**Table 2.3.2.2(Reviewer's) Recurrence of VTE within 48 hours of treatment discontinuation**

| Population | Enoxaparin b.i.d. (E.) rec.*/Total | % | Heparin (H.) rec./Total | % | Treatment Difference (E .- H.) Along with Exact 95% C.I. |
|---|---|---|---|---|---|
| All Treated | 2/247 | 0.8% | 3/254 | 1.2% | -0.4% (-4.0%; 2.6%) |
| Evaluable | 2/228 | 0.9% | 3/241 | 1.2% | -0.3% (-4.1%; 2.9%) |

*: rec. - recurrence; Asy.: Asymptotic.

From Table 2.3.2.2, we notice that the upper bounds of the exact 95% confidence intervals are less than 3% for both all-treated and evaluable patients (2.6% for all-treated patients; 2.9% for evaluable patients). Therefore, Enoxaparin is not inferior to Heparin by 3% or more on the recurrence rate of VTE occurred within 48 hours of treatment discontinuation.

4. Insufficient analysis on the Enoxaparin heparinized patients versus Enoxaparin non-Heparinized patients

**Sponsor's Response** [redacted] BEST POSSIBLE

In response to the comparison of the Enoxaparin effects on the pre-Heparinized patients versus non-heparinized patients, the sponsor performed the following odds ratio analysis.

Due to the low recurrence rates in most of the analyses addressed in this document, the sponsor used the StatXact Software Version 2.02 to compute the exact odds-ratios along with their associated 95 percent and 90 percent confidence intervals. The sponsor presented the results first by Study; then, the sponsor presented the results analyzed by the data pooled from both studies (Study# 529 and 2091).

The following remarks made by the sponsor based on the results using data pooled from the two studies (combined analysis) were related to the Enoxaparin Heparinized patients versus Enoxaparin non-Heparinized patients:

1. Enoxaparin once-daily (o.d.) heparinized vs Enoxaparin (o.d.) non-heparinized on study drug: 90% CI=(1.003; ∞) indicated a higher risk of recurrence in heparinized patients.
2. Enoxaparin (bid) heparinized vs Enoxaparin twice-daily (bid) non-heparinized at 3 months; 95% CI=(0.08; 0.084) indicated a higher risk of recurrence in non-heparinized patients.

**Reviewer's Comment.**

Remark 2 made by the sponsor based on the combined analysis of the 95% confidence interval on the odds ratio between the two patient populations, Enoxaparin twice-daily Heparinized vs. Enoxaparin twice-daily non-Heparinized, at month 3 follow-up indicates that a higher risk of VTE recurrence in non-Heparinized patients.

In response to the medical officer's concern about the equality of the VTE recurrence rates between pre-Heparinized and non-Heparinized patients treated by Enoxaparin, this reviewer has performed Fisher Exact tests to explore this issue based on the data pooled from the two studies for all-treated patients. Table 2.3.2.3 (below) presents the VTE recurrence rates and the results of Fisher Exact test on the equality of the VTE recurrence rates between pre-Heparinized and non-Heparinized patients for both Enoxaparin once-daily and Enoxaparin twice-daily doses, using all-treated patient data set.

**Table 2.3.2.3 (Reviewer's) The recurrence of VTE along with Fisher Exact test using data pooled from two studies: Studies 2091 and 529 for all-treated patients**

**✓Enoxaparin Once Daily Dose**

| Recurrence of VTE | Heparinized Enoxaparin (N=168) | | Non-Heparinized Enoxaparin (N=130) | | Two-Sided Fisher Exact Test P-value |
|---|---|---|---|---|---|
| | rec.# | no rec. | rec. | no rec. | |
| on study drug | 4 | 164 | 0 | 130 | 0.135 |
| At 1 Month | 6 | 162 | 2 | 128 | 0.473 |
| At 3 Months | 9 | 159 | 4 | 126 | 0.402 |

**#: rec. - Recurrence.**

**✓Enoxaparin Twice Daily Dose**

| Recurrence of VTE | Heparinized Enoxaparin (N=275) | | Non-Heparinized Enoxaparin (N=284) | | Two-Sided Fisher Exact Test P-value |
|---|---|---|---|---|---|
| | rec.# | no rec. | rec. | no rec. | |
| on study drug | 1 | 274 | 3 | 281 | 0.624 |
| At 1 Month | 5 | 270 | 8 | 276 | 0.577 |
| At 3 Months | 5 | 270 | 17 | 267 | 0.015* |

