Anti IIa Activity - Mean Pharmacokinetic parameters (Day 5) for males and females ±SD

	Treatment A		Treatment B		Treatment C	
	Male	Female	Male	Female	Male	Female
Amax IU/mL	0.23±0.05	0.22±0.04	0.23±0.05	0.24±0.04	0.27±0.05	0.24±0.05
tmax h*	4.5	3.8	4.0	4.0	4.5	4.0
AUC_{0-8h}	1.29±0.32	1.17±0.22	1.26 ±0.30	1.24±0.25	1.47±0.35	1.30±0.29
AUC_{0-t}	1.81 ±0.73	1.27 ±0.30	1.67±0.71	1.38±0.33	2.04±0.79	1.499±0.39
CL/F L/h mL/min	1.68±0.73 28.0±12.2	1.67±0.36 27.8±6.0	1.80±0.70 30.0±11.7	1.55±0.35 25.8±5.8	1.47±0.52 24.5±8.7	1.46±0.29 24.3±4.8
t1/2 h	2.7±1.0	2.3±0.7	2.0±0.5	2.0±0.7	2.5±0.7	2.1±0.5

*median

[redacted]

AUC from treatment C was about 6% higher than the AUC from treatment A. A slightly higher clotting time prolongation was observed for treatment C vs. treatment A. There is a significantly lower extent of absorption ($p<0.001$) in females vs. males and the MRT of [redacted] activity is significantly longer in males vs. females ($p<0.001$). The average exposure in females is lower than in males ($p<0.001$) and the apparent elimination half-life is prolonged in males vs. females.

[redacted] - Mean parameters (Day 5) for males and females ±SD

	Treatment A		Treatment B		Treatment C	
	Male	Female	Male	Female	Male	Female
A(Δt)max s	115.8±14.6	93.2±9.0	116.9±16.5	99.9±9.8	122.6±14.6	99.3±10.1
A ave s	61.8±6.4	48.2±5.7	59.8±6.3	50.2±6.1	64.7±8.3	52.1±5.7
tmax h*	3.0	2.5	2.5	2.5	3.5	3.0
AUC_{0-84h} h.s	1484±153	1158±136	1456 ±119	1190±1435	1552±199	1250±137
AUC h.s	1961 ±314	1327 ±226	1966±226	1367±239	2009±341	1454±238
MRT h	16.4±2.7	11.5±2.3	17.2±2.1	11.5±2.0	15.7±2.0	12.1±2.5
t1/2 h	11.7±2.4	7.1±2.0	12.5±1.8	7.3±1.8	11.1±1.9	7.6±2.2

*median

No significant gender effects were observed for aPTT.

Two one sided tests procedure results:

Anti-Xa activity (log transformed)

Parameter	TRT	90% CI*	Estimate
Amax IU/mL	B vs. A C vs. A C vs. B	102-110 102-110 96-103	106 106 99
AUC_{0-24h} IU.h/mL	B vs. A C vs. A C vs. B	100-106 105-112 102-108	103 109 105
$AUC_{0-\infty}$ IU.h/mL	B vs. A C vs. A C vs. B	100-106 104-111 101-108	103 107 104

* Confirmed by reviewer

Note that all of these comparisons except one show the lower bound of the 90% CI >100%

Anti-IIa activity (log transformed):

Parameter	TRT	90% CI*	Estimate
Amax IU/mL	B vs. A C vs. A C vs. B	97-111 104-120 100-115	104 112 108
$AUC_{0-8\,h}$ IU.h/mL	B vs. A C vs. A C vs. B	95-109 105-121 103-119	102 112 110
AUC_{0-t} IU.h/mL	B vs. A C vs. A C vs. B	92-108 107-126 107-126	100 116 116

Note that most of these comparisons show the lower bound of the 90% CI >100%

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[redacted]

Parameter	TRT	90% CI	Point Estimate
A(Δtmax) s	B vs. A C vs. A C vs. B	100-108 102-111 98-106	104 106 102
AUC_{0-24h} h*s	B vs. A C vs. A C vs. B	98-103 103-110 103-108	101 106 106

Note that all these comparisons except two show the lower bound of the 90% CI >100%.

