

**B. PIVOTAL STUDIES ENOX 491001 AND PK-537**

**6.0 STUDY ENOX 491001**

(NDA Volumes: M43.2-8)

- 6.1 Study Protocol
- 6.2 Statistical Analysis
- 6.3 Study reports

**TITLE:** *Efficacy and safety evaluation of enoxaparin (Lovenox®) 40 mg/day in the prophylaxis of late-occurring deep venous thrombosis following total hip replacement from week 2 until week 5 after surgery. A randomized, double-blind, placebo controlled study.*

Study Start Date: 08/24/91  
Study Completion date: 07/28/94  
Study Report Date: 11/22/95

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**Identity of Test Material**

1. Open-label phase:

Enoxaparin, Injectable solution 100 mg/mL, 40 mg/0.4 mL.  
Lots No. 4329, 4351, 4354, 4428, 4469, 4475, 4584,  
4496, and 207-1

2. Double-blind phase

Enoxaparin, Injectable solution 100 mg/mL, 40 mg/0.4 mL sc, qd  
Lots No. CB4733, 4475, 4917  
Placebo, Injectable solution saline, 0.4 mL, sc, qd,  
Lots CB4863P, CB4905P, F94A27

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## 6.1 STUDY PROTOCOL

### 6.1.1 Objective

The sponsor has defined for the objective of this study to evaluate the efficacy and safety of 21 days post-hospital treatment with enoxaparin 40 mg, sc, qd, versus similarly administered placebo (saline), in the prevention of late-occurring (week 2 to week 5) venous thromboembolism following total hip replacement.

### 6.1.2 Study Design

The study was conducted as phase IV (new indication, duration), prospective, single-center, randomized, double-blind, placebo-controlled two parallel group clinical trial to assess safety and efficacy of enoxaparin to prevent late-occurring venous thromboembolism

Eligible patients who underwent total hip replacement surgery (THR), from surgery to randomization were to receive, in an open-label fashion, enoxaparin 40 mg, sc, qd for 14±1 days. At hospital discharge all patients were subject to ascending venography. Patients who were negative for DVT, were randomly allocated to receive as outpatients, subcutaneously, once daily either enoxaparin 40 mg (4000 aXa IU) or placebo (isotonic saline) for 21±1 days. All patients were scheduled for a follow-up visit at day 21±1 post discharge for clinical, laboratory, treatment compliance, and venographic assessment. A 3-month follow-up period was reserved for reporting new DVT and/or PE.

The study efficacy endpoint was represented by the development of VTE (DVT and/or PE) and it was considered as treatment efficacy failure. Surveillance for DVT (efficacy assessment) was performed by ascending contrast venography. A symptomatic PE was to be confirmed by lung scan or pulmonary angiography or, in case of death, by autopsy (if permitted).

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

There was neither administrative changes of this protocol, nor amendment for change.

**Assignment**

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**6.1.3 Study Population**

Male and female patients, aged 45 or older, body weight between \_\_\_\_\_ kg, who have completed total hip replacement [THR] surgery and perioperative enoxaparin prophylaxis for 14±1 days, who were venographically negative for DVT, who had the ability to walk unassisted with full weight-bearing on the operated leg using crutches, and who signed informed consent, were eligible for this study.

Exclusion criteria included total hip replacement [THR] more than 15 days before inclusion, DVT prophylaxis interrupted for more than 24 hours, history of known VTE within the previous 6 months, cancer in progression, hemorrhagic syndrome or hemostatic abnormality outside limits, renal insufficiency and any condition putting patients at risk of hemorrhage.

No concomitant medication were permitted. Preventive daily use of elastic bandaging or support stockings as well as physiotherapy were encouraged. All other treatment, if necessary in case of concomitant disease, was recorded (starting date, indication, dosage regimen, date of end) in the case report forms.

There were no predetermined criteria for treatment discontinuation.

**Treatment Assignment and Randomization**

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The investigator had to establish the eligibility of each patient. 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 (SAS software package). Patients were given a treatment pack containing 25

identical syringes and labeled with the corresponding randomization number.

*Study Duration*

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The planned duration of treatment for each patient was 21±2 days following hospital-discharge. A successful perioperative prophylaxis was considered if no DVT were found on a control phlebography.

*Study Medication and Blinding*

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The study medication was prepared by the sponsor as ready-for-use prefilled syringes containing 40 mg in 0.4 mL of enoxaparin injectable solution (strength: 100 mg/mL) or 0.4 mL isotonic saline.