**#: rec. - Recurrence; *: Significance at the level of 0.05.**

Table 2.3.2.3 indicates that at the third month follow-up, the recurrence rate 6.0% (17/284) in the non-heparinized Enoxaparin twice-daily group is significantly higher than that 1.8% (5/275) in the pre-heparinized Enoxaparin twice-daily group under the significance level of 0.05 (p-value = 0.015).

## 3.0 STUDY PK529

### 3.1 Background Information

**Study objective:** The objective of the study was to show that the efficacy and safety of weight-adjusted dose Enoxaparin administered once or twice daily subcutaneously is as good as intravenous continuous infusion adjusted-dose Heparin in the treatment of lower extremity deep vein thrombosis with or without pulmonary embolism. [Both Enoxaparin and Heparin were to be used on conjunction with Warfarin, an approved treatment for venous thromboembolic disease.]

**Study Design**: This was an international multi center, randomized, open labeled, parallel-group clinical trial involving about 80 centers in the United States, Europe, and other regions of the world. There were three treatment groups in this trial: 1) Enoxaparin 1.5 mg/kg once daily, 2) Enoxaparin 1.0 mg/kg twice daily, and 3) Heparin therapy.

In order to have 200 evaluable patients in each treatment group, approximately, nine hundred (900) patients were to be enrolled. Each center was to enroll at least 18 patients. Each patient's participation was to last for approximately three months.

**Study Population:** Patients entered into this study must have had the following condition: 1. Male or female; 2. Eighteen (18) years and older; 3. Symptomatic, venographically diagnosed lower extremity deep vein thrombosis or symptomatic pulmonary embolism diagnosed by ventilation perfusion lung scan or pulmonary angiography. 4. Life expectancy of greater than six months; 5. Written informed consent prior to beginning protocol specific procedures indicating that they understood the purpose of this study and were willing to adhere to the procedures described in this protocol . (Inclusion Criteria).

Patients were excluded from entry into this study if they met any of the following exclusion criteria: 1. Treatment with therapeutic doses of heparin (unfractionated heparin or low molecular weight heparin) for more than 24 hours prior to randomization; 2. Oral anticoagulant treatment within the previous five days; 3. Need for thrombolytic therapy; 4. Active hemorrhage, active ulcerative disease or known angiodysplasia of the intestinal tract; 5. Known disease with a hemorrhagic risk (e.g. hemophilia); 6. Eye, spinal cord or central nervous system surgery within one month; 7. Severe renal insufficiency; 8. Disorders contraindicating anticoagulant therapy including oral anticoagulant therapy, that is, severe hepatic insufficiency; 9. Allergy to heparin, protamine sulfate or chloride, swine products, iodine or radiopaque contrast media, that would contraindicate treatments or evaluations required by the protocol; 10. History of heparin associated thrombocytopenia or heparin or warfarin associated skin necrosis; 11. Treatment with other investigational therapeutic agents within the previous four weeks; 12. Patients with previous or requiring inferior vena cava interruption; 13. Known pregnancy or lactation. (Exclusion Criteria).

**Treatment Assignment and Pan:** Study drug administration was to begin as soon as possible after confirmation of deep vein thrombosis or pulmonary embolism. All patients were to be hospitalized during the initial treatment phase of the study. In the event confirmation was delayed, pre-study

Heparin (unfractionated or low molecular weight) at therapeutic doses was to be permitted for a maximum of 24 hours prior to randomization.

Patients were to be randomly assigned to one of the three treatment groups in a 1:1:1 ratio by a computer generated randomization program. All treatments were to continue for a minimum of five days and were to be discontinued when the International Normal Ratio (INR) was between 2.0-3.0 on two consecutive measurements not performed on the same day.