Comments:

1. An alternate model to use for gender analysis would be:

Y = Weight sequence gender sequence*gender subject(sequence*gender) period product product*gender weight*product *sequence*product*period*gender*

Using this model if the interaction term *"sequence*product*period*gender"* is not significant at the $p<0.1$ level, this term could be dropped from the model and the data re-analyzed. If no terms show significance at the 0.05 level then the analysis could then be repeated dropping the weight term. It is noted that to some extent weight is taken into account through the dose being given on a weight basis. The model further explores gender effects in terms of the gender*product interaction.

2. The results from the two one-sided test show that many of the parameter comparisons had the lower bound of the 90% CI greater than 100%. This lends some doubt as to the conclusions of bioequivalence, however, an earlier submission showed bioequivalence of the single to double strength enoxaparin (PK129, reviewed in April 1996 (NDA 20-164/SE1 (008)).

Protocol Report RP 54563Q-260

Title: An open-label pilot study, randomized trial of 5 weeks enoxaparin 60 mg sc plus aspirin alone following conventional medical therapy in patients admitted to hospital with diagnosis of unstable angina or acute non-Q-wave myocardial infarction

[redacted]

Study dates: Aug. 25, 1994 - Aug 08, 1995

Objective: To evaluate the safety and efficacy of 5 weeks enoxaparin therapy in combination with aspirin.
To assess the pharmacokinetic profile of 60 mg repeated dose, once daily enoxaparin in patients.

Assay dates: Not supplied
Assay site: Not supplied

Batches: Aspirin RT 991 -US841
Enoxaparin CB05871, CB05992

Demographics:
Overall patient population: not PK patients

	MEAN ± SD	RANGE
AGE (YEARS) MALE FEMALE	63.5 ± 9.6 67.8 ± 4.5	44 - 80 62 -73
WEIGHT (KG) MALE FEMALE	81.9 ± 15.6 68.3 ± 8.2	64 - 115 57 - 78
HEIGHT (CM) M ALE FEMALE	174.2 ± 6.1 159.0 ± 6.2	167 - 188 150 - 166

METHODOLOGY:

Study design:
Patients with unstable angina or non-Q-wave myocardial infarction were included in the study. The patients were stabilized by conventional therapy for a minimum of 2 and a maximum of 5 days. Enoxaparin 60 mg (0.3 mL) was administered sc once daily with aspirin 100 mg po once daily. Patients were randomized to one of two treatment groups, aspirin alone or enoxaparin plus aspirin. This was also a clinical study in which efficacy and safety were addressed.

Biological Measurements:
Anti-Xa and anti-IIa activities, Heptest^{R} and aPTT were measured.

Blood sampling:
Day 1, 2 and 3: pre-dose and 3 hour post-dose
Day 4: pre-dose, 1, 3, 4, 6, 9, 12, 16 and 24 hours post dose.
Day 28: 3 hours post-dose

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RESULTS:

Summary of mean pharmacokinetic/pharmacodynamic parameters at steady-state (Day 4) ±SD:

	Anti Xa activity	Anti IIa activity
Amax IU/mL	0.58±0.15	0.052±0.20
t max (h)	4.0*	4.0*
AUC_{0-t} (h.IU/mL)	5.74±1.35	0.33±1.45
AUC (h.IU/mL)	6.18±1.46	NA
MRT (h)	9.3±1.3	NA
Vz/F (L)	7.5±1.4	NA
Vss/F (L)	9.3±2.0	NA
CL/F L/h mL/min	1.02±0.33 17.0±5.5	NA
t1/2 (h)	5.2±0.8	NA
A ave = $AUC_{0-\tau}/\tau$(IU/mL)	0.24±0.6	NA
r=A(3h) day 28/A (3h) Day 2	1.07±0.22	1.27±0.38

*median NA=not applicable

Summary of mean [redacted] and aPTT parameters at steady-state (Day 4) ±SD:

	[redacted]	aPTT
A t=0h (s) on Day 4	29.3±6.5	32.0±3.4
Amax (s)	82.6±7.9	39.6±4.1
A(Δt)max (s)	+69.5±7.4	NA
t max (h) - median, N=19	4.0	3.0
AUC(0-24h) (h.s), N=13	995.4±102.5	NA
t1/2 (h), N=13	8.9±2.1	NA
r=A(3h) day 28/A (3h) Day 2 N=13	1.12±0.13	NA