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.

*Study Drug Administration*

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After hospital-discharge, eligible patients received study drug medication as a package with 25 syringes for subcutaneous injection. Twenty-one of them should have been used on daily basis. Patients were instructed to call the investigator in case of any adverse reaction that might appear any time during the next 3 weeks, and to report for evaluation 21 days after discharge.

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#### 6.1.4 Assessment of Efficacy and Safety

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##### *Efficacy*

DVT: Initially, a bilateral ultrasonography was considered for assessment of DVT. It was changed to the ascending contrast venography as "the most reliable procedure for detection of leg venous thromboembolism." DVT negative bilateral venography at the end of hospital treatment (day 14±2) was mandatory for patients to enter the study. The same procedure was repeated at the end of post-hospital treatment period (day 21±2), or earlier if clinical signs and symptoms of DVT have been appeared. All venographies were read by investigators and by two independent radiologists blinded for treatment assignments. If necessary, agreement was to be reached during an expert consensus meeting.

DVT was diagnosed when the venogram revealed a constant intraluminal filling defect in the deep vein in at least two projections. It was classified as proximal if the thrombus was in popliteal and proximal veins, and distal if it was in calf veins.

PE: Symptomatic pulmonary embolism was to be confirmed by lung scan or pulmonary angiography, or in case of death, by autopsy (if permitted). In patients surviving PE a bilateral ascending venography had to be performed. Everyone involved in this study was instructed to perform daily assessment for the presence or absence of clinical suspicion of pulmonary embolism, and to report it to the investigator. This period of observation was extended for additional three-month follow-up beginning the end of 21 days period of treatment.

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##### Primary Efficacy Criteria

Because DVT and PE are considered to be the expression of the same disease process, the primary efficacy criterion in this study was the occurrence of a documented VTE (venous thromboembolic event including a confirmed DVT, PE and death due to thromboembolism). The occurrence of VTE was referred as "treatment failure."

### *Safety Outcomes*

Safety outcomes were defined in terms of occurrence or non-occurrence of death, major or minor hemorrhage, adverse event other than VTE and hemorrhage, and change of laboratory parameters.

Hemorrhage: location, intensity (major: Hb level reduction >2g/dL, need for transfusion of >2 units of PRC, any intracranial or retroperitoneal; minor: overt, but none of the above). Intraocular hemorrhage was missed from this list.

Adverse events: Any adverse event, either reported by patients or elicited by investigator was judged according to severity (mild, moderate or severe) and relationship to study medication (none, possible, or probable). The type, dates of onset and resolution, outcome and instituted therapy (if any) were recorded in the case report forms.

Separate group was formed for "serious" adverse events. This category included all events that met any of the following criteria: death occurring within 4 weeks of the last day of study drug administration; life-threatening events; events resulting in disability or incapacity; events requiring or prolonging hospitalization; any event resulting from a drug overdose; and any event that resulted in cancer or congenital anomaly.

### Laboratory Tests

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Blood samples were collected for blood cell counts, hematocrit and hemoglobin levels (day of discharge and day of evaluation, D1 and D21 of this study). Platelet count was assessed weekly to detect drug-induced thrombocytopenia.

## 6.2 Statistical Methods

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### Sample Size

Sample size determination was based on the assumption of a DVT rate of 13% in the placebo group and 2% in the enoxaparin group.

With  $\alpha=0.05$  (two-tailed) and a power of 80%, it was calculated that 80 patients per group would be needed to detect a difference of this magnitude.

A plan for statistical analysis was completed "before data were unlocked and evaluated".

#### Study population

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Two study populations were analysed separately:

- Intent-to-treat analysis (all randomized patients having received at least one dose of study medication), and
- per-protocol analysis (evaluatable patients who completed the study).

Patients considered as not evaluatable and in violation of the protocol were analyzed separately.

Any of the following criteria have qualified patients as non-evaluatable for the per-protocol analysis of efficacy: Presence of confirmed DVT, or venography not performed at inclusion; bilateral venography not done or not assessable at day 21; patients not having received enoxaparin for  $14 \pm 3$  days between surgical procedure and inclusion; body weight  $>100$  kg; venography at inclusion performed 5 or more days before actual inclusion; venography at the end performed 5 or more days after the last study drug injection; patient having received concomitant anticoagulant treatment during the double-blind period.