Each patient in the Enoxaparin once daily treatment group was to receive one subcutaneous injection of Enoxaparin daily; each dose was to be weight-adjusted, based on a 1.5 milligrams per kilogram daily dosing regimen. Similarly, each patient in the Enoxaparin twice daily treatment group was to receive two subcutaneous injections of 1.0 milligram per kilogram Enoxaparin at 12 hour intervals; each dose was to be weight-adjusted, based on a total daily dose of 2.0 milligrams per kilogram. Moreover, the Enoxaparin once daily treatment group was to be blinded in comparison to the Enoxaparin twice daily treatment group. Finally, each patient in the Heparin treatment group was to receive one initial intravenous bolus injection of 5000 units of heparin followed by a continuous intravenous infusion of Heparin at a rate of 1250 units hourly. This treatment was to be administered in an open-label manner.

All randomized patients were to receive an oral anticoagulant therapy (Warfarin) within 72 hours after initiation of treatment and were to continue therapy for at least three months. The first dose (Warfarin) was to be administered within 72 hours after study drug administration.

**Follow-Up Visits:** All patients were to be followed on a regular basis. Visits were to be conducted at monthly intervals for three consecutive months after randomization. Visits were to occur within one week of the specified time. During the follow-up period, patients were required to report to the hospital immediately if recurrent symptoms of deep vein thrombosis or pulmonary embolism developed. The diagnosis of deep vein thrombosis was to be confirmed by venography or ultrasonography. The diagnosis of pulmonary embolism was to be confirmed by ventilation perfusion lung scan. All ultrasonograms venograms, and those ventilation perfusion lung scans or pulmonary angiograms performed to assess recurrence or progression of disease were to be read by a clinical Outcome Adjudication Committee who remained blinded to the patient's treatment group. The determination of this Committee was to be used to identify those patients who had a recurrence of venous thromboembolic event within three months of randomization. This Committee had to assess the recurrence in a consistent way with the rules indicated in the protocol. In particular they were to take into account the investigator and experts assessment of the venographies, ultrasonographies, pulmonary angiographies, perfusion ventilation lung scans that were available.

**Primary Efficacy Parameter:** The primary efficacy parameter is the incidence of clinically symptomatic recurrent venous thromboembolism within three months following randomization. A patient is considered a failure if any of the following occurs: 1) there are clinical signs or symptoms that require related corrective therapy (either surgical or pharmacological) within the initial 72 hours after first dose of study medication, 2) there are clinical signs or symptoms beyond the initial 72 hour period and an objective test indicates a worsened condition (venography, ultrasonography,

ventilation perfusion lung scan, or pulmonary angiography), 3) there are clinical signs or symptoms that require related corrective therapy (either surgical or pharmacological) beyond the initial 72 hour period and there are no objective test results, 4) death occurs and the clinical Outcome Adjudication Committee determines that a venous thromboembolic event caused or is associated with the patient's death, or 5) it can not be confirmed that the patient is alive. Otherwise, a patient is considered a success.

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

The secondary efficacy analysis was performed on the evaluable patient population. The evaluable patient population excluded those patients who presented at least one of the non-evaluability criteria. The sponsor emphasized that the evaluability of the endpoint was not based on the objective tests but was based on the assessment of the Outcome Adjudication Committee.

**Safety Parameters:** The primary safety parameter, analyzed for all patients who received at least one dose of study medication, is the incidence of major and minor hemorrhagic episodes. In addition, the incidence of adverse events and abnormal laboratory findings were to be evaluated.

### 3.2 Sponsor's statistical analysis and results

Table 3.2.1 summarizes the demographic characteristics for the 501 patients included in the all-treated patient population.

