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APPROVAL PACKAGE FOR:

**APPLICATION NUMBER
20-718/S-010**

**Clinical Pharmacology and Biopharmaceutics
Review**

Clinical Pharmacology/Biopharmaceutics Review

NDA: 20-718, SE2(C)010
Integrillin® (Eptifibatide)
Cor Therapeutics, Inc.

Submission Date: March 14, 2001

Reviewer: Gabriel J. Robbie, Ph.D.

Type of Submission: This is a response to FDA's request for information regarding standard curve and quality control samples used for assay of eptifibatide in PRIDE study.

BACKGROUND:

Eptifibatide reversibly inhibits platelet aggregation by binding to glycoprotein (GP) IIa/IIIb platelet receptor complex. This action prevents thrombosis and leads to a reduction in acute ischemic events after percutaneous coronary intervention (PCI). On February 13, 2001, the Agency requested additional information for the analytical method used in NDA 20-718/SE2-010 to determine eptifibatide concentrations in the PRIDE study (Protocol 96-023b). Specifically additional information regarding standard curve range, quality control samples and intra- and inter-day assay variability was requested.

SPONSOR'S RESPONSE:

Supplement SE2-010 includes the requested information regarding quality control and standard curve samples. The following table provides a summary of the analytical information.

Compound	Matrix	Range (ng/ml)	QC (ng/ml)	CV%		Accuracy (% Bias)
				Intra	Inter	
Eptifibatide	Plasma			5.1	6.9	+14.3
				5.4	3.9	+6.5
				3.6	2.0	-9.0
				3.1	6.3	-1.3

The intra-run and inter-run %CV were below 7%. The accuracy at the lowest concentration was slightly higher at 14%, but this value is within QC.

RECOMMENDATION:

The Office of Clinical Pharmacology and Biopharmaceutics finds the quality control and standard curve data acceptable. No further action is warranted at this time.

RD/FT by Angelica Dorantes, Ph. D.

Gabriel J. Robbie, Ph. D.

Cc: NDA 20-718, HFD 110, HFD 860 (Mehta, Robbie), CDER document room: Attn: Biopharm (CDER)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 20718
Integrillin® (Eptifibatide), SE2-010
Cor Therapeutics

Submission Date: June 29, 2000

Reviewer: Gabriel J. Robbie

Type of Submission: Efficacy supplement to support double bolus dosing of eptifibatide in patients receiving percutaneous coronary intervention.

INTRODUCTION:

Eptifibatide, a disulfide-linked cyclic heptapeptide, reversibly inhibits platelet aggregation through specific binding to the glycoprotein (GP) IIa/IIIb platelet receptor complex. This action prevents thrombosis and leads to a reduction in acute ischemic events after percutaneous coronary intervention (PCI). Eptifibatide is administered intravenously and has a rapid onset of action with a short half-life. The effects of platelet aggregation are observed soon after administration of eptifibatide and are rapidly reversed upon cessation of drug infusion. Inhibition of ADP-induced platelet aggregation is used for assessing drug effect and, receptor occupancy is the pharmacological marker. The sponsor has determined that 80% receptor occupancy is obtained at a concentration of 1600 ng/ml, at which concentration a majority of the patients would exhibit adequate platelet inhibition. The goal of the program was to develop a regimen that achieved this target concentration at all time points.

For patients undergoing PCI the present label recommends an intravenous bolus (B) dose of 135 µg/kg followed by an infusion (I) of 0.5 µg/min-kg for 20 to 24 hours. However, in the PRIDE study (Study 96-023), where 3 regimens of Integrillin were studied, 135 µg/kg (B)/0.75 µg/min-kg (I), 180 µg/kg (B)/2.0 µg/min-kg (I), and, 250 µg/kg (B)/3.0 µg/min-kg (I), it was observed that platelet inhibitory activity at 1-h was less than that seen immediately after the bolus or at steady state. The percentage of patients with ≥80% inhibition of platelet aggregation was 86% at 5 min, 51% at 1 h, and 83% at 8 h. This was attributed to the rapid decrease in plasma eptifibatide concentrations immediately following the bolus dose to below 1600 ng/ml and the subsequent rise in concentrations to steady-state because of the infusion. Since the greatest thrombogenic stimulus during angioplasty occurs during device deployment and in the periprocedural period, the sponsor intends to administer a second bolus dose of integrillin 10-min following the initial bolus administration to maintain eptifibatide concentrations above 1600 ng/ml.

