7.9. 2 Efficacy Results: Analysis of measures of effectiveness

a. Primary efficacy endpoint

The primary efficacy endpoint was the incidence of recurrent thromboembolism (VTE, venous thromboembolic event) in the ITT population within three months of randomization.

Table 7.9-6
SUMMARY OF RECURRENT VTE FOR ALL TREATED PATIENT POPULATION

Patient Outcome ITT Population		HEPARIN		ENOXAPARIN qd		ENOXAPARIN bid		COMBINED	
		N=290	%=100	N=298	%=100	N=312	%=100	N=900	%=100
No recurrence		278	95.9	285	95.6	303	97.1	866	96.2
VTE	VTE	12	4.1	13	4.4	9	2.9	34	3.8
	DVT	8	2.7	11	3.7	7	2.2	26	2.9
	PE	1		1		2		4	
	Both	3		1		0		4	
Thrombus location									
DVT	Proximal	7		9		6		22	
	Proximal /distal	3		4		4		11	
	Iliac	1		0		0		1	
	Unilateral	10		10		4		24	
	Bilateral	0		2		2		4	

From Table 11 (Vol.25, p.77)

The primary efficacy endpoint was statistically analyzed using the confidence interval approach (Table 7.9-7)

Table 7.9-7
ANALYSIS OF EQUIVALENCE BETWEEN THREE TREATMENTS BASED ON 95% CI APPROACH

ITT Population		Heparin		Enoxaparin qd		Enoxaparin bid	
VTE incidence		12/290	4.14%	13/298	4.36%	9/312	2.88%
Difference	E1-H			0.22%			
	E2-H					-1.25%	
95% Confidence interval				[-3.04%; 3.49%]		-4.20%; 1.70%]	
CONCLUSION		EQUIVALENCE		EQUIVALENCE		EQUIVALENCE	
90% Confidence Interval				[-2.51%; 2.96%]		[-3.73%; 1.22%]	
Observed Odd-Ratio				1.06		0.69	
95% Confidence interval				[0.47; 2.36]		[0.29; 1.66]	
90% Confidence Interval				[0.54; 2.07]		[0.33; 1.44]	

From Table B.5.05 (Vol.31,p.153), and Table B.5.06 (Vol.31, p.155). *= Equivalence was claimed if the upper limit of the 95% confidence interval of the difference was less or equal to 10% and lower limit greater or equal to -10%

b. Secodary efficacy analyses

Secondary efficacy endpoints included: incidence of VTE in the evaluable patient population within three months of randomization, subgroup analyses such as influence of risk factors and study centers to VTE, and analysis of patients who underwent sequential venography during treatment period (a group of 227 patients).

1) *Incidence of recurrent VTE in the Evaluable population*

Table: 7.9-8
RECURRENCE OF VTE IN EVALAUBLE PATIENT POPULATION

Recurrent VTE		Heparin N=235	Enoxaparin qd N=247	Enoxaparin bid N=258	Combined N=740
No recurrence		225 (95.7%)	236 (95.5%)	250 (96.%)	711 (96.1%)
VTE	Any	10 (4.1%)	11 (4.4%)	8 (2.9%)	29 (3.8%)
	DVT	7	9	6	22
	PE	1	1	2	4
	DVT + PE	2	1	0	3

From Table B.5.02 (Vol. 31, p.154)

Incidence rate of VTE in the Evaluable population was comparable to ITT population. There was no signficiant difference between treatment groups, and the sponsor was able to demonstrate a statistical equivalence. This secodary efficacy evaluation has confirmed the primary analysis of efficacy.

2) *Site of the recurrence*

Table 7.9-9
LOWER EXTREMITY THROMBUS LOCATION

Thrombus Location			Heparin N=290	Enoxaparin qd N=298	Enoxaparin bid N=312	Combined N=900
No recurrence			278 (95.9%)	287 (95.6%	303 (97.1%)	866 (96.2%)
VTE	Total		12	13	9	34
	DVT	Leg	7	9	6	22
		Arm	1	0	1	2
	PE		1	1	2	4
	DVT + PE		3	1	0	4
DVT	Proximal	Any	7	9	6	22
		Only	4	5	2	11
	Proximal/Distal		3	4	4	11
	Any Iliac		1	0	0	1
	Unilateral		10	10	4	24
	Bilateral		0	2	2	4

From Table 11: Summary of Recurrent VTE Outcome for ITT (Vol.25, p.77).

There was no signifciant interaction between treatment groups and the site of recurrence of VTE.

3) *Time to First Recurrent VTE*

A special analysis of time to first recurrent VTE was performed using the methods of survival analysis. Results are presented as survival distribution plots (Figure 1: Analysis of time to first recurrence of VTE: Product limit estimates: All-treated patient [Vol.25, p.69]). According to the sponsor's interpretation, the enoxaparin twice-daily group shows both a slight delay in onset of recurrence when compared to the enoxaparin once-daily and heparin groups, as well as plateau phase beginning after day 55. Both the enoxaparin-once-daily and heparin groups show accelerated occurrence of events as well as a failure to enter a plateau phase throughout the entire 97 day follow-up period (Submission: Table B.5.09 and B.5.10). The sponsor did not provide explanation for this result, and had no comment on it.

