

Table of Contents

Volume 1

Tab 1- Tirofiban Medical and Statistical Review

Volume 2

Tab 1- Eptifibatide Medical Review (PURSUIT Study)

Tab 2- Eptifibatide Medical Review (PERIGREE Study)

Tab 3- Eptifibatide Medical Review (PRIDE Study)

Tab 4- Eptifibatide Medical Review (IMPACT I and II Studies,
IMPACT High-Low Study)

Tab 5- Meta-analysis of IIb/IIIa antagonists

MEDICAL OFFICER REVIEW

NDA #: 20-718
DRUG NAME: Integrilin
SPONSOR: COR Therapeutics
TYPE OF DOCUMENT: Supplement (AZ)
DATE RECEIVED: 10-1-97
DATE COMPLETED: Draft
MEDICAL OFFICER: Isaac W. Hammond, MD, Ph.D.

The following table, lists the submissions and regulatory actions for NDA 20-718 (Integrilin™). The original application was submitted on 4/1/96. The application was reviewed by the Division of Gastrointestinal and Coagulation Drug Products. The clinical studies were discussed before the Cardio-Renal Advisory Committee on 2/27/97. On 3/21/97, the application was Not Approved pending the submission of additional clinical studies. Subsequent to the Not Approved regulatory action, the application was transferred from the Division of Gastrointestinal and Coagulation Drug Products to the Division of Cardio-Renal Drug Products. On 10/1/97, the sponsor submitted additional clinical information, primarily the results from the PURSUIT Trial, to support the approval of Integrilin™. A listing of new clinical studies is provided in the appendix 8. This document will provide a medical review of the PURSUIT trial.

NDA History

Date Received	Information
4-1-96	NDA Submitted
8-2-96	Safety Amendment
10-15-96	Clinical/Statistical Amendment to NDA
11-21-96	Clinical/Statistical Amendment to NDA
2-27-97	Cardio-Renal Advisory Committee Review
3-21-97	FDA Action Letter - Not Approveable
5/15/97	Transfer of NDA from HFD-180 (Division of Gastrointestinal and Coagulation Drug Products) to HFD-110 (Division of Cardio-Renal Drug Products)
10-1-97	Clinical Amendment - PURSUIT Study Submitted

In addition to the archival copies of the NDA, the clinical trial reports and the data (SAS data files) for the PURSUIT trial were provided on CD-ROM

General Information

Name of Drug

Generic: Eptifibatide

Trade: Integrilin™

Pharmacologic Category: Inhibitor of Platelet GP IIb/IIIa complex

Proposed Indications:

1. Prevention of Death and myocardial infarction (MI) in patients with Unstable Angina or non Q-wave MI;

2. Adjunct to percutaneous transluminal coronary angioplasty (PTCA) for the prevention of abrupt closure of the treated coronary vessel

Dosage Form: sterile solution for intravenous administration

Route of Administration: intravenous injection

Table of Contents	Page
Summary of the PURSUIT Protocol	2
Summary of Efficacy	10
Subgroup Analyses	13
Summary of Safety	18
Deaths	18
Bleeding	18
Transfusions	26
Serious Non-bleeding Adverse Events	27
Strokes	29
Review Summary	32
Appendix	34

PURSUIT Protocol (#94-016)

A Randomized, Double-Blind Evaluation Of The Efficacy And Safety Of Integrilin™ Versus Placebo For Reducing Mortality And Myocardial (Re)Infarction In Patients With Unstable Angina Or Non-Q Wave Myocardial Infarction

PROTOCOL

The original PURSUIT protocol (submitted on 1/10/95) was a randomized, double-blind, placebo controlled trial in patients with unstable angina or non-Q wave myocardial infarction to assess the effect of eptifibatide on mortality and MI. Eligible patients were randomized to placebo or one of two doses of eptifibatide, 135 ug/kg bolus followed by a continuous infusion for 72 hours of 1.0 ug/kg or 1.25 ug/kg. After the randomization was initiated, drastic changes were made in the protocol (amendment #2) with regard to the dosing regimens, interim analysis and data analysis plan. These changes were of such significance that the investigators chose to treat the patients randomized prior to amendment #2 as a separate trial. The 118 patients randomized in accordance with the original protocol and amendment #1 have been characterized as the PRE-PURSUIT Trial. Those patients randomized in accordance with amendment #2 and subsequent amendments have been characterized as the PURSUIT Trial. An additional substudy evaluating pharmacokinetics was performed and denoted as the PERIGEE Substudy. Table P.1 provides the chronology of events in relation to study conduct.