Based on the reasons listed previously and the results of ESPRIT study, the sponsor proposed the following dosing regimen for incorporation into the label for patients undergoing PCI, initial bolus of 180 µg/kg with 2.0 µg/min-kg for 20-24 hours and a second bolus dose of 180 µg/kg administered 10 minutes after the initial bolus dose. However, in the ESPRIT study eptifibatide concentrations were not measured. Because

of the lack of plasma concentration data from ESPRIT, the sponsor alternatively submitted data from a substudy of PRIDE (the present submission) where the following dosing regimens were studied (none of which are the present proposed regimen of 180 (B)/2 (I)/180 (B) (10 min)); 180 (B)/2 (I), 180 (B)/2 (I)/90 (B) (30 min), 250 (B)/3 (I), and 250 (B)/3 (I)/125 (B) (30 min). The reviewer therefore simulated the concentrations which would result from the proposed dose of 180 (B)/2 (I)/180 (B) (10-min) and compared them to concentrations resulting from the highest dose of 250 (B)/3 (I)/125 (B) (30-min) studied in the PRIDE sub-study. A detailed summary of the results of PRIDE sub-study and the results of modeling and simulation are attached in Appendix II of this review.

RESULTS:

The mean concentration (simulated) at 10-min (immediately following administration of II^{nd} bolus) with the new proposed dosage regimen of 180 $\mu\text{g}/\text{kg}$ (B) + 2 $\mu\text{g}/\text{min}\cdot\text{kg}$ (I) + 180 $\mu\text{g}/\text{kg}$ (10-min) is about 3000 ng/ml, which is above the target concentration of 1600 ng/ml, and the 95th percentile is expected to be about 4500 ng/ml. The expected mean steady-state concentration of 2100 ng/ml with the new proposed regimen is about 4-fold higher than those expected with the current labeled regimen for PCI patients of 135 $\mu\text{g}/\text{kg}$ (B) + 0.5 $\mu\text{g}/\text{min}\cdot\text{kg}$ (I) of 535 ng/ml.

The mean expected concentration at 10-min of 3000 ng/ml obtained with the proposed new regimen is similar to that seen at 30-min (time of II^{nd} bolus) with the 250 $\mu\text{g}/\text{kg}$ (B) + 3 $\mu\text{g}/\text{min}\cdot\text{kg}$ (I) + 125 $\mu\text{g}/\text{kg}$ (30-min) dosing regimen used by Group I in Study 96-023b. The 95th percentile concentration at 10-min following the 180 $\mu\text{g}/\text{kg}$ bolus is higher, by about 500 ng/ml, compared to the 95th percentile concentration at 30-min after the 125 $\mu\text{g}/\text{kg}$ bolus.

COMMENTS:

1. The sponsor is requested to provide information regarding details of the standard curve range, quality control sample information, intra- and inter-day assay variability for Study 96-023b.
2. The sponsor should have collected sparse plasma samples from a representative sub-group of patients undergoing PCI in the ESPRIT study instead of simulating plasma concentrations.

