6.9.2 Efficacy Analyses Results

a. Primary Efficacy Endpoint

1) Incidence of recurrent VTE during three months after randomization.

The primary efficacy endpoint was the incidence of VTE (DVT, PE or deaths) between the beginning of the study and either the occurrence of the event or the end of the follow-up period (3 months following randomization).

Records of VTE objective assessment (venogram, duplex ultrasound, pulmonary scan, and angiogram) were read by investigators and by an adjudication committee. There were 40 patients with VTE during the study period. They had 42 VTE events. The Adjudication Committee confirmed 30. The Committee's report is used for study analysis. Twenty-four of them were considered as events by investigators, too. This makes a 87% congruence between assessors. Four events (H=2/E=2) were considered VTE by the Committee, but not so by the investigator, and ten events (H=6/E=4) were not considered to be events by the Committee, but were considered as such by the investigator.

Majority of events occurred within 21 days of study (25, 59.5%). In first two weeks (14, 33%) there were more events than in the following two weeks (11, 26%). Only five events (11.9%) occurred during the treatment period (first week). Three events were in the enoxaparin and two in the heparin group.(From Table 37, Vol.22,pp.89-90).

Only 6% of patients experienced VTE. DVT was present in 86.7%, PE in the remaining patients. Summary of recurrent VTE is presented on Table 6.9-9

Table 6.9-9
SUMMARY OF RECURRENT VTE. ALL-TREATED PATIENTS

Venous thromboembolic event [VTE]			Heparin		Enoxaparin		Combined	
			N	%	N	%	N	%
No VTE			237	93.3	234	94.7	471	94.0
VTE	Total		17	6.7	13	5.3	30	6.0
	DVT		14	5.5	11	4.5	25	5.0
	PE		2	0.8	1	0.4	3	0.6
	DVT + PE		1	0.4	1	0.4	2	0.4
DVT Location	Unknown		3	?	2	?	5	?
	Unilateral	Proximal	11	78.6	10	90.9	21	84.0
		Proximal & distal	3	21.4	0	0.0	3	12.0
	Bilateral		0	0.0	1	9.0	1	4.0
PE (pulmonary embolus)		Total	3	17.6	2	15.3	5	16.7
		Fatal	2	11.7	0	0.0	2	6.7
		Nonfatal	1	5.8	2	15.4	3	10.0

From Table 14 (Vol.22, p.50)

The table shows relatively high incidence (6.0%) of VTE recurrence, with extension of DVT (DVT, unilateral, proximal) being the most frequent event (84.0%). This incidence of VTE is considered as an expected failure of the therapeutic regimens. There was no significant difference between two treatments (heparin+warfarin vs. enoxaparin+warfarin). Majority of DVT extensions occurred during the second week (days [1-7]:3 events, days [8-14]:9, days [15-21]:5). Is it possible that the change of therapy (anticoagulation controlled by heparin or enoxaparin with warfarin shifted to warfarin alone) occurring in the second week, contributed to reduction of the level of prophylaxis before warfarin protection was completely established? The submission does not address this question.

The three PE occurred within first 2 days of study. Two of them were massive and fatal. It is not clear whether they occurred independently of the therapy, or how much the beginning of therapy (eventual incomplete thrombolysis and separation of clot particles, resulting in embolization), and other common measures, i.e., caval filter (if they were in effect at this time), have contributed to the event.

It is of interest to note that 25/30 (83.4%) VTE (DVT/PE) occurred in patients who had at least one of risk factors present at baseline(Table6.9-6 and Table 15 [Vol.22, p.51]). There was no significant difference between distribution of risk factors and incidence of recurrent VTE between treatment groups.

The incidence of VTE during three months following randomization in the all-treated population was analyzed for statistical equivalence of enoxaparin (outpatient) and heparin(in hospital) prophylaxis of VTE recurrence in all-treated and evaluable population of patients with acute symptomatic DVT with or without PE. Table 6.9-10 summarizes this analysis.

