difference in the rates of DVT between the two groups was significant (asymptotic p-value= 0.018). The following Table gives a comparison between the enoxaparin and the placebo group in terms of odds ratio (extracted from sponsor's summary in page 8-2-147 and 8-2-149, Volume 3).

Table 2.3/ Comparisons in Terms of Odds Ratio (Placebo vs Enoxaparin)

Odds Ratio for the Failure Rate	95% Confidence Interval
3.549 (All randomized patients)	(1.337, 9.424) (all randomized patients)
3.153 (All evaluable patients)	(1.178, 8.437) (All evaluable patients)

Note that the 95% confidence intervals for the odds ratios do not contain 1; indicating that the treatment groups are different with respect to failure rates in favor of enoxaparin.

One hundred and fifty-five patients were evaluated in the per protocol analysis. The incidence of DVT (no PEs) is summarized in the Table below (extracted from sponsor's summary in page 8-2-149, Volume 3) .

Table 2.4/ Failure Rates Based on Per Protocol

DVT	Enoxaparin (N=75)	Placebo (N=80)	Overall (N=173)
Yes	2(2.7%)	17 (19.3%)	18 (11.6%)
No	73 (97.3%)	64 (80%)	137 (86.7%)
Sample Size	75	80	155

The frequency of DVT was higher in the placebo group than in the enoxaparin group. The difference in the rates of DVT between the two groups was significant (asymptotic chi-square p-value=0.001) in favor of enoxaparin. The odds ratio for the incidence of DVT was 9.695. The two-tailed 95% confidence interval was (2.157, 43.587).

The sponsor also provided analytic results on patients in the two groups according to DVT site. In this trial, all patients with both proximal and distal DVT were considered as having proximal DVT. No caval thrombosis was detected. The sites of diagnosed DVT are presented below (extracted from sponsor's Volume 3, page 8-2-149)

Table 2.5/ Failure Rates by DVT Sites For Evaluable Patient Population)

Level	Enoxaparin	Placebo	Overall
Proximal DVT	5 (5.9%)	7 (7.95%)	12 (6.9%)
Distal DVT	1 (1.2%)	10 (11.4%)	11 (6.4)
Sample Size	85	88	173

There was no significant difference in the incidence of proximal DVT between the two groups (asymptotic chi-square p-value .0592). The rate of distal DVT was significantly higher in the placebo group (11.4%) than in the enoxaparin group (1.2%) (asymptotic chi-square p-value=.006). Similar conclusions are valid for the all treated population (see Table 3.2 of this review).

The rate of distal DVT was significantly higher in the placebo group (11.4%) than in the enoxaparin group (1.2%) (asymptotic chi-square p-value=0.006). The odds ratio (placebo versus enoxaparin) for the incidence of distal DVT was 10.769 and the two-tailed 95% confidence interval was (1.347, 86.082). The distal DVT observed in the enoxaparin group occurred in patients who underwent general anesthesia, nine out of the ten distal DVT (90%) in the placebo group occurred in patients who underwent general anesthesia.

2.4 *Sponsor's Safety Event Summary Results/ Reviewer's Evaluation and Comments:*

Safety analyses were based on all 179 patients included in the study. No patient died during the study. Twenty one out of 179 patients (11.7% of the treated patients) experienced a bleeding complication. Among these, 17 patients experienced hematomas at injection site. None of the hemorrhage resulted in death. All the hemorrhages were classified as minor.

The incidences of hemorrhages in each treatment group are presented below (extracted from sponsor's Volume 3,8-2-158):

Table 2.7/ Bleeding Data by Treatment Group

Bleeding	Enoxaparin (N=90)	Placebo (N=89)	Overall (N=179)
Yes	17 (18.9%)	4 (4.5%)	21 (11.7%)
No	73 (81.1%)	85 (95.5%)	158 (88.3%)

The incidence of hemorrhages (including hemorrhage at injection site) was significantly higher in the Enoxaparin group (asymptotic chi-square p-value =0.003). The corresponding odds ratio was 4.95. The two-tailed 95% confidence intervals was (1.59,15.4).

The distribution of hemorrhage site is summarized in the following Table (extracted from page 8-2-159,Volume 3).

