enoxaparin thromboprophylactic

therapy.

The primary endpoint was the occurrence of thromboembolism. Patients experiencing thromboembolism were considered to present with a "treatment failure." The evaluation of the primary endpoint was based on phlebography. All phlebograms were to be reviewed by a panel of two independent experts. If there was an agreement consensus was obtained in a meeting with two experts. If the experts' opinion was not available, the opinion of the center in the case report form was taken into account. If the phlebogram was not available, the Doppler ultrasound examination was used. In the absence of Doppler ultrasonography, patients with clinical signs causing the investigator to change the anticoagulant treatment within 24 hours following the onset of the clinical signs were considered to be treatment failures. In the absence of clinical information, patient survival was considered as a success and patient death a failure.

The secondary endpoints for efficiency analyses were as follows:

1) the incidence of VTE in each group,
2) the incidence of PE in each group'
3) the incidence of proximal VTE in each group
4) the incidence of distal VTE in each group
5) the incidence of study withdrawal in each group.

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Analyses of secondary endpoints consisted of comparing the two groups in terms of the above parameters.

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2.2 *Sponsor's Analysis Method And Results*

2.2.1 Data Set Analyzed and Statistical Analysis Plan

Five hundred and thirty two patients were eligible for the trial. One hundred and seventy nine (57% males and 43% females) were actually randomized 14 ± 1 days after surgery. Only patients with negative bilateral venogram were eligible for randomization. Thirty one out of 353 patients who had VTE detected by venography were excluded from the second phase. Thus the VTE incidence rate after the first phase was about 14.76% (31/210, extracted from page 8-2-130, Volume 3). The reported incidence rate in this study is approximately 12.89% higher than the VTE rate reported in study PK 537. Out of 179 patients who qualified for the second phase 90 were allocated to treatment group and 89 to placebo group. Fifty two percent of the patients assigned to the treatment group were male compared to 61.8% in the placebo group. Two-tailed Fisher's exact test indicated the proportion of the males in the two groups were not different (p-value = 0.228).

All patients were in good general condition at baseline. The two groups were comparable in terms of all the baseline parameters (sex, age, height, weight, BMI,....,etc.) recorded during

the physical examination, except for obesity. The rate of obesity was higher in placebo group 36% vs 22% (asymptotic chi-square p-value 0.049).

2.2.2 Sponsor's Analysis Results/ Reviewer's Evaluation and Comments

In this study, a total of 179 patients underwent elective hip replacement surgery and were administered enoxaparin for 14 ± 1 days. Only patients with negative bilateral venogram were eligible for randomization into the second phase of the study. Ninety patients received enoxaparin and 89 received placebo. Descriptive statistics for the efficacy measures are presented in the following Table (extracted from sponsor's Volume 3, page 8-2-147).

Table 2.1/ DVT Rates in the All Treated Patients

Treatment Failure	Enoxaparin (N=90)	Placebo (N=89)	Overall (N=179)
Yes	6 (6.7%)	18 (20.2%)	24 (13.4%)
No	84 (93.3%)	71 (79.8%)	155 (86.6%)
Sample size	90	89	179

We see from the above Table that for the all-treated patients, 6 out of 90 patients (6.7%) in the enoxaparin group and 18 out of 89 patients (20.2%) in the placebo group had a thromboembolic event. The failure rate was significantly higher in the placebo group than in the enoxaparin group (p-value 0.008 based on asymptotic chi-square). Note that there were no patients who developed PE in this study.

Analyses of the evaluable subgroup of patients gave similar results. Note that the most common reason for patients being designated as unevaluable was that the mandatory venography was either inadequate or not done. The following Table (extracted from page 8-2-149. Volume 3) summarizes efficacy results corresponding to the evaluable patient population.

Table 2.2/ DVT Rates for All Evaluable Patients

Treatment Failure	Enoxaparin (N=85)	Placebo (N=88)	Overall (N=173)
Yes	6 (7.1%)	17 (19.3%)	23 (13.3%)
No	79 (92.9%)	71 (80.7%)	150 (86.7%)
Sample Size	85	88	173

The frequency of DVT was higher in the placebo group than in the enoxaparin group. The