Table 6.9-10

STATISTICAL ANALYSIS OF THE EFFICACY OUTCOMES: INCIDENCE OF VTE. INTENT-TO-TREAT AND EVALUABLE (PER PROTOCOL) POPULATION

Analysis	Primary: Intent-to-Treat	Secondary: Evaluable
Incidence on Enoxaparin	13/247 (5.26%)	12/228 (5.26%)
Incidence on Heparin	17/254 (6.69%)	16/241 (6.64%)
Observed Difference Heparin-Enoxaparin	1.43%	1.38%
95% Confidence Interval of Difference*	-2.72%; 5.58%	-2.90%; 5.65%
90% Confidence Interval of Difference	-2.05%; 4.91%	-2.21%; 4.96%
CONCLUSION	EQUIVALENCE*	EQUIVALENCE*
Observed Odd-Ratio	1.29	1.38
90% Confidence Interval of Odd-Ratio	0.69; 2.41	0.67; 2.45
95% Confidence Interval of Odd-Ratio	0.61; 2.72	0.59; 2.77
Significance of Interaction (α=0.15) Treatment*Center Treatment*Stratification	 p= 0.552 p= 0.518	 p= 0.529 p= 0.482
Reviewer's Assessment of Efficacy: Primary efficacy endpoint. Enoxaparin vs. Heparin. Odds-Ratio	E H Total VTE 13 17 30 NoVTE 234 237 471 Total 247 254 501	Odds-Ratio E/H = 0.7862 95% Confidence interval: ±0.7443 CI= (0.0419, 1.5305]

From Table B.5.5 (Vol.23, p.231) and Table B.5.6 (Vol.23, p.232). * Equivalence was claimed if the lower limit of CI was greater than -3%.

Based on these data, the sponsor concluded that enoxaparin was equivalent to heparin for DVT treatment. The FDA statistician after evaluation of the same data, concluded enoxaparin was not inferior to heparin by 3% or more, but the results are not robust enough for this claim.

This reviewer has used Odds-Ratio method to assess efficacy of enoxaparin vs. heparin regimen. The result demonstrates that there is a significant difference between two treatments favoring enoxaparin as a more protective. However, since therapy was administered in an open-label manner, and the enoxaparin regimen was given only to patients whose clinical condition at baseline had allowed outpatient therapy (otherwise they dropped out of study prior to receive the first dose of study medication), it is possible that the better clinical condition at baseline, rather than the drug itself, has contributed to the better prognosis of outpatients. Therefore, I would conclude that the enoxaparin outpatient regimen was at least as good as or not worse than the heparin regimen for the selected group of patients.

2) Incidence of recurrent VTE and the location of DVT

This is a subanalysis of the primary efficacy endpoint. Because patients at baseline had a proximal DVT (almost all unilateral), this analysis provides information of extension of DVT, and occurrence of new VTE in other sites (Table 6.9-11).

Table 6.9-11

SUMMARY OF RECURRENT VTE BY LOCATION. ALL-TREATED POPULATION

VTE LOCATION			Heparin N=254	Enoxaparin N=247	Combined N=501
VTE			17 (6.69%)	13 (5.26%)	30 (5.98%)
DVT	Total		14 (5.5%)	11 (4.45%)	25 (4.99%)
	Unknown		3	2	5
	Unilateral	Total	12 (4.7%)	8 (3.24%)	20 (3.99%)
		External iliac	2	1	3
		Common femoral	1	1	2
		Superficial femoral	3	2	5
		Popliteal	4	0	4
	Bilateral	Total	0	2	2
PE	Total		3 (1.2%)	2 (0.8%)	5 (1.0%)
	Fatal		2	0	2
	Non-fatal		1	2	3

From table 14: Summary of recurrent VTE for All-treated patients (Vol. 22, p.50).

In this table all parameters are in favor of enoxaparin prophylaxis but, in the opinion of this reviewer, the numbers are too small for any conclusive distinction between two treatments.

b. Secondary efficacy analyses

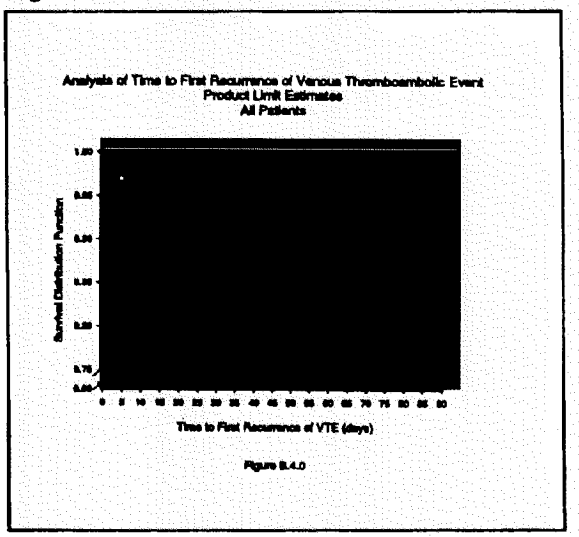
1) VTE incidence in evaluable patient population

Data are summarized on Table 6.9-2. The sponsor has reported this data on Table B.5.1, Appendix IV, Part B of the submission. They confirm that enoxaparin was equivalent to heparin protecting against VTE recurrence in the evaluable patient population. This result supports the conclusion based on the analysis of the primary efficacy endpoint.

