There was no significant influence of the risk factors studied to the distribution of VTE in treatment groups.

Rehospitalization, treatment and duration

Fifty-one patients required additional treatment or rehospitalization. Forty-five of them were found to have positive VTE outcome (E=10/P=35). They were treated with heparin for 5.8 (mean duration) days (E=5.9/P=5.8), and/or warfarin for 73 days (E=57/P=79). Mean hospital stay was significantly shorter in the enoxaparin group (E=mean 99 days for 11 patients/P= mean 269 days for 32 patients).

Comment: It is an important observation indicating that clinical oucome of DVT may be better if patients had have received prophylactic treatment, as it is proposed in ths Supplement.

7.7.3 *Safety Analysis*

In this study the safety analysis referred to intent-to-treat population (262 patients) and included DVT and hemorrhage as adverse events. Some analyses were done on all-enrolled (pre-randomization) population (total of 288 patients), simply because all these patients have recieved at least one dose of enoxaparin during the open-label period of the study.

Patients exposure to study medication was slightly different than planned (Table 7-8).

Table 7-8

ENOXAPARIN EXPOSURE AND COMPLIANCE DURING TWO PHASE OF THE STUDY PK-537

PHASE	CATEGORY	PARAMETER	ENOXAPARIN	PLACEBO	OVERALL
OPEN-LABEL	Time from preoperative dose to surgery	(hrs) mean range	12.5	12.8	12.7
	Time from surgery to postoperative dose	(hrs) mean range	8.0	7.8	7.9
	Treatment duration	(days) mean range	9.7	10.1	9.9
	Compliance	(%) mean range	100.0	100.1	100.0
DOUBLE-BLIND	Treatment duration	(days) mean range	18.6	18.1	18.3
	Compliance*	(%) mean range	100.0	100.0	100.0

From Table 17 (Vol.9, p.8-8-62);
*= (number of doses administered/number of days exposed) x 100

Time from the pre-operative dose to surgery and from surgery to the post-operative dose was at average within the range of 24 hours what as it was planned. However, few patients waited for surgery more than 24h, and few have received the 2d dose of study medication more than 24h after surgery.

Treatment duration was longer than planned in the open-label period(mean 9.9 *vs* 7±2), and shorter than planned in the double-blind period (18.3 *vs*. 21±2).

These discrepances with the study Protocol were equally distributed within treatment groups.

Deaths

There was no death among the patients who had been randomly assigned to double-blind treatment. In the pre-randomization, hospital period, two patients died after starting enoxaparin therapy. For more information see above.

Discontinuation

Table 7-9

SUMMARY OF PATIENTS WHO DISCONTINUED STUDY

EVENT	CLASSIFICATION	OPEN-LABEL	DOUBLE-BLIND		OVERALL
			ENOXAPARIN	PLACEBO	
DISCONTINUATION		26	15	22	37/262 14% 63/288 22%
DEATH		2	-	-	2/288 <1%
ADVERSE EVENT	Total	9	3	12	24/288 8% 15/262 6%
	DVT + PE	4 (1PE)	3	10 (2PE)	17/288 6% 13/262 5%
	PE	1	-	2	3/288 2/262 -
	Major hemorrhage	1	-	-	1/288 0/262
	Other	4	-	2	6/288 2% 2/262
CONSENT WITHDRAWAL		8	10	5	23/288 8% 15/262 6%
PROTOCOL VIOLATION	Non-compliance	6	1	1	7/288 2% 2/262 <1%
	Venography not performed	-	1	4	5/262 2%
OTHER		1	-	-	1/288

From table 18 (Vol.9, pp.8-8-64/65)

Adverse Experiences

In this study, the two primary study outcomes DVT for efficacy and hemorrhage for safety, were also included in reports on adverse experiences.

During the analysis, the sponsor recognized that there was no uniformity in event classification and allocation. Therefore, for decision on outcomes the sponsor used the suggestion by an adjudication committee, and for classification of adverse events, priority was given to invistigator's assessment. Due to this intervention, number of DVT and hemorrhagic events, presented as study outcomes and as adverse events, differ in this report.