Comment:

During the first five days of treatment only five VTE were registered (E1=3, E2=2, H=0). During the next ten days 3 VTE were recorded (H=2, E1=1). A slightly better outlook gives E2 after day 15. How much one can relate this VTE delay to E2 regimen? Probably very little. Two weeks after randomization and beginning of treatment, and one week after cessation of heparin and enoxaparin therapy, during warfarin treatment, many variables could have been involved (not discussed in this submission) and become unclear for data interpretation.

4) *Subgroup of Patient who Underwent Sequential Venography on Day 8. Change of Thrombus Size.*

Another interesting analysis of efficacy included those patients who had baseline venogram, and a control venogram performed eight days later (completion of the treatment period). Those venograms were analyzed after the visual information was translated into a venogram score (Table 7.9-10)

Table 9-10
DVT RESPONSE TO 7-DAY TREATMENT WITH HEPARIN AND ENOXAPARIN

A. THROMBUS (MARDER'S SCORE) PER LEG					
Patients		Heparin	Enoxaparin qd	Enoxaparin bid	Combined
N		70	84	73	227
Baseline	Mean	20.8	19.8	18.7	19.8
	Median	24	22	20	22
	Range	1.0-40.0	1.0-40.0	1.0-40.0	1.0-40.0
Day 8	Mean	18.5	18.4	17.4	18.1
	Median	21	19	17	19
	Range	1.0-40.0	-6.0-12.0	-6.0-17.0	-6.0-40.0
Difference Base-Day 8		2.3	1.5	1.4	1.7

B. EXPERT PANEL ASSESSMENT OF PATIENTS CONDITION								
Patients	Heparin		Enoxaparin qd		Enoxaparin bid		Combined	
N*	83		94		87		264	
	N	%	N	%	N	%	N	%

Improved	44	53	34	36.2	35	41.2	113	43.1
Unchanged	25	30.1	43	45.7	37	43.5	105	40.1
Worsened	4	4.8	4	4.3	0	0	8	3.1
Inconclusive	10	12	13	13.8	13	15.3	36	13.7
Missing	0	-	0	-	2	-	2	-

From Table 13.2 (Vol.25, p.84. *= Only adjudicated patients.

This analysis indicates that during the treatment period the majority of primary thromboses did not change or improved for some percent. Heparin was slightly better than both enoxaparin regimens. Less than five percent of treated patients worsened.

Comment: This is a conclusive evidence that this type of treatment (anticoagulation with heparin or LMWH) is necessary to halt extension of symptomatic thrombosis once it has been formed. However, the 8-day treatment may not be sufficient for major improvement (revascularisation).

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5) *Subgroup of Patients who Underwent Sequential Ventilation Perfusion Lung Scan.*

Data are presented on Table 13.3 Summary of Lung Scan Assessment Shifts for All-Treated Patients Undegoing Sequential Ventilation Perfusion Lung Scan During Treatment Period (Vol.25, p.67).

A significant number of patients, 287 (31.9%) in all, presented with PE, defined as a high probability lung scan or positive pulmonary angiogram. Since both procedures were performed on symptomatic patients (to confirm diagnosis), this is a very high incidence of PE. The scan was repeated after 8 day therapy in 265 patients (Table 13.3 [Vol.25, p.85]). Patients who were classified as with "high probability" at the baseline, improved during the study in about 40%. Patients who were with "intermediate and low probability" sustained in this category (>30%), improved for one category (10%-30%), or worsened (<10%). There was no significant difference between treatment groups, indicating that other factors might be involved.

Number of patients who developed high probability lung scans during treatment period was similar in the three treatment groups.

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6) *Interaction: Demographic characteristics and Risk factors*

Table 7.9-11
INTERACTION BY DEMOGRAPHIC CHARACTERISTICS AND RISK FACTORS

Patients with recurrent VTE			Heparin	Enoxaparin qd	Enoxaparin bid	Combined
			N=290	N=298	N=312	N=900
Total			12	13	9	34
Gender	Male		7	4	6	17
	Female		5	9	3	17
Risk Factors	Age	<40-	3	1	2	6
		40-69	6	9	5	20
		≥70	3	3	2	7
	Obesity		3	10	5	18
	Prior DVT and/or PE		4	3	5	12
	Varicose veins		2	1	1	4
	Cancer		3	6	3	12
	Recent surgery		1	2	0	3
	Radio/Chemotherapy during study		1	1	2	4
Presence of PE at baseline	No		8	8	4	20
	Yes	Asympt.	0	1	2	3
		Symptom.	4	5	5	14

From Table: Summary of VTE Outcome by Subgroup for All-Treated Patients (Vol.25, p.62).

The sponsor did not find that any of these groups could influence the incidence of VTE, the primary efficacy endpoint.

7) *Interaction by Country and Investigator*

Results are presented in Appendix 3 and Table 13.1: Summary of VTE Outcome by Country and Center for All-Treated Patients (Vol.25, p.63-64). The recurrences were reported in the U.S.A in 5.0%, Sweden 5.6%, France 4.4% and Norway 3.4%. Apparently there was no interaction by country.

8) *Subgroup analysis – Confidence interval approach*

The incidence of recurrent VTE by sex, age, weight group and predefined risk factors for the all-treated population did not show treatment preference, except for obese patients (E1=7.3%/E2=3.4%/H=2.5%). Patients with a qualifying DVT in the iliac vein had VTE reccurrence in E1=13.0%, E2=0%, and H=0%.

