(E=20/P=19) were found as unevaluable at the end of the double-blind period. At the end of the study, the evaluable population (223) was equally distributed within the study groups (E=111/P=112).

8.2 Integrative Analysis of Efficacy

At present, Lovenox is approved for perioperative prophylaxis of DVT and PE (Europe: 40mg, to start h before surgery; USA: 30mg BID, to start h after surgery) in a period up to 14 days. Approval for post-hospital discharge prophylaxis was requested with this supplement. In both studies submitted to support this request, enoxaparin prevented occurrence of new DVT (during a period of 21 days post hospital discharge) better than placebo (Table 8-2a and 8-2).

8.2.1 Primary Efficacy Analysis

To demonstrate the success of both studies in achieving reduction of VTE the sponsor has submitted the following table (Table 8-2a)

Table 8-2a

DISTRIBUTION OF VENOUS THROMBOEMBOLIC DISEASE OUTCOME FOR ALL-TREATED PATIENT POPULATION

	ENOX		PK537		COMBINATION	
	Placebo	Enox	Placebo	Enox	Placebo	Enox
	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)
Patient	89(100)	90(100)	131(100)	131(100)	220(100)	221(100)
No VTE	71(80)	84(93)	86(66)	110(84)	157(71)	194(88)
DVT	18(20)*	6(6.7)*	43(33)*	21(16)*	61(28)	27(12)
PE	0(0)	0(0)	2(1.5)	0(0)	2(0.9)	0(0)
DVT+PE	18(20)	6(6.7)	45(34)	21(16)	63(29)	27(12)

From table 11 Vol. 1, p.2-1-195. * Sigmnificant defference

Comment: At randomization, the baseline difference between patient populations entering the double-blind period had affected the results of efficacy. Frequency of DVT in the PK-537 enoxaparin group (16%) was close to this in the placebo group of ENOX study (20%). The incidence of DVT in ENOX study appeared to be a half of the frequency in PK537 study. Data from both studies show that, at the end of the double-blind period (venographic assessment), enoxaparin was found better than the placebo in

preventing development of DVT. The relative difference (enoxaparin vs. placebo) was statistically significant granting the sponsor a permission to submit these two studies for review.

However, a more detailed analysis of primary efficacy endpoints and without summing data provides some different results and conclusions (Table 8-2).

Table 8-2

PRIMARY EFFICACY ANALYSIS. INTENT-TO-TREAT POPULATION

Study Period			ENOX		PK-537	
Open-label	Patients		253		288	
	Days with enoxaparin		14		10 (6-12)	
	Evaluation		Phlebography		Clinical signs for DVT	
	Dropouts n(%)		DVT	Other	DVT	Other
			33 (13.0%)	41 (16.2%)	4 (1.4%), 1PE	22 (7.6%)
Double-blind	Patients		179		262	
	Randomized Patients		Enoxaparin 90	Placebo 89	Enoxaparin 131	Placebo 131
	Days on study		21		21	
	Evaluation		Phlebography		Phlebography	
	DVT n(%)	Total	6 (6.7%)*	18 (20.2%)*	21 (16%)*	43 + 2PE (34.3%) *
		Proximal	5 (5.9%)	7 (8.0%)	8 (6.1%)*	28 (21.4%)*
		Distal	1 (1.2%)*	10 (11.4%)*	13 (9.9%)	15 (11.5%)
Duble-blind Conclusion	Difference between treatments, P=value		6.7% - 20.2% = -13.5%		16% - 34.3% = -18.3%	
			p=0.008*		p=0.001*	

From Table 18 (Vol.8; p.8-8-64), Table 6-7, and Table 7-6. * Significant difference between enoxaparin and placebo treated groups ($p<0.05$)

In ENOX, the overall treatment failure occurred in 24 of 179 patients (13.4%). Data show six DVT out of 90 patients (6/90 or 6.7%) in the enoxaparin, and 18/89 (20.2%) in the placebo group. This clinical difference was statistically significant (p=0.008). Treatment failure was presented only with DVT. There were no deaths or PE.

