CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020164, S015

STATISTICAL REVIEW(S)

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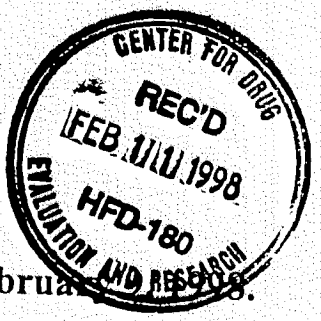
STATISTICAL REVIEW AND EVALUATION
NDA Supplement

FEB 11 1998



Date: February [redacted]

NDA: 20-164/SE1 015

APPLICANT: Rhone-Poulenc Rorer Pharmaceuticals Inc.

NAME OF DRUG: Lovenox (enoxaparin sodium) Injection

INDICATION: The treatment of a deep vein thrombosis [redacted]

USER FEE DUE DATE: 2/28/1998.

PRIORITY CONSIDERATION: Standard.

DOCUMENTS REVIEWED: NDA Vol. 1 and Vol. 15 - 41 dated Feb. 28, 1997; sponsor's documents dated Oct. 8, 1997 and Oct. 23, 1997.

MEDICAL REVIEWER: This review has been discussed with medical officer, Nenad Markovic, M.D.

STATISTICAL REVIEWER: Wen-Jen Chen, Ph.D.

1.0 INTRODUCTION

Patients with acute deep vein thrombosis (DVT) are treated in a hospital with Standard Heparin (SH) administered by continuous intravenous infusion. Recent studies in hospitalized patients with acute DVT have shown that there is no loss of antithrombotic efficacy when subcutaneous low molecular weight heparin (LMWH) is used. Enoxaparin is an LMWH (average weight 4500 Daltons) derived [redacted] The objective of this submission is to establish the efficacy and safety of outpatient anticoagulant therapy with LMWH in the management of patients with acute proximal DVT.

This statistical review covers two pivotal studies, Study # CPK2091 and Study# PK529, which the sponsor submitted in support of the claim for the proposed indication. These two studies compared

the efficacy and safety of Enoxaparin at doses of 1.0 mg/kg twice a day or 1.5 mg/kg once a day (Study# PK529) administered subcutaneously with unfractionated Heparin administered intravenously, in the treatment of lower extremity deep vein thrombosis (Study# CPK 2091 and Study# PK529), and lower extremity deep vein thrombosis associated with a pulmonary embolism (Study# PK529).

The primary efficacy outcome variable was the incidence of recurrent venous thromboembolic disease within three months of randomization. Patients with symptoms or signs of recurrent venous thrombosis underwent objective testing using a combined approach of impedance plethysmograhy, duplex ultrasonography and venography. Patients suspected of having a pulmonary embolism were to undergo a lung scan or a pulmonary angiography.

2.0 STUDY CPK2091

2.1 Background Information

Objectives: The primary objective in this study was to compare the efficacy and safety of an outpatient anticoagulant regimen consisting of a fixed-dose subcutaneous Enoxaparin injection with a standard inpatient anticoagulant regimen consisting of unfractionated Heparin administered by continuous intravenous infusion in patients with acute proximal deep vein thrombosis. [Both Enoxaparin and Heparin were to be used on conjunction with Warfarin, an approved treatment for venous thromboembolic disease.]

Study Design: This study was conducted as a parallel-group, multi-center, open-label, and randomized clinical trial. This study was conducted in Canada from 1992 to 1994. Although this was an open-label study, the study report indicated that all outcome events (recurrent venous thromboembolism and hemorrhage) were judged by a Central Adjudication Committee (CAC) which was unaware of the treatment allocation.

All patients were assessed daily by the study nurse either at the outpatients' thrombosis clinic or at the patient's home (for an outpatient) or in the hospital for inpatients. Clinical laboratory evaluations were performed on all patients at study entry and at the end of study treatment.