RECOMMENDATIONS:

The Office of Clinical Pharmacology and Biopharmaceutics simulated expected plasma concentrations following treatment with the new proposed dosage regimen of 180 $\mu\text{g}/\text{kg}$ (B) + 2 $\mu\text{g}/\text{min}\cdot\text{kg}$ (I) + 180 $\mu\text{g}/\text{kg}$ (10-min). The expected steady-state concentration of 2100 ng/ml with the new proposed regimen is about 4-fold higher than the steady-state concentration of 535 ng/ml expected with the currently labeled regimen of 135 $\mu\text{g}/\text{kg}$ (B)

+ 0.5 $\mu\text{g}/\text{min}\cdot\text{kg}$ (I) for patients undergoing PCI. The expected peak concentration at 10-min (immediately following the IInd bolus) is about 3000 ng/ml, this concentration is similar to that observed at 30-min (immediately following the IInd bolus) with the highest dose of 250 $\mu\text{g}/\text{kg}$ (B) + 3 $\mu\text{g}/\text{min}\cdot\text{kg}$ (I) + 125 $\mu\text{g}/\text{kg}$ (30-min) used in Study 96-023b. From a pharmacokinetic perspective, the new dosing regimen of 180 $\mu\text{g}/\text{kg}$ (B) + 2 $\mu\text{g}/\text{min}\cdot\text{kg}$ (I) + 180 $\mu\text{g}/\text{kg}$ (10-min) proposed by the sponsor is acceptable and is expected to maintain plasma concentrations above the target concentration of 1600 ng/ml during the entire treatment.

/S/

Gabriel J. Robbie, Ph. D.

RD/FT by Emmanuel O. Fadiran, Ph. D.

Cc: NDA 20718, HFD 110, HFD 860 (Mehta, Robbie), CDER document room: Attn: Biopharm (CDER)

APPENDIX I

STUDY 96-023b – A RANDOMIZED OPEN LABEL EVALUATION OF THE PHARMACODYNAMICS AND SAFETY OF FOUR DOSING REGIMENS OF INTEGRILLIN IN PATIENTS UNDERGOING PERCUTANEOUS CORONARY INTERVENTION: A SUB-STUDY OF THE PRIDE PROTOCOL

STUDY INVESTIGATORS AND SITES: Multicenter/Multiple Investigators

Volumes: 38.2 to 38.3

OBJECTIVES:

- 1) To evaluate the safety and pharmacodynamic effects of integrillin (eptifibatide) on 20 μ M ADP-platelet induced ex vivo platelet aggregation and GP IIb/IIIa receptor occupancy in patients undergoing PCI who received a regimen of eptifibatide characterized by an initial bolus, a continuous infusion and a second bolus of eptifibatide compared with those receiving a single bolus plus infusion of eptifibatide.
- 2) To determine the prolongation and recovery of Simplate bleeding time in patients undergoing PCI who received eptifibatide at the current infusion rates.

FORMULATIONS:

Integrillin[®], Eptifibatide injection, COR Therapeutics

Bolus: Sterile intravenous injection containing 20 mg eptifibatide, 52.5 mg citric acid monohydrate USP and 10 ml water for injection, USP

Infusion: Sterile intravenous injection containing 75 mg eptifibatide, 525 mg citric acid monohydrate USP and 100 ml water for injection USP.

STUDY DESIGN:

This was an open-label, randomized, multicenter, dose-escalation study in 39 subjects (33 M/6 F) less than 75 years of age (mean: 60 yr) who have known coronary artery disease and are scheduled to undergo percutaneous coronary intervention. Subjects are to be randomized to each of the following treatments,

Dosing Group	Initial Bolus (μg/kg)	Continuous Infusion Rate (μg/min-kg)	Second Bolus (μg/kg)
F (n=7)	180	2.0	None
G (n=13)	180	2.0	90
H (n=6)	250	3.0	None
I (n=13)	250	3.0	125

Patients in Groups H and I were treated based on the safety and pharmacodynamics in patients in Groups F and G.

Patients received 81-325 mg aspirin within 1-12 hours before eptifibatide administration, then daily thereafter.

ASSAY:

... as the internal standard was used for quantitation of eptifibatide concentrations. The LOQ of eptifibatide was ... ng/ml. Details of the standard curve range, quality control sample information, intra- and inter-day assay variability were not provided by the sponsor.