Comment: These criteria are slightly different from exclusion criteria, and allow more flexibility.

Summary tabulations by treatment group and statistics were provided for age, gender, weight, height, medical history, physical examination, hip disease, surgical procedure, type of hip prosthesis, type of anesthesia, total intraoperative and postoperative blood loss, laboratory parameters at inclusion, and duration of enoxaparin prior to randomization.

#### Efficacy Evaluation

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The primary study efficacy criterion was "treatment failure" as previously defined. Decision three used to classify patients as "success" or "failure" is presented (Table 6-1)

Table 6-1

YES ↓	← VENOGRAPHY →	NO ↓
Expert's consensus ⌞		Ultrasonography This was abandoned later
YES ⌞	NO ↓	
FAILURE/SUCCESS	Investigator Conclusion ⌞	
	FAILURE/SUCCESS	

This plan defined secondary criteria for analysis of efficacy: incidence of DVT and PE in each group; incidence of proximal and distal DVT (patients with both were evaluated as having proximal), and incidence of dropouts.

Descriptive statistics was provided for both populations.

Safety Evaluation

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Safety analysis was performed only on the intent-to-treat population. Safety analyses were based on a between-group comparison of the incidence of hemorrhage, adverse events other than thrombosis and hemorrhage, and changes in laboratory parameters. Changes of laboratory parameters were summarized by treatment group in shift tables (baseline values at inclusion vs. values at the end of treatment). For each laboratory parameter, the observed values were coded as: below normal, normal and above normal based on the normal ranges redefined in the case report forms. The within-group evolution of each parameter was assessed using McNemar's Chi-Square t-test. Between group comparison of changes in laboratory parameters were performed using Student's t-test.

Statistical analyses were carried out using the SAS® software package, version 6.08.

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### 6.3 Study Report

#### 6.3.1 Distribution of Patients

Five hundred thirty-two (532) consecutive patients of both sexes, aged more than 45 years, body weight between \_\_\_\_\_ kilograms, having undergone 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 DVT as assessed by an initial bilateral ascending contrast venography of the lower extremities performed within the 5 days preceding randomization were screened for inclusion/exclusion criteria. Three hundred and fifty-three (353) were ineligible mostly because of refusal to sign an informed consent (165, 47%), inadequate body weight (43, 12%), DVT detected by inclusion venography (13%, or 33 of 253 patients who have undergone adequate initial venography), and medical need for long-term treatment with antiplatelet agents or oral anticoagulants (29, 8.2%). Other reasons for non-inclusion of screened patients are presented on Table 2 (Vol.2, p.8-1-73).

Comment: N.B. 13% patients who were on adequate prophylaxis during the first part of this study, have shown a "study efficacy failure" outcome.

One hundred seventy-nine (179) were selected for inclusion in the double-blind phase of the study. They were considered in the ITT analysis of efficacy and analysis of safety. All 179 selected patients were randomized, 90 in the enoxaparin and 89 in the placebo group. They all received at least one dose of the study drug and were considered in the ITT analysis of primary efficacy and in the analysis of safety.

During the study, 24 patients (15 in the enoxaparin, and 9 in the placebo group) failed to satisfy one or more criteria and they were not included in ITT secondary efficacy, and/or per-protocol analysis (Table 6-2: Disposition of patients).

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Table 6-2

## DISPOSITION OF PATIENTS

PATIENTS	ENOXAPARIN		PLACEBO		OVERALL	
	N	%	N	%	N	%
Pre-selected	-	-	-	-	532	100
Randomized	90	50.3	89	49.7	179	100
Evaluable for safety	90	50.3	89	49.7	179	100
Evaluable for primary efficacy criteria (ITT)	90	50.3	89	49.7	179	100
Evaluable for secondary efficacy criteria (ITT)	85	49.1	88	50.9	173	100
Evaluable for efficacy (per-protocol) Completed-evaluable	75	48.4	80	51.6	155	100

From Vol.2 p.8-1-80

One hundred fifty-five patients (E=75/P=80) or 86.6% of randomized, were evaluable in the per-protocol analysis of efficacy. They constitute the group of evaluable patients who were included into the study and have completed it in full compliance with the protocol.