Table P.1. Chronology of protocol submission, Study Conduct and Data and Safety Monitoring Committee

Date	Protocol Submissions	Study Conduct	DSMC
9-23-94	Draft PURSUIT protocol (#107)		
1-10-95	Original PURSUIT protocol (#117)		
3-27-95	Amendment #1		
7-10-95		1st Patient Randomized to Pre-PURSUIT	
9-21-95	Amendment # 2		
11-29-95		1st Patient Randomized into PURSUIT	
2-12-96	Amendment #4		
3/21/96			Safety Review
4/27/96			Safety Review
5/21/96			Safety Review
5/29/96			Safety Review

Table P.1. Chronology of protocol submission, Study Conduct and Data and Safety Monitoring Committee

Date	Protocol Submission	Study Conduct	DSMC
6-21-96			Teleconference
6-26-96	Amendment #5		
6-27-96		PERIGEE Substudy Started	
7-19-96	Amendment #6		
7/22/96			Select Eptifibatide Dose Interim Analysis
12/19/96			Interim Analysis
1-20-97		Last Patient Randomized into PURSUIT	
1-23-97		PERIGEE Substudy Completed	
7-22-97	Amendment #7		

* all protocol related submissions were made to IND¹

PERIGEE Substudy is a pharmacokinetic/pharmacodynamic substudy

The following description of the protocol is based on the protocol submitted as amendment 2 and subsequent protocol amendments.

Study Design and Description

This study was a randomized, multicenter, double blind, placebo controlled, parallel dose trial in patients with Unstable Angina or Non-Q wave Myocardial Infarction. The primary objectives were to demonstrate the efficacy of a single dosing regimen of Integrilin compared to placebo and to determine the safety of the dosing regimen of Integrilin selected. Patients were eligible for enrollment if they had experienced at least 10 minutes of cardiac ischemia at rest within the previous 24 hours and fulfilled CK or ECG criteria. Table P.2. lists the inclusion and exclusion criteria. After screening, eligible patients were randomized¹ to one of two Integrilin regimens (180 µg/kg as a bolus followed by a continuous infusion of either 1.3 or 2.0 µg/kg/min) or to a matching placebo bolus and infusion for 72 hours in a 1:1:1 ratio. All patients should have received aspirin unless contraindicated. Heparin use was optional. After 2100 patients were randomized into the trial, the Data and Safety Monitoring Committee (DSMC) was responsible for reviewing the safety data (e.g. bleeding incidence) and choosing a single eptifibatide dose regimen to continue².

Table P.2. Inclusion/Exclusion Criteria (Based on Criteria in Amendment 2)

Inclusion Criteria
<ul style="list-style-type: none"> • Have experienced symptoms of cardiac ischemia (angina or anginal equivalent) at rest, with episodes lasting at least 10 minutes, within 24 hours of enrollment, AND • Have either transient ST segment elevation > 0.5 mm, <u>or</u> transient or persistent ST segment depression of > 0.5 mm, <u>or</u> definitive T wave inversion of >1 mm, <u>or</u> persistent ST segment elevation > 0.5 mm but not requiring reperfusion therapy (because of small ischemic area)^c

¹ Investigators contacted the Duke Coordinating Center (U.S. and Canada) or the Cardialysis Coordinating Center (European). A kit number at the site was assigned by the randomization center.

² This is described in more detail in the description of the interim analysis. Originally, the DSMC only had the option of selecting one dose. Amendment 6, however, gave them the option to continue both doses.

during or within 12 hours of an episode of chest pain^B and obtained within 36 hours of an episode OR

- Have subsequent associated positive CK-MB > the upper limit of normal
- ≤ 75 years of age^A

[NOTE: Transient means < 30 minutes duration and no thrombolytics or direct PTCA.]