Overall, there were no significant differences in patients across treatment groups with respect to individual risk factor or for risk factors grouped into low and high risk patient categories. Visual displays of the confidence intervals are summarized (Fig.1).

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c. Summary of efficacy analysis

Based on the analysis of

- primary efficacy endpoint,
- revention of VTE recurrence (measured by the incidence of VTE) within three months after randomization for treatment of VTE, and
- support from secondary efficacy analyses,

the sponsor concluded that both enoxaparin regimens, 1.5 mg/kg qd, and 1.0 mg/kg bid, given within first seven days of clinical symptoms and followed by warfarin maintenance, are equivalent to heparin intravenous infusion followed by the same warfarin regimen. Results of the evaluable patient population were similar to those for the all-treated patient population.

Because heparin is approved for treatment of DVT, this equivalence means that enoxaparin (both regimens) can be accepted as alternative for heparin in this indication.

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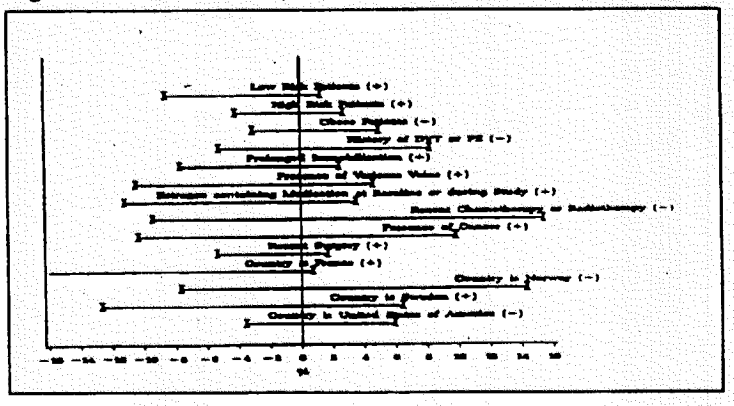
7.9.3 Safety Evaluation

Safety was evaluated on all-treated patient population. It includes a total of 900 patients assigned to heparin (290), enoxaparin once daily (298) and enoxaparin twice daily (312). Study medication exposure, hemorrhage, transfusion requirements, death, serious clinical adverse events, and clinical laboratory values were monitored for three months (during warfarin exposure). A similar safety profile was found for all three treatment regimens. The number of deaths was similar (H=9/E1=11/E2=7). An increased number of minor hemorrhage at injection site was reported for enoxaparin treated patients. Only one case of immune thrombocytopenia was reported for one enoxaparin treated patient.

a. Extent of Exposure

Heparin was given pre-randomization as an emergency therapy to more than a half of enrolled patients. Regardless to this exposure, the patients were subsequently randomized to enoxaparin (one of two doses) or to continue on heparin. Sixty (6.6%) patients received heparin for two and more days (Table 14.[Vol.25, p.90]).

Figure 1: 95% CI Analysis of VTE Recurrence in Subgroups



Duration of these three treatments was planned for 5 days. However, the majority of patients (466, 51.8%) received treatment for 6-7 days. Three hundred-twenty (35.6%) patients were treated longer (8-10 and more days). One hundred-fourteen (12.7%) patients did not reach the planned duration of treatment. Heparin was planned for six days. It was considered as a compliance criterion. Enoxaparin compliance was estimated on 10 injections (5 days). These criteria for compliance were met by 73.4% of patients (H= 50.3% vs. E~84.2% [E1=83.6%/E2=85.3%]). It seems there was a lack of compliance with postrandomization heparin therapy. Perhaps, it is largerly due to the

prerandomization heparin and an early achievement of the targeted INR in the heparin group, leading to early transfer to warfarin alone.

At least 80 percent of patients in each treatment group initiated warfarin therapy within two days of randomization. Compliance based on a patient achieving INR between 2.0-3.0 prior to discontinuation of study medication was achieved by approximately 90% of patients in each treatment group. Majority of patients (61.6%) continued warfarin beyond 90 days. Less than 5.5% received this drug for only one month (Table 17.[Vol.25,p.97]). Daily dose of warfarin necessary to maintain INR was similar in all treatment groups.

b. Incidence of hemorrhagic episodes as the primary safety endpoint

Hemorrhagic episodes were assessed separately for the treatment period and for the entire study period (Table 7.9-12).

Table 7.9-12
INCIDENCE OF HEMORRHAGE BY SEVERITY AND STUDY PERIOD

HEMORRHAGE	Heparin		Enoxaparin qd		Enoxaparin bid		Combined	
Treatment Period	N=290	%	N=298	%	N=312	%	N=900	%
Any	39	13.4	46	15.4	54	17.3	139	15.4
Major	6	2.1	5	1.7	4	1.3	15	1.7
Minor only	33	11.4	41	13.8	50	16.0	124	13.8
Leading to Discontinuation	5	1.7	4	1.3	1	0.3	10	1.1
Requiring Transfusion	4	1.4	2	0.7	2	0.6	8	0.9
Serious	4	1.4	3	1.0	3	1.0	10	1.1
Study Period								
Any	68	23.4	77	25.8	81	26.0	226	25.1
Major	15	5.2	10	3.4	6	1.9	31	3.4
Minor only	53	18.3	67	22.5	75	24.0	195	21.7
Leading to Discontinuation	5	1.7	4	1.3	1	0.3	10	1.1
Requiring Transfusion	10	3.4	6	2.0	4	1.3	20	2.2
Serious	15	5.2	7	2.3	6	1.9	28	3.1
Hemorrhagic Episodes during the Follow-up Period (Difference between Study - Treatment)								
Any	29	10.0	31	10.4	27	8.6	87	9.7
Major	9	-	5	-	2	-	16	1.8
Minor only	20	6.9	26	8.7	25	8.0	71	7.8
Leading to Discontinuation	0	0	0	0	0	0	0	0
Requiring Transfusion	6	-	4	-	2	-	12	1.4
Serious	11	3.8	4	1.3	3	1.0	18	2.0

From Table 23 (Vol.25, p.108) and Table 22 (Vol.25, p.107).