Table 2.8/ Distribution of Hemorrhage by Sites

Hemorrhage site	Enoxaparin	Placebo	Overall
Epsilaxis	1 (5.9%)	0	1 (4.8%)
Gastrointestinal	1 (5.9%)	0	1(4.8%)
Wound Hematoma	1(5.9%)	1(25%)	2(9.5%)
Injection-site hematoma	14 (82.4%)	3(75%)	17(81%)
Sample Size	17	4	21

Only one hemorrhage was considered as a "Serious Adverse Event" in the Enoxaparin group. Only one hemorrhage led to a temporary discontinuation of treatment in the Enoxaparin group. None of the hemorrhages observed necessitated transfusion during surgery.

III INTEGRATED SUMMARY:

3.1 *Integrated Efficacy Summary/Reviewer's Summary and Comments*

The following Table is based on sponsor's summarization of the efficacy results of both studies PK537 and ENX491001 (extracted from sponsor's Volume 14, page 8-13-5).

Table 3.1/ Combined Failure Rates

Treatment Group/Study	Study PK537	ENX491001	PK537+ENX491001
Placebo	34.4%(45/131)	20.2%(18/89)	28.6%(63/220)
Enoxaparin 40mg	16%(21/131)	6.7% (6/90)	12.2%(27/221)

Analyses of the combined efficacy data showed an overall incidence of venous thromboembolic incidence rate of 12.2 percent (27 of 221 patients) in the enoxaparin treated population and 28.6 percent (63 out of 220 patients) in the placebo-treated population. This difference was statistically significant (asymptotic chi-square p-value=0.001). The resulting

estimated odds ratio was 2.94 with a 95% confidence interval of (1.77,4.87).

It is to be noted here that in study PK537, 16.0 percent (21 out of 131 patients) of the enoxaparin-treated patients and 34.45 percent (45 out of 131) of the placebo treated patients developed venous throembolic complications. This difference was significant (asymptotic chi-square p-value=0.001). The observed placebo: enoxaparin odds ratio was 2.74 with a 95% confidence interval of (1.52,4.94). However in study ENX 491001 the incidence of venous thromboembolism in the all treated patient population was 6.7% (6 out of 90 patients) in the enoxaparin group and 20.2% (18 out of 89 patients) in the placebo group. This clinical difference was also statistically significant (asymptotic chi-square p-value=0.008). The observed placebo:enoxaparin odds ratio was 3.55 with a 95% confidence interval of (1.34,9.42).

In order to assess the appropriateness of pooling placebo:enoxaparin venous thromboembolic incidence rates across the two studies, a statistical analysis of the homogeneity of the enoxaparin to placebo odds ratio (ENX 491001:3.55, PK 537:2.4) was performed. The results of the Breslow-Day test was not significant (p-value= 0.657), indicating the two studies were not significantly different with respect to the relative odds (between treatments) of venous thromboembolism.

The following Table summarizes deep vein thrombosis by site (extracted from sponsor's Table 8, page 8-13-22, Volume 14).

Table 3.2/Combined Failure Rates by Sites

	ENX491001		PK537		Combined	
	P N(%)	E N(%)	P N(%)	E N(%)	P N(%)	E N(%)
No. Patients	89	90	131	131	220	221
Site of Thrombi: All proximal	7 (7.9%)	5 (5.6%)	28 (21.4%)	8 (6.1%)	35 (15.9%)	13 (5.9%)
Only Distal	10 (11.2%)	1 (1.1%)	15 (11.5%)	13 (9.9%)	25 (11.4%)	14 (6.3%)
Indeterminate	1 (1.1%)	0 (0.0%)	2 (1.5%)	0 (0.0%)	3 (1.4%)	0 (0.0%)
No thrombus	71 (79.8%)	84 (93.3%)	86 (65.6%)	110 (84.%)	157 (71.4%)	194 87.8%)

Overall, 48 of 441 (10.9%) patients developed proximal deep vein thrombosis; 35 out of 220 (15.9%) among placebo-treated patients and 13 out of 221 (5.9%) among enoxaparin-treated patients.

Individual odds ratios were found homogenous (asymptotic chi-square p-value =0.146) and the combined odds ratio is estimated to be 2.96 with a 95% confidence interval of (1.50, 5.83). Treatment group combined incidences of proximal deep vein thrombosis are significantly different in favor of enoxaparin. See also Table A.2 in the appendix for combined subgroup information.

