Table 3.3.1 (Sponsor's) Recurrent VTE by Treatment Group and Country for All-Treated Patients

Once-daily Enoxaparin vs. Heparin

Country	Enoxaparin N rec. / N total		Heparin N rec. / N total		Exact Odds Ratio with 95% CI.	Exact Odds Ratio with 90% CI
France	1	31	3	29	0.29 (0.01; 3.93)	0.29 (0.01 ; 2.84)
Norway	0	27	1	30	0 (0; 21.11)	0 (0; 10)
Sweden	3	37	2	34	1.41 (0.15; 17.85)	1.41 (0.21; 11.97)
United States	9	112	3	104	2.93 (0.70; 17.29)	1.93 (0.85; 12.94)
Other	0	91	3	93	0 (0; 1.74)	0 (0; 1.17)

Exact Zelen p-value for homogeneity of odds-ratios: p=0.077.

Twice-daily Enoxaparin vs. Heparin

Investigator	Enoxaparin N rec. / N total		Heparin N rec. / N total		Exact Odds Ratio with 95% CI.	Exact Odds Ratio with 90% CI
France	0	30	3	29	0 (0; 1.61)	0 (0; 1.08)
Norway	2	30	1	30	2.05 (0.10; 126.4)	2.05 (0.15; 62.06)
Sweden	1	36	2	34	0.46 (0.01; 9.28)	0.46 (0.02; 6.15)
United States	5	123	3	104	1.42 (0.27; 9.40)	1.42 (0.34; 6.99)
Other	1	93	3	93	0.33 (0.01; 4.17)	0.33 (0.01; 3.03)

Exact Zelen p-value for homogeneity of odds-ratios: p=0.378; Rec.: Recurrence

Table 3.3.2 (Sponsor's) Recurrent VTE by Treatment Group and Country for Evaluable Patients

Once-daily Enoxaparin vs. Heparin

Country	Enoxaparin N rec. / N total		Heparin N rec. / N total		Exact Odds Ratio with 95% CI.	Exact Odds Ratio with 90% CI
France	1	29	3	28	0.30 (0.01; 4.06)	0.30 (0.01; 2984)
Norway	0	26	1	27	0 (0; 19.73)	0 (0; 9.35)
Sweden	3	35	2	31	1.35 (0.14; 7.27)	1.35 (0.20;11.58)
United States	7	93	1	76	6.05 (0.75; 278.7)	6.05 (0.94; 137.3)
Other	0	64	3	73	0 (0;1.94)	0 (0; 1.30)

Exact Zelen p-value for homogeneity of odds-ratios: p=0.067.

Table 3.3.2 (Sponsor's) Recurrent VTE by Treatment Group and Country for Evaluable Patients (Continued)

Twice-daily Enoxaparin vs. Heparin

Investigator	Enoxaparin N rec. / N total		Heparin N rec. / N total		Exact Odds Ratio with 95% CI.	Exact Odds Ratio with 90% CI
France	0	29	3	28	0 (0; 1.61)	0 (0; 1.08)
Norway	2	28	1	27	1.98 (0.10; 122.5)	1.98 (0.15; 60.14)
Sweden	1	33	2	31	0.46 (0.01; 9.24)	0.46 (0.02; 6.13)
United States	4	103	1	76	3.01 (0.29;152.2)	3.01 (0.38; 74.41)
Other	1	65	3	73	0.37 (0.01; 4.70)	0.37 (0.01; 3.42)

Exact Zelen p-value for homogeneity of odds-ratios: p=0.290; Rec. Recurrence.

The sponsor claimed that the p-values for testing homogeneity of odds-ratios between treatments Enoxaparin once-daily and Heparin across the above five countries were only slightly greater than 0.05 for both all-treated and evaluable patients (p=0.077 for all-treated patients; p=0.067 for evaluable patients). However, the results for testing homogeneity of odds-ratios between treatments Enoxaparin twice-daily and Heparin across the above five countries were non-significant, under the significance level of 0.05, for the both all-treated and evaluable patients.

Reviewer's Comment.