2) Time to recurrence

Another secondary efficacy endpoint was the time to first recurrence of VTE. Product Limit Estimates analysis was performed. Patient having a recurrence were considered as failures. Patients who did not have a recurrent VTE were censored at their last visit data or at 90 days. The plot has shown more events for enoxaparin group later on in the follow-up period (Fig. 6.9-11). The survival distribution plot for the evaluable patient population is comparable and can be found in Fig. B.5.), Appendix IV, Part B of this submission.

Figure 6.9-11



Both plots also show that the frequency of VTE events was identical in both treatment groups during the treatment period (1-8 days). The true difference began to occur during the third week, when all subjects were outpatients receiving warfarin maintenance. The sponsor has not provided any explanation for this observation.

3) Subgroup Analysis

A confidence interval approach was used for subgroup analysis with -3% as the lower limit of significance. Data are presented in the submission on Table 15 (Vol.22, p.51). Subgroups as age, gender, previous VTE, recent surgery, active malignancy, and recent trauma, were all of a small size. Results cannot be used to prove any specific inference of difference between two treatment groups.

4) Investigator and Strata Interaction

Another analysis was performed on the investigator and strata interaction. Data are presented in the submission on Table 16 (vol.22, p.53). The treatment effect was found independent of investigators, and strata interactions were nonsignificant for all-treated (p=0.516) and evaluable patient population (p=0.482). These results reduced the number of possible confounding variables for interpretation of the study primary efficacy variables.

5) Investigator and Adjudication Committee Assessment

Table 37 in this submission (Vol.22, p. 90) presents a listing of VTE. It includes VTE considered adverse events by investigators, and those decided by the Adjudication Committee to be outcome events. There was 87% concurrence between these two groups of assessors of VTE data.

c. Summary on Efficacy Results

Based on these data the sponsor concluded that the outpatient treatment of acute symptomatic DVT with enoxaparin for initial anticoagulation, is a regimen equivalent to the standard in hospital regimen employing intravenous heparin for the same purpose. In both regimens, the maintenance therapy should be given to oral warfarin.

The sponsor did not indicate, but it was clear from these data, that the outpatient regimen can be applied only to patients whose clinical condition allow home treatment, and who are willing to use self-injection procedure for the subcutaneous administration of Lovenox injection.

6.9.3 Safety Evaluation

OVERVIEW

Safety was studied only on all-treated or intent-to-treat (ITT) patient population. Hemorrhage, coagulation factors, adverse events and clinical laboratory values were monitored in this trial. The safety assessment was divided between evaluation of hemorrhagic episodes, adverse events (clinical and laboratory) and evaluation of deaths. Sponsor's conclusion on Safety:". . . In general, with the exception of the significantly higher incidence of headache, pain, and insomnia in the heparin group, there were no differences in any of the safety factors between the treatment groups."

a. Extent of exposure

1) Study medication: enoxaparin and heparin

Enoxaparin and heparin were given to rapidly achieve an anticoagulation state that will slow or stop further extension of venous thrombosis. Whenever randomization had to be deferred more than a day for objective assessment of DVT, i.e. venography, patients with acute symptomatic DVT received heparin infusion as an emergency measure. This intervention created the Pre-randomization Period. Exposure of patients to heparin during this period and to enoxaparin and heparin during the Treatment Period is summarized on table 6.9-12

Table 6.9-12
STUDY DRUG EXPOSURE FOR ALL-TREATED PATIENTS INCLUDING THE PRE-RANDOMIZATION HEPARIN

		Heparin		Enoxaparin		Combined	
Study Period	Days on heparin	N=254	%	N=247	%	N=501	%
Pre-Randomization	No prior heparin	162	63.8	153	61.9	315	62.9
	1-2 days	74	29.1	71	28.5	145	28.9
	>2 days	17	6.7	7	6.9	24	4.7
	Unknown duration	1	0.4	6	2.4	7	1.4
	Prior heparin total pts	92	36.2	84	34.0	176	35.1
Treatment Period	Days on Study Medication	N=254	%	N=247	%	N=501	%
	<4 days	5	1.9	5	2.0	10	2.0
	4-5 days (Protocol)	49	19.2	45	18.2	95	18.9
	6-7 days	170	78.7	146	79.8	316	79.2
	> 7 days	30		51		81	
	Median (days)	6.0		6.0		6.0	
	Range (days)	1-12		1-17		1-17	

From Table 17: Summary of pre-randomization heparin and study drug exposure for all-treated patients (Vol. 22, p.58).

More than one third of patients received heparin as initial treatment. After confirmation of venography, they were randomly assigned to both treatment groups. The randomization resulted in a comparable distribution of these patients between heparin and enoxaparin regimens. Apparently, those patients who proceeded with heparin could have not been affected by the pre-randomization period therapy. However, for patients who, after randomization, proceeded with enoxaparin treatment, the baseline coagulation status was different in comparison with patients who started with enoxaparin (other 2/3 of total 247 patients in this group).