**Table 3.2.1 (Sponsor's) Summary of Patient Characteristics for All-Treated Patients***

| | Heparin N=290 | | Enoxaparin Once-daily N=298 | | Enoxaparin Twice-daily N=312 | | Combined N=900 | |
|---|---|---|---|---|---|---|---|---|
| | N | (%) | N | (%) | N | (%) | N | (%) |
| Sex | | | | | | | | |
| Male | 150 | (51.7) | 161 | (54.0) | 181 | (58.0) | 492 | (54.7) |
| Female | 140 | (48.3) | 137 | (46.0) | 131 | (42.0) | 408 | (45.3) |
| Age | | | | | | | | |
| Less than 40 years | 40 | (13.8) | 38 | (12.8) | 38 | (12.2) | 116 | (12.9) |
| 40 to 49 years | 28 | (9.7) | 31 | (10.4) | 38 | (12.2) | 97 | (10.8) |
| 50 to 59 years | 50 | (17.2) | 52 | (17.4) | 54 | (17.3) | 156 | (17.3) |
| 60 to 69 years | 70 | (24.1) | 73 | (24.5) | 74 | (23.7) | 217 | (24.1) |
| 70 to 79 years | 71 | (24.5) | 72 | (24.2) | 83 | (26.6) | 226 | (25.1) |
| ≥ 80 years | 31 | (10.7) | 32 | (10.7) | 25 | (8.0) | 88 | (9.8) |

*: Extracted from Table 7, Volume 25.

Statistical inferences were performed to compare the differences among the treatment groups by sex, age, and body mass index. Fisher's exact test and one-way analysis of variance were used for

categorical variables and continuous ones, respectively. The results of the comparisons among the three treatment groups on sex (p-values=0.292 for male and female), age (p-value=0.986), and body mass index (p-value=0.38) were all non-significant under significance level of 0.05 for all-treated patients. Results for the evaluable population were similar to those for the all-treated group.

**Analysis of risk factors**

Table A.2 (Appendix A) summarizes risk factors for venous thromboembolic disease in the all-treated population. The most common risk factor was a history of antecedent venous thromboembolic disease (217 patients, 24.1%). Seventy-seven (26.6%) Heparin patients, 66 (22.1%) Enoxaparin once-daily patients and 74 (23.7%) Enoxaparin twice-daily patients had this risk factor. The second most common risk factor was recent surgery (177 patients; 19.7%), followed by the presence of cancer (141 patients; 15.7%). The treatment groups were comparable with respect to the presence of all prospectively defined risk factors. Results for the evaluable population were similar to those for the all-treated patient population.

**Statistical methodology for efficacy analysis**: The statistical objective of the study was to demonstrate that the incidence rate of clinically symptomatic recurrent venous thromboembolic events in each Enoxaparin group was not different from the Heparin incidence rate by more than 10%. An asymptotic 95% confidence interval of the difference in incidence rates between each Enoxaparin group and the Heparin group was to be calculated using a normal approximation of the binomial probability law. An Enoxaparin regimen was to be declared equivalent to Heparin if the upper limit of the 95% confidence interval of their difference did not exceed 10% and the lower limit did not fall below -10%. If a large number of recurrences occurred in the study, the interaction, treatment*country, was to be tested using a logistic regression model, with an $\alpha$-level of 0.15. The interaction, treatment*center, was also to be investigated. In case of empty cells, centers and/or countries were to be pooled.

**Results of the efficacy analysis**: Table 3.2.2 (extracted from sponsor's Table B5.01 of Volume 31) and Table 3.2.3 (extracted from sponsor's Table B5.02 of Volume 31) present the recurrent venous thromboembolic events developed in the three treatment groups (Enoxaparin once-daily, Enoxaparin twice daily, and Heparin) for all-treated patients and evaluable patients, respectively.

**Table 3.2.2 (Sponsor's) Recurrent Venous Thromboembolic Outcome for All-Treated Patients**
**Enoxaparin once-daily versus Heparin**

| | Heparin (H) No. of patient | % | Enoxaparin OD* (E) No. of patient | % | Treatment Difference % Diff. (H - E) | 95% Asym.* C. I. |
|---|---|---|---|---|---|---|
| Event | 290 | | 298 | | | |
| None (Success) | 278 | 95.9 | 285 | 95.6 | | |
| VTE[1] | 12 | 4.1 | 13 | 4.4 | -0.22% | (-4.49%, 3.04%) |
| DVT[1] | 8 | 2.8 | 11 | 3.7 | -0.92% | (-3.8%, 2.0%) |
| PE[1] | 1 | 0.3 | 1 | 0.3 | | |
| DVT and PE | 3 | 1.0 | 1 | 0.3 | | |