From the results of the sponsor's odds-ratio analysis, we notice that the p-value for testing the homogeneity of VTE odds-ratios across countries is only slightly greater than 0.05 in the comparison of Enoxaparin once-daily with Heparin for the all-treated (p=0.077) and evaluable (0.067) patient populations, implying heterogeneity of VTE odds ratios for the two treatment groups, Enoxaparin once-daily versus Heparin, across countries. In order to assess the robustness of the clinical equivalence between Enoxaparin once-daily and Heparin, this reviewer performed the following subset analysis.

Since for both all-treated and evaluable patient populations, only the two odds ratios computed for Sweden and United States are greater than 1, indicating that the two odds of the VTE recurrence rates calculated from the above two countries have the same direction, this reviewer calculated the 95% confidence interval of the treatment difference (Enoxaparin-once-daily - Heparin) for both of the all-treated and evaluable patients using data only from Sweden and United States. However, due to low VTE recurrence rates, the exact 95% confidence intervals on the two treatment differences, Enoxaparin once-daily versus Heparin, for both of the all-treated and evaluable patients are calculated. Table 3.3.3 (below) presents these results.

Table 3.3.3 (Reviewer's) 95% Confidence Intervals for Enoxaparin-once-daily - Heparin
(Using Data Only From Sweden and United States)

Patient Population	Dif. Of P-Values (%) (E.o.d.* - H#)	Lower Bound of Exact 95% C.I.	Upper Bound of Exact 95% C.I.
All-Treated	4.5%	-2.8%	12.4%
Evaluable	5.0%	-3.1%	13.6%

E.o.d.: Enoxaparin once-daily; H: Heparin.

From Table 3.3.3, it can be noted that the upper bounds for both the all-treated and evaluable patients calculated using data only from Sweden and United States are greater than the clinical delta 10% (12.4% for all-treated patients; 13.6% for evaluable patients). Therefore, the efficacy of Enoxaparin once-daily considered not to be inferior to that of Heparin by 10% or more is at best marginal when it is analyzed using more homogeneous data pooled from Sweden and United States.

3. Improper analysis on the first treatment period

Sponsor's Response

In response to the comparison of the treatment groups in the first treatment period, the sponsor conducted the following odds ratio analysis.

Patients with a recurrent venous thromboembolic event (VTE) were counted in these analyses if the recurrence occurred within 48 hours of treatment discontinuation. An exact odds-ratios with their associated 95% and 90 % confidence intervals were calculated using the StatXact Software Version 2.02. Table 3.3.4 presents the results of the analyses on both all-treated and evaluable patients.

Table 3.3.4 (Sponsor's) Recurrence of VTE within 48 hours of treatment discontinuation Enoxaparin Twice Daily versus Heparin

Population	Enoxaparin b.i.d.* N rec.#/N total		Heparin N rec./N total		Exact Odds Ratio with 95% CI	Exact Odds Ratio with 90% CI
All Treated	2	312	2	290	0.93 (0.07 - 12.90)	0.93 (0.10 - 8.64)
Evaluable	2	258	2	235	0.91 (0.07 - 12.70)	0.91 (0.10 - 8.48)

b.i.d.: twice daily; rec.: recurrence.

APPEARS THIS WAY ON ORIGINAL

Table 3.3.4 (Sponsor's) Recurrence of VTE within 48 hours of treatment discontinuation (Continued)

Enoxaparin Once Daily versus Heparin

Population	Enoxaparin o.d.* N rec.#/N total		Heparin N rec./N total		Exact Odds Ratio with 95% CI	Exact Odds Ratio with 90% CI
All Treated	4	298	2	290	1.96 (0.28 - 21.79)	1.96 (0.36 - 14.69)
Evaluable	4	247	2	235	1.92 (0.27 - 21.34)	1.92 (0.35 - 14.40)

o.d.: once daily; rec.: recurrence.