Study Population: Patients entered into this study must have had their deep vein thrombosis confirmed by either venography or duplex ultrasonography (Inclusion Criterion).

Patients were excluded from entry into this study if they met any of the following exclusion criteria: 1. previous history of two or more episodes of a deep vein thrombosis or pulmonary embolism; 2. presence of current active hemorrhage, active peptic ulcer disease, or familial hemorrhage diathesis; 3. concurrent symptomatic pulmonary embolism; 4. had received more than 48 hours of unfractionated heparin therapy for the qualifying deep vein thrombosis; 5. inability to receive outpatient heparin therapy because of associated co-morbid conditions or potential for non-compliance; 6. inability to attend follow-up visits as an outpatient because of geographic inaccessibility; 7. known history of Protein C or Protein S deficiency; 8. pregnant or lactating

women; 9. women of childbearing potential who were not covered by a medically recognized contraceptive method; 10. unwilling to give informed consent.

Treatment Assignment and Plan: Qualified patients with acute proximal deep vein thrombosis were randomly assigned to either a fixed dose subcutaneous Enoxaparin 1.0mg/kg administered twice daily on an outpatient basis (outpatient Enoxaparin group) or the usual treatment of unfractionated Heparin administered in the hospital by continuous intravenous infusion and adjusted to maintain the activated partial thromboplastin time within a defined therapeutic range (inpatient Heparin group).

A total of 500 patients were randomized into inpatient and outpatient treatment groups. The randomization will be stratified by hospital center, by hospitalization status, and by method of diagnosis. In the conduct of the trial, central randomization was performed through [redacted].

Patients assigned to outpatient therapy received Enoxaparin 1.0mg/kg twice daily. The dose was based on body weight. Outpatients must have received Enoxaparin therapy for a minimum of five days. Patients assigned to in-hospital therapy were admitted to the hospital where parenteral unfractionated Heparin therapy was begun. The unfractionated infusion was discontinued when the targeted therapeutic range for the International Normalized Ratio was achieved; however, unfractionated Heparin must have been administered for at least five days. Warfarin was commenced on the second day of Heparin or Enoxaparin therapy.

Follow-Up Visits: Follow-up evaluation was required for all randomly-assigned patients. From the start of the study until March 9, 1994, the duration of the follow-up period was six months following the date of randomization. Since the assessments of the primary safety and efficacy measures were all completed within three months, the duration of the follow-up period was reduced from six months to three months. At monthly follow-up visits for three months after completing study drug treatment, patients underwent a history, physical examination, laboratory testing, and impedance plethysmography.

Adverse Events: Adverse events were defined as any undesirable clinical event, whether observed by the investigator, reported by the patient or elicited by general questioning, as well as those based on signs and/or symptoms detected during the physical examination and clinical evaluation of patients, between the first dose of study medication and final evaluation. All serious adverse events occurring during study treatment or during the follow-up period were to be reported to the sponsor.

Primary Efficacy Parameter: The primary efficacy parameter was the incidence of recurrent venous thromboembolism within three months (90 days) of randomization. A patient who had a recurrence of venous thromboembolism was considered a treatment failure.

Efficacy Assessment: The primary analysis was performed on the all-treated patient population, which consisted of all randomized patients who received at least one dose of study medication. A

secondary analysis was performed on evaluable patients who completed the study in accordance with the protocol.

2.2 Sponsor's statistical analysis and results

Analysis of demographics

Table 2.2.1 summarizes the demographic characteristics for the 501 patients included in the all-treated patient population.

Table 2.2.1 (Sponsor's) Summary of Patient Characteristics for All-Treated Patients*

	Heparin (N=254)		Enoxaparin (N=247)		Combined (N=501)	
	N	(%)	N	(%)	N	(%)
Sex						
Male	149	58.7	154	62.3	303	60.5
Female	105	41.3	93	37.7	198	39.9
Age						
Less than 40 years	39	15.4	50	20.2	89	17.8
40 to 49 years	24	9.4	31	12.6	55	11.0
50 to 59 years	54	21.3	41	16.6	95	19.0
60 to 69 years	65	25.6	56	22.7	121	24.2
70 to 79 years	54	21.3	52	21.1	106	21.2
≥ 80 years	18	7.1	17	6.9	35	7.0

*: Extracted from sponsor's Table 8, Volume 22.