Sample Collection:

Blood samples were collected at baseline and at 1, 2, 3, 4, 6 and 8 hours after initial bolus administration for assessment of pharmacokinetic parameters of Integrillin, and for determination of ex vivo platelet aggregation (induced by 20 µM ADP) and for determination of receptor occupancy.

RESULTS

Mean plasma concentrations of eptifibatide from the various regimens are presented in the following table.

Table 1: Mean (SD) Plasma Concentrations (ng/ml) of Eptifibatide

Time after 1st Bolus (h)	Group F 180/2.0 (n=4)	Group G 180/2.0/90 (n=12)	Group H 250/3.0 (n=5)	Group I 250/3.0/125 (n=12)
1.0	1222.8 (327.0)	1766.0 (443.4)	1287.8 (363.5)	2305.3 (700.6)
2.0	1404.3 (171.9)	1575.5 (314.4)	1715.0 (292.0)	2311.5 (831.3)
3.0	1329.5 (96.8)	1655.6 (286.8)	2116.6 (634.0)	2226.6 (561.5)
4.0	1458.0 (120.3)	1675.9 (425.3)	2271.8 (504.2)	3175.6 (3033.0)
6.0	1431.5 (34.7)	9560.0 (17696.9)*	2448.4 (589.3)	2226.5 (825.2)
8.0	1645.3 (250.4)	2599.1 (2342.1)	3453.3 (2880.6)	2520.4 (790.9)

*includes outlier with plasma concentration of 14313 ng/ml

Eptifibatide plasma concentration at 1-h was lower than the steady-state (8 h) concentration in all Groups. Administration of a second bolus dose 30 minutes after the initial bolus resulted in higher 1-h plasma concentrations compared to administration of a single bolus dose. The mean plasma concentration at 1-h in Groups G and I receiving the second bolus was greater than 1600 ng/ml required for 80% receptor occupancy of GP IIb/IIIa receptors, while mean 1-h concentrations in Groups F and H were below 1600 ng/ml. The observed concentrations exhibited an average %CV of approximately 25 to 30%. The cause of the variability is not known because the sponsor has not provided details of the analytical method and the variability associated with the assay.

The sponsor has modeled the data and has obtained mean estimates and standard errors of the estimates. These are presented in the table below.

Table 2: Estimated Mean (Std Error) Eptifibatide Pharmacokinetic Parameters

Parameter	Group F 180/2.0 (n=4)	Group G 180/2.0/90 (n=12)	Group H 250/3.0 (n=5)	Group I 250/3.0/125 (n=12)
A (ng/ml)	18326 (25060)	21828 (54095)	33458 (84412)	32998 (130412)
B (ng/ml)	7666 (14972)	10794 (3833)	13799 (61959)	13792 (6955)
α (1/h)	1.34 (3.96)	2.42 (5.16)	3.06 (42.7)	2.41 (7.86)
β (1/h)	0.256 (0.36)	0.256 (0.10)	0.270 (0.672)	0.263 (0.143)
CL (ml/min.kg)	1.17 (0.027)	1.03 (0.126)	1.23 (0.47)	1.17 (0.19)
Css (ng/ml)	1710	1946	2441	2560

The observed concentrations best fit a two-compartment model with a clearance of 1.2 ml/min.kg. Pharmacokinetic parameter estimate of clearance in Group F (180 (B)/2 (I)) had the lowest standard error.

Table 3: Mean (SD) ADP-Induced Platelet Aggregation as a Percentage of Baseline by Treatment Group

Time after 1st Bolus (h)	Group F 180/2.0 (n=4)	Group G 180/2.0/90 (n=12)	Group H 250/3.0 (n=5)	Group I 250/3.0/125 (n=12)
Baseline	100.0	100.0	100.0	100.0
1.0	12.1 (9.8)	8.4 (7.9)	5.7 (6.9)	1.2 (2.1)
2.0	9.7 (5.5)	8.8 (7.2)	3.9 (4.5)	2.5 (4.7)
3.0	7.5 (4.7)	6.0 (5.4)	4.1 (4.7)	1.1 (2.1)
4.0	6.1 (3.5)	7.1 (6.1)	2.2 (2.9)	0.7 (1.9)
6.0	6.4 (5.2)	8.0 (11.4)	2.4 (3.5)	1.6 (3.0)
8.0	6.5 (7.1)	6.8 (7.9)	3.0 (4.2)	0.7 (1.4)