Reviewer's Comment. BEST POSSIBLE

Instead of applying the 95% confidence intervals on the two sets of two treatment differences (set 1. Enoxaparin once-daily - Heparin and set 2. Enoxaparin twice-daily - Heparin) to perform the clinical equivalence analysis as defined in the protocol for the above two sets of the two treatment groups, the sponsor computed two sets of 95% confidence intervals on the odds ratios for each set treatment group to compare differences. This reviewer therefore, computed the 95% confidence intervals on the two sets of the two treatment differences to assess the clinical equivalence for the above two sets of two treatment groups, as defined in the protocol using the first treatment period data. Due to low VTE recurrence rates, the exact 95% confidence intervals are calculated. The results are presented in Table 3.3.5.

Table 3.3.5 (Reviewer's) Recurrence of VTE within 48 hours of treatment discontinuation
Enoxaparin once-daily vs. Heparin

Population	Enoxaparin o.d. (E.) rec.*/Total	%	Heparin (H.) rec./Total	%	Treatment Difference (E .- H.) Along with Exact 95% C.I.
All Treated	4/298	1.34%	2/290	0.69%	0.65% (-2.0%; 3.9%)
Evaluable	4/247	1.62%	2/235	0.85%	0.77 (-2.5%; 4.6%)

rec.: recurrence.

Enoxaparin twice-daily vs. Heparin

Population	Enoxaparin b.i.d. (E.) rec.*/Total	%	Heparin (H.) rec./Total	%	Treatment Difference (E .- H.) Along with Exact 95% C.I.
All Treated	2/312	0.64%	2/290	0.69%	-0.049% (-2.8%; 2.5%)
Evaluable	2/258	0.78%	2/235	0.85%	-0.075% (-3.5%; 2.9%)

rec.: recurrence.

For Enoxaparin twice-daily versus Heparin, Table 3.3.5 shows that the upper bounds of the exact 95% confidence intervals are all less than 3% for both all-treated and evaluable patients (2.5% for

all-treated patients; 2.9% for evaluable patients). Therefore, Enoxaparin twice-daily is not inferior to Heparin by 3% or more on recurrence of VTE within 48 hours of treatment discontinuation. However, for Enoxaparin once-daily versus Heparin, the upper bounds of the exact 95% confidence intervals are all less than 10% but greater than 3% for both all-treated and evaluable patients (3.9% for all-treated patients; 4.6% for evaluable patients). Therefore, one can only declare that Enoxaparin once-daily is not inferior to Heparin by 10% or more on recurrence of VTE within 48 hours of treatment discontinuation.

4.0 CONCLUSION

For Study# 2091, the sponsor's claim that, based on the clinical delta of 3%, Enoxaparin twice-daily is equivalent to Heparin is not supported by the efficacy data in this trial. The result of the efficacy analysis only indicates that Enoxaparin twice-daily is not inferior to Heparin by 3% or more and the conclusion is at best marginal.

For Study# 529, the efficacy data support the sponsor's claim that both Enoxaparin once-daily and Enoxaparin twice-daily are clinically equivalent to Heparin according to the 10% clinical delta margin. However, upon using the clinical delta of 3% (as in Study# 2091), only Enoxaparin twice-daily can be shown to be not inferior to Heparin by 3% or more.

Even if the delta of 10% was acceptable for Study# 529, the claim that Enoxaparin once-daily is not inferior to Heparin by 10% or more is at best marginally supported when analysis is restricted to more homogeneous data pooled from Sweden and United States. The clinical reviewer may need to address the selection of a more relevant clinical delta for this study.

The result of the Fisher Exact test based on data pooled from the two studies (Study# 2091 and Study# 529) indicates that the recurrence rate at the third-month follow-up in the non-Heparinized Enoxaparin twice-daily group is significantly higher than that in the pre-Heparinized Enoxaparin twice-daily group.

Due to the different characteristics among drugs, the Division of Anti-Infective Drug Product Guideline should not have been used to provide the basis for the clinical delta in Study# 529. The sponsor should have based their choice of delta on historical studies on Heparin.