The baseline characteristics of age and sex were compared between the two treatment groups (Heparin and Enoxaparin) using the Chi-square test or Student's t-test. The results indicated that the two treatment groups did not differ significantly with respect to age or sex ($p=0.132$ for age by two sided t-test; $p=0.452$ for sex by chi-square test). Results for the evaluable population were similar to those for the all-treated group.

Analysis of risk factors

Table A.1 (Appendix A) summarizes risk factors for venous thromboembolic disease in the all-treated population. A chi-square test was used to test for the treatment group comparability regarding risk factors. The results indicated that there were no statistically significant differences between the treatment groups with respect to risk factors at the 0.05 significance level ($p=0.095$ for Previous History of DVT or PE, $p=0.325$ for Recent Trauma, $p=0.344$ for Presence of Cancer, and $p=0.472$ for Recent Surgery). Similarly, for the evaluable population, there were no statistically significant differences between the treatment groups with regard to risk factors.

Statistical methodology for efficacy analysis

For the all-treated and evaluable patient populations, the sponsor provided the incidence of recurrent venous thromboembolism and a 95 percent confidence interval for the differences in rates between the Enoxaparin and Heparin groups. The primary objective of this analysis was to demonstrate equivalence between the two treatments using a clinical delta of 3%. Based on this 3% clinical delta, the new treatment, Enoxaparin, was to be claimed statistically equivalent to Heparin if the lower limit of the 95 % confidence interval of the difference in mean incidence rates was greater than -3% and the upper limit was less than 3%.

To test the interaction, the sponsor applied logistic regression analysis to assess the following two types of interactions: 1. interaction between treatment and investigator and 2. Interaction between treatment and strata (defined previously) for both the all-treated and evaluable patient populations. The significance level of the interaction effect was α=0.15.

Results of efficacy analysis

Table 2.2.2 (extracted from sponsor's Table 14 of Volume 22) and Table 2.2.3 (extracted from Table B.5.2 of Volume 23) present the recurrent venous thromboembolic events by treatment group for all-treated Patients and evaluable patients, respectively.

Table 2.2.2 (Sponsor's) Recurrent Venous Thromboembolic Outcome for All-Treated Patients

	Heparin (H) N= 254		Enoxaparin (E) N= 247		Treatment Difference % Diff. (H - E)	95% Asym.* C. I.
	No. of patient	%	No. of patient	%		
Event						
None (Success)	237	93.3	234	94.7		
VTE[1]	17	6.7	13	5.3	1.43%	(-2.72, 5.58)
DVT[1]	14	5.5	11	4.5	1.0%	(-2.75, 4.87)
PE[1]	2	0.8	1	0.4		
DVT and PE	1	0.4	1	0.4		

1: VTE - venous thromboembolic event; DVT - deep vein thrombosis; PE - pulmonary embolism.
***: Asym. - Asymptotic.**

Table 2.2.3 (Sponsor's) Recurrent Venous Thromboembolic Outcome for Evaluable Patients

	Heparin (H) N= 24 No. of patient	%	Enoxaparin (E) N= 228 No. of patient	%	Treatment Difference % Diff. (H - E)	95% Asym.* C. I.
Event						
None (Success)	225	93.4	216	94.7		
VTE[1]	16	6.6	12	5.3	1.3%	(-2.90, 5.65)
DVT[1]	13	5.4	10	4.4	1.0%	(-2.89, 4.91)
PE[1]	2	0.8	1	0.4		
DVT and PE	1	0.4	1	0.4		