*includes outlier with plasma concentration of 14313 ng/ml

Group F receiving 180 $\mu\text{g}/\text{kg}$ (B) + 2 $\mu\text{g}/\text{min.kg}$ (I) exhibited the highest mean ADP-induced platelet aggregation at 1-h (12% of baseline) and Group I receiving 250 $\mu\text{g}/\text{kg}$ (B) + 3 $\mu\text{g}/\text{min.kg}$ (I) + 125 $\mu\text{g}/\text{kg}$ (B) exhibited the lowest mean 1-h and 8-h ADP-induced platelet aggregation (1% from baseline) compared to other groups. Administration of an additional 90 $\mu\text{g}/\text{kg}$ (B) 30 min following the first 180 $\mu\text{g}/\text{kg}$ (B) in Group G resulted in a decrease in ADP-induced platelet aggregation at 1-h (8% of baseline), but this value was higher than the mean value (6% of baseline) of Group H receiving 250 $\mu\text{g}/\text{kg}$ (B) + 3 $\mu\text{g}/\text{min.kg}$ (I).

Table 4: Mean (SD) Percentage of GP IIb/IIIa Receptors Occupied at Different Time Points

Time after 1st Bolus (h)	Group F 180/2.0 (n=4)	Group G 180/2.0/90 (n=12)	Group H 250/3.0 (n=5)	Group I 250/3.0/125 (n=12)
Baseline	0.00	0.00	0.00	0.00
1.0	67.4 (10.9)	81.6 (5.8)	75.3 (10.3)	80.5 (10.0)
2.0	73.6 (9.1)	76.3 (7.8)	65.2 (9.7)	77.5 (10.5)
3.0	74.0 (10.5)	72.6 (10.7)	80.2 (8.3)	80.6 (12.4)
4.0	72.4 (10.8)	75.4 (9.3)	68.4 (13.6)	83.5 (12.9)
6.0	82.5 (13.8)	80.4 (9.3)	83.0 (10.9)	84.4 (8.3)
8.0	73.4 (9.8)	76.4 (16.2)	80.5 (12.0)	82.7 (8.8)

GP IIb/IIIa receptor occupancy 1-h after commencement of therapy was lower in Group F receiving 180 µg/kg (B) + 2 µg/min.kg (I) compared to other groups. Administration of an additional 90 µg/kg (B) 30 min following the first 180 µg/kg (B) in Group G increased mean receptor occupancy by 14%. Mean receptor occupancy at 1-h in Group H receiving the higher dose of 250 µg/kg (B) + 3 µg/min.kg (I) was 75%, which increased to 81% with the administration of an additional bolus dose of 125 µg/kg (B). Mean receptor occupancy at 8-h was about 5% higher in Groups H and I receiving a higher dose compared to Groups F and G.

Baseline bleeding times of 6-8 minutes increased to >30 minutes following continuous infusion of eptifibatide in all 4 groups. Bleeding times decreased from >30 minutes to 19, 16, 22 and 20 minutes in Groups F, G, H and I, respectively, about 4 hours after termination of infusion.

Minor bleeding events (n=1) were observed in Groups G, H and I and none in Group F.

CONCLUSIONS:

The present sub-study of PRIDE shows that observed concentrations 1-h after the initial bolus were higher in Groups G and I receiving a second bolus administration of 90 and 125 µg/kg at 0.5 h. The observed mean 1-h concentration in the Groups receiving the second bolus was above the target concentration of 1600 ng/ml for 80% receptor occupancy.