/S/

Wen-Jen Chen Ph.D.,
Mathematical Statistician

Concur: Dr. Sankoh /S/ 2/9/98

/S/ 2/9/98
Dr.Welch

cc: Archival NDA 20-164/SE1 015
HFD-180 Div File
HFD-180/Dr. Talarico
HFD-180/Dr. Markovic
HFD-180/Ms. Oliver
HFD-720/Dr. Welch
HFD-720/Dr. Sankoh
HFD-720/Dr. Chen
HFD-720/File Copy
HFD-344 Dr. Barton.

[This review contains 27 pages of text and tables.]

Appendix A

Table A.1 (Sponsor's) Summary of Risk Factors for Venous Thromboembolic Disease in All-Treated Patient Population for Study# 2091

RISK FACTORS FOR-DVT/PE[b]	Heparin N = 254		Enoxaparin N = 247		Combined N = 501	
	N	%	N	%	N	%
VENOUS THROMBOEMBOLISM						
History of prior DVT or PE[c]	37	14.6	51	20.6	88	17.6
History of prior DVT	31	12.2	50	20.2	81	16.2
History of prior PE	13	5.1	9	3.6	22	4.4
Hospitalization prior to DVT	23	9.1	21	8.5	44	8.8
RECENT TRAUMA[c]	27	10.6	19	7.7	46	9.2
Genitourinary system	1	0.4	1	0.4	2	0.4
Complications pregnancy and childbirth	0	0.0	1	0.4	1	0.2
Injury and Poisoning	26	10.2	17	6.9	43	8.6
PRESENCE OF CANCER[c]	57	22.4	46	18.6	103	20.6
Neoplasms	56	22.0	46	18.6	102	20.4
Gastrointestinal	11	4.3	9	3.6	20	4.0
Colon and Rectum	7	2.8	5	2.0	12	2.4
Esophagus	0	0.0	2	0.8	2	0.4
Stomach	3	1.2	0	0.0	3	0.6
Pancreas	1	0.4	2	0.8	3	0.6
Breast	8	3.1	7	2.8	15	3.0
Prostate	9	3.5	5	2.0	14	2.8
Pulmonary	5	2.0	6	2.4	11	2.2
Brain	6	2.4	5	2.0	11	2.2
Lymphoma	5	2.0	3	1.2	8	1.6
Ovary	5	2.0	0	0.0	5	1.0
Other	8	3.1	11	4.5	19	3.8
Digestive system	1	0.4	0	0.0	1	0.2
RECENT SURGERY[c]	45	17.7	51	20.6	96	19.2
Neoplasms	0	0.0	1	0.4	1	0.2
Nervous system and sense organs	0	0.0	1	0.4	1	0.2
Digestive system	1	0.4	0	0.0	1	0.2
Complications pregnancy/childbirth	0	0.0	1	0.4	1	0.2
Musculoskeletal system connective tissue	1	0.4	0	0.0	1	0.2
Operations nervous system	0	0.0	2	0.8	2	0.4
Operations eye	0	0.0	1	0.4	1	0.2
Operations cardiovascular system	3	1.2	1	0.4	4	0.8
Operations urinary system	4	1.6	1	0.4	5	1.0
Operations male genitals	3	1.2	1	0.4	4	0.8
Operations female genitals	3	1.2	1	0.4	4	0.8
Operations musculoskeletal system	27	10.6	38	15.4	65	13.0
Operations integumentary system	1	0.4	0	0.0	1	0.2
Misc[d] diagnostic/therapeutic procedures	0	0.0	1	0.4	1	0.2
Operations digestive system	2	0.8	2	0.8	4	0.8

Appendix A (Continued)

Table A.2 (Sponsor's) Summary of Risk Factors for Venous Thromboembolic Disease in All-Treated Patient Population for Study# 529