Exclusion Criteria

- Persistent (> 30 minutes) ST segment elevations of > 1.0 mm on ECG suggesting acute Q-wave myocardial infarction.
- A history of bleeding diathesis (either primary or secondary), gastrointestinal bleeding, hematemesis, hematochezia, or melena or gross genitourinary bleeding within the past 30 days, or evidence of active bleeding (except menstrual bleeding).
- Severe hypertension (systolic blood pressure > 200 mm Hg or diastolic blood pressure > 100 mm Hg on therapy). Patients will become eligible upon control of their blood pressure.
- Had major surgery within 6 weeks of enrollment.
- History of stroke, other central nervous system damage, or structural abnormalities of the central nervous system.
- If female, a lack of adequate contraception during the previous menstrual cycle or pregnant. Premenopausal females should have a pregnancy test performed prior to enrollment.
- Known prothrombin time > 1.2 times control (or INR ≥ 2.0).
- Known platelet count < 100,000/mm³.
- Known hematocrit < 30%.
- Participated in a study of experimental therapy within the previous 30 days.
- Concomitant or planned administration of an anti-GP IIb/IIIa or thrombolytic agent.
- Thrombolytic therapy within 24 hours.
- Renal failure (serum creatinine level ≥ 2.0 mg/dL or renal dialysis).

^A after 300 patients were accrued, it was determined by the Data and Safety Monitoring Committee that patients > 75 years could be enrolled if their body weight was > 50 kg (amendment 5).

^B Amendment 5 eliminated the 12 hours requirement.

^C changed to persistent

Study drug administration could be discontinued in patients who went for coronary artery bypass grafting, ischemic stroke or neurological deficit and due to an adverse event or for significant bleeding. Patients also received standard medical therapy, including heparin and aspirin. All patients were followed until hospital discharge and re-evaluated 30 days after enrollment for the occurrence of any component of the composite primary endpoint of death or myocardial (re)infarction.

If (re)infarction was suspected, patients had total CK and CK-MB measured during, at 8 and 16 hours after the event and 12 lead ECG during, at 30 minutes and 24 hours after the event. In patients undergoing percutaneous coronary revascularization and coronary artery bypass³, total CK and CK-MB⁴ was obtained immediately before and at 8 and 16 hours post-procedure.

³ CABG added with amendment 5

⁴ Amendment 5 specified that CK-MB should be obtained regardless of the Total CK.

Diagnostic coronary cath and PTCA could be performed at any time. Study drug should have been continued during the procedures. In patients who undergo percutaneous coronary intervention late in the infusion course, the infusion could be continued for 96 hours. In patients who received thrombolytic therapy, study drug was discontinued. Concurrent use of other GP IIb/IIIa inhibitors was not permitted.

The schedule of routine evaluations performed during the study are outlined in table P.3. Patients will have a day 30 follow-up visit and a 6 month phone call to assess the occurrence of clinical endpoints.

Table P.3. Schedule of Evaluations

Evaluation	Pre-Enrollment (Within 24 hours of enrollment) *	At Enrollment	During Infusion				Post-Infusion ^A	
			8 hr.	16 hr.	24 hr.	daily	Hosp. Discharge	30 FU
12 lead ECG		X			X		X	X
PT	X							
aPTT	X	X**	X** *		X			
CPK & CK-MB		X	X	X				
Troponin T		X	X	X				
Serum Creatinine	X							
Platelet Count	X				X	X		
Hematocrit	X				X	X		
Hemoglobin	X					X		

* Study drug initiation does not need to wait until these labs have returned.

** If patient is on heparin at time of enrollment; *** only if heparin is initiated at time of enrollment.

^A ECGs and Enzyme determinations are added if the patient experiences percutaneous procedure or CABG.

Primary Efficacy Endpoint

The primary endpoint was the composite of death from any cause or myocardial (re)infarction during the first 30 days after randomization (see specific definition for MI). The endpoints used in this analysis are those determined to fulfill the pre-specified definition of an event as adjudicated by the Clinical Events Committee.

Secondary Efficacy Endpoints

There were numerous secondary endpoints specified as outlined in table P.4. The events occurring between 30 days and 6 months after treatment were not adjudicated by the Clinical Events Committee⁵.

