Reference is also made to a series of requests dated July 24, 1997 regarding the biopharmaceutics information in this supplement. With this letter we are responding to these requests.

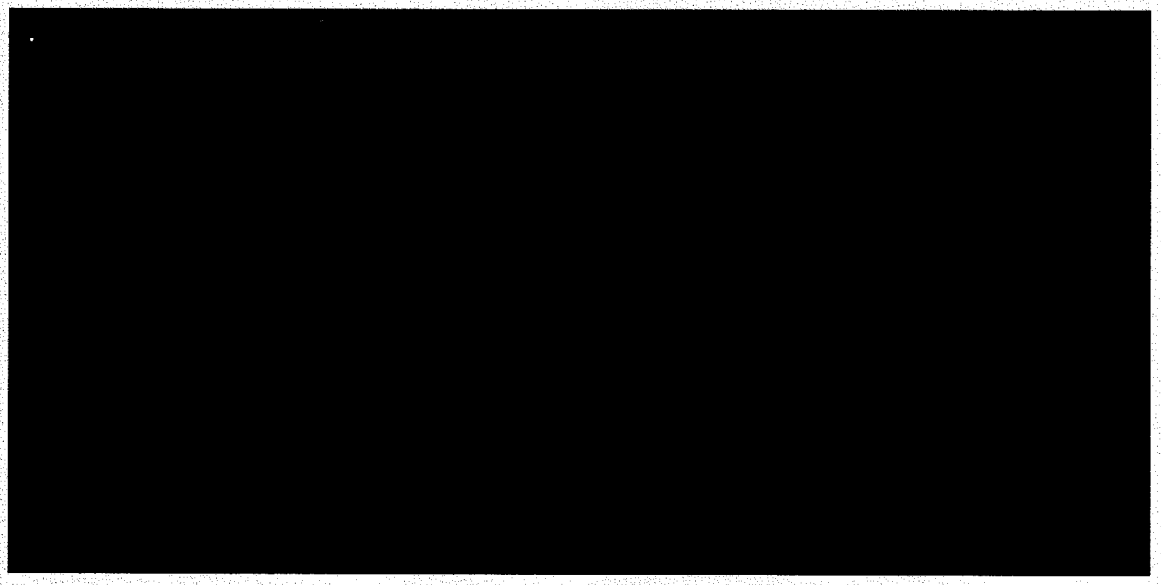
1. **FDA Request: Please submit the statistical analysis on the data, the SAS code, and the ASCII data sets in Study RP 54563Q-133 using the following gender analysis model:**

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

- **Using the 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 be repeated dropping the weight term. It is noted that to some extent, weight is taken into account through the weight based dosing. The model further explores gender effects in terms of the gender*product interaction.**

1. RPR Response:

A statistical analysis was performed on the data from Study RP 54563Q-133 to assess the effect of gender on the ln transformed steady-state AUC(0-24), AUC(0-36), AUC, and AMAX (activity maximum) parameters.



[redacted]

The statistical analysis demonstrates that the treatment*gender term does not reach statistical significance ($p < 0.05$). Therefore, a gender effect as described by the treatment*gender interaction term is not present for the AUC and AMAX (αXa activity maximum) parameters of enoxaparin.

2. **FDA Request: Please comment on the following:**

a. The difference in mean clearance of anti-Xa activity in the population studied under Protocol Report RP 54563Q-260 as NDA 20-164/S-015 NDA 20-164/S-016 compared to earlier studies. Consider consistency in units when comparing mean clearance across studies, i.e. whether clearance is based on "IU anti-Xa" or "mg" of enoxaparin. Avoid comparison of ranges since these are dependent on the number of subjects used in the analyses.

b. The present study suggests that clearance is 70% higher than shown previously in healthy subjects.

c. The higher ratio of anti-Factor Xa to anti-Factor IIa activity (14±3.1) shown in these studies than in the original submission.

2a and 2b. RPR Response: RPR concurs that the mean clearance estimate of anti-Xa activity observed in patients in Study RP 54563Q-260 is higher than that observed in healthy human subjects in studies included in this submission (Study RP 54563Q-K91006 and RP 54563Q-K91107 and RP 54563Q-133). However, Study RP 54563Q-260 included only a limited number of patients for pharmacokinetic determination (n=16) and the variability for pharmacokinetic parameter estimates was higher in this study than usually observed. For example, the %CV for the clearance estimate was 33% in Study RP 54563Q-260 versus the 15 - 20% typically seen in Phase 1 studies in healthy subjects. In addition, the terminal half-life estimate in Study RP 54563Q-260 is comparable (5.2 hr) to that typically observed in Phase 1 studies in healthy subjects, and, consequently, a significant volume of distribution difference would also have to be postulated in patients based upon the data obtained in this study.