	Heparin N = 290 N (%)	Enoxaparin Once-daily N = 298 N (%)	Enoxaparin Twice-daily N = 312 N (%)	Combined N = 900 N (%)
RISK FACTORS FOR DVT/PE (1)				
Obesity (2)	122 (42.1)	137 (46.0)	146 (46.8)	405 (45.0)
DVT and/or PE (excluding present episode)	77 (26.6)	66 (22.1)	74 (23.7)	217 (24.1)
DVT (excluding present episode)	72 (24.8)	62 (20.8)	73 (23.4)	207 (23.0)
PE (excluding present episode)	22 (7.6)	16 (5.4)	16 (5.1)	54 (6.0)
Prolonged Immobilization	38 (13.1)	38 (12.8)	40 (12.8)	116 (12.9)
Presence of Varicose Veins	41 (14.1)	45 (15.1)	52 (16.7)	138 (15.3)
Presence of Congestive Heart Failure	9 (3.1)	12 (4.0)	8 (2.6)	29 (3.2)
Chronic Obstructive Pulmonary Disease	25 (8.6)	19 (6.4)	28 (9.0)	72 (8.0)
Estrogen Containing Medication	26 (9.0)	21 (7.0)	25 (8.0)	72 (8.0)
Acquired and Inherited Thrombophilia	7 (2.4)	4 (1.3)	3 (1.0)	14 (1.6)
Recent Chemotherapy/Radiotherapy	19 (6.6)	27 (9.1)	21 (6.7)	67 (7.4)
Presence of Cancer	45 (15.5)	49 (16.4)	47 (15.1)	141 (15.7)
Gastrointestinal	5 (1.7)	10 (3.4)	7 (2.2)	22 (2.4)
Colon and Rectum	3 (1.0)	6 (2.0)	6 (1.9)	15 (1.7)
Esophagus	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.1)
Stomach	1 (0.3)	2 (0.7)	0 (0.0)	3 (0.3)
Pancreas	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.1)
Other	1 (0.3)	3 (1.0)	0 (0.0)	4 (0.4)
Breast	8 (2.8)	7 (2.3)	7 (2.2)	22 (2.4)
Prostate	5 (1.7)	4 (1.3)	5 (1.6)	14 (1.6)
Pulmonary	5 (1.7)	9 (3.0)	8 (2.6)	22 (2.4)
Brain	0 (0.0)	1 (0.3)	2 (0.6)	3 (0.3)
Hematopoietic/Lymphoma	8 (2.8)	9 (3.0)	9 (2.9)	26 (2.9)
Ovary	1 (0.3)	0 (0.0)	1 (0.3)	2 (0.2)
Skin	3 (1.0)	0 (0.0)	2 (0.6)	5 (0.6)
Genitourinary	7 (2.4)	6 (2.0)	5 (1.6)	18 (2.0)
Other	6 (2.1)	7 (2.3)	9 (2.9)	22 (2.4)
Recent Surgery	55 (19.0)	57 (19.1)	65 (20.8)	177 (19.7)
Circulatory System	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.1)
Digestive System	9 (3.1)	5 (1.7)	10 (3.2)	24 (2.7)
Injury and Poisoning	1 (0.3)	5 (1.7)	0 (0.0)	6 (0.7)
Mental Disorders	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.1)
Neoplasms	1 (0.3)	1 (0.3)	0 (0.0)	2 (0.2)
Obstetrical Procedure	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)
Operation Cardiovascular System	3 (1.0)	3 (1.0)	5 (1.6)	11 (1.2)
Operation Digestive System	9 (3.1)	5 (1.7)	10 (3.2)	24 (2.7)
Operation Female Genital Organs	5 (1.7)	4 (1.3)	4 (1.3)	13 (1.4)
Operation Integumentary System	5 (1.7)	0 (0.0)	2 (0.6)	7 (0.8)
Operation Male Genital Organs	3 (1.0)	2 (0.7)	5 (1.6)	10 (1.1)
Operation Musculoskeletal System	29 (10.0)	36 (12.1)	34 (10.9)	99 (11.0)
Operation Nervous System	2 (0.7)	2 (0.7)	4 (1.3)	8 (0.9)
Operation Nos	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)
Operation Respiratory System	0 (0.0)	0 (0.0)	4 (1.3)	4 (0.4)
Operation Urinary	2 (0.7)	3 (1.0)	2 (0.6)	7 (0.8)