**Enoxaparin twice-daily versus Heparin**

| | Heparin (H) No. of patient | % | Enoxaparin BID* (E) No. of patient | % | Treatment Difference % Diff. (H - E) | 95% Asym.* C. I. |
|---|---|---|---|---|---|---|
| Event | 290 | | 312 | | | |
| None (Success) | 278 | 95.9 | 303 | 97.1 | | |
| VTE[1] | 12 | 4.1 | 9 | 2.9 | 1.2% | (-1.7%, 4.2%) |
| DVT[1] | 8 | 2.8 | 7 | 2.2 | 0.54% | (-2.0%, 3.1%) |
| PE[1] | 1 | 0.3 | 2 | 0.6 | | |
| DVT and PE | 3 | 1.0 | 0 | 0.0 | | |

***: OD - once daily; BID - twice daily; Asym. - Asymptotic.**
**1: VTE - venous thromboembolic event; DVT - deep vein thrombosis; PE - pulmonary embolism.**

**Table 3.2.3 (Sponsor's) Recurrent Venous Thromboembolic Outcome for Evaluable Patients**
**Enoxaparin once-daily versus Heparin**

| | Heparin (H) No. of patient | % | Enoxaparin OD* (E) No. Of patient | % | Treatment Difference % Diff. (H - E) | 95% Asym.* C. I. |
|---|---|---|---|---|---|---|
| Event | 235 | | 247 | | | |
| None (Success) | 225 | 95.7 | 236 | 95.5 | | |
| VTE[1] | 10 | 4.3 | 11 | 4.5 | -0.2% | (-3.84%, 3.45%) |
| DVT[1] | 7 | 3.0 | 9 | 3.6 | -0.66% | (-3.9%, 2.6%) |
| PE[1] | 1 | 0.4 | 1 | 0.4 | | |
| DVT and PE | 2 | 0.85 | 1 | 0.4 | | |

**Enoxaparin twice-daily versus Heparin**

| | Heparin (H) No. of patient | % | Enoxaparin BID* (E) No. of patient | % | Treatment Difference % Diff. (H - E) | 95% Asym.* C. I. |
|---|---|---|---|---|---|---|
| Event | 235 | | 258 | | | |
| None (Success) | 225 | 95.7 | 250 | 96.9 | | |
| VTE[1] | 10 | 4.3 | 8 | 3.1 | 1.15% | (-2.18%, 4.49%) |
| DVT[1] | 7 | 3.0 | 6 | 2.3 | 0.7% | (-2.2%, 3.6%) |
| PE[1] | 1 | 0.4 | 2 | 0.78 | | |
| DVT and PE | 2 | 0.85 | 0 | 0.0 | | |

***: OD - once daily; BID - twice daily; Asym. - Asymptotic.**
**1: VTE - venous thromboembolic event; DVT - deep vein thrombosis; PE - pulmonary embolism.**

Table 3.2.2 indicates that 278 (95.9%) Heparin patients, 285 (95.6%) Enoxaparin-once-daily patients, and 303 (97.1%) Enoxaparin-twice-daily patients did not develop recurrent venous thromboembolism, whereas 12 (4.1%) Heparin patients, 13 (4.4%) Enoxaparin-once-daily patients, and 9 (2.9%) Enoxaparin-twice-daily 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. A claim of treatment equivalence between the two treatments was to be made if the lower limit of the 95 percent confidence interval was greater than -10 percent and the upper limit of the 95 % confidence interval was less than 10%. For the all-treated patients, the resulting asymptotic 95 percent confidence

interval for the treatment difference (Heparin - Enoxaparin-once-daily) of -0.22 % was (-3.49%, 3.04%). Since the lower limit of the asymptotic confidence interval was greater than -10 percent and the upper limit was less than 10%, the sponsor concluded that the two treatments, Heparin and Enoxaparin-once-daily, were equivalent. Similarly, the resulting asymptotic 95% confidence interval for the treatment difference (Heparin - Enoxaparin-twice-daily) of 1.2 % was (-1.7%, 4.2%). Since the lower limit of the asymptotic confidence interval was greater than -10 percent and the upper limit was less than 10%, again, the sponsor concluded that the two treatments, Heparin and Enoxaparin-twice-daily, were equivalent.