Due to the arguments presented above, RPR has relied more on pharmacokinetic data obtained by pharmacokinetic sampling in Study RP 54563Q-261, in which peak and trough anti-Xa activity plasma concentrations were obtained in over 350 patients (over 200 and 150 patients at 1.25 and 1.0 mg/kg, respectively) on administration of the third weight adjusted dose of enoxaparin (steady-state). As in Study RP 54563Q-260, aspirin was coadministered with enoxaparin. In this study, peak and trough anti-Xa activity plasma concentrations measured were within the range anticipated based upon repeat dose pharmacokinetic modeling of single dose data from Study RP 54563Q-K91006 in normal healthy subjects. Mean peak concentrations were 1.5 and 1.0 IU anti-Xa/ml, and mean

trough concentrations were 0.6 and 0.5, for 1.25 and 1.0 mg/kg enoxaparin, respectively. In comparison, the limited data obtained in RP 54563Q-260 demonstrated a mean peak activity of 0.58 IU anti-Xa/ml. Thus the data from a significantly larger number of patients in Study RPR 54563-261 suggests that any differences between the pharmacokinetics of enoxaparin in healthy subjects and patients is significantly overestimated in Study RP 54563Q-260.

RPR is currently planning analyses to explore these issues further (see question 3 and 4 below).

Response 2C

The human *in vivo* ratio of anti-Factor Xa to anti-Factor IIa (αXa/αIIa ratio) of 3.95 quoted in the original submission (NDA #20-164) was based upon intravenous administration of enoxaparin. The αXa/αIIa ratio following subcutaneous administration of enoxaparin has generally been observed to be higher. In those studies in which the anti-Xa and anti-IIa biological assays are similar to those used in the current submission, similar αXa/αIIa ratios following subcutaneous administration were observed.

For example, in Study RP 54563-105640 (NDA #20-164, Vol. 2.12 p 12), αXa/αIIa ratios in the range of 6-15 were observed for the 16 healthy subjects in this study (see p 60-61, Tables XIV and XV on p 105-106, Figure M1 on p 132).

Other pertinent subcutaneous studies in the original NDA include Study RP 54563-100535 (Vol. 2.13, p 334), (see Figure 1, p 384) and Study RP 54563-100493 (Vol. 26, p 330), (see Figure 3, p 373).

Thus the αXa/αIIa ratios reported in the current submission are comparable to those typically observed in the original submission.

3. FDA Request: **Consider conducting a drug-interaction study in healthy elderly subjects with two treatment arms: enoxaparin and enoxaparin with aspirin.**

3. RPR Response: Although the biopharmaceutical mechanism by which an interaction with aspirin would be anticipated is currently unclear, Rhône-Poulenc Rorer will conduct a drug-interaction study of enoxaparin, and enoxaparin and aspirin at steady-state in healthy elderly subjects.

4. FDA Request: **Consider conducting a non-linear mixed effect modeling of the data in the healthy elderly subject study and other studies where sampling for determination of anti-Xa activity etc. has occurred. Properly conducted, non-**

linear mixed effect modeling studies could identify enoxaparin effects on different populations and the influence of cofactors such as age and co-administered drugs.

•4. **RPR Response:** Rhône-Poulenc Rorer is currently planning the analysis of the existing enoxaparin data using nonlinear mixed effects modeling. The significant patient data from the recent study RP 54563Q-261 will be included in this analysis.

Should you have any additional questions or require any additional information during the review of this application, please contact me at (610) 454-3023

Sincerely yours,

Thomas E. Donnelly, Jr., Ph.D.
Group Director
Worldwide Regulatory Affairs

TED/bnh
Attachments

APPEARS THIS WAY ON ORIGINAL

ATTACHMENT 2:

PROPOSED REVISED PACKAGE INSERT (DATED FEBRUARY 10, 1998)

27 pages
Redacted
DRAFT
LABELING

ATTACHMENT 3:

PRINTOUTS OF STATISTICAL ANALYSES OF DATA FROM STUDY RP54563Q-133

Model 1 Effects:
Weight, Sequence, Gender, Gender*Sequence, Subject(Sequence), Period, Treatment, Treatment*Gender, Weight*Treatment

Model 2 Effects:
Weight, Sequence, Gender, Gender*Sequence, Subject(Sequence), Period, Treatment, Treatment*Gender, Weight*Treatment, Period*Treatment*Gender*Sequence

Note: gender effect was determined using Type III MS from subject(sequence) as error term in both models

General Linear Models Procedure
Class Level Information

Class	Levels	Values
PERIOD	3	1 2 3
TREAT	3	1 2 3
GENDER	2	1 2
SEQUENCE	6	1 2 3 4 5 6

Number of observations in data set = 72

APPEARS THIS WAY ON ORIGINAL

General Linear Models Procedure

Dependent Variable: LAUC24

Source	[redacted]	Sum of Squares	Mean Square	F Value	Pr > F
Model	26	2.54584103	0.09791696	7.30	0.0001
Error	45	0.60382807	0.01341840		
Corrected Total	71	3.14966910			