NA=not applicable

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Comparison of CL/F to other studies:

Study PK9001006:

DOSE mg/Kg	Cls/F L/h
1.0	0.72 ±0.09 range=0.59-0.84
1.25	0.65 ±0.06 range=0.54-0.73
1.5	0.64 ±0.06 range=0.59-0.81
2.0	0.64 ±0.07 range=0.55-0.77

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Study RP554563Q-133:

All given 1.5 mg/Kg sc enoxaparin:

	Males	Females	Males	Females	Males	Females
CL/F L/h	0.61±0.12	0.60±0.12	0.61±0.12	0.56±0.10	0.59±0.12	0.55±0.09
mL/min	10.2±2.0	10.0±2.0	10.2±2.0	9.3±1.7	9.8±2.0	9.2±1.5

Other parameters are more difficult to compare across studies, since this study used a fixed dose, whereas the other studies used a weight-adjusted dose.

Note:

The mean clearance values shown in these two studies are much lower than in the present Study RP54563-260. The sponsors concluded that the clearance is within that found in earlier studies, however this would only be the case where AUC was in IU μg/mL and dose was in mg units, but the AUC reported in Study RP54563Q-260 was reported as IU anti-Xa/mL and presumably dose was also considered as IU anti-Xa/mL. It is erroneous for the sponsors to report ranges of clearance since these are highly dependent on the number of subjects in the study analyses. The present study shows a mean clearance about 70% longer than that reported in previous studies, which may be due to aspirin being present, or may reflect on a difference between the activity in patients vs. healthy volunteers. Since clearance is a hybrid term it is difficult to understand the underlying mechanism unless other tests/studies are undertaken. For instance, the possibility of a drug interaction could be explored from a crossover study in elderly healthy subjects in which there are two treatment arms: enoxaparin given alone and enoxaparin with aspirin. This study could not be undertaken in the patient population (unstable angina) since aspirin is administered to

these patients routinely.

Conclusion:
1. The sponsors need to explain the difference in mean clearance in this population for anti-Xa activity as compared to earlier studies. The sponsors should be aware of consistency in units when comparing mean clearance across studies i.e. whether clearance is a based on IU anti-Xa or mg enoxaparin. Comparison of ranges should be avoided since these are dependent on the number of subjects used in the analyses. The present study suggests that clearance is 70% higher than shown in healthy subjects.

2. The sponsors may want to consider conducting a drug-interaction study in healthy elderly subjects with two treatment arms: enoxaparin and enoxaparin with aspirin. Another possibility would be to compare the populations and the influence of cofactors using individual plasma data and a non-linear fixed mixed effect model.

Protocol Report RP 54563Q-261
Title: A multi center trial of safety and tolerability of two doses of enoxaparin in patients with unstable angina and non-Q-wave myocardial infarction.

[redacted]

Study dates: July-06-1995 to Feb.-02-1996
Objective: To compare the safety and tolerability of two weight adjusted regimens of subcutaneous injections of enoxaparin in patients with unstable angina and non-Q-wave myocardial infarction.

Assay dates: Oct 1995-March, 1996
Assay site: RPR, Antony, France
Batches: Lot # 9505717 100mg/mL enoxaparin, Lot # 9505729 40 mg/0.4 mL enoxaparin, Lot # 9405175, 9406198, 9505719 30 mg/0.3mLenoxaparin.

Demographics:

Overall patient population: not just the PK patients

	MEAN ± SD	RANGE
AGE (YEARS)	62.7 ± 11.5	33 - 92
WEIGHT (KG)	83.8 ± 18.4	40 - 169

63.3% were male and 36.7% were female.

METHODOLOGY:

Study design:
Although this was primarily a clinical safety study, blood specimens were collected during the trial for anti-Xa activity measurements.

Patients received a 30 mg intravenous bolus then a weight-adjusted dose of either 1.25 mg/Kg or 1.0 mg/Kg subcutaneous dose of enoxaparin every 12 hours. After hospital discharge, patients received a fixed dose of 60 mg (weight≥65 Kg) or 40 mg (weight < 65 Kg) subcutaneous dose of enoxaparin every 12 hours. The duration of treatment was for a total of 14 days on the fixed dose regimen.