In a separate analysis, performed upon the Agency's request, the sponsor provided data showing no influence of pre-randomization heparin to the VTE recurrence rate between treatment groups. Exception was seen at the third month follow-up. At this time, the VTE recurrence rate 6.0% (17/284) in the non-Heparinized Enoxaparin was significantly higher than in the pre-Heparinized Enoxaparin group, under the significance level of 0.05 (p-value=0.015). For more details see the Statistical Review.

The majority of patients received heparin (heparin or enoxaparin) more than planned. Median duration was 6 vs. 5 days. Almost 80% patients were treated for 6-7 days, instead of 5. The overall range was 1-17 days.

2) Study medication 2 - Warfarin Exposure

Information about warfarin exposure during the treatment and the follow-up period is provided in this submission on Table 20 (Vol.22, p.62). Most of the patients began warfarin therapy on Day 2 as planned (H=69.7%/E=72.9%). One heparin and one enoxaparin patients (0.4%) began this therapy on Day -2. Warfarin maintenance continued until the end of the 3-month period follow-up. Warfarin dose was adjusted (monthly) to maintain INR between 2.0 and 3.0. The mean number of days on such a warfarin treatment was 81.9 days for the heparin and 82.3 days for the enoxaparin group. Overall range was 1 - 90 days.

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There was no significant difference in duration of exposure to warfarin between heparin and enoxaparin treatment groups.

b. Hemorrhage

1) Hemorrhage as the primary safety variable

Hemorrhage was assessed as any episode, major episode, leading to discontinuation, and requiring transfusion, during the treatment period (1-7 days) and the entire study (1-90 days).(Table 6.9-13)

Table 6.9-13
HEMORRHAGIC EPISODES DURING TREATMENT PERIOD AND ENTIRE STUDY

Number of Hemorrhagic Episodes	Heparin N=254		Enoxaparin N=247		Combined N=501	
	Treatment	Study	Treatment	Study	Treatment	Study
Any episode	10 (3.9%)	24 (9.4%)	11 (4.5%)	18 (7.3%)	21 (4.2%)	42 (8.4%)
Major episode	3 (1.2%)	6 (2.4%)	5 (2.0%)	8 (3.2%)	8 (1.2%)	14 (2.8%)
Leading to discontinuation	4	na	3	na	7	na
Requiring transfusion	2	4	1	3	3	7

From Table 26 and 27 (Vol.22, p.75). na= non applicable

There was no statistically significant difference of the incidence of hemorrhagic episodes between the treatment groups. This conclusion is for the duration of the treatment period, and the entire study.

A summary of hemorrhagic episodes sites and symptoms for the treatment period for all-treated patients by severity of the event and the study drug is provided in the submission on Table 28 (Vol.22, p.77-78).

The sponsor concluded that there was no statistically significant difference in the incidence of hemorrhagic episodes (all parameters observed) between treatment group for the treatment period or the full three months study period.

Comment: Hemorrhagic episodes were reported on CRF-Bleeding Event Form. This form was written to emphasize only major hemorrhage. There is a possibility that many minor hemorrhages could have been overlooked (spontaneous epistaxis that stopped after compression, microscopic hematuria, petechiae, small ecchymoses, skin hematoma, etc.). These forms were adjudicated, and the decision (no bleed, minor bleed, major bleed) was reported as safety endpoint. Therefore, the low incidence of "any" hemorrhagic episodes in this report, could be due to under-reporting.

2) Hemorrhage as adverse event

Other signs/symptoms of hemorrhage were collected from adverse event reports (Table 29, Vol.22, p.78). They include minor anemia (1 case), major coagulation disorder (1), unspecified hemorrhage (4), GI hemorrhage (4), rectal hemorrhage (2), melena (2), hematuria (2) and hemoptysis (1).

Characteristically, all hemorrhagic episodes were comparably distributed between the heparin and enoxaparin treatment groups.

C. Adverse Events as Secondary Safety Endpoints

Clinically relevant adverse events were reported on CRF-Daily Treatment Form (heparin and enoxaparin) in a block at the end of the page. The Follow-up Assessment form was designed to collect data for fatal outcomes, VTE including bilateral IPG, bleeding event, compliance with warfarin therapy, and other, unscheduled medical attention for reasons related to VTE.

Adverse events reported in CRF have been translated by RPR staff members into COSTART (Coding Symbol of Thesaurus of Adverse Events) terminology for presentation in this submission.

1) Adverse events during the treatment period

Overall 140 (27.9%) patients (H=93[36.6%]/E=47[19.0%]) presented at least one adverse event during the treatment period. There is no information how many adverse events have been reported during the whole study period of three months. Due to COSTART terminology, only four non-related adverse events (headache, pain, nausea and insomnia) occurred 36 times (each ≥3%). However, hemorrhage (a composite adverse event comprising of COSTART terms such as hematuria, ecchymosis, hemorrhage) appeared in 21 events (4.2%), more than any of the leading four alone (Table 6.9-14).