Ten major hemorrhages leading to discontinuation occurred during the treatment period. None of them happened during the follow-up. This indicates that warfarin, within the targeted INR range is safer than both heparin and enoxaparin within their targeted ranges. Incidence of other major hemorrhage during treatment period was neglectably low (H=1/E1=1/E2=3)

Incidence of "minor only" hemorrhage was higher in enoxaparin groups (E2>E1) during the treatment period. Perhaps, it is due to injection site reactions. It is not clear why this difference continued to exist during the follow-up period.

During the follow-up period, significantly more serious hemorrhage were registered in heparin group, and they required transfusion (H=11/E=4/E=3). Because all three groups in this period received only warfarin, this incidence is probably due to factors not related to study medications.

One hundred thirty-nine hemorrhagic episodes occurred during the treatment period. It is between 17-18 per a day of therapy. Eighty-seven appeared during the 90 days of follow-up. It is less than one daily.

Comment: Heparin and enoxaparin treatment carry a serious risk of bleeding. This should be judged against the benefit. Insignificant, but still present difference exists between heparin and enoxaparin, with enoxaparin twice-daily being the most risky regimen for bleeding .

Significant difference was found between enoxaparin and heparin treated patients in the location of hemorrhagic episodes (Table. 7.9-13)

Table 7.9-13 BEST POSSIBLE

DISTRIBUTION OF HEMORRHAGIC EVENTS BY BLEEDING LOCATION

Hemorrhage by Site	Heparin	Enoxaparin qd	Enoxaparin bid	Combined
Any hemorrhage	68	77	81	226
GI	11	12	13	36
Retroperitoneal	-	1	-	1
Epistaxis >5 min	4	5	4	13
Ecchymosis/Hematoma Injection Site	1	17	17	35
Subconjunctival	1	2	2	5
Ecchymosis, Other	10	11	10	31
Hematoma, Other	6	9	7	22
Hematuria	16	13	21	50
Other	31	23	25	79

From Table 25 (Vol. 25, p.112)

Thirty-five hematomas (7.74%) appeared on injection site in 452 patients who received enoxaparin. In comparison with only one event (0.45%) in the heparin group, this incidence is highly significant. Clinically, it means that patients who will benefit from once daily injection of enoxaparin have probability to experience more injection site hemorrhage (1:14) than patients receiving heparin (1:100). None of these events was considered serious and all were managed at site with standard clinical measures.

Transfusion Needs

Twenty (6.9%) heparin patients, 22 (7.4%) enoxaparin once-daily patients and 21 (6.7%) enoxaparin twice-daily patients received one or more transfusions. The mean total amount of blood transfusion products given to heparin patients was 4.0 units (range 1 to 8 units) compared to 4.7 units (range 2 to 19) for enoxaparin once-daily patients and 3.3 units (range 1 to 19 units) for enoxaparin twice-daily patients.

c. Secondary safety analysis: Incidence of adverse events.

In this analysis, VTE and hemorrhage (all categories) were included into the adverse event class. Number of patients with at least one adverse event during the treatment period was 444 (49.3%). They were distributed almost equally between treatment groups (H=136[46.9%]/ E1=150[50.3%]/ E2=158[50.6%]). Only 58 of these adverse events that appeared in 45 patients were classified as serious (Submission: Table 31, Vol.25, p.124). Only nine serious events appeared in more than one patient (Table 7.9-14).

Table 7.9-14
SERIOUS ADVERSE EVENTS DURING TREATMENT PERIOD THAT APPEARED IN MORE THAN ONE PATIENT

Adverse Event	Heparin	Enoxaparin qd	Enoxaparin bid	Combined
Gastrointestinal hemorrhage	1	2	2	5
Chest pain	1	1	2	4
Deep Thrombophlebitis	1	2	1	4
Hemorrhage	2	-	1	3
Pain	2	-	-	2
Anemia	1	-	1	2
Dizziness	1	-	1	2
Dyspnea	-	1	1	2
Prostatic carcinoma	-	1	1	2
Total	9	7	10	29

From Table 31 (Vol.25, p.124)

Serious adverse events were also recorded during the entire study period of 3 months. The majority of events occurred during the treatment period (H=7[70%], E1=7[58%], E2=8[57%]). In the heparin group all early events were classified as hemorrhage. In E1 group, two events were classified as deep thrombophlebitis, two hemorrhage and three were unrelated (pain, edema, and hypotension). In E2 group, one thrombophlebitis, two GI hemorrhage, two allergic reactions, two chest pain, one duodenitis and one apnea events were recorded. One case of thrombocytopenia occurred in this group with onset on day 9. In the follow-up period thrombophlebitis occurred once in the heparin group, three times in E1 group, and no in E2 group. There was no difference of incidence and category of adverse event between treatment groups during the follow-up period.

d. Adverse events leading to discontinuation

According to Table 29 (Vol.25, p.119. Summary of Adverse Clinical Events Leading to Study Medication Discontinuation During the Treatment Period for All-Treated Patients), 21 patients (2.3%) discontinued

treatment due to at least one adverse event. The most frequent was GI hemorrhage which occurred six times. Less frequent were chest pain and hemorrhage (3 times each) and dyspnea (twice). No significant difference between treatment groups was found.