In PK 537, an overall treatment failure occurred in 66 of 262 patients(25.2%). Between-group analysis showed that patients

receiving enoxaparin did better than the placebo. VTE incidence in the enoxaparin group was 21/131 (16%) *versus* 45/131 (34.3%) in the placebo group. This difference was statistically significant (p=0.001; Odds' ratio was 2.74; The 95% confidence interval [1.51-4.94]). Treatment failure was presented by DVT. The only two PE were recorded in the placebo group.

Based on data from the primary efficacy analysis in the double-blind period (Table 8-2a) the sponsor concluded that *"enoxaparin 40mg was significantly more efficacious than placebo for preventing DVT during the double-blind phase of both pivotal studies."* There is no comment on the open-label phase of the study and the randomization procedure before the double-blind period. The sponsor did not comment on whether and how much the difference in randomization procedure (DVT negative patients were selected by two methods) has influenced the outcome, or the interpretation of the outcome in these two studies.

Therefore, this conclusion deserves few comments.

A. *Study Reproducibility*

The word reproducibility has been derived from the verb *to reproduce* meaning to produce a counterpart, a copy or a duplicate. In Live Sciences, this term has been used as a measure to estimate the probability of an instrument, assay or a drug, to produce similar results under identical conditions. In clinical trials, the reproducibility is usually interpreted as "more than one adequate and well-controlled study with similar results."

Both studies, ENOX and PK-537 are adequate and well controlled. In both studies the patient populations were comparable by main parameters at the beginning of the open-label period (hip replacement surgery, age, gender, previous medical history). In both studies, the enrolled patients underwent comparable, if not identical, peri-operative prophylaxis for DVT (enoxaparin 40mg, qd for 9 or 12 days), had identical extended prophylaxis (two groups to receive enoxaparin 40 mg or placebo qd, for 21 days) and, at the end of the double-blind period, had an identical primary efficacy endpoint (incidence of DVT assessed by an ascending bilateral phlebography). The null hypothesis was that there is no difference between enoxaparin and placebo treated groups in both studies. In both studies this hypothesis was rejected with a power sufficient to claim significant difference in favor of enoxaparin as a better drug than placebo for extended prophylaxis of DVT in patients who underwent hip replacement surgery and peri-operative prophylaxis with enoxaparin. However, the frequency of documented DVT in both, enoxaparin and placebo treated, populations in PK-537 was more than twice larger than in ENOX, respectively. This finding showed that a "systematic error" must have occurred in either of the two studies.

A consecutive analysis has shown that here, a "systematic error" was created by the randomization procedure performed before the double-blind period. It was substantially different between two studies.

In ENOX, patients at hospital discharge were examined by a bilateral ascending contrast venography. Only those who were negative for DVT (including clinically symptomatic and asymptomatic thrombosis) were randomized to the double-blind period. At the end of the double-blind period patients were again examined by a bilateral ascending contrast venography (study endpoint). Patients with documented DVT (phlebography) were considered as study "failures" in comparison with study "successes," patients with normal bilateral phlebograms at the end of the study. Thus, DVT detected in the period between two phlebographies became a true incidence (all new DVT appearing during a definite time) of this event.

In PK-537, patients at hospital discharge were examined for clinically symptomatic DVT only. Asymptomatic patients were randomized for the double-blind period. At the end of the double-blind period these patients were examined by a bilateral ascending contrast phlebography (first time). Again, patients with documented DVT (phlebography) were considered as study "failures" in comparison with study "successes," patients with normal bilateral phlebograms at the end of the study. However, a single phlebography performed at the end of the study has recorded all, new and old, DVT. Findings have shown DVT that might have been present before surgery, or have developed during either of the two study periods. Therefore, in PK-537, DVT present prevalence (total number of DVT [new and old] at a certain point of time) of this event in the population entered/completed the double-blind period.

It is known, from epidemiological studies that incidence and prevalence are two complementary parameters that cannot be compared directly or used interchangeably. Therefore, as the result of efficacy assessment, the study ENOX has produced an incidence of DVT, a parameter different from the prevalence that was produced in the PK-537 study. This is the explanation for the difference in absolute number of frequency of DVT in both studies, and for the unveiled "systematic error."

Can one consider ENOX and PK-537 as two reproducible studies in spite of this evident "systematic error" in measurement of the efficacy endpoint? For those who might be satisfied with demonstration of the tendency only, the answer coming from these studies is positive. A tendency of enoxaparin to protect patients from DVT better than the placebo can do, has been well documented. This is also in congruence with other studies (under the same NDA), and the suggested new Guidelines for Efficacy Measurement in supplemental applications for new indication.