Table 6.9-14
SUMMARY OF THE MOST FREQUENT ADVERSE EVENTS DURING THE TREATMENT PERIOD

Event		Heparin, N=254		Enoxaparin, N=247		Combined, N=501		p-value
		N	%	N	%	N	%	
Headache		16	6.3	2	0.8	18	3.6	0.001*
Pain		13	5.1	4	1.6	17	3.4	0.046*
Nausea		11	4.3	4	1.6	15	3.0	0.113
Insomnia		15	5.9	0	0.0	15	3.0	c*
Hemorrhage	Total	12	4.4	10	4.0	21	4.2	na
	Hematuria	5	2.0	4	1.6	9	1.8	1.0
	Ecchymosis	3	1.2	3	1.2	6	1.2	1.0
	Hemorrhage	3	1.2	3	1.2	6	1.2	1.0
Total	Reviewer's assessment	67	26.4	20	8.1	87	14.4	H/E (OR)= 4.1 95%CI: [3.5, 4.7]

From Table 31 (Vol.22, p.80) and Table 32 (Vol.22, p.82). * = Statistically significant difference. c*= The sponsor considers this statistical significance to be related to the in hospital monitoring rather than to drug difference. na= non applicable. (OR)= Odds-Ratio.

Adverse events reported from hospitalized patients (heparin group) were four times more than from outpatients (enoxaparin group). The difference is due to general, non-specific adverse events. It is not clear whether outpatients did not report or did not experience adverse events such as insomnia, pain, headache and nausea. Almost no difference between treatment groups was found for hemorrhage as adverse event.

2) Adverse events leading to discontinuation during the treatment period.

During the treatment period 16 (3.2%) patients experienced serious adverse event leading to treatment discontinuation. These adverse events are summarized in the submission on Table 33 (Vol.22, p.84). Nine of them (3.5%) were in the heparin group, and seven (2.8%) in the enoxaparin group. The events included pulmonary embolus, hematemesis, decreased prothrombin time, and joint disorder (one patient per a treatment group). Other adverse events occurred in single patients (intracranial hemorrhage, epistaxis, hematuria, nausea, chest pain, pneumothorax, accidental injury, fever, anxiety).

3) Adverse events related to study medication that occurred during the treatment period

As a part of this safety analysis, investigators were requested the adverse events, that occurred during the treatment period, to relate to the study medication (heparin or enoxaparin). Warfarin was excluded from this assessment. It was a simplified assumption that warfarin had added a balanced effect on both treatment groups.

Table 6.9-14
ADVERSE EVENT RELATED TO STUDY MEDICATION DURING TREATMENT PERIOD

RELATED ADVERSE EVENT		Heparin, N=254		Enoxaparin, N=247		Combined, N=501	
		N	%	N	%	N	%
Hemorrhage	Total	17	6.7	14	5.7	31	6.2
	Hematuria	5	2.0	4	1.6	9	1.8
	Ecchymosis	3	1.2	3	1.2	6	1.2
	Hemorrhage	3	1.2	3	1.2	6	1.2
	Epistaxis	2	0.8	1	0.4	3	0.6
	Rectal hemorrhage	1	0.4	1	0.4	2	0.4
	Intracranial hemorrhage	0	0.0	1	0.4	1	0.2
	hematemesis	1	0.4	1	0.4	2	0.4
	Gum hemorrhage	1	0.4	0	0.0	1	0.2
	Gastrointestinal hemorrhage	1	0.4	0.	0.0	1	0.2
Thrombocytopenia		2	0.8	1	0.4	3	0.6
Prothrombin decreased		1	0.4	1	0.4	2	0.4
DVT		0	0.0	1	0.4	1	0.2
Allergic reactions	Total	2	0.8	1	0.4	3	0.6
	Pruritus	1	0.4	0	0.0	1	0.2
	Rash	0	0.0	1	0.4	1	0.2
	Fever	1	0.4	0	0.0	1	0.2
Nausea		2	0.8	0	0.0	2	0.4
Reviewer's assessment	Total	24*		18*		42	H/E (OR)= 1.33 [0.68,1.96]

From Table 34 (Vol. 22, P.85). *= Significant difference.

More adverse events recorded in hospital (heparin group) were related to the study medication than the adverse events collected from outpatients (enoxaparin group). Although being not large, this difference was statistically significant.

4) Serious adverse events during the study

Serious adverse events were recorded during the treatment period and during the 3-month period of study. The following table summarizes sponsor's reports (Table 6.9-15).