Related adverse events during the treatment period were classified according to COSTART dictionary. They are summarized on Table 30 (Vol. 25, p.120. Summary of Adverse Clinical Events Related to Study Medication During the Treatment Period for All-Treated Patients Again, the only significant difference was found between injection site hemorrhage in heparin and both enoxaparin groups. All other hemorrhages were distributed non significantly between these groups. However, there was a tendency for E2 group to have less events, and for E2 and heparin group to have events distributed more evenly.

e. Clinical laboratory evaluations

Platelet count, hemoglobin level and abnormal values of bilirubin, potassium, ALT and AST were evaluated at baseline and during treatment period. Change of these parameters was summarized on table 34 (Vol.25, p.132. Table 34: Summary of Clinically Significant Laboratory Test Values, Thrombocytopenia and Thrombocytosis for All-Treated Patients), table 35 (Vol. 25, p.133. Table 35: Summary of Clinically Significant Laboratory Test Values, Hemoglobin, for All-Treated Patients), and table 36 (Vol. 25, p.135. Table 36: Summary of Clinically Significant Laboratory Test Values, Biochemistry, for All-Ttreated Patients). No difference in occurrence of any abnormal parameter was observed between the three treatment groups.

- *HIT*

One patient (1/900, <0.1%) developed immune thrombocytopenia. Two patients, one in each enoxaparin treatment group, developed severe thrombocytopenia for an incidence of 0.3% for each group.

- *Thrombocytopenia*

It may be of interest to note that 71 patients had thrombocytopenia at baseline (mild=57; moderate=13; severe=1). This number decreased to 53 during treatment, but the category has worsened (mild=37; moderate=14; severe=2). During the follow-up period the total number of patients with thrombocytopenia was 68 (mild=51; moderate=8; severe=8).

- *Thrombocytosis*

Thrombocytosis was recorded at baseline in 56 (6.2%) patients. This number increased to 136 (15.1%) during the treatment period, and reset to 69 (7.8%) during the follow-up period.

- *ALT and AST*

During the treatment period a trend toward increased frequency of substantial ALT and AST elevation was observed for enoxaparin patients. No other difference was noted between treatment groups for laboratory parameters.

The sponsor has submitted table 37: Listing of Patients with Serious Laboratory Events Related to Study Medication During the Study Period (Table 37, Vol. 25, p.138). In this table, 6/7 (85%) events (decrease of hemoglobin and RBC, increase of APTT, and PT) in the heparin group appeared during the treatment period. In other groups only 50% of events occurred in this period. All other events (cited above plus platelet decrease, and AST and ALT increase) occurred immediately after this period.

f. Deaths

Incidence of deaths by any cause was considered as a special section of the safety analysis. This is not analysis of mortality related to enoxaparin. It was only registration of all deaths that occurred during the study period of three months.

Twenty-eight patients died during this study Table 20(Vol.25, p.104). Only two of them died during the treatment period (E1 group). One of them (pt#01044) died by pulmonary edema associated with pulmonary embolism chronic obstructive pulmonary disease and pulmonary hypertension. Another (pt#20016) died due to retroperitoneal hemorrhage associated with parenchymal hemorrhage. Twenty-six deaths occurred during the follow-up period. None of them was associated with the study medication. They are shortly presented in Narratives (see Appendix 3).

g. Discontinuation by any reason

Another aspect of the safety analysis was the discontinuation by any reason. Again, it was only registration, and investigator's assessment of the probability of any relation of the discontinuation with each of three study medications. Table 21 (Vol. 25, p.106. Listing of Patients with Adverse Clinical Events Who Discontinued Study Medication) summarizes these data.

Twenty-three patients discontinued study medication due to adverse events (H=8/E1=10/E2=5). Accidental overdose occurred in the heparin group. Six out of eight (75%) events were bleeding (hematuria, vagina, GI, and hemorrhage). In E1 group, four events (40%) were hemorrhage, two were recurrence of thrombophlebitis (20%) and other included dyspnea, bradycardia, myocardial infarction, asthenia, hypotension, vomiting, and peripheral edema. Two of them died (pt#01044: dyspnea, cardiac arrest; pt#20016: hypotension). In E2 group, only one event (20%) was hemorrhage. Two events (40%) were PE or reoccurrence of VTE. Two were classified as chest pain (microembolisation was not ruled out). Others include allergic reactions (urticaria, and pruritus). All other patients recovered after discontinuation of the study medication during the treatment period. Rechallenge has not been performed. Association is classified as possible.