Table P. 4. Secondary Endpoints

Secondary Efficacy Endpoints
<ul style="list-style-type: none"> • The primary composite endpoint and its individual components 96 hours, 7 days and 30 days after enrollment. • The composite of death, non-fatal MI or recurrent ischemia at 96 hours, 7 days and 30 days. • A comparison of the primary composite endpoint in patients who undergo a revascularization procedure [This endpoint was deleted with amendment 4].

⁵ Originally, these endpoints were to be adjudicated. Amendment 5 specified that they would not be adjudicated.

- A comparison of the primary composite endpoint in patients who do not undergo a revascularization procedure.
- Individual components of the primary endpoint within 30 days of enrollment.
- Efficacy analysis by gender.
- Efficacy analysis by ethnicity.
- Efficacy analysis by age.
- Rehospitalization for cardiac symptoms within 30 days.
- A comparison of severity of myocardial (re)infarction using CK-MB values.
- Death, MI, recurrence of ischemic symptoms, repeat attempt at coronary revascularization and readmission for ischemic symptoms at 6 months after enrollment.

Secondary Safety Endpoints

- Comparison of Integrilin to placebo in patients who undergo percutaneous cardiac interventions while on study drug and in those who do not.
- Incidence of stroke (all cerebrovascular events, all cerebrovascular events associated with intracranial hemorrhage, all cerebrovascular events associated with residual functional impairment)
- Incidence of bleeding while on study drug
- Differences in bleeding index* while on study drug
- Safety endpoints by gender, age and ethnicity

* Bleeding Index = # Units PRBCs transfused + (observed drop in hematocrit/3)

Statistical Analysis Plan

After 300 patients were accrued, the DSMC was responsible for evaluating the safety data to determine whether patients > 75 years of age could be enrolled. After 2100 patients were enrolled, the DSMC was responsible for evaluating the safety data and selecting a dose of eptifibatide to continue in the study. In the original protocol, the high dose group would be selected if there was no substantial difference (e.g. 5 percentage points) in the major bleeding incidence between the two eptifibatide groups and the proportion of patients with events also showed no untoward safety risk⁶. In amendment 6, the protocol was changed so that the DSMC could permit both eptifibatide groups to continue enrollment. Additional interim analyses assessing efficacy were specified after accrual of 1/3 and 2/3 of the patients in the two treatment arms. The interim analysis for efficacy of the primary endpoint followed O'Brien Fleming Boundaries. The decision to stop early for benefit also required a consistent trend toward improved mortality.

In the original protocol, assuming that a single eptifibatide dose would be selected, the study would enroll approximately 4691 patients⁷ in each treatment arm (placebo and one eptifibatide arm). This provided an 80% power to detect a 20% reduction in event rate between the placebo and eptifibatide arms (based on placebo event rate of 8.0%, one-sided binomial with alpha = .025, adjustment for 4 looks).

Table P.5. lists the statistical testing specified in the protocol for the various endpoints.

⁶ The use of the MI and death data as a means of determining which dose to continue in the trial suggests that the first interim analysis is simply not based on safety issues alone and some adjustment of the significance level may be required. The original protocol seemed rather clear that the higher dose would be used if there were no difference in safety (major bleeding) between the eptifibatide doses. Amendment 6 changed this when it added that the DSMC could permit both doses to continue without providing the circumstances under which this could occur.

⁷ if both eptifibatide doses were continued, 3850 patients would be enrolled in each treatment group

Table P.5. Statistical Analysis Plan

Endpoint	Statistical Analysis
Primary Endpoint	<ul style="list-style-type: none"> the statistical test procedure was not specified for the primary analysis the level of alpha to determine statistical significance was not specified for the primary analysis analysis for all patients randomized ^A and all patients treated ^B logistic regression models will be utilized to identify prognostic variables influencing overall response <p>[Note: the interim analysis would use a one sided binomial test with alpha = .025]</p>
Secondary Endpoint	<ul style="list-style-type: none"> Calculate two sided 95% confidence intervals Incidences and proportions will be evaluated assuming binomial distributions Counts will be assessed by non-parametric rank procedures
Safety Endpoints	<ul style="list-style-type: none"> Confidence Intervals will be constructed to estimate the difference of the incidence of adverse events

^A All Randomized Population = Total number of subjects allocated to an assigned treatment regimen, regardless of whether they received any portion of study drug.