R-Square	C.V.	Root MSE	LAUC24 Mean
0.808288	4.333930	0.11583782	2.67281268

Source	[redacted]	Type III SS	Mean Square	F Value	Pr > F
WEIGHT	1	0.37501592	0.37501592	27.95	0.0001
SEQUENCE	5	0.64099756	0.12819951	9.55	0.0001
GENDER	1	0.13358206	0.13358206	9.96	0.0029
GENDER*SEQUENCE	5	0.63882117	0.12776423	9.52	0.0001
SUBJECT(SEQUENCE)	6	0.64624590	0.10770765	8.03	0.0001
PERIOD	2	0.00033779	0.00016890	0.01	0.9875
TREAT	2	0.00196276	0.00098138	0.07	0.9296
TREAT*GENDER	2	0.01232654	0.00616327	0.46	0.6346
WEIGHT*TREAT	2	0.00341558	0.00170779	0.13	0.8808

Tests of Hypotheses using the Type III MS for SUBJECT(SEQUENCE) as an error term

Source	[redacted]	Type III SS	Mean Square	F Value	Pr > F
SEQUENCE	5	0.64099756	0.12819951	1.19	0.4125

Tests of Hypotheses using the Type III MS for SUBJECT(SEQUENCE) as an error term

Source	[redacted]	Type III SS	Mean Square	F Value	Pr > F
GENDER	1	0.13358206	0.13358206	1.24	0.3080

BEST POSSIBLE

General Linear Models Procedure

Dependent Variable: LAMAX

Source	[redacted]	Sum of Squares	Mean Square	F Value	Pr > F
Model	26	1.35324045	0.05204771	5.20	0.0001
Error	45	0.45036836	0.01000819		
Corrected Total	71	1.80360881			

R-Square	C.V.	Root MSE	LAMAX Mean
0.750296	29.24204	0.10004092	0.34211329

Source	[redacted]	Type III SS	Mean Square	F Value	Pr > F
WEIGHT	1	0.15877004	0.15877004	15.86	0.0002
SEQUENCE	5	0.30421244	0.06084249	6.08	0.0002
GENDER	1	0.02054800	0.02054800	2.05	0.1588
GENDER*SEQUENCE	5	0.30251584	0.06050317	6.05	0.0002
SUBJECT(SEQUENCE)	6	0.30709504	0.05118251	5.11	0.0004
PERIOD	2	0.00122906	0.00061453	0.06	0.9405
TREAT	2	0.00520849	0.00260424	0.26	0.7720
TREAT*GENDER	2	0.02055897	0.01027949	1.03	0.3663
WEIGHT*TREAT	2	0.00446861	0.00223430	0.22	0.8008

Tests of Hypotheses using the Type III MS for SUBJECT(SEQUENCE) as an error term

Source	[redacted]	Type III SS	Mean Square	F Value	Pr > F
SEQUENCE	5	0.30421244	0.06084249	1.19	0.4130

Tests of Hypotheses using the Type III MS for SUBJECT(SEQUENCE) as an error term

Source	[redacted]	Type III SS	Mean Square	F Value	Pr > F
GENDER	1	0.02054800	0.02054800	0.40	0.5497

APPEARS THIS WAY ON ORIGINAL

General Linear Models Procedure

Dependent Variable: LAUC36

Source	[redacted]	Sum of Squares	Mean Square	F Value	Pr > F
Model	26	2.82931108	0.10881966	7.27	0.0001
Error	45	0.67341778	0.01496484		
Corrected Total	71	3.50272886			

R-Square	C.V.	Root MSE	LAUC36 Mean
0.807745	4.469404	0.12233086	2.73707313

Source	[redacted]	Type III SS	Mean Square	F Value	Pr > F
WEIGHT	1	0.38818721	0.38818721	25.94	0.0001
SEQUENCE	5	0.73015521	0.14603104	9.76	0.0001
GENDER	1	0.15112032	0.15112032	10.10	0.0027
GENDER*SEQUENCE	5	0.72788417	0.14557683	9.73	0.0001
SUBJECT(SEQUENCE)	6	0.73984381	0.12330730	8.24	0.0001
PERIOD	2	0.00134050	0.00067025	0.04	0.9562
TREAT	2	0.00085138	0.00042569	0.03	0.9720
TREAT*GENDER	2	0.01094409	0.00547205	0.37	0.6958
WEIGHT*TREAT	2	0.00256813	0.00128407	0.09	0.9179

Tests of Hypotheses using the Type III MS for SUBJECT(SEQUENCE) as an error term

Source	[redacted]	Type III SS	Mean Square	F Value	Pr > F
SEQUENCE	5	0.73015521	0.14603104	1.18	0.4146

Tests of Hypotheses using the Type III MS for SUBJECT(SEQUENCE) as an error term

Source	[redacted]	Type III SS	Mean Square	F Value	Pr > F
GENDER	1	0.15112032	0.15112032	1.23	0.3107