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h. Summary of safety analysis

Summarizing the risk/benefit assessment of this study, the sponsor has made the following conclusion: " Enoxaparin as a 1.0 mg/kg twice daily regimen or a 1.5 mg/kg once-daily was equivalent to adjusted-dose, continuous infusion heparin therapy for the prevention of recurrent venous thromboembolic disease in patients with acute deep vein thrombosis with or without pulmonary embolism. The safety profile of both enoxaparin once-daily and enoxaparin twice-daily treatment was comparable to that of continuous infusion heparin therapy."

7.10 STUDY 529: REVIEW SUMMARY

The Study 529 is an adequate and well controlled clinical trial. Both the efficacy and safety analyses have demonstrated equivalence between enoxaparin once-daily + warfarin, enoxaparin twice-daily + warfarin, and heparin + warfarin regimens for prevention of VTE recurrence in patients who presented with acute DVT with or without PE. Data obtained in this study are admissible as evidence in support of the sponsor's claim that Lovenox can be used for treatment of acute DVT.

The lack of statistical significance for difference between enoxaparin once-daily and enoxaparin twice-daily suggests that, the more convenient once-daily regimen, should be recommended as treatment for a limited number of patients who present with acute DVT and with clinical condition permiting outpatient

treatment. For in hospital treatment of acute DVT with or without PE the three regimens may be considered as interchangeable.

8.0 SUPPLEMENT N-015: INTEGRATED SUMMARY OF EFFICACY AND SAFETY (RISK/BENEFIT ASSESSMENT)

To support their claim, the sponsor submitted two adequate and well controlled clinical trials, and additional evidence for efficacy and safety of Lovenox in the requested indication. In both pivotal studies enoxaparin successfully replaced heparin. The overview of both trials is presented on table 8-1.

This table (8-1: Overview of Studies in the treatment of Acute DVT [Vol.1; p.172]) presents data in support that both studies were designed and conducted in a manner allowing meta-analitical analysis.

A total of 1401 patients were treated in both trials. They received intravenous heparin (544 patients - both trials), enoxaparin once-daily 298 patients - study '529' only), enoxaparin twice-daily (559 patients - both trials).

More than 95% of patients did not have reccurrence VTE within three months. This result supports use of enoxaparin for DVT treatment.

Table 8-1

Table 1 : Overview of Studies in the Treatment of Acute Deep Vein Thrombosis[a]

	CPK 3991	529
Study Design	Hospitalization or ambulatory; open-label, parallel, modestly-enlarged, multicenter	Hospitalization; partially blinded (enoxaparin double regimen), parallel group, modestly-enlarged, multicenter
Study Phase	III	III
Location	Canada	United States, Europe, Australia, Israel
Start of Treatment	After confirmation of diagnosis of deep vein thrombosis and randomization process	After confirmation of diagnosis of deep vein thrombosis with or without pulmonary embolism and randomization process
Duration of Treatment	Outpatients and inpatients; at least 5 days (treatment period); follow-up 90 days (study period)	Inpatients; at least 5 days (treatment period); follow-up 97 days (study period)
Treatment Group, Dose & Regimen	Enoxaparin 1 mg/kg bi-twice-daily Unfractionated heparin bolus 5000 units I.v., then continuous infusion of 1250 units hourly. Warfarin sodium therapy adjusted to an INR[b] of 2 to 3 was begun within two days of randomization for all treatment groups and continued for three months.	Enoxaparin 1.5 mg/kg qd once-daily Enoxaparin 1 mg/kg bi-twice-daily Unfractionated heparin bolus 5000 units I.v., then continuous infusion of 1250 units hourly. Warfarin sodium therapy adjusted to an INR[b] of 2 to 3 was begun within three days of randomization for all treatment groups and continued for three months.
Objective	To compare the efficacy and safety of an outpatient anticoagulant regimen consisting of a weight-adjusted dose subcutaneous enoxaparin injection with a standard inpatient anticoagulant regimen consisting of unfractionated heparin administered by continuous infusion	To compare the safety, efficacy and cost benefit of enoxaparin administered once or twice-daily subcutaneously to intravenous continuous infusion heparin therapy in the treatment of lower extremity deep vein thrombosis and pulmonary embolism
Number of randomized patients	301: Heparin = 154 Enoxaparin once-daily = na[c] Enoxaparin twice-daily = 147	900: Heparin = 290 Enoxaparin once-daily = 298 Enoxaparin twice-daily = 312
Criterion for randomization	Patients with acute proximal deep vein thrombosis confirmed by either venography or duplex ultrasonography	Patients with symptomatic lower extremity deep vein thrombosis diagnosed by venography or ultrasonography

[a] Extracted from studies CPK 3991 and 529 Comprehensive Medical Reports
[b] INR: International Normalized Ratio
[c] na: not applicable

Integrated Summary of Benefits and Risks
Protocol Numbers CPK 3991 and 529
Enoxaparin IM 20-164/s
18 February 1997