It is worth mentioning that the two studies differ regarding how the patients were diagnosed at the end of the hospital period(open label phase). In study ENX491001, the patients were evaluated for venous thrombotic event by venography whereas the events in study PK537 patients were evaluated for venous thrombotic disease by the presence of clinical signs. Two percent (actually 1.87%) of the patients in PK537 were classified as having VTE after the open label phase of the study whereas 15% (actually 14.76%) of the patients in ENX491001 were classified as having VTE after the open label phase. This may raise concerns that the clinical diagnosis of VTE may be less effective than the diagnosis by venography. The sponsor did share this concern. The sponsor reported that this difference was explained by the difference in the design of the studies because only patients proven to be free of deep vein thrombi by venography were randomized in study ENX 491001. As a result one could suspect that 13% (15% - 2%) percent of the 262 patients (about 34 patients) in PK537 had entered into the double blind phase with VTE. That is, it is likely that the higher VTE rates in PK537 (in the placebo group and the treatment group) were due to the presence of patients who already had VTE at the end of the first phase of the study and were not detected by the clinical signs method. It is thus possible that these VTE patients did not improve at all and were diagnosed as having VTE (by venography) at the end of the double blind phase. It is also worth mentioning that in study PK537 there were 2 PEs found in the placebo group whereas no PEs were found in the Enoxaprin treated group. On the contrary no PEs were found in study ENX491001.

This reviewer did not find any problems with the randomization plan and/or process. Chances are very small that all the VTE patients (if any) from the first phase went to one group (placebo or enoxaparin treated) only. The randomization process, when properly carried out, should ensure "averaging out" of the effects of extraneous factors that may be present. It is worth mentioning that in PK537 the VTE rates were inflated in both groups (8.3 percent in the placebo group and 14.2 percent in the treatment group) compared to ENX491001.

IV OVERALL REVIEWER's COMMENTS/CONCLUSIONS

Comments:

1. Assuming that the 15% incidence rate observed in ENX491001 is the true VTE rate after the open phase period, then one could assume that 13% additional (about 34 VTE patients) VTE patients entered the second phase of study PK537. Because of randomization one could assume that these 34 VTE patients were divided evenly between placebo and the treatment group. Upon removing these additional VTEs from the observed events, the hypothetical failure rate would look as in the following Table.

Table 4.1/ Would be VTE Rates in PK537 When All 34 VTE Patients Are Evenly Distributed

	Overall N(%)	Enoxaparin N(%)	Placebo N (%)
Number of patients	262	131	131
Total VTE	66-34=32 (38%)	21-17=4 (10.7%)	45-17=28 (47%)

In this scenario, it can still be concluded that VTE rate is significantly higher (asymptotic chi-square p-value=.001) in the placebo group than that of the enoxaparin group.

Scenario 2: If we assume the VTE rates in study (ENX491001) to be the true rate (which is 6.7% for enoxaparin and 20% for placebo) we see that nine of 131 enoxaparin treated patients would have had VTE compared to twenty six of 131 placebo treated patients. So that the additional 13% (15%-2%) more VTE patients per treatment group (about 17 patients) due to poor 1st phase screening would bring down the VTE rates as in the following Table:

Table 4.2/Would be DVT Rates Assuming ENX491001 is the True Study.

	Overall N(%)	Enoxaparin N(%)	Placebo N (%)
Number of patients	262	131	131
Total VTE patients	69 (26.33%)	26 (19.84%) (9+17)	43 (32.82%) (26+17)

Under this scenario, it can still be concluded that VTE rate is significantly higher (asymptotic chi-square p-value .017) in the placebo group than that of the enoxaparin treated group.

2. Finally, one could find the number of patients with VTE in placebo group (or enoxaparin group) that would lead to borderline significance by varying the number of VTE patients in

the placebo group (or enoxaparin group). Note that 21 is the observed number VTE patients in the enoxaparin group and 45 is the observed number of VTE patients in the placebo group. In the following table we summarize this scenario.

Table 4.3/ Hypothetical Number of DVT Patients Required to Nullify Observed Enoxaparin Benefit in PK537

	Enoxaparin N(%)	Placebo N(%)	P-value (Fisher's exact)
Number of patients	131	131	
(Fixed Enox, Varied Pla Events) Number of VTEs	21 (16.03%)	30 (22.9%)	.211
(Fixed Enox, Varied Pla Events) Number of VTEs	21 (16.03%)	35 (26.71%)	.049
(Varied Enox, Fixed Pla Events) Number of VTEs	30 (22.9%)	45 (34.35%)	.0553
(Varied Enox, fixed Pla Events) Number of VTEs	29 (22.13%)	45 (34.35%)	.0392

Thus to nullify the observed enoxaparin benefit, one would have had to observe 10 more enoxaparin VTEs or 10 less placebo VTEs.