However, if one wants more, e.g., accuracy of measurement, than the answer should be 'no' unless additional relevant information is provided. It was done by the statistical reviewer and this reviewer independently and in cooperation.

In his part of this analysis, the medical reviewer has evaluated data as there was only one phlebography at the end of the double-blind period (Table 8-3). Patients, who were excluded from the ENOX study after the open-label period because of DVT (13% of enrolled), were included in calculations of the study efficacy outcome. Three possible scenarios (best, worst, and common) were considered. The statistical reviewer has taken the same approach using another direction. He reduced double-blind phase VTE[DVT] in PK-537 by the percent (13%) taken from the ENOX study. (**See Statistical Report**). As a result, in both analyses, the two studies were shown to be comparable regarding the efficacy analysis, thus reproducibility was confirmed and approvability was conceived.

Table 8-3

PRIMARY EFFICACY ANALYSIS. PER-PROTOCOL POPULATION

Study Period			ENOX		PK-537	
Open-label	Patients		212		266	
	Days with enoxaparin		14		10 (6-12)	
	Evaluation		Phlebography		Clinical signs for DVT	
Double-blind "Common" Scenario	Randomized Patients		Enoxaparin 106	Placebo 106	Enoxaparin 133	Placebo 133
	Days on study		21		21	
	Evaluation		Phlebography		Phlebography	
	DVT	Total n(%)	23 (21.7%)*	35 (33%)*	23 (17.3%)*	45 + 2PE (33.8%) *
Double-blind "Worst" Scenario	Randomized Patients		Enoxaparin 123	Placebo 89	Enoxaparin 135	Placebo 131
	Days on study		21		21	
	DVT	Total n(%)	39 (31.7%)*	18 (20.2%)*	25 (18.5%)*	43 + 2PE (34.0%)*

* Significant difference between enoxaparin and placebo treated groups ($p<0.05$)

The "common scenario" calculations (Table 8-3) have shown that the per-protocol populations have responded to the extension of prophylaxis comparably to the response of the intent-to-treat population (Table 8-2). In both studies, the enoxaparin treated groups performed significantly better than the placebo. There was no major difference of the incidence of DVT in related treatment groups (enoxaparin or placebo) between ENOX and PK-537 studies. These data support conclusion on efficacy made above.

However, in the "worst possible" scenario calculations (Table 8-3), with all failures assigned to the enoxaparin group, data are opposite. In this setting, the worst performing group was the one in ENOX that was the best in the intent-to-treat population (Table 8-2). *This information indicates that venography may be thrombogenic; fewer invasive procedures should be considered for interim evaluation of DVT in patients undergoing extended enoxaparin prophylaxis.*

B. *One or Two Phase Prophylaxis*

Another question for consideration of efficacy is whether one may consider the double-blind phase independently from the open-label phase in these two studies? According to data presented in the supplement and summarized below, the double-blind phase efficacy was dependent upon the open-label phase procedures in both studies.

An early phlebography at the end of the open-label period in ENOX has excluded from randomization 13% of patients with "silent" DVT. This exclusion rate was almost 10 times larger than in PK-537 (only 1.4% patients with DVT assessed by clinical signs were excluded).

Patients with "silent" DVT entered the double-blind period in PK-537. Their number is not known. In the event that their percent was 13% (as in ENOX), this would have been presented at the end of the study, as 17 DVT positive patients.

Actually, after the double-blind period in the enoxaparin group of PK-537, there were 21 (16%) patients with DVT. The difference of 4 DVT (21-17=4) would be close to number of patients who developed new DVT at the end of the double-blind period. It would resemble the situation found in ENOX with six new DVT during this double-blind period.

An early discontinuation of enoxaparin prophylaxis (without prior selection of patients with DVT), resulted in a high incidence rate of DVT (34.3%) in PK-537 (placebo group). This incidence rate was larger almost twice than in the placebo (20.2%), and five times in the enoxaparin (6.7%) group of the ENOX study during the double-blind period.