1: VTE - venous thromboembolic event; DVT - deep vein thrombosis; PE - pulmonary embolism.
***: Asym. - Asymptotic.**

Table 2.2.2 indicates that 237 (93.3%) Heparin patients and 234 (94.7%) Enoxaparin patients did not develop recurrent venous thromboembolism, whereas 17 (6.7%) Heparin patients and 13 (5.3%) Enoxaparin patients developed recurrent venous thromboembolic events. In addition, the sponsor provided the 95 percent confidence interval to assess treatment differences between Heparin and Enoxaparin recurrent venous thromboembolism incidence. For the all-treated patients, the resulting asymptotic 95 % confidence interval for the treatment difference (Heparin - Enoxaparin) of 1.43 percent was (-2.72, 5.58). Since the lower limit of the asymptotic confidence interval was greater than -3 percent, the sponsor concluded that the two treatments were statistically equivalent. Furthermore, the sponsor emphasized that the result of the analysis for the asymptotic 95% confidence interval on the treatment difference (Heparin - Enoxaparin) of the recurrent incidence rates for the evaluable patients was similar to that of the all-treated patients. However, from Table 2.2.3, we notice that the asymptotic 95% confidence interval for the evaluable patients was (-2.90%, 5.65%); the lower limit -2.90% is very close to -3%: the negative of the selected clinical delta.

For the all-treated population, the result of the logistic regression test showed that there was no significant interaction between treatment and investigator (p=0.552). Moreover, the result of the logistic regression analysis indicated that the interaction between treatment and stratification factors was also non-significant (p=0.518). Similarly, theses two interaction tests for the evaluable patients were not significant (p=0.529 for the interaction between treatment and investigator; p=0.482 for the interaction between treatment and stratification).

Clinical Overview of Drug Safety: The all-treated population 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. The sponsor claimed that 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.

2.3 Reviewer's Analyses and Comments

In reviewing the biostatistical section of the submission, this statistical reviewer made two sets of information requests, dated 8/14/97 and 10/9/97, with regard to Study# 2091 to clarify some issues encountered in the review. This reviewer will first comment on the issue of the sponsor's efficacy analysis performed in the original submission and then on the issues of the sponsor's responses from the two sets of information requests.

2.3.1 Comment on the Efficacy Analysis

1. Issue on the clinical equivalence analysis using asymptotic confidence interval

The asymptotic 95% confidence interval of the treatment difference (Heparin - Enoxaparin) for the all-treated patients shows that the lower bound (-2.72%) is greater than -3%, the pre-specified clinical delta, and the upper bound (5.58%) is greater than 3%. Therefore, based on this result, one should only declare that Enoxaparin is not inferior to Heparin by 3% or more. Similarly, the result from the evaluable patients also indicates that Enoxaparin is not inferior to Heparin by 3% or more.

However, the two lower bounds (-2.72% and -2.90%) of the asymptotic 95% confidence intervals calculated from the data of the all-treated and evaluable patients, respectively, are close to -3%, especially the result for the evaluable patients. In addition, due to the low VTE recurrence rates (less than 7% for the two treatment groups in the all-treated patient population), this reviewer performed an exact 95% confidence interval on the treatment difference (Heparin - Enoxaparin) for the all-treated patients to further assess the non-inferiority of the Enoxaparin versus Heparin. The lower bound of the exact 95% confidence interval is -3.69% for the all-treated patients, which is less than -3%. Therefore, the exact tests show that the study result (Enoxaparin is not inferior to Heparin by 3% or more) is not robust.

2.3.2 Comment on the sponsor's Responses

In this section, this reviewer will comment on the following four issues with respect to the sponsor's responses dated 10/8/97 and 10/23/97.

1. Issue on the active (Lovenox + Warfarin) vs. active control (Heparin + Warfarin) for both studies (Study# 2091 and Study# 529),
2. Issue on the selection of the clinical delta for Study# 2091,
3. Improper analysis on the first treatment period for Study# 2091, and
4. Insufficient analysis on the Enoxaparin Heparinized patients versus Enoxaparin non-Heparinized patients.