From these three scenarios, it can be concluded that the observed treatment difference reflects true enoxaparin benefit.

Conclusions:

In this reviewer's assessments, the efficacy data in studies PK537 and ENX491001 indicate that enoxaparin is effective in the prevention of deep vein thrombosis during the first three post-discharge weeks in patients who had previously undergone total hip replacement surgery and who had received conventional enoxaparin (40 mg) during hospitalization period as well as 12 ± 2 hours before surgery.

2. In this reviewer's assessments, the safety data in study ENX491001 indicate that there were significantly more bleeding complications among the enoxaparin treated patients than the placebo treated patients (19% in enoxaparin group and 5% placebo group); these bleedings are classified as minor. However, the safety data in study PK537 indicate that there were no significant differences in the incidence rates of hemorrhagic episodes between the two

treatment groups (minor incidence rates: 6% enoxaparin group and 2% placebo group; major incidence rates: 0.0%).

3. Because the minimum age requirement for the two studies is at least 40 years old, it is not known what implications this trial will have for patients who are less than forty years old.

/S/

M. Mushfiqur Rashid, Ph. D. 12/23/96

Mathematical Statistician

Concur:

Dr. Huque /S/ 12/23/96

for Dr. Smith /S/ 12/23/96.

cc: Archival NDA #s 20-164/SE1-010
HFD - 180
HFD - 180/Dr. Fredd
HFD - 180/ Ms. Oliver
HFD - 344/ Dr. Lisok
HFD - 720/ Dr. Smith
HFD - 720/ Dr. Huque
HFD - 720/ Dr. Sankoh
HFD - 720/ Dr. Rashid
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Appendix

Table A.1: Summary of Demographic and Background Characteristics (Extracted From Sponsor's Table B.5.1, Page 8-9-40, Volume 10)

	Overall N(%)	Enoxaparin N(%)	Placebo N(%)
Number of Patients	262	131	131
Sex Male Female	 113 (43.1%) 149 (56.9%)	 56 (42.7%) 75(57.3%)	 57 (43.5%) 74 (56.5%)
Race Caucasian	262 (100.0%)	131(100.0%)	131 (100.0%)
Age(Years) Average Less than 65 65 and over	 68.5 88 (33.6%) 174 (66.4%)	 69.0 38 (29.0%) 93 (71.0%)	 68.1 50 (38.2%) 81 (61.8%)
Weight(kg) (1 missing) Average	77.5	76.4	78.5
Height(cm)(1 missing) Average	169.8	169.5	170.1
Body Mass Index(1 missing) Average	26.9	26.6	27.2
Body Surface Area(1 missing)Average	1.92	1.91	1.94
Blood Pressure(one missing):(Sys.,Dias.)Average	(151.9,80.0)	(152.1,80.0)	(151.8,85.0)
Pulse (6 missing) Average	71.6	71.6	71.7

Table A.2/ Combined Failure Rates by Subgroups (extracted from sponsor's Table 10, page 8-13-25, Volume 14)

	Placebo		Enoxaparin		Combined	
	n/N	%	n/N	%	n/N	%
Number of Patients	220		221		441	
Patients with VTEs	63	28.6%	27	12.2%	90	20.4%
Sex:						
Male	23/112	20.5%	8/103	7.8 %	31/215	14.4%
Female	40/108	37.0%	19/118	16.1%	59/226	26.1%
Obesity (based on BMI)						
Obese	33/100	33.0 %	13/74	17.6 %	46/174	26.4%
Non-obese	30/120	25.0 %	14/147	9.5 %	44/267	16.5%
Surgical procedures:						
Unilateral Primary THR	51/191	26.7%	21/183	11.5%	72/374	19.3%
Unilateral Revision THR	3/9	33.3%	1/12	8.3%	4/21	19.0%
Unilateral pri. THR (Contra. THR hx.)	0/5	0.0%	1/10	10.0%	1/15	6.7%
Bilateral Primary THR	9/15	60.0%	4/16	25.0%	13/31	41.9%
Age:						
Less than 65	17/87	19.5%	4/63	6.3%	21/150	14.0%
65 years and over	46/133	34.6%	23/158	14.6%	69/291	23.7%