This presentation of findings enlightens an implicit aspect of this supplement. Both studies were indeed similar, and the open-label period procedures (perioperative enoxaparin prophylaxis and phlebography prior to randomization) had an important impact to the outcome of the double-blind period. This effect should be considered whenever an extension of prophylaxis with enoxaparin is planned.

C. *What Type of Prophylaxis for the Perioperative Period*

The two studies in this supplement have used a European type prophylactic procedure: enoxaparin 40mg/qd, sc, for 10-14 days. Prophylaxis was planned to begin within 12 hours before surgery, and to end after the hospital discharge. In the U.S. the recommended dose of enoxaparin is 30mg/q12h, sc, for up to 14 days. Prophylactic dose in the U.S., to begin within 24 hours after surgery when hemostasis has been established. The main difference includes time when prophylaxis begins (before surgery vs. after surgery), daily dose (40mg vs. 60mg), and administration (full dose once daily vs. ½ dose q12h). The difference between two approaches is historical and based on the surgeon's preference rather than the scientific evidence. There have not been efforts to compare the efficacy/safety of these two procedures for enoxaparin prophylaxis in a single trial. On the other side, these procedures have been in practice for years, and both have been confirmed as effective and reasonably safe. *Can both approaches be recommended as equal to precede the extended prophylaxis soon after hospital discharge as suggested in this supplement*?

In a dose ranging study (NDA#20-164/S001; PK-526) the sponsor compared the safety and efficacy of enoxaparin 10mg/qd, 40mg/qd and 30mg/q12h. It was a phase III, multicenter, parallel group, randomized, double-blind clinical trial performed in the U.S. (1989-90, 572 patients). Prophylaxis started within two days after surgery and continued up to seven days after surgery. It was reviewed by DGCDP. The reviewing medical officer (L. Talarico, M.D.) found the comparable efficacy results between 40mg/qd and 30mg/q12h regimens. She recommended 30mg/q12h regimen and suggested that 40mg/qd "could represent an alternate regimen for patients in whom single daily injections are preferred. " The 30mg/q12h regimen was approved because, at this time, the sponsor had available only syringes pre-filled with 30mg/0.3mL enoxaparin (**See: M.O. Review NDA#20-164, p. 161**). Today, syringes pre-filled with enoxaparin 40mg/0.4mL are also available. Subsequently, it may be considered that, based on this study (PK-526), both regimens (30mg/q12h and 40mg/qd) are equivalent for patients undergoing hip replacement surgery.

In another study (NDA#20-164/S008; PK-567 and PK-568) the sponsor compared safety and efficacy of enoxaparin 40mg/qd versus heparin 5000 IU/t.i.d., sc in patients undergoing major abdominal surgery. The supplement included two pivotal and several supportive studies (other indications, same dose). The two pivotal studies were Phase III, multicenter, randomized, double-blind clinical trials including 2,643 patients. Prophylaxis began between 12 and 2 hours before surgery and continued for 6-12 days. The supplement was reviewed by DGCDP (M.O.: N. Markovic, M.D.) and was found to be *"approvable."*.

The Table 8-4 summarizes the primary efficacy and safety variables in those studies.

Table 8-4:

INCIDENCE OF PRIMARY STUDY OUTCOMES IN PATIENTS WHO STARTED ENOXAPARIN PROPHYLAXIS PRIOR OR AFTER SURGERY

Enoxaparin dose		Patients	Any hemorrhage	Major hemorrhage	VTE
PK-526*	40mg/qd	149	11%	4%	14%
	30mg/q12h	143	13%	5%	11%
PK-567@	40mg/qd	1115	17%	3.5%	10%
PK-568@	40mg/qd	1347	16.8%	3.6%	7.13%

* Prophylaxis begins within 24 hours after surgery. @ Prophylaxis begins within 12 hours prior to surgery.

It is difficult to compare patients on hip replacement surgery (PK-526) and those undergoing major abdominal surgery mostly for cancer (PK-567 all cancer patients, and PK-568 one-third cancer patients). Many unwanted confounding variables may be involved. Study duration may be accounted for the percent of "any" hemorrhage (PK-526 7 days/6-12 days in two other studies). However, the incidence of major hemorrhage seems to be equal. The incidence of VTE, study failures, is also comparable with data obtained in study ENOX (13%, *[vide supra]* table 8-2).