The recommended dosage change in the label is for administration of a second 180 µg/kg bolus 10-min after the initial bolus of 180 µg/kg. This new dosage regimen was not studied in the present Study. Therefore, the biopharmaceutics reviewer simulated the concentrations which are expected with the new dosage regimen of 180 µg/kg (B) + 2 µg/min.kg (I) + 180 µg/kg (B) 10-min and compared the concentrations to those

simulated following administration of 250 µg/kg (B) + 3 µg/min.kg (I) + 125 µg/kg (30-min). The details and results of the simulation are attached in Appendix II.

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APPENDIX II

SIMULATION OF CONCENTRATIONS EXPECTED WITH RECOMMENDED NEW DOSAGE REGIMEN OF 180 µg/kg (B) + 2 µg/min.kg (I) + 180 µg/kg (B) 10-min AND COMPARISON WITH HIGHEST DOSE OF 250 µg/kg (B) + 3 µg/min.kg (I) + 125 µg/kg (30-min) USED IN PROTOCOL 96-023b

OBJECTIVE:

To simulate and compare plasma eptifibatide concentrations resulting from the recommended dose of 180 µg/kg (B) + 2 µg/min.kg (I) + 180 µg/kg (B) 10-min and the maximum dose of 250 µg/kg (B) + 3 µg/min.kg (I) + 125 µg/kg (30-min) used in Protocol 96-023b.

STUDY DESIGN:

Eptifibatide plasma concentrations were modeled to a 2-compartment open model using the pharmacokinetic parameters obtained from Group F receiving 180 µg/kg bolus and 2 µg/min.kg infusion in Study 96-023b. The values of the pharmacokinetic parameters (intercepts normalized to 1 µg/kg) were: A = 6.36 ng/ml, B = 2.66 ng/ml, $\alpha = 1.34 \text{ h}^{-1}$, $\beta = 0.256 \text{ h}^{-1}$ and $K_{21} = 0.575712 \text{ h}^{-1}$. Equations 1, 2 and 3 listed below were used for simulation of bolus and infusion concentrations and the sum total of concentrations from the bolus and infusion doses were calculated using the super-position principle.

$$C_{p,bolus} = A \cdot e^{-\alpha \cdot t} + B \cdot e^{-\beta \cdot t} \quad \text{Eq. 1}$$

$$C_{p,inf} = \frac{R_0(K_{21} - \alpha)(1 - e^{-\alpha \cdot t})}{\alpha(\beta - \alpha)V_c} + \frac{R_0(K_{21} - \beta)(1 - e^{-\beta \cdot t})}{\beta(\alpha - \beta)V_c} \quad \text{Eq. 2}$$

$$C_{p,inf} = \frac{R_0(K_{21} - \alpha)(e^{+\alpha \cdot T} - 1)e^{-\alpha \cdot t}}{\alpha(\beta - \alpha)V_c} + \frac{R_0(K_{21} - \beta)(e^{+\beta \cdot T} - 1)e^{-\alpha \cdot t}}{\beta(\alpha - \beta)V_c} \quad \text{Eq. 3}$$

Where, t = time after initiation of infusion/bolus dose (h), T = infusion duration (h), R_0 = infusion rate (µg/h.kg) and V_c = central volume of distribution (ml/kg). Equations 2 and 3 were used for simulating concentrations during and after termination of infusion, respectively.

For each dose, plasma concentrations of 1000 subjects were simulated using Monte-Carlo sampling at the following time points: 0, 0.166, 0.25, 0.5, 1, 2, 3, 4, 6, 8, 24, 26 and 30 h