Note that the proposed dosage regimen for this indication is 1 mg/Kg S.C. every 12 hours in conjunction with oral aspirin therapy (100 to 325 mg once daily). Treatment with enoxaparin would be for a minimum of 2 days and continued until clinical stabilization with a usual duration of treatment of 2 to 8 days.

Blood sampling:
Blood was collected for measurement of anti-Xa activity pre-dose and 3 to 5 hours post-dose following the third and last enoxaparin weight -adjusted dose and after fixed dose administration.

RESULTS:
Because of a high rate of major hemorrhage the 1.25mg/Kg dose group was discontinued and the subsequent patients were placed on 1.0 mg/Kg dose. Samples were collected from 281/321 patients in the 1.25 mg group and from 244/309 patients in the 1.0 mg group.

Table 1 summarizes the anti-Xa activities measured in patients at predose (trough) and at about 3 hours postdose (peak). Comparison of median trough and peak levels for the third vs. last dose shows similar values, indicating lack of accumulation for bid dosing. No formal pharmacokinetic study was submitted for this dosing regimen. Currently enoxaparin is approved for prevention of deep vein thrombosis following knee or hip replacement at a recommended dose of 30 mg twice daily.

The trough anti-Xa activities were 20 to 33% higher in the 1.25 mg/Kg group compared to the 1.0 mg/Kg group. Also "peak" anti-Xa activities were 45 to 50% higher in the 1.25 mg/Kg group compared to the 1.0 mg/Kg group. The "peak" activity is not an exact figure since single samples were taken approximately 3 hours postdose. Protocol Report K 9001006 in this submission showed that there was dose linearity between 1.0 to 2.0 mg/Kg in healthy adults.

After the third dose of 1.25 mg/Kg there was a statistically significant higher "peak" anti-Xa activity ($p<0.01$) in patients experiencing major hemorrhage than those without major hemorrhage. Also, the rate of major hemorrhage was 6.5 % in the 1.25 mg/Kg group compared to a rate of 1.9% in the 1.0 mg/Kg group of patients.

Mean Amax levels from pharmacokinetic studies in healthy subjects showed similar levels to the "peak" values obtained in patients at the 1.0 mg/Kg dose. Mean Amax levels from pharmacokinetic studies in healthy subjects showed lower levels to the "peak" values obtained in patients at the 1.25 mg/Kg dose.

Conclusions:

1. The sponsors have shown that the 1.0 mg/Kg dose has a more favorable safety profile in these patients. The dosing regimen used in this study is different from the proposed regimen in that an initial bolus dose was given, however the subsequent doses were given every 12 hours which is the proposed dosing regimen.

2. Sampling activities at trough and "peak" times gives some information on the possible accumulation of enoxaparin in this population.

3. The sponsors are encouraged to undertake non-linear mixed effect modeling of the data in this study and studies where sampling for determination of anti-Xa activity and aPTT has occurred. If undertaken correctly this would give a much better picture of the handling of enoxaparin by different populations and the influence of cofactors such as age, co-administered drugs.

Table 1 : Summary data of anti-Xa activity (IU anti-Xa/ml)

Weight adjusted dose 1.25 mg/kg bid or 1.0 mg/kg bid

- All patients

		Enoxaparin 1.25 mg group (dose tier 1)	Enoxaparin 1.00 mg group (dose tier 2)
Third dose	Trough	0.6 (0.3, 1.0) [n= 216]	0.5 (0.3, 0.7) [n= 164]
	Peak	1.5 (1.2, 1.7) [n= 227]	1.0 (0.9, 1.2) [n= 163]
Last	Trough	0.8 (0.4, 1.0) [n= 115]	0.6 (0.4, 0.9) [n= 45]
	Peak	1.6 (1.1, 1.8) [n= 103]	1.1 (1.0, 1.2) [n= 46]