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Different reasons for non-compliance of other patients were:

- Violation of the study protocol - Violation of study criteria and inadequate study treatment compliance such as: inadequate body weight (E=2/P=0), hemostatic abnormality at inclusion (E=1/P=0), presence of DVT at inclusion (E=1/P=1), heparin treatment other than enoxaparin before inclusion (E=2/P=0), incomplete treatment (E=1/P=3), no or incomplete venography at inclusion (E=1/P=1). Data extracted from Vol. 1, p.8-1-75.
- Violation of time elapsed between initial venography and actual inclusion (total 8; E=6/P=2), or time elapsed between final venography and last study drug administration (total 4; E=1/P=3),
- Premature study treatment discontinuation - withdrawal. Three patients (E=2/P=1) discontinued the study prematurely (Table 6-3: Description of patients with premature treatment discontinuation).

Table 6-3

PATIENTS WITH PREMATURE TREATMENT DISCONTINUATION

PATIENT(n), GROUP	DAY OF DISCONTINUATION	REASON	SEVERITY	DRUG RELATION
13 ENOX	19	Pain in the lower extremities following drug injection	severe	possible
232 ENOX	8	Physician's decision (study dangerous)	?	?
63 PLACEBO	3	Angina-type chest pain	severe	possible

From Table 7(Vol.2, p.8-1-78)

Population Characteristics

Between-group comparison as regards patient characteristics were performed considering both patients evaluable for the ITT analysis (179 patients) and for per-protocol analysis of efficacy (155 patients). Overall, the 2 treatment groups did not differ in baseline characteristics whatever the study population considered.

Demographic Data

Table 6-4

PATIENTS DEMOGRAPHIC CHARACTERISTICS. INTENT-TO-TREAT POPULATION

GENDER	PARAMETER	ENOXAPARIN		PLACEBO		OVERALL		P= VALUE
		N	%	N	%	N	%	
TOTAL	N/%	90	100%	89	100%	179	100%	.196
MALE	N/%	47	52.2	55	61.8	102		
FEMALE	N/%	43	47.8	34	38.2	77		
AGE	Mean±SD	70.66	9.08	68.25	8.21	69.46	8.72	.653
	RANGE							
HEIGHT (cm)	Mean±SD	1.64	0.086	1.64	0.072	1.64	0.079	.585
	RANGE							
WEIGHT (kg)	Mean±SD	68.66	11.09	70.06	11.73	69.35	11.04	.412
	RANGE							
BMI (kg/m <sup>2</sup> )	Mean±SD	25.55	3.189	25.85	3.490	25.70	3.336	.552
	RANGE							

From table 10 and 11 (Vol.2, pp. 8-1-81/82)

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## Prior Medical History

Overall, the prevalence of prior medical history for various body systems was similar in both treatment groups, and typical of a middle-age to elderly patient population. Hypertension (45%), GI (35%) and metabolic/endocrine disorders (mostly diabetes mellitus) were leading diagnosis recorded in the case report forms (Table 6-5: Distribution of patients with prior medical history). All other diagnosis were less frequent. There was no significant difference between treatment groups in any category or diagnosis.

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Table 6-5

DISTRIBUTION OF PATIENTS WITH PRIOR MEDICAL HISTORY

CATEGORY	DIAGNOSIS	ENOXAPARIN	PLACEBO	OVERALL	P=VALUE
ITT PATIENTS	TOTAL NUMBER	90	89	179	
VTE	DVT	1	1	2	1.00
	DVT sequelae	0	0	0	NA
	Recurrent DVT	0	0	0	NA
	PE	1	0	1	1.00
	Phlebitis superficialis	3	3	6	1.00
CARDIOVASCULAR	MI	2	0	2	.497
	Angina pectoris	9	9	18 (10%)	.980
	Valvular disease	4	1	5	.368
	Hypertension	39	41	80 (45%)	.713
	Rhythm disorders	8	2	10	.100
RESPIRATORY DISORDERS	Chronic respiratory insufficiency	11	7	18 (10%)	.332
	Asthma	7	1	8	.064

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OTHER MEDICAL	GI	29	33	62 (35%)	.495
	Renal	11	8	19 (11%)	.499
	Metabolic/endocrine	15	19	34 (19%)	.425
	Autoimmune	1	0	1	1.000
	Hematological	5	5	10	1.000
	Seizure	2	1	3	1.000
	Paralysis of legs	1	0	1	1.000
	Neoplasia	2	2	4	1.000

From Table 12-15 (Vol.2, pp.8-1-82/87)

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### Physical Examination

Physical examination considered an assessment of general condition, obesity, hypertension, varicose veins, leg ulcers, operative wound hematoma, and other abnormalities. Obesity was identified in 52 (29.1%) patients, significantly more in patients on placebo group (32 vs. 20 in enoxaparin group) ( $P=0.043$ ). Hypertension was the most frequent finding (40.8%), but it was distributed almost equally between two groups ( $P=0.928$ ). Other parameters were distributed similarly.  $P$ -values were in the range of 0.156 (other abnormalities) to 0.621 (wound hematoma). The details of physical examination characteristics are provided in Table 16 (Vol.2, p 8-1-89) table POPDESC-4, Appendix III, and data listings INDIV-4, Appendix IV.