Table 6.9-15
SERIOUS ADVERSE EVENTS DURING THE TREATMENT PERIOD AND FOLLOW-UP

Serious Adverse Event		TREATMENT PERIOD			FOLLOW-UP PERIOD		
		Heparin	Enoxaparin	Combined	Heparin	Enoxaparin	Combined
DVT		1	2	3	4	1	5
PE		1	1	2	0	0	0
Hemorrhage	Total	6	5	11 (2.2%)	0	0	0
	Hematuria	2	0	2	0	0	0
	Hemorrhage	0	2	2	0	0	0
	Hematemesis	1	1	2	0	0	0
	Intracranial	0	1	1	0	0	0
	GI	1	0	1	0	0	0
	Abdominal	0	1	1	0	0	0
	Epistaxis	1	0	1	0	0	0
	Intra articular	1	0	1	0	0	0
Thrombocytopenia		1	1	2	0	0	0

From Table 35 (Vol.22, p.86) and Table 36 (Vol.22, p.87)

Other serious adverse events recorded during the treatment period include carcinoma of lung, carcinoma, pneumonia, chest pain, myocardial infarction, pneumothorax, kidney failure, liver test abnormal, urinary tract infection, confusion, cellulitis. There were no reports of such adverse events during the follow-up period.

The above table shows that the expected adverse event hemorrhage did not occur during the INR controlled warfarin treatment in the follow-up period. Although rare (2.2%), hemorrhagic adverse events occurred only within the treatment period and may be attributed equally to either heparin or enoxaparin.

d. Clinical Laboratory Evaluations as Secondary Safety Endpoint

Clinical Laboratory tests were evaluated for detection of abnormal values of two "expected" and several "unexpected" parameters. Change of platelet count (thrombocytopenia and thrombocytosis) may be related to direct and immune heparin and LMWH effect. Change of hemoglobin may be related to blood loss.

1) Thrombocytopenia

Mild to moderate thrombocytopenia was registered in 36 patients at the baseline. Patients randomized to heparin had the mild form of this syndrome significantly more than patient on enoxaparin (7.1% vs. 2.8%). At the end of the treatment period, thrombocytopenia was found in 21 patient. Is it recovery? The sponsor does not provide comments.

Comment: These data indicate that neither heparin or enoxaparin induced direct thrombocytopenia in this trial. Less than five days make a period insufficient for occurrence of immune thrombocytopenia in previously unsensitized patients.

2) Thrombocytosis

In this study a particular attention was given to thrombocytosis. At baseline, 45 patients presented mild (39) or moderate (6) thrombocytosis. At the end of treatment period, their number increased to 70 (58 mild, 12 moderate). More cases of mild thrombocytosis was recorded in patients who received enoxaparin (E=15%/H=8.3%).

Comment: During a phase of acute thrombosis and/or pulmonary embolism platelet count may differ in relation to the actual state of coagulation due to the disorder. Analysis of individual data may indicate whether heparin or enoxaparin induced thrombocytosis in these patients. The sponsor did not comment.

3) Hemoglobin

Only change of hemoglobin for more of 20g/L (major hemorrhage) was recorded. Few patients (9, 1.8%) presented this change. Enoxaparin contributed in 7/9 (77.8%) cases.

4) Other Laboratory Values

Most of other laboratory results appeared to be insignificant. In both groups there was an insignificant increase in AST and ALT during the course of the treatment period.

e. Death as Secondary Endpoint for Safety

Deaths were analyzed separately of adverse events.

1) Deaths During the Treatment Period (Day 1-6)

Three patients died during the treatment period. One patient (pt#124010) died of PE (autopsy confirmed) the first day heparin therapy was started and immediately discontinued. One enoxaparin treated patient (pt#112014) died on day six from "catastrophic hemorrhage." A day before, this patient experienced massive hematemesis. One heparin patient (pt#021018) died on day seven from metastatic lung cancer complicated by PE (autopsy confirmed).

In summary two patients on heparin died as consequence of study drug failure. One patient on enoxaparin died because of drug induced adverse event (hemorrhage).

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2) Deaths During the Study (Day 1-90)

Forty-three patients died during this study. Three of them died during the treatment period. Twenty-five died during the follow-up period (day 8-90). Six patients died during the first 30 days of therapy, eight between 31-60 days, and 11 between 61-90 days. Fifteen patients died after study termination between 91 and 209 days.

Twelve events of study failure occurred in 19 patients who died. One patient had both VTE and hemorrhage. This number is an incidence rate of almost 60% of outcomes in patients who died, as declared, by cause non related to study medication. Efficacy failure (DVT, PE, VTE) occurred in eight patients (42.1%). Safety failure (major hemorrhage) occurred in four patients (21%). There was no difference between heparin and enoxaparin groups. However, the event appeared during or after warfarin treatment, and was related to this study medication.