Median, 25th and 75th percentiles

- Patients experiencing any hemorrage or not

		Enoxaparin 1.25 mg group (dose tier 1)		Enoxaparin 1.00 mg group (dose tier 2)	
		Any hemorrhage number of patients : 22	No hemorrhage number of patients : 299	Any hemorrhage number of patients : 8	No hemorrhage number of patients : 303
Third dose	Trough	0.6 (0.3,1.0) [n=15]	0.6 (0.3,1.0) [n=201]	0.6, 0.7 and 1.0 [n=3]	0.5 (0.3,0.7) [n=161]
	Peak	1.7 (1.5,2.1) [n=15]	1.4 (1.2,1.7) [n=212]	1.2 and 1.9 [n=2]	1.0 (0.9,1.2) [n=161]
Last dose	Trough	0.6 (0.3,0.8) [n=8]	0.8 (0.4,1.0) [n=107]	0.3 and 1.5 [n=2]	0.6 (0.4,0.9) [n=43]
	Peak	1.7 (1.7,2.2) [n=5]	1.6 (1.1,1.8) [n=98]	1.0 and 1.8 [n=2]	1.1 (0.9,1.1) [n=44]

Median, 25th and 75th percentiles
extracted from table 9.1 (Appendix IV)

- Patients experiencing major hemorrage or not

		Enoxaparin 1.25 mg group (dose tier 1)		Enoxaparin 1.00 mg group (dose tier 2)	
		Major hemorrhage number of patients : 21	No major hemorrhage number of patients : 299	Major hemorrhage number of patients : 6	No major hemorrhage number of patients : 303
Third dose	Trough	0.5 (0.3,1.0) [n=14]	0.6 (0.3,1.0) [n=202]	0.7 and 1.0 [n=2]	0.5 (0.3,0.7) [n=162]
	Peak	1.8 (1.6,2.1) [n=14]	1.4 (1.2,1.7) [n=213]	1.2 and 1.9 [n=2]	1.0 (0.9,1.2) [n=161]
Last dose	Trough	0.6 (0.3,0.8) [n=7]	0.8 (0.4,1.0) [n=106]	0.3 and 1.5 [n=2]	0.6 (0.4,0.9) [n=43]
	Peak	2.0 (1.3,2.3) [n=4]	1.6 (1.1,1.8) [n=99]	1.0 and 1.8 [n=2]	1.1 (0.9,1.1) [n=44]

Median, 25th and 75th percentiles
extracted from table 9.2 (Appendix IV)

Fixed dose : 40 mg bid (weight < 65 kg) ; 60 mg bid (weight > 65 kg)

		Enoxaparin 1.25 mg group (dose tier 1)	Enoxaparin 1.00 mg group (dose tier 2)
Fixed dose treatment	Trough	0.4 (0.3, 0.8) [n= 13]	0.4 (0.3, 0.6) [n= 41]
	Peak	1.2 (1.0, 1.4) [n= 12]	0.9 (0.7, 0.9) [n= 43]

Median, 25th and 75th percentiles

Table 2 : Anti-Xa Activity of patients experiencing any hemorrage (IU anti-Xa/ml)

Patient number	Enoxaparin 1.25 mg group (dose tier 1)				Enoxaparin 1.00 mg group (dose tier 2)			
	Third dose		Last dose		Third dose		Last dose	
	Trough	Peak	Trough	Peak	Trough	Peak	Trough	Peak
03-202					1.033	1.905	1.512	1.811
04-201								
05-104	NA	NA						
06-104	0.328	1.700	0.318	1.360				
07-209								
08-119								
10-106	0.267	1.961						
13-101	0.211	2.100						
13-102	0.788	1.309	0.768	1.652				
17-109	0.185	1.211						
17-112	0.836	1.540						
17-204					0.727	1.228	0.276	1.020
18-102	0.359	1.582						
20-115	0.254	1.850						
21-101	1.139	1.231						
24-101	NA		0.640					
32-105	NA	2.135	NA	NA				
32-118	0.228		0.325					
32-130	0.618		NA					
32-227								
32-230								
39-102	0.984	1.554	0.224	0.854				
41-101	NA	NA	0.847	1.747				
47-101		2.240						
47-205					0.607			
47-208								
48-112								
48-127	1.664	2.256	0.563					
49-101	1.012	1.638						
56-103	1.820	2.233	1.617	2.156				
median	0.618	1.700	0.602	1.747				
25th percentile	0.261	1.547	0.323	1.652				
75th percentile	0.998	2.118	0.788	2.156				
n	15	15	8	5	3	2	2	2

NA = not applicable