^B As Treated Population = Total number of subjects who correctly received any portion of study drug that was intended by their randomization schedule.

Definition of Endpoints

Death was defined as all-cause mortality. Myocardial (re)infarction was determined by clinical, ECG and enzymatic criteria. The specific criteria varied according to the clinical situation [i.e., time from enrollment, post-procedure, presence of Non Q wave MI (NQMI) pre-enrollment, etc.]. The presence of a NQMI at randomization represents a baseline feature and was not considered a primary endpoint of the study. Since patients with NQMI could be enrolled, the protocol provides criteria for distinguishing an MI at enrollment from an MI as a post-randomization event. Table P.6 outlines the criteria for diagnosing an enrollment MI. Patients could have any one of the ECG or enzyme criteria for the diagnoses of an enrollment MI.

Table P.6. Criteria for MI at Enrollment [MI if one criteria is met].

ECG Criteria	Enzyme Criteria
<ul style="list-style-type: none"> ECG findings of new, significant Q waves of > 0.04 seconds duration in at least 2 contiguous leads on ECG obtained either at or 24 hours after enrollment. 	<ul style="list-style-type: none"> An elevation of the CK-MB above normal to $\geq 3\%$ of total CK at 0 and/or 8 hours after enrollment If CK-MB is not available, an elevation of total CK >2.0 times the upper limit of normal (ULN) at baseline and/or 8 hours after enrollment If the baseline and 8 hour CK-MB are normal but elevation of the CK-MB above normal and to $\geq 3\%$ of total CK is recorded at 16 hours after enrollment and no symptoms consistent with MI have occurred since enrollment. In the event of an elevation of the CK-MB above normal and $\geq 3\%$ of total CK occurs at only the 16 hour point after enrollment and symptoms consistent with MI did occur after enrollment, the clinical events committee will code the event

after reviewing the ECG, symptoms and enzyme deviations.

Tables P.7a - P.7e list the endpoint MI criteria for patients who had an enrollment MI [(re)infarction], no enrollment MI, percutaneous coronary intervention and coronary bypass surgery. Please note that in all cases, CK-MB measurements take precedence over total CK values.

Table P.7a. Endpoint MI Criteria: Post-Randomization, without Enrollment MI [MI if one criteria is met].

ECG Criteria	Enzyme Criteria
<ul style="list-style-type: none"> • ECG finding of new, significant Q waves of > 0.04 seconds duration in at least 2 contiguous leads on ECG obtained either at or 24 hours after an episode of known or suspected myocardial ischemia 	<ul style="list-style-type: none"> • An elevation of the CK-MB above normal and to $\geq 3\%$ of total CK at 0, 8 and/or 16 hours after an episode of known or suspected myocardial ischemia.

Table P.7b. Endpoint MI Criteria: Within 18 hours of enrollment [MI if one criteria is met].

ECG Criteria	Enzyme Criteria
<ul style="list-style-type: none"> • The occurrence of recurrent, severe ischemic pain at rest and new ST segment elevation of ≥ 0.1 mV (1.0 mm) in two contiguous leads. Either the pain or the ST elevations must be documented to persist for > 30 minutes 	

Table P.7c. Endpoint MI Criteria: More than 18 hours after enrollment [MI if one criteria is met].

ECG Criteria	Enzyme Criteria
<ul style="list-style-type: none"> • The finding of new, significant Q waves (> 0.04 seconds) in at least two contiguous leads and distinct from both the enrollment and the 24-hour post-enrollment ECGs 	<ul style="list-style-type: none"> • If the immediately prior CK-MB level was within the normal range, elevation of the CK-MB level above the normal range and to $\geq 3\%$ of total CK. • If the immediately prior CK-MB was above the normal range, an increase of $\geq 50\%$. • If CK-MB is not available and the total CK is > 2X ULN it must be at least 25% increased over the immediately prior level. • If CK-MB is not available and the total CK is > 1.5 and < 2X ULN, it must be at least 100% increased over the immediately prior level.