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### Laboratory tests

The two treatment groups were comparable with regards to hematological parameters. Mean values of hemoglobin and platelet count are reported in section "General safety: laboratory parameters".

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### Surgery

Surgery was assessed as Type of Hip Disease, Surgical Procedure, type of Anesthesia, Type of Revision Surgery, Type of Anesthesia and Intraoperative Complications, and the Duration of the Surgical Procedure (Table 6-6: Distribution of patients with regard to Surgery).

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Table 6-6

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

CATEGORY	SUBCATEGORY	ENOXAPARIN	PLACEBO	OVERAL	P=VALUE
HIP DISEASE	PATIENTS	80	81	161	.250
	Osteoarthritis	79	80	159	
	Rheumatoid arthritis	0	1	1	
	Congenital dislocation	1	0	1	
	Unknown	10	8	18 (10%)	
SURGICAL INTERVENTION	Total	90	89	179	.741
	Anterior	5	6	11	
	Posterior	85	83	168	
	Prosthesis	6	3	9	.144
	Acetabular	2	0	2	
	Femoral	82	86	168	
	Both				
	Cemented prosthesis	88	88	176	1.000
REVISION SURGERY	Femoral	2	2	4	.383
	Acetabular	8	3	11	
	Both	2	4	6	
ANESTHESIA	General	52	52	104	.930
	Local	38	37	75	
INTRAOP. COMPLICATIONS	YES	0	0	0	NA
DURATION OF SURGERY (hours)	Mean ± SD Range	2.13 ± 0.327	2.06 ± 0.324	2.08 ± 0.325	.539

From Table 17-21 (Vol.2, pp 8-1-90/93)

The type of hip disease was not classified in 10% of patients (E=11.%/P=9.8%). It could not have had impact to study groups.

## Blood loss before randomization

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Since normal hemoglobin and hematocrit were not considered as inclusion criteria, the pre-study blood loss (peri- and post-operatively) might have had impact on safety and efficacy results during the study. This problem was properly addressed.

Intraoperative blood loss was measured by weighing compresses (g). Postoperative wound drainage was measured in mL (after 24h, between 24 and 48, 48 and 72, and total wound drainage). Number

characteristics, the sponsor decided to present them separately. The review will follow this orientation.

Intent-to-treat analysis of efficacy

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Table 6-7

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

CATEGORY			ENOXAPARIN		PLACEBO		OVERALL		P=VALUE
			N	%	N	%	N	%	
FAILURE <sup>a</sup>		T	90	100	89	100	179	100	.008*
		No	84	93.3	71	79.8	155	86.59	
		Yes	6	6.7*	18	20.2*	24	13.4	
DVT <sup>b</sup>	Total	T	85	100	88	100	173	100	.018*
		Yes	6	7.1*	17	19.3*	23	13.3	
	Proxi mal	T	85	100	88	100	173	100	0.592
		Yes	5	5.9	7	8	12	6.9	
	Distal	T	85	100	88	100	173	100	.006*
		Yes	1	1.2*	10	11.4*	11	6.4	

From Table 25-27 (Vol.2, p.8-1-98/105)

<sup>a</sup> Primary efficacy variable; <sup>b</sup> Secondary efficacy variable; \* Significant difference between enoxaparin and placebo treated groups

Comment: Enoxaparin was significantly better than placebo in prevention of "treatment failure", but this "failure" was due to a difference in distal venous thrombosis category only. The difference between two groups in proximal vein category was not significant. Since proximal vein thrombosis are considered to be related more than distal veins, to development of massive PE, it is not clear, whether this study can provide efficacy data to be regarded as pivotal for the purpose of this submission.

Per-protocol analysis of efficacy

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of red blood cell units transfused (intra-, post-operatively and total) was another measuring parameter (Table 22, Vol. 2, p 8-1-94).