These findings arouse suspicion that data on efficacy (incidence of VTE) and safety (incidence of major hemorrhage) of enoxaparin vs. heparin treatment, other than those obtained from endpoints measured during the treatment period, may not be related to either of these drugs but to warfarin, INR levels and coagulopathy due to cancer.

3) Study Discontinuation Due to Hemorrhage and Deaths

Fourteen patients discontinued the study because of a major hemorrhagic episode (H=6/E=8). Five died (H=2/E=3). Selected information from narratives of survivors are included in Appendix 2.

It is apparent that enoxaparin dose in this trial was safe unless the drug was used under increased risk for bleeding conditions such as gastrointestinal or genitourinary disease. Two discontinuations due to the injection site hematoma indicate to unrecognized hemorrhagic diathesis (aspirin or other drugs?). In many other patients, injection site hematoma were of little, if any, clinical significance.

4) Study Discontinuation Due to VTE and Deaths

Thirty-one patients discontinued the study because of VTE (mostly DVT). Seventeen (54.8%) died. In the heparin group there were 18 with VTE (58.0%). Thirteen of them (72.3%) died. In the enoxaparin group there were 13 (41.9%) patients with VTE. Four of them (30.7%) died. The selected narratives of survivors are included in Appendix 2.

Comment: High incidence of deaths in the heparin group may be related to better clinical status of patients treated at home by enoxaparin.

Summaries of narratives for all deaths and patients who discontinued study 2091 are presented in Appendix 2.

f. Summary of Safety Analyses

The sponsor has summarized all safety analyses in the following paragraph: "The all-treated population (ITT) was analyzed for safety effects. This included 254 heparin patients and 247 enoxaparin patients. Hemorrhage, coagulation factors, adverse events, and clinical laboratory values were monitored in this trial. In general, with the exception of the significantly higher incidence of headache, pain, and insomnia in the heparin group, there were no differences in any of the safety factors between the treatment groups."

This conclusion is in congruence with data presented in the submission.

6.10 STUDY 2091 REVIEW SUMMARY

The pivotal study CPK-2091 is an adequate and well controlled clinical trial. Both the efficacy and safety analyses have demonstrated equivalence between heparin+warfarin and enoxaparin+warfarin treated patients. Data obtained in this study are admissible as evidence in support of the sponsor's claim that Lovenox Injection can be used for treatment of acute DVT.

The FDA efficacy analysis allows the sponsor, instead of claiming the clinical equivalence, to declare that enoxaparin is not inferior to heparin by 3% or more. However, data were not robust enough to support this claim. (See Statistical Review)

This study does not allow the sponsor to claim enoxaparin for treatment of DVT and PE as stated. The inference can be made only to the sampled population (who satisfied inclusion/exclusion criteria) and only for persons whose clinical condition allows outpatient treatment.

7.0 STUDY 529
(Submission Vol. 25-33,52-70,71-87, 105-139)

7.1 TITLE PAGE

Study Phase and Drug Identifiers: Phase III, RP 54563q.

Protocol Number: **529**

Protocol Title: *A multicenter, randomized, partially-blind, parallel-group, clinical trial to compare the efficacy and safety of twice and once-daily subcutaneously administered enoxaparin and continuous infusion heparin in the treatment of patients with deep vein thrombosis with and without pulmonary embolism.*

Author: Theodore E. Spiro, RPR

Investigators:

A total of 17 countries, and 74 centers and investigators participated in this multicenter trial. A list if participating countries, centers, investigators, and number of patients assigned per treatment group and investigator, is included in Appendix 3.

Study Start Date:	05/19/94
Study Completion Date:	07/17/96
Date of Report:	01/30/97
Date of Submission:	02/28/97