This summary on perioperative prophylaxis suggests a trend of "no difference" between orthopedic and abdominal patients at risk who underwent major surgery. The same trend can be seen between patients who have received the first prophylactic dose of enoxaparin 40mg/qd *prior to* or *within 24 hours after* surgery. This trend needs further confirmation. New studies are warranted.

8.2.2 Secondary criteria:

During the double-blind period in ENOX study, DVT was detected in 23/179 (13.3%) patients. In the enoxaparin group DVT was found in 6/85(7.1%), and in the placebo group in 17/88(19.3%). This difference was statistically significant. However, in the enoxaparin group 5/6 (83%) DVT were proximal, while 1/6 (17%) were distal DVT. This distribution was opposite in the placebo group: proximal 7/17 (41%), and 10/17(59%) distal. Statistically significant difference was only between distal DVT (p=0.008), and not between proximal DVT (p=0.592).

Per-protocol analysis of efficacy included 155 evaluable patients and has demonstrated comparable results.

During the corresponding period in PK-537 study, DVT was recorded in 64/262 patients (24.2%). Twenty-one out of 131, or 16.0% patients with DVT were found in the enoxaparin group, and 43/131 (32.8%) in the placebo group. This difference was statistically significant (p=0.001). However, in the enoxaparin group, eight (6.1) DVT were proximal, 13 (9.9%) distal. It was opposite in the placebo group, 28 (21.4) proximal, and 15 (11.5%) distal. Difference between distal DVT in two treatment groups was not significant.

The evaluable patient population included 111 patients in the enoxaparin, and 112 in the placebo group. The incidence of VTE in the evaluable placebo group was 45/112 (40%) and VTE in the evaluable enoxaparin group was 20/111 (18%), result comparable to intent-to-treat analysis.

A special attention was given to subgroup analyses and their influence to the analysis of treatment failure. It was found that, at the baseline and during the open-label period, both groups were well balanced. It includes the distribution of patients by age, sex, surgical diagnosis, operated extremity, and risk factors such as obesity, varicose veins, congestive heart failure, estrogen containing medications, and history of PE and/or phlebitis. The distribution of patients by site was also well balanced between treatment groups.

An additional analysis should be mentioned at this time. Fifty-one patients required treatment or rehospitalization. Forty-five of them had positive VTE outcome. Mean hospital stay was significantly lower for patients in the enoxaparin group (E=mean 99 days for 11 patients/ P= mean 269 days for 32 patients).

Secondary efficacy analyses were complementary to the primary efficay analysis.

8.2.3 *Conclusion on Efficacy*

1. Enoxaparin 40mg/qd was better than placebo for prophylaxis of late occurring DVT in patients who
- underwent hip replacement surgery,
- have received perioperative prophylaxis with enoxaparin, and
- at hospital discharge, were negative for DVT by any of the objective methods of assessment.

This **extension of prophylaxis** began within 24h of the last enoxaparin injection.

2. Clinical assessment of DVT at the end of perioperative prophylaxis was not sufficient. Bilateral ascending contrast phlebography is the best method available for detection of asymptomatic DVT, but may be thrombogenic. Ultrasound based methods may be acceptable (Need further studies).

3. **Extended prophylaxis** of DVT with enoxaparin 40mg/qd for up 35 days following hip replacement surgery was better than if the perioperative prophylaxis ended after 9 or 14 days. Drug administration began within 12h prior to surgery. Frequency of DVT in patients who received a continuous prophylaxis for days was significantly lower than in patients who received 21 days shorter prophylaxis (placebo group during the double-blind period)

4. All peripherative prophylactic regimens based on enoxaparin should be acceptable for introduction of patients into the 21-days outpatient extension of prophylaxis regimen. However, it is dependent upon an objective confirmation that no DVT is present at hospital discharge. Attempts to extend perioperative prophylaxis without objective assessment of DVT should be discouraged because it may delay treatment of clinically silent, but not less dangerous DVT.

   A single regimen (see #3), beginning before operation and ending five weeks after surgery, appears to be a preferable solution for prevention of DVT (early and late) in patients undergoing hip replacement surgery.

This conclusion on efficacy analysis is in support of the sponsor's request and has substantiated basis for another new indication for enoxaparin: extended prophylaxis in patients undergoing hip replacement surgery. It also suggests the necessity to investigate into DVT prophylactic procedures already approved and practiced in other surgeries with high risk for developing DVT.