The title Adverse Experiences includes: Overview (discussing hemorrhage as primary outcome for safety), Deaths and Discontinuations, Analysis of all adverse events by severity and incidence (hemorrhagic episodes: peri- and post-operative), Incidence of adverse events as secondary safety analysis, Incidence of serious adverse events, and Listing of patients with VTE using COSTART terms.

Primary Safety Analyses: Hemorrhagic Episodes

Hemorrhagic episodes were reported as perioperative, postoperative and during the double-blind period. The table 7-10 presents these data in extension.

Table 7-10

DISTRIBUTION OF HEMORRHAGES BY PHASE OF STUDY, SEVERITY, LOCATION, AND RELATION TO SURGERY

CATEGORY	ENOXAPARIN			PLACEBO			OVERALL		
Patients with:	open N=288	double N=131	total N=288	open[a] N=288	double N=131	total N=288	open N=288	double N=262	total N=288
Any bleeding	16	8	24	14	3	17	30	11	41
Major bleding	2	0	2	1	0	1	3	0	3
Non-operative site	1	7	8	1	3	4	2	10	12
Operative site	14	1	15	13	0	13	27	1	28
Perioperative bleeding	3	-	3	2	-	2	7*	-	7
Postoperative bleeding	10	-	10	10	-	10	22*	-	22

*= Non-randomized patient included. [a]= Patients received enoxaparin and were randomized into placebo group
From table 19, 20,21 and 22 (Vol.9, pp.8-8-66/69)

A total of 41 hemorrhagic episodes (14%, 41/288) were reported by all-treated patient during a period of 35 days of study. Only 3 episodes were considered major hemorrhage resulting in study discontinuation. Twenty-eight of them occurred at the operative site (68%, 28/41), almost all developed postoperatively (79%,22/28). Twelve episodes (29%, 12/41) occurred at non-operative site (almost all at injection site). Ten of them (83%, 10/12) developed during the double-blind period. Both peri- and post-operative bleeding was equally distributed between treatment groups, due to the unique treatment during the open-label phase (all patients received enoxaparin).

The sponsor has underlined the following conclusion: "Eleven (4.2%) of 262 randomized patients experienced at least one hemorrhagic episode during the double-blind period, three (2.4%) patients in the placebo group, eight (6.1%) patients in the enoxaparin group. This difference was not statistically significant (p=0.217). No major hemorrhagic episodes occurred during this period."

Comment: There was a clinically clear difference between two groups with respect to minor hemorrhages occurring during the double-blind phase. Most of them were injection site hematomas. Patients receiving enoxaparin developed twice the number of hematoma than patients receiving saline injection. However, the sponsor did not find that this difference was significant (ed. Probably the injection technique had some influence on the frequency of hematoma in placebo group).

Secondary Safety Analyses: Incidence of Adverse Events

Incidence of adverse events was reported using COSTART system. However, according to the sponsor, listings of adverse events are insufficient because COSTART terms were not consistently recorded by investigators, and minor hemorrhages were not reported consistently as adverse events. There was no investigators' compliance with sponsor's instructions (Comment made by the sponsor: Vol.9, p.8-8-69).

Results of investigators' assessment of adverse events are summarized on table 23 "Incidence of adverse events by body system regardless of relationship to study drug for all treated patients", table 24 "The incidence of adverse events reported by greater than two percent of patients in either treatment group regardless of relationship to study drug for all-treated patients", table 25 "Summary of adverse event related to study drug with a frequency of greater than one percent in either treatment group by body system and intensity for all-treated patients",

Serious adverse events were analyzed separately. They are summarized on table 26 "Listing of patients with serious adverse events, excluding patients with VTE, as the only serious adverse event." Serious adverse events were assessed for intensity (mild, moderate and severe) and relation to the study drug (none, remote, possible and probable). During the double-blind period,

49 patients (18.7%) reported serious adverse events, 38 in the placebo and 11 in the enoxaparin group. Of these 49 patients, 45 reported VTE (COSTART terms: thrombophlebitis, deep thrombosis, pulmonary embolus), 34 in the placebo and 11 in the enoxaparin group. Thirty-nine patients (31 placebo, 8 enoxaparin) reported VTE as the only serious adverse event. The remaining five patients reported a total of 9 serious adverse events. They all were in the placebo group. None of these adverse events was considered related to study medication by the investigator.