7.2 TABLE AND CONTENT OF THE STUDY

STUDY 529: CONTENT			
7.1	Title Page	7.9	**Study Results**
7.2	Table and Content of the Study	7.9.1	**Data Sets Analyzed**
7.3	Identity of the Test Material	a.	Patients Disposition
7.4	**Synopsis**	b.	Demographics
7.5	Study Objective	c.	Risk Factors
7.6	**The Investigational Plan**	d.	Diagnostic Method Presenting Symptoms
a.	Study design	e.	Prior Medication
b.	Discussion on the Design & Choice of Control Group.	f.	Concomitant Medication
c.	Study Population (Eligibility Criteria)	7.9.2	**Efficacy Analyses Results**
d.	Patient Assignment (Randomization)	a.	Primary Efficacy Endpoint
e.	Dose Selection (Study Medication)	b.	Secondary Efficacy Analyses
f.	Blinding	1)	Recurrence VTE in Evaluable Population
g.	Efficacy and Safety Variables	2)	Site of VTE Recurrence
•	Efficacy: VTE	3)	Time to First VTE
•	Safety: Hemorrhage, Adverse Events	4)	Subgroup -Sequential Venography
•	Laboratory Tests	5)	Subgroup - Sequential Lung Scan
h.	Concomitant medication	6)	Interaction - Demographics and Risk Factors
7.7	**Statistical Methods**	7)	Interaction - Country, Investigator
a.	Statistical Plan	8)	Subgroup - Confidence Interval
b.	Efficacy Analysis	c.	Summary of Efficacy Analyses
c.	Safety Analysis	7.9.3	**Safety Evaluation**
d.	Non-evaluability criteria	a.	Extent of Exposure
7.8	**Disposition of Patients Entered**	b.	Incidence of Hemorrhage
a.	Demographics	c.	Serious Adverse Events
b.	Risk Factors	d.	Discontinuation Due to Adverse Events
c.	Exposure to Study Medication	e.	Clinical Laboratory Evaluation
d.	Concomitant Medication	f.	Deaths
e.	Dropouts	g.	Discontinuation by any cause
f.	Protocol Violations	h.	Summary of Safety Analyses
g.	Study Discontinuation	7.10	**Review Summary and Recommendation**
h.	Deaths		

For details see Appendix 1: Study 529 Report (Vol. 25-33), Case Report Tabulations (Vol.52-70), Patient Profiles (Vol.71-87), Case Report Forms for Patient who Discontinued (Vol.105-139). ISE (Vol.37), ISS (Vol.38), ISE and ISS Summary Tables (Vol. 39-41), Drug Abuse and Overdose (Vol.41), and Integrated Summary of Benefits and Risks (Vol..41).

7.3 IDENTITY OF THE TEST MATERIALS

Study Medications: Lovenox®(enoxaparin sodium) Injection; Heparin sodium injection.

Table 7-1
STUDY 529: IDENTITY OF TEST MEDICATIONS

STUDY MEDICATION	LOT NUMBER
1. Enoxaparin 200 mg/mL	CB05827, CB05952, CB05984, CB06031, CB06053, CB06074.
2. Enoxaparin 100 mg/mL	CB05826, CB05951, CB05983, CB06071, CB06091, CB06092.
3. Placebo	CB05829P, CB05953P, CB05985P, CB06073P, CB06095P.
4. Heparin Sodium 5000 units/mL (multiple use vials containing 50,000 units per 10 mL. Wyeth-Ayerst No.	113010, 014008, 034052, 094031, 055158.
5. Warfarin	Coumadin® (DuPont Merck) was used by all except 43 patients (Austria, Belgium, Netherlands) who were treated with phenprocoumon.

All study medication was supplied by the sponsor and packaged individually for each patient. Within each enoxaparin patient box, daily boxes were supplied. Patients who used phenprocoumon were classified as non-evaluable ("wrong therapy").

7.4 INTRODUCTION - SYNOPSIS

The study 529 is included in the Supplement No.015 as the second pivotal trial to support the sponsor's claim that Lovenox injection can be used for treatment of DVT and PE. This indication has been already approved in Europe. In the U.S., Lovenox is approved for use in prophylaxis against postoperative DVT which may lead to PE in orthopedic and abdominal surgery.

The study was designed to demonstrate equivalence between two subcutaneous enoxaparin regimens (weight adjusted two enoxaparin doses [once- and twice-daily]) and a conventional intravenous infusion heparin regimen. Both enoxaparin and heparin regimens were used to achieve an initial (first 1-5 days), rapid increase of anticoagulation and to prevent further extension of DVT and PE. Both regimens included warfarin (beginning the second day and with INR adjusted thereafter) for maintenance of anticoagulation over a period of three months. Initial medications (enoxaparins and heparin) were ceased after the warfarin targeted INR (2.0 - 3.0) was achieved (5-10 days after randomization). Only patients with acute symptomatic DVT (venography confirmed) with or without PE (ventilation-perfusion lung scan confirmed) were included in this trial.

The study was conducted as multicenter, randomized, enoxaparin dose level blinded, parallel group, active treatment controlled clinical trial which included 900 patients randomly assigned in the three treatment groups. Efficacy was measured as the incidence of recurrent VTE (DVT, PE or death by venous thromboembolism) among the intent-to-treat population within three months following randomization. Statistical analysis of VTE recurrence rates, based on 95% confidence interval approach, demonstrated equivalence between enoxaparin once-daily and heparin, and enoxaparin twice-daily and heparin regimens.

Safety was assessed by means conventional for the enoxaparin studies: incidence of hemorrhage (any, major), adverse events (COSTART terminology), mortality (by all causes), abnormal laboratory test values (hemoglobin, platelet counts, AST & ALT), and registration of any unexpected side effect that could have been related to any of the study medications. This study did not demonstrate any unexpected adverse event, or any increased frequency or severity of the expected adverse events or hemorrhage between treatment groups.