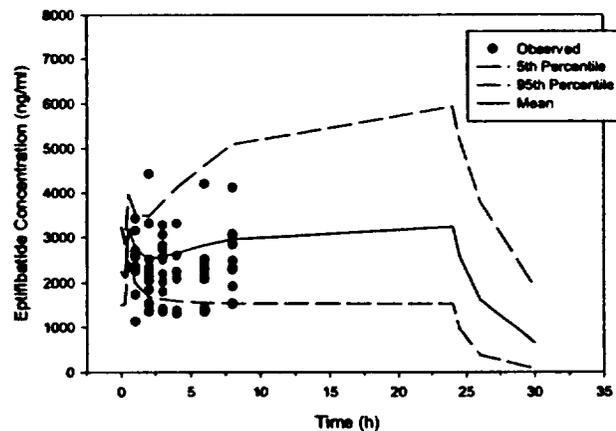
after initiation of infusion. The pharmacokinetic parameters A, B, α and β were simulated with a log-normally distributed inter-individual variability with a mean of 30%; this was based on the approximately 30% inter-subject variability reported for the observed concentrations in Study 96-023b. The mean, maximum, minimum, 5th percentile and 95th percentile concentrations were plotted for the different doses.

RESULTS

The simulated concentrations for dosing regimen 250 $\mu\text{g}/\text{kg}$ (B) + 3 $\mu\text{g}/\text{min.kg}$ (I) + 125 $\mu\text{g}/\text{kg}$ (30-min) received by subjects in Group I in Study 96-023b were similar to observed concentrations. Observed concentrations from most subjects, except 2, were within the 95th and 5th percentile limits obtained by simulating mean inter-individual variability of 30% (see Figure 1. below). The 95th percentile for the 30-min concentration (immediately following the IInd bolus) was about 4000 ng/ml. The mean concentration at 30-min was 3200 ng/ml and the mean steady-state concentration was about 3237 ng/ml.

Figure 1.

250 mcg/kg bolus + 3 mcg/min.kg infusion (24-h) + 125 mcg/kg bolus (30-min)

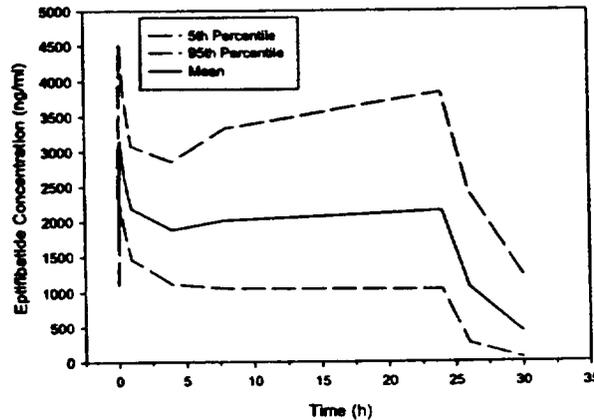


The expected mean, 5th and 95th percentile concentrations following the proposed dosage regimen of 180 $\mu\text{g}/\text{kg}$ (B) + 2 $\mu\text{g}/\text{min.kg}$ (I) + 180 $\mu\text{g}/\text{kg}$ (B) 10-min is presented in the following figure. The mean concentration at 10-min (immediately following administration of IInd bolus) is about 3000 ng/ml, which is above the target concentration of 1600 ng/ml, and the 95th percentile is about 4500 ng/ml. The mean expected concentration with the new proposed dosage regimen is similar to that seen at 30-min (time of IInd bolus) with the 250 $\mu\text{g}/\text{kg}$ (B) + 3 $\mu\text{g}/\text{min.kg}$ (I) + 125 $\mu\text{g}/\text{kg}$ (30-min) dosing regimen used by Group I in Study 96-023b. The 95th percentile concentration at 10-min following the 180 $\mu\text{g}/\text{kg}$ bolus is higher, by about 500 ng/ml, compared to the 95th percentile concentration at 30-min after the 125 $\mu\text{g}/\text{kg}$ bolus. This difference, however, is not expected to be significant in terms of adverse effects because of, a) transient nature of

increase in concentration and, b) absence of serious adverse events in individuals in Group I of Study 96-023b whose observed concentrations were above 4000 ng/ml.

Figure 2.