A listing of patients with VTE as serious adverse event is provided.

Comment: The information provided in this Section is questinable due to sponsor's doubts in data reliability (*vide supra*).

Clinical Laboratory Evaluations

a. Platelet Count

Thrombocytopenia was found in one patient on enoxaparin during the double-blind period (pt#...). It was mild and resolved without discontinuation of study medication.

Thrombocytosis (defined as greater than $400*10^9/L$) occurred in a total of 85 patients (Table 7-11)

Table 7-11

PLATELET COUNT AT BASELINE AND CHANGES DURING STUDY

STUDY PERIOD	DIAGNOSIS	CLASSIFICATION	ENOXAPARIN	PLACEBO	OVERALL
BASELINE	Thrombocytopenia	Mild	1	1	2
	Thrombocytosis	Mild	0	4	4
OPEN-LABEL*	Thrombocytopenia		0	0	0
	Thrombocytosis	Mild	36	48	84
		Moderate	0	1	1
DOUBLE-BLIND	Thrombocytopenia		0	0	0
	Thrombocytosis	Mild	77	64	141
		Moderate	39	42	81

From table 28 (Vol.9, p.8-8-83)
* Values are allocated to treatment groups after randomization

Thrombocytosis that was observed at the end of the open-label period and was returned to normal during the double-blind period, was referred by the sponsor to "reactive thrombocytosis after hip operation".

Comment: This explanation does not seem to be sufficient, and needs more supportive evidence. However, patients with thrombocytosis were equally distributed between treatment groups.

Hemoglobin changes were related to operation and blood replacement. Only 6 patients were reported to have decrease of >20 g/L (4 in placebo, and 2 in-the enoxaparin group).

Changes of Biochemistry parameters were minor, except for aminotransferase activity during the open-label period. SGOT was increased in 26 patients (10.2%, E=15/P=11), but was normalized during the next period of study. SGPT was increased in 6 patients (2.4%, E=5/P=1) and returned to normal in the double-blind period.

Comment: In summary, no substantial difference between treatment groups was observed for the incidence of shifts in laboratory parameters from within to outside the normal range during either of the study periods, except for platelets (see above) and hemoglobin (shift from below normal at the end of open-label period, to normal at the end of double-blind period).

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C. REVIEW SUMMARY AND CONCLUSIONS

8.0 INTEGRATED SUMMARY OF TWO PIVOTAL STUDIES

8.1 Summary of Study Reports

The sponsor has submitted two independent studies, ENOX 491001 (single center, France) and PK-537(single center, Sweden), to support a new indication for Lovenox® injection. This indication includes a new dose (40 mg/0.4 mL) and new duration (21 days) "after hospital discharge for long term prevention of DVT following hip replacement surgery."(Citation from Labeling Annotated, Vol.1, p.2-1-5)

The two studies had a similar design and their own specificities (Table 8-1).

Table 8-1

TWO PIVOTAL STUDIES FOR EXTENDED LOVENOX PROPHYLAXIS OF DVT AFTER HOSPITAL DISCHARGE FOLLOWING HIP REPLACEMENT SURGERY

TABLE OF CONTROLLED CLINICAL TRIALS		
Protocol No. Investigator Publications	ENOX 491001 Planes,A.,La Roshelle, France single-center No publications	PK-537 Bergquist, Malmo, Sweden single-center No publications
Completion status	June 28,1994 November 22, 1995	March 20, 1995
Study design	Double-blind, randomized, parallel groups following an open-label phase	Double-blind, randomized, parallel groups following an open-label phase
Treatment, doses	Open-label period: enoxaparin 40 mg/0.4 ml qd (all patients). Double blind period: enoxaparin 40 mg/0.4 ml, or Placebo 0.4 ml, od.	Open-label period: enoxaparin 40 mg/0.4 ml qd (all patients). Double blind period: enoxaparin 40 mg/0.4 ml, or Placebo 0.4 ml, od.
a) Number entered open-label period b) number entered double-blind period c) enoxaparin (ITT/EVA) d) placebo (ITT/EVA)	a) 253 b) 179 (evaluable: 155) c) 90 (75) d) 89 (80)	a) 288 b) 262 (evaluable: 233) c) 131 (111) d) 131 (112)