Comment: These parameters were not equally distributed within treatment groups. Thus, wound drainage and total number of packed RBC units were significantly greater in enoxaparin group than in placebo. However, one may assume that increased blood loss was compensated with transfusion because, at inclusion, there was no significant difference between hemoglobin content in patients distributed in two treatment groups.

Two treatment groups were comparable with regards to the number of days of daily administration of enoxaparin before randomization (Table 23, Vol. 2, p.8-1-95), number of study treatment injections (Table 24, Vol. 2, p.8-1-96), and the concomitant venous prophylaxis with elastic bandaging or stockings. A summary of concomitant therapy is provided in Table POPDESC-8, Appendix III, and details are given in data listings INDIV-13, INDIV-17, Appendix IV.

Comment: According to data presented, the two treatment groups did not differ significantly in baseline characteristics (demographics, medical and surgical history, physical examination, surgical procedure, duration of pre-randomization and study treatment, or concomitant therapy) and the results of efficacy and safety assessment should not be influenced by baseline confounding variables (at least those that are discussed)

6.3.2 Efficacy Results

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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 including a venography confirmed DVT, a lung scan confirmed PE, and autopsy confirmed death by thromboembolism. No deaths or PE occurred in this study. Also, there was no symptomatic DVT prior to venography performed per protocol on day 21.

Comment: This approach taken by the sponsor, allows analysis of "treatment failure" to be made only on the incidence of "silent" DVT that occurred between hospital discharge and day 21, end of study, in both placebo and enoxaparin group.

Efficacy was analyzed in two populations: intent-to-treat (179 patients), and per-protocol (155 evaluable patients). Although both populations were similar with regard to baseline

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Table 6-8

INCIDENCE OF DVT AS TREATMENT FAILURE IN PER-PROTOCOL POPULATION								
CATEGORY		ENOXAPARIN		PLACEBO		OVERALL		P=VALUE
		N	%	N	%	N	%	
FAILURE <sup>a</sup>	T	75	100	80	100	155	100	.001*
	No	73	97.3	64	80.0	137	88.38	
	Yes	2	2.7*	16	20.0*	18	11.6	
DVT <sup>b</sup>	T	75	100	80	100	155	100	.001*
	Yes	2	2.7*	16	20.0*	18	11.6	
Proximal DVT	T	75	100	80	100	155	100	.064
	Yes	1	1.3	7	8.8	8	5.2	
Distal DVT	T	75	100	80	100	155	100	.018*
	Yes	1	1.3*	9	11.3*	10	6.5	

From Table 32-34 (Vol.2, p.8-1-106/109)

<sup>a</sup> Primary efficacy variable; <sup>b</sup> Secondary efficacy variable; \* Significant difference between enoxaparin and placebo treated groups

Again, in per-protocol population, enoxaparin was significantly better than placebo in preventing DVT, and this effect was due to the significant difference in distal vein thrombosis incidence between the two treatment groups.

Some discrepancy was found on day 21 between patients complain, venography reading by investigator and radiologist. A thorough evaluation followed and the concensus data are presented on tables. More information can be found in Section 6.2.1.2.2 page 8-1-101/102.

*Study Discontinuation*

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Table 6-9

PATIENTS WHO DISCONTINUED STUDY TREATMENT							
CATEGORY		ENOXAPARIN		PLACEBO		OVERALL	
		N	%	N	%	N	%
ITT population	T	90	100	89	100	179	100
	Yes	2	2.2	1	1.1	3	1.7
Per-protocol analysis	T	75	100	80	100	155	100
	Yes	1	1.3	0	0.0	1	0.6

From Table 31 and 35(Vol.2, pp8-105 and 110)

Reason for discontinuation was an adverse event for two patients (#13-E=1/#63-P=1), and physician's decision "study dangerous" without more detailed explanation (#232). Both adverse events were considered to be non-related to study drug. Patient #13 had pain in lower extremities after enoxaparin injection (?), and patient #63 had an angina-type chest pain.

*Three months follow-up*

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A 73-year-old woman (pt#...), two months after a negative second venography, presented with symptomatic and venographically confirmed billateral DVT and a documented asymptomatic pulmonary embolism. No other thromboembolic events were noted. According to the sponsor, this event may be related to the second venography (?).

Sponsor's conclusion on efficacy: "Results of the intent-to-treat and per-protocol analyses of the primary efficacy criterion were consistent and showed that enoxaparin was more effective than placebo in preventing late-occurring deep venous thrombosis after total hip replacement when administered 40 mg subcutaneously, once daily, on an out-patient basis from week 2 to week 5 after surgery."