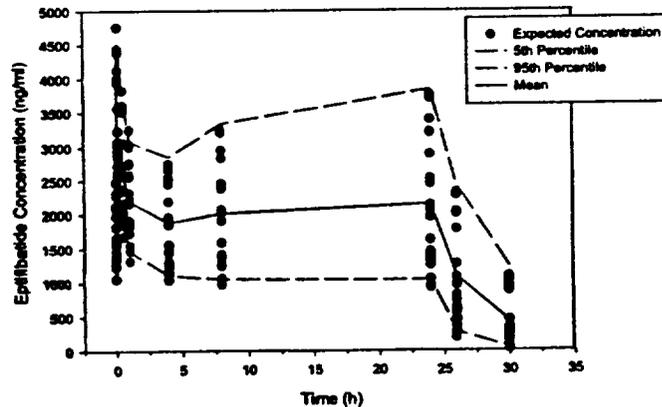
180 mcg/kg bolus + 2 mcg/min.kg infusion (24-h) + 180 mcg/kg bolus (10-min)



The simulated plasma concentrations of eptifibatid from a random group of 20 subjects receiving the proposed dosing regimen of 180 $\mu\text{g}/\text{kg}$ (B) + 2 $\mu\text{g}/\text{min.kg}$ (I) + 180 $\mu\text{g}/\text{kg}$ (B) 10-min is presented in Figure 3.

Figure 3.

180 mcg/kg bolus + 2 mcg/min.kg infusion (24-h) + 180 mcg/kg bolus (10-min)

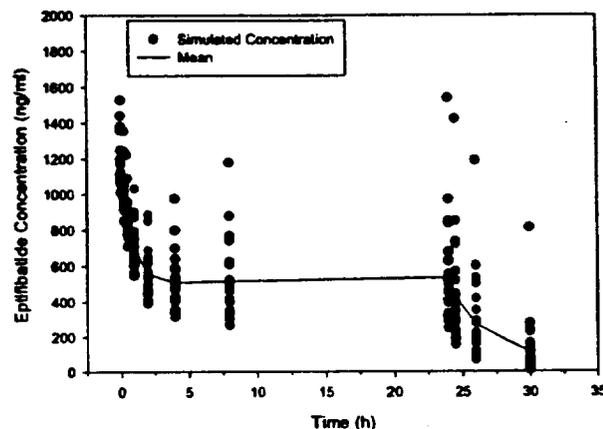


The above concentrations were contrasted with the simulated plasma concentrations of eptifibatid from a random group of 20 subjects receiving the currently labeled dosing regimen for PCI patients of 135 $\mu\text{g}/\text{kg}$ (B) + 0.5 $\mu\text{g}/\text{min.kg}$ (I) (no IInd bolus). As seen in Figure 4, the mean concentration during the Ist hour after bolus (700 ng/ml) and at steady-

state (535 ng/ml) with the current labeled dosing regimen is about 1/4 of the concentrations expected with the new dosing regimen of 180 µg/kg (B) + 2 µg/min.kg (I) + 180 µg/kg (B) (10-min).

Figure 4.

Simulated Conc. following 135 mcg/kg bolus + 0.5 mcg/min.kg infusion (24-h)



CONCLUSIONS:

The mean concentration at 10-min (immediately following administration of IInd bolus) with the new proposed dosage regimen of 180 µg/kg (B) + 2 µg/min.kg (I) + 180 µg/kg (10-min) is about 3000 ng/ml, which is above the target concentration of 1600 ng/ml, and the 95th percentile is about 4500 ng/ml. The expected mean steady-state concentration with the new proposed regimen is 2100 ng/ml which is about 4-fold higher than the steady-state concentration expected with the current labeled regimen for PCI patients of 135 µg/kg (B) + 0.5 µg/min.kg (I).

The mean expected concentration with the proposed new dosage regimen is similar to that seen at 30-min (time of IInd bolus) with the 250 µg/kg (B) + 3 µg/min.kg (I) + 125 µg/kg (30-min) dosing regimen used by Group I in Study 96-023b. The mean steady-state concentration, however, was higher (3200 ng/ml) because of the larger dose (3 µg/min.kg (I) vs. 2 µg/min.kg (I)).