1. Issue on the active (Lovenox + Warfarin) vs. active control (Heparin + Warfarin) for both studies (Study# 2091 and Study# 529)

Sponsor's Response

In response to this reviewer's concern about the effectiveness of Heparin in the two studies (Study# 2091 and Study# 529), the sponsor reported that non-pharmacological treatment of venous thromboembolic disease was replaced by pharmacological therapy during the first half of the 20th century, and at the present time both Heparin and Warfarin are approved by the Agency for treatment of venous thromboembolic disease.

The sponsor also responded that data published in the 1940s showed the incidence of recurrence was between 31.4 percent and 51.7 percent for patients treated with strict bed rest only. Moreover, one recent study has addressed the question of the requirement for Heparin therapy in addition to Warfarin for the initial treatment of patients with symptomatic proximal deep vein thrombosis. The result showed that asymptomatic extension of thrombus was 39.6% of patients treated with oral anticoagulants alone and 8.2% of patients treated with heparin and oral anticoagulants.

Reviewer's Comment.

Based on the historical evidence provided by the sponsor, the patients treated with Heparin and oral anticoagulants had significantly reduced recurrence rates when compared with the patients treated with oral anticoagulants alone or treated with strict bed rest only. However, the patient population used in the historical study may not be similar to that of the current study. The sponsor has not presented evidence that the active control in each of the two given trials is effective for the patient populations and the indication studied in these two trials.

2. Issue on the selection of the clinical delta

Sponsor's Response

In response to the adequacy for the selection of the clinical delta, the sponsor replied that in the original protocol, 400 patients per arm were to be enrolled. An equivalence approach based on 95% confidence limits was to be used but the definition of the equivalence (delta) was not unique. A 6% recurrence rate for heparin was assumed. Power calculations were made for delta =5% and delta =6% if treatment were truly equivalent (84% and 95% power, respectively), and for delta =2% and delta =3% if in fact Enoxaparin was truly better than heparin by 3% instead of being equivalent (92% and 98% power, respectively).

The sample size was amended from 800 patients in the original protocol to 500 patients because of new information that had been published in 1992 and 1993. The expected recurrence rate on Heparin

remained at 6%. A delta value of 3% was selected, but power calculations were redone under the alternative hypothesis that Enoxaparin would be truly better than heparin by 3% .

Reviewer's Comment

Besides providing information on power and sample size calculations, the sponsor should also have supplied evidence from historical studies to demonstrate the adequacy of the selected delta.

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 events (VTE) were counted in this analysis 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 [redacted] Table 2.3.2.1 presents the results of the analyses on both all-treated and evaluable patients.

Table 2.3.2.1 (Sponsor's) Recurrence of VTE within 48 hours of treatment discontinuation

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	247	3	254	0.68 (0.06 - 6.02)	0.68 (0.08 - 4.43)
Evaluable	2	228	3	241	0.68 (0.06 - 6.01)	0.68 (0.08 - 4.42)

*: rec. - recurrence.

Reviewer's Comment.

Instead of applying the 95% confidence interval on the treatment difference (Heparin - Enoxaparin) to perform the clinical equivalence analysis as defined in the protocol for the two treatment groups (Enoxaparin versus Heparin), the sponsor computed the 95% confidence interval on the odds ratios of Enoxaparin versus Heparin to compare the difference of the two treatment groups. This reviewer therefore, computed the 95% confidence interval on the two treatment difference (Enoxaparin - Heparin) of VTE recurrence rates to perform the clinical equivalence analysis as defined in the protocol. Due to low VTE recurrence rates, the exact method was employed to calculate the 95% confidence intervals on the two treatment difference (Enoxaparin - Heparin) of VTE recurrence rates for both all-treated and evaluable patients and the results are demonstrated in Table 2.3.2.2.