Comment: Study data do not provide basis for such an extrapolation in the sponsor's conclusion. The sample size in this study was too small to present PE and deaths related to thromboembolism. Only DVT were recorded. Incidence of proximal DVT in both treatment groups was not significantly different. Only significant difference between groups was found in the incidence of distal DVT. Extrapolation beyond this fact is not based on data in this study.

### 6.3.3 Safety Results

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ON ORIGINAL

Safety results are reported for the intent-to-treat population of 179 patients (E=90/P=89) who received at least one dose of the double-blind medication. Endpoints for assessment of safety were: deaths, premature discontinuation of study because of treatment related events, hemorrhage (major and minor), adverse events other than thrombosis and hemorrhage, and change of laboratory parameters. An overview of safety results is presented on table 6-10.

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ON ORIGINAL

Table 6-10

## SAFETY RESULTS. INTENT-TO-TREAT POPULATION.

EVENT	CLASS	ENOXAPARIN	PLACEBO	OVERALL
DEATH	-	0	0	0
DISCONTINUATION		0(2)*	0(1)*	0(3)*
BLEEDING	TOTAL	17	4	21
	MAJOR	0	0	0
	MINOR	17	4	21
	- local	15	4	19
	- general	2	0	2
ADVERSE EVENTS	-	6	9	15
Hgb (g/dL) Mean ± SD	Before randomization	10.5 ± 1.0	10.4 ± 1.0	-
	On day 21±2	11.8 ± 1.0	11.7 ± 1.0	-
Platelet count (10 <sup>6</sup> /mL) Mean ± SD	Before randomization	475 ± 141	484 ± 127	-
	On day 21±2	281 ± 73	288 ± 77	-

From table 36 (Vol.2, p.8-1-112) and data from section 7.3.6 (Vol.2, p. 8-1-118). \* Events classified by investigators. Classification rejected by the sponsor.

## Deaths

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ON ORIGINAL

No patients died during the study period, and the three-month follow-up.

## Premature study treatment discontinuation due to adverse events

Three patients were discontinued from study because of adverse events by the judgement of investigator. However, the sponsor did not accept this judgement because of the following:

- Patient #13 (enoxaparin) was declared undergoing premature discontinuation (pain in lower extremities after enoxaparin injection) on day 19 when he received more than 80% of medication.
- Patient #63 (placebo) discontinued study after only 3 doses of study medication because of angina-type chest pain.
- Patient #68 (enoxaparin) underwent only temporary discontinuation (wound hematoma) and received more than 80% of the scheduled treatment.

## Hemorrhage

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ON ORIGINAL

No major hemorrhage was reported.

Twenty-one out of 179 patients (11.7%) experienced a bleeding complication observed as minor. The distribution of hemorrhage sites is summarized on table 6-11.

Table 6-11

APPEARS THIS WAY  
ON ORIGINAL

DISTRIBUTION OF HEMORRHAGE SITES

HEMORRHAGE SITE	ENOXAPARIN		PLACEBO		OVERALL	
	N	%	N	%	N	%
Epistaxis	1	5.9	0	0.0	1	4.8
Hematemesis	1	5.9	0	0.0	1	4.8
Wound hematoma	1	5.9	1	25	2	9.5
Injection- site hematoma	14	82.4	4	75	17	81.0
Total	17	-	4	-	21	-

From Statistical report (Vol.3,p. 8-2-159)

Patient #25 experienced one episode of epistaxis after 13 doses of study drug. This hemorrhage was minor and did not result in study discontinuation or rehospitalization.

Patient #53 was rehospitalized for 1 episode of hematemesis (100 mL) after 14 doses of the study medication. Esophagitis and active gastric ulcer were found on endoscopy. It was considered as a serious adverse event, but did not cause study discontinuation.

Wound hematoma appeared in patients #68 (enoxaparin) and #271 (placebo). Both episodes were mild and did not cause surgery or rehospitalization. Study drug was temporarily discontinued for patient #68 (see above). Both patients completed the study.

The incidence of hemorrhages (including hematoma at injection site) was significantly higher in enoxaparin group ( $p=0.003$ ). The corresponding odds ratio was 4.95. The two-tailed 95% confidence interval was 1.59 - 15.4.

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ON ORIGINAL