8.1 EFFICACY (BENEFITS)

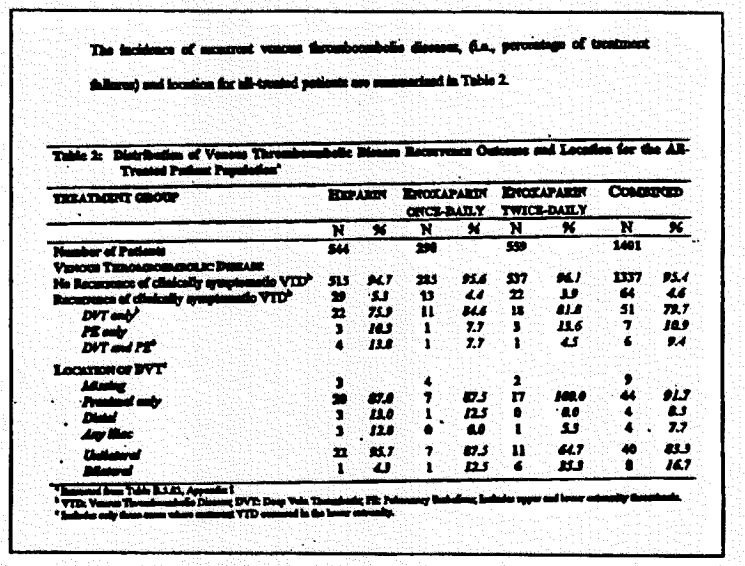
(Integrated Summary of Benefits and Risks [Vol.1, p.165-211], and Integrated Summary of efficacy [Vol. 37], and Integrated Efficacy and safety Summary tables [Vol.39-41])

Treatment of DVT and Prophylaxis of VTE reccurrence

The sponsor has proposed Lovenox® (enoxaparin sodium) injection for "Treatment of Deep Vein Thrombosis [redacted] The recommended dose in patients with acute DVT with or w/o PE is 1.5 mg/kg qd or 1.0 mg/kg q12h for a minimum of 5 days and until a therapeutic oral anticoagulant effect has been achieved (INR 2.0-3.0). Warfarin therapy should be initiated when appropriate.

Table 8-2 (Distribution of VTE outcome and location for the all-treated patient population) is to demonstrate the dominance of enoxaparin vs. heparin regimens in this indication.

Table 8-2



The incidence of recurrent venous thromboembolic disease, (i.e., percentage of treatment failures) and location for all-treated patients are summarized in Table 2.

Table 2: Distribution of Venous Thromboembolic Disease Recurrence Outcome and Location for the All-Treated Patient Population[a]

TREATMENT GROUP	HEPARIN		ENOXAPARIN ONCE-DAILY		ENOXAPARIN TWICE-DAILY		COMBINED	
	N	%	N	%	N	%	N	%
Number of Patients	344		298		559		1401	
VENOUS THROMBOEMBOLIC DISEASE								
No Recurrence of clinically symptomatic VTE[b]	313	94.7	283	95.6	537	96.1	1337	95.4
Recurrence of clinically symptomatic VTE[b]	29	5.3	13	4.4	22	3.9	64	4.6
DVT only[c]	22	75.9	11	84.6	18	81.8	51	79.7
PE only	3	10.3	1	7.7	3	13.6	7	10.9
DVT and PE[c]	4	13.8	1	7.7	1	4.5	6	9.4
LOCATION OF DVT[c]								
Missing	3		4		2		9	
Proximal only	20	87.0	7	87.5	17	100.0	44	91.7
Distal	3	13.0	1	12.5	0	0.0	4	8.3
Any Site	3	13.0	0	0.0	1	5.9	4	7.7
Untreated	22	95.7	7	87.5	11	64.7	40	83.3
Bilateral	1	4.3	1	12.5	6	35.3	8	16.7

[a] Extracted from Table E.3.1.01, Appendix 1
[b] VTE: Venous Thromboembolic Disease; DVT: Deep Vein Thrombosis; PE: Pulmonary Embolism; Includes upper and lower extremity thrombosis.
[c] Includes only those cases where confirmed VTE occurred in the lower extremity.

Only 64 or 4.6% patients had reccurrence of symptomatic VTE. While heparin regimen allowed recurrent VTE within the expected rate (observed 5.3% vs. expected 5%-7%), both enoxaparin regimens were below the incidence rate expected for heparin regimen (E1=4.4%, E2=3.9%).

Recurrence of DVT appeared in 51 (79.7% of all VTE) patients (H=75.9%/E1=84.6%/ E2=81.8%). Local extension was the most frequent type of reccurrence. It occurred in 44 (91.7% of all DVT) patients (H=87.0%/E1=87.5%/E2=100.0%). VTE type (DVT, PE or both) and location of DVT were distributed comparably among treatment groups. Pulmonary embolism occurred in 13 patients (20.3% of recurrent VTE). Two fatal outcomes occurred in the heparin group. No death was directly related to study medications, and no thromboembolic death occurred as recurrent VTE.

As per these data, the primary efficacy parameter, the incidence of recurrent VTE, was higher in heparin, than in enoxaparin treated groups. Enoxaparin twice-daily performed better than once-daily. However, this difference was not statistically signficant. In conclusion, the sponsor declared equivalence between either one of the two enoxaparin and the heparin treatment group.

All patients experiencing reccurrent VTE had additional risk factors. The sponsor submitted evidence (confidence interval testing) that some risk factors (gender, weight over 90 kilos, "low risk", location, cancer, and age) had statistically different effect on one or the other treatment regimen. However, the difference was small, the number of patients per subset also small, and without further work and explanation, these results appeared to be insignificant.

According to the sponsor, these two pivotal trials unequivocally support using enoxaparin instead of heparin in therapeutic regimens (with warfarin) for initial treatment of acute (symptomatic) DVT (confirmed by venography or duplex ultrasound) when thrombolysis is not required and therapy is aimed toward prevention of DVT extension and pulmonary embolism.