In addition, based on the results from Table 3.2.3, the sponsor emphasized that the results of the clinical equivalence analysis using the evaluable patient data set for the asymptotic 95% confidence intervals on the recurrent incidence rates for the two sets of treatment differences, (Enoxaparin once-daily - Heparin) and (Enoxaparin twice-daily - Heparin), were similar to those of the all-treated patients.

### 3.3 Reviewer's Analyses and Comments

As stated in section 2.3, this statistical reviewer made two sets of information requests, dated 8/14/97 and 10/9/97, with regard to Study# 529 to to clarify issues encountered in the review. To complete the biostatistical review, this reviewer will comment on the sponsor's responses to the following three issues:

1. Issue on the selection of clinical delta,
2. Issue on the analysis of two treatment equivalence using data across countries, and
3. Improper analysis on the first treatment period.

1. Issue on the selection of clinical delta

**Sponsor's Response**

In response to the adequacy of the selection of the clinical delta, the sponsor replied that the guideline for designing equivalence studies was proposed by the Division of Anti-Infective Drug Products, CDER/FDA, in 1992. This guideline provides the following criteria to select the differences (delta) for various proportions: **" For effectiveness endpoints with values greater than 90 percent for the better of the two agents, a confidence interval that crosses zero and remains within a lower bound delta of -0.10 or less will usually be required to establish equivalence."**

The sponsor explained that at the original protocol stage, March 10, 1994, a 10% recurrence rate for Heparin was assumed, based on the criteria stated in the above guideline, and so a 10% delta was selected for this study. However, the observed recurrence rate turned out to be lower than the expected one (about 4.5% instead of 10% originally planned). The sponsor indicated that they could not change the pre-planned definition after the results were known. They decided to keep 10% as a maximal acceptable difference. However, the sponsor also assessed the clinical equivalence between Enoxaparin and Heparin using a clinical delta of 3% and declared that Enoxaparin-twice-daily was

clinically equivalent to Heparin, and Enoxaparin once-daily almost met the clinical equivalence relationship with Heparin.

**Reviewer's Comment**

The sponsor's selection of a 10% clinical delta for equivalence in Study 529 was based on the guideline proposed by the Division of Anti-Infective Drug products; however, the characteristics of the anti-coagulant drug may be different from that of anti-infective drug. The sponsor should have referred to historical studies on Heparin to select the clinical delta for the equivalence study. Instead of using the historical information to capture the recurrence rate for Heparin, the sponsor assumed a 10% recurrence rate for Heparin without any reference.

Since in the response to the selection of clinical delta, the 3% delta was used by the sponsor to evaluate the clinical equivalence for Study 529, the comment on the clinical delta of 3% is given below. Firstly, the asymptotic 95% confidence interval of the treatment difference (Enoxaparin-twice-daily - Heparin) for the all-treated patients was (-4.20%; 1.70%); the lower bound (-4.20%) is less than -3%, the negative of the clinical delta, and the upper bound (1.70%) is less than 3%. Following the result from all-treated patients, instead of claiming the clinical equivalence for these two drugs: Enoxaparin-twice-daily and Heparin, one should only declare that Enoxaparin-twice-daily is not inferior to Heparin by 3% or more. Secondly, the asymptotic 95% confidence interval of the treatment difference (Enoxaparin-once-daily - Heparin) for the all-treated patients was (-3.04%; 3.49%); the upper bound (3.49%) is greater than 3%. The result from all-treated patients clearly indicates that Enoxaparin-once-daily is inferior to Heparin by 3% or more. Therefore, based on the above two results, only Enoxaparin-twice-daily can be considered not inferior to Heparin by 3% or more if the clinical delta of 3% is selected.

2. Issue on the analysis of two treatment equivalence using data across countries

**Sponsor's Response**

In response to the issue of heterogeneity for the treatment effects across the countries, the sponsor proposed to display the results by country, pooling those countries in which less than 20 patients per arm were included. Consequently, results are displayed separately for United States, Sweden, Norway, France and all other countries pooled. Exact odds-ratios with associated 95% and 90% confidence intervals were calculated. Tests of homogeneity of odds-ratio across countries were performed using the exact Zelen's p-value. Table 3.3.1 (below) and Table 3.3.2 (below) provide the results on recurrent venous thromboembolic events (VTE) by treatment group and country for all-treated and evaluable patients, respectively.