8.3 Integrative Analysis of Safety

Safety data are presented in details and analyzed in the corresponding study (*vide supra*). Only risk/benefit assessment related information is presented here.

In ENOX no patient died in the study period. There was no major hemorrhage. Minor hemorrhages occurred in 21/179 (11.7%) patients. Seventeen hematomas appeared at the injection site (14 enoxaparin, 3 placebo group). This difference was statistically significant. None of the hemorrhages led to blood transfusion, surgery or premature study disconitunation.

Other adverse events (other than DVT or hemorrhage) were observed in 15/179(8.4%) patients. Six patients in the enoxaparin and nine in the placebo group presented with one adverse event (p=0.405). Two patients, each in another group,

presented with "severe" adverse events, one of them led to premature study discontinuation. Adverse event relationship to study treatment was considered as "possible" for one patient in enoxaparin group, and 2 patients in the placebo group.

General laboratory tests, observed along the study, did not show statistical differences between the two treatment groups regarding the longitudinal changes of the main laboratory parameters.

In PK-537 safety information comprised both study periods. No patient died during the double-blind period. Two patients died during the open-label phase. They are discussed earlier. Upon the investigator's assessment, these two deaths were not related to the study medication (enoxaparin). Two patients in the placebo group developed PE. They are included in the VTE efficacy analysis. A total of 63 patients discontinued the study. Twenty-six of them during the open label period (26/288, 9%), 37 during the double blind period (37/262, 14%). More in the placebo (22/131, 17%), than the enoxaparin (15/131, 11%) group. Most of the discontinuations were due to consent withdrawal (E=10/P=5) and to the adverse events as assessed by investigators (E=3/P=12).

A total of 41 hemorrhagic episodes (41/288, 14%) was reported by all-treated patients during the 35 days of this study. Only three episodes were considered major hemorrhage and resulted in the discontinuation. There was no major hemorrhage during the double-blind period. Eleven (4.2%) of 262 randomized patients experienced at least one hemorrhagic episode during this period (E=6|6.1%|/P=3|2.4%|). This difference was not statistically significant (p=0.217).

Among secondary safety analyses, the incidence of adverse events was not considered as a consistent analysis. It was because of the lack of investigators' compliance to fulfill all terms as requested by COSTART system. During the double-blind period 49 patients (18.7%) reported serious adverse events (38 in the placebo and 11 in the enoxaparin group). Thirty-nine patients

(31 placebo and 8 enoxaparin) reported VTE as the only serious adverse event. None of other adverse events (all in the placebo group) was considered as related to the study medication.

The sponsor included efficacy and primary safety parameters into the Adverse Event Section of Safety Analysis. Because they were reported more frequently than other adverse events, the major impact to results in this analysis came from endpoints used for assessment of study failure (e.g., the incidence of VTE [DVT, PE, death] and hemorrhage [major and minor bleeding]). This resulted in numerically more adverse events to occur in the placebo group, but this difference was not statistically compared.

A mild thrombocytopenia occurred in one patient on enoxaparin during the double-blind period. It resolved spontaneously and the drug was not discontinued.

There were two major trends in laboratory variables. First, average hemoglobin level was below normal at the end of the open-label, and its levels returned to normal in both groups during the double-blind period. Second, a thrombocytosis (reactive, according to the sponsor) occurred at the end of the open-label period, and resolved during the double-blind period. Other laboratory tests, from randomization to the end of study, did not show statistical difference between the two treatment groups.

In summary for safety, there was no a single parameter that may be attributed (statistically significant) to better, or worse safety of enoxaparin than placebo in the double-blind period. Safety during the open-label period (perioperative prophylaxis with enoxaparin 40mg/qd) was within the limits known from previous studies.

9.0 RISK/BENEFIT ASSESSMENT AND REVIEW CONCLUSION

9.1 *Benefit*

Hip arthroplasty is still a major surgical procedure carrying a postoperative mortality risk of . More than 50% of mortality is due to thromboembolism. In patients who have not been prophylactically protected against thrombosis, DVT appeared in about 40%-70% with fatal PE in 2%. This risk was five times greater than in patients after abdominal and thoracic surgery at