8.2 SAFETY (RISKS)

(Integrated Summary of Benefits and Risks [Vol.41, p.283], and Integrated Summary of Benefits and Risks [Vol.1, p.165-211]).

Both physicians and patients have to be aware that patients on enoxaparin treatment carry on increased risk for injection site hematomas, and bleeding at any site. In particular, this risk is increased for patients who suffer from diseases that may bleed locally: peptic ulcer, cancer (locations including GI, urinary system, gynecological, respiratory etc.).

In two controlled clinical trials ('2091' and '529') 1401 patients were exposed to at least one dose of study medications. Five hundred forty-four were randomized to heparin+warfarin, 298 to enoxaparin qd + warfarin, and 559 to enoxaparin bid + warfarin. Assessments of hemorrhage, adverse clinical events and clinical laboratory evaluations were compared across the three treatment groups during the treatment (Day 1 - Day 14) and study periods (Day 1 - Day 90).

The sponsor has concluded that the two clinical trials have demonstrated that the safety profile of both enoxaparin regimens was comparable to that of continuous infusion of heparin.

Hemorrhage

Hemorrhage was the primary safety parameter.

Table 8-3 (Submission Vol.1, p.183. Table 4: Summary of the Incidence of Hemorrhagic Episodes During the Treatment Period for the All-Treated Patient Population) and table 8-4 (Vol.1, p. 185, Table 5: Summary of the Incidence of Hemorrhagic Episodes During the Study Period for All-Treated Patient Population) present that patients exposed to anticoagulant study medications (heparin or enoxaparin with warfarin, or warfarin alone) are prone to bleeding episodes up to 20% of exposures.

However, categories such as major hemorrhage, or hemorrhage leading to discontinuation, occurred rarely and were comparably distributed beteen treatment groups. Minor hemorrhage (9.8%) was significantly more frequent among enoxaparin groups than heparin, and during the treatment period.

Ecchymosis/hematoma group was the major component of minor hemorrhage (61/137; 44.5%). With enoxaparin twice-daily being the regimen with the most hemorrhagic episodes, this result can be attributed to the increased frequency of the injection site reactions (bleeding, pain, masses, etc.) due to subcutaneous route of administration of a LMWH.

Table 8-3

Table 4: Summary of the Incidence of Hemorrhagic Episodes during the Treatment Period for the All-Treated Patient Population[a]

TREATMENT GROUP	HEPARIN		ENOXAPARIN ONCE-DAILY		ENOXAPARIN TWICE-DAILY		COMBINED	
	N	%	N	%	N	%	N	%
Number of Patients	544		298		559		1401	
NUMBER OF PATIENTS WITH HEMORRHAGIC EPISODES								
Any Episode	49	9.0	46	15.4	65	11.6	160	11.4
Major[b]	9	1.7	5	1.7	9	1.6	23	1.6
Minor only[c]	40	7.4	41	13.8	56	10.0	137	9.8
Leading to Discontinuation	9	1.7	4	1.3	4	0.7	17	1.3
Requiring Transfusion	6	1.1	2	0.7	3	0.5	11	0.8
SITE OF HEMORRHAGIC EPISODES								
Any Episode	49	9.0	46	15.4	65	11.6	160	11.4
Gastrointestinal	7	1.3	5	1.7	9	1.6	21	1.5
Retroperitoneal			1	0.3			1	0.1
Intracranial								
Epistaxis	1	0.2	4	1.3	3	0.5	8	0.6
Ecchymosis/Hematoma	11	2.0	26	8.7	24	4.3	61	4.4
Subconjunctival	1	0.2			1	0.1	0.1	0.1
Hematuria	16	2.9	8	2.7	17	3.0	41	2.9
Other	17	3.1	9	3.0	18	3.2	44	3.1

[a] Extracted from Table 4.4.01 and 4.4.02, Appendix]
[b] Severity as defined by the Outcome Adjudication Committee

Table 8-4

Table 5: Summary of the Incidence of Hemorrhagic Episodes during the Study Period for the All-Treated Patient Population[a]

TREATMENT GROUP	HEPARIN		ENOXAPARIN ONCE-DAILY		ENOXAPARIN TWICE-DAILY		COMBINED	
	N	%	N	%	N	%	N	%
Number of Patients	544		298		559		1401	
NUMBER OF PATIENTS WITH HEMORRHAGIC EPISODES[b]								
Any Episode	92	16.9	77	25.8	99	17.7	268	19.1
Major[c]	21	3.9	10	3.4	14	2.5	45	3.2
Minor only[d]	71	13.1	67	22.5	85	15.3	223	15.9
Leading to Discontinuation	9	1.7	4	1.3	4	0.7	17	1.2
Requiring Transfusion	14	2.6	6	2.0	7	1.3	27	1.9
MAJOR HEMORRHAGIC DURING FOLLOW-UP[e]								
Month 1	15	2.8	7	2.3	11	2.0	33	2.4
Month 2	3	0.6	2	0.7	2	0.4	7	0.5
Month 3	3	0.6	1	0.3	1	0.2	5	0.4

[a] Extracted from Table 5.4.01, Appendix]
[b] Excludes episodes of hemorrhage which occurred after confirmed occurrence of venous thromboembolic disease
[c] Severity as defined by the Outcome Adjudication Committee

Adverse Events

The combined incidence of all