Duration of drug treatment a) open-label b) double-blind	a) 14±1 b) 21±2	a) 9±3 b) 21±2
Efficacy Outcome	Incidence of VTE(DVT) between two phlebographies (end of phase I and phase II)	Incidence of VTE(DVT) at the end phase II
FAIL (DVT+PE) phase II a) placebo b) enoxaparin	a) 20(22.5%) b) 6(6.7%) P<0.05	a) 45(34%) b) 21(16%) P<0.05

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ENOX 491001

In ENOX, first, 253 eligible patients who underwent elective hip surgery received 14-days in-hospital prophylaxis with 40mg enoxaparin. This phase was open-label, single active treatment group, no control was included. At the end of this period, a mandatory bilateral ascending contrast phlebography was performed to exclude patients with DVT. There were 33 patients (13.0%) with asymptomatic DVT. They received intensive DVT treatment. Patients who were DVT negative (documented by phlebography), and who met other criteria were included into the second (double-blind) phase. According to the sponsor, "other criteria" involved patients at age above 45 years, both sexes, body weight between kg, completed hip replacement surgery, and a perioperative Lovenox prophylaxis for 14 days (last injection within 24 hours). A total of 179 eligible patients were randomized into an enoxaparin (90 patients) and a placebo (89 patients) treatment group.

Patients who entered the double-blind phase had the following demographic characteristics: 179 patients, 102 male, 77 female, mean age 69±9 (range), mean height 1.64±0.08 m (range , mean weight 69.3±11.4 kg (range). They were randomized (enoxaparin 90, placebo 89) and the two treatment groups did not differ in baseline characteristics. All randomized patients received at least one dose of study medication and were evaluable for safety (179), and for primary efficacy criteria (intent-to-treat, 179). At the end of tihs period there were 155 patients (enoxaparin 75, placebo 80) evaluable for the efficacy analyses (per protocol/completed)were.

PK-537

In PK 537, first 288 eligible patients who underwent elective hip surgery received about 10 days in-hospital prophylaxis with 40mg enoxaparin daily. This phase was open-label, single active treatment group, no control was included. At the end of this period, investigators were to decide, based on clinical symptoms of DVT and/or PE (confirmed by venography if present) who of patients will be randomized for the second, an outpatient phase. There were 26 (9%) patients who discontinued study at this point. Two, of them died while on enoxaparin. One probably of MI (autopsy not performed), another probably of TIA complicated by MI (confirmed on autopsy). Both reasons were considered by the investigator as non related to the study medication. Four patients had DVT and one PE. They received intensive treatment. Nine patients withdrew their consent, and six did not comply with the protocol. Two hundred sixty-two patients (91%) qualified for the double-blind (outpatient) phase of the study. They were randomized into an active treatment group (enoxaparin, 131 patients), and a placebo control group (131 patients). The placebo group received 0.4 mL saline solution (NaCl 0.9%), sc, qd, for 21±2 days.

Patients who entered the double-blind period had the following demographic characteristics: number 262 (E=131/P=131), 113 male, 149 female; mean age 68 (range), with 67% (174 patients) over the age of 65; average height 169.8 cm (range ; average weight 77.5 kg (range); and BMI (body mass index) at average of 26.9 (range). The two treatment groups did not differ in the baseline characteristics. Separate analyses determined that the other possible confounding variables at the baseline, e.g., risk factors and surgery related factors (type of hip disease, operated extremity, anesthesia, duration of operation and blood loss), were also distributed almost equally between the two treatment groups. The within-group analyses did not show any significant difference.

All qualified patients (262) were randomized (enoxaparin 131, placebo 131). All randomized patients received at least one dose of study medication and were eligible for primary efficacy and safety analysis (intent-to-treat, 262). Thirty-nine patients