Table P.7d. Endpoint MI Criteria: Within 24 hours of Percutaneous Coronary Intervention [MI if one criteria is met].

ECG Criteria	Enzyme Criteria
<ul style="list-style-type: none"> • ECG changes consisting of new significant Q waves of > 0.04 seconds duration in at least 2 contiguous leads. 	<ul style="list-style-type: none"> • An elevation of CK-MB (or total CK in the absence of CK-MB values) to $\geq 3X$ ULN and at least 50% increased over the value preceding the procedure.

Table P.7e. Endpoint MI Criteria: Peri-Operative MI [MI if one criteria is met].

ECG Criteria	Enzyme Criteria
<ul style="list-style-type: none"> • New, significant Q waves (≥ 0.04 seconds) in at least two anatomically contiguous leads 	<ul style="list-style-type: none"> • CK-MB $\geq 5X$ ULN (or CK in the absence of CK-MB), and at least 3% of total CK if both CK and CK-MB are available. • New regional wall motion abnormality documented by echocardiogram may be considered as collaborative evidence.

Table P.8 outlines the various committees involved in the conduct of the trial and their respective functions.

Table P.8. PURSUIT Committees

Committee	Function	Composition
Clinical Events	Responsible for performing central blinded adjudication of patient data to determine whether a non-fatal MI or stroke had occurred within 30 days of enrollment.	Physicians organized and trained at Duke Clinical Research Institute. They came from Baylor Univ., Cleveland Clinic, Duke & Mayo Clinic. Vol 2.53
Data Safety Monitoring	Responsible for evaluation of the safety and efficacy of eptifibatide at predetermined interim analyses.	Joseph Albert, M.D. George Beller, M.D. Robert Bonow, M.D. Bruce Brundage, M.D. Lloyd Fisher, Ph.D. Robert Hardy, Ph.D. Jurgen Meyer, M.D. Thomas Ryan, M.D. Kerry Lee, Ph.D.* Beth Weatherley, MS*
Executive	Responsible for the overall administration of the study, resolution of recruitment issues, study progress, policies and procedures	Michael Bergman, M.D. Robert Califf, M.D. Jaap Deckers, M.D. Daniel Gretler, M.D. Robert Harrington, M.D. Michael Kitt, M.D. Kerry Lee, Ph.D. Michael Lincoff, M.D. Bruce Rodda, Ph.D. Maarten Simoons, M.D. Eric Topol, M.D.
Steering	Responsible the overall scientific direction of the study. protocol and sub-study design, creation of trial policies, monitoring of trial progress, response to recommendations of the Data safety monitoring committee, in conjunction with the executive committee, and reporting of trial results	Regional and national coordinators for the PURSUIT trial; these were prominent physicians with expertise in the study of unstable angina or in areas related to use of eptifibatide. See vol 2.52; 4- 6

* = Non Voting Members

FDA Review of PURSUIT Data

Introduction

The first patient was randomized to the pursuit trial on 11-29-95, and the last patient was randomized on 11-20-97. Initially, patients were randomized to one of three groups (placebo, integrilin 180/1.3 µg/kg infusion, and integrilin 180/2.0 µg/kg infusion). On 7-22-96 after the first interim analysis (3218 subjects enrolled), the DSMC discontinued the low dose group as provided for in the study protocol.

The PURSUIT trial report included several secondary endpoints which were analyzed as a function of time (96 hours, 7 days, 30 days, and 6 months) and population ("all randomized", "treated as randomized", "as treated"). Due to the tremendous amount of data available for analyses, it is beyond the capability of the review to validate all the reported comparisons. Thus, the primary purpose of this review is to validate the data from the PURSUIT trial supporting the primary efficacy endpoint, selected secondary endpoints, and safety of Integrilin™ (eptifibatide) injection.

The protocol specified primary efficacy endpoint was the composite of death from any cause or CEC adjudicated Myocardial infarction at 30 days. The primary efficacy endpoint will be analyzed by region of study, gender, age, and ethnicity.

The randomization procedure in North America required the investigator to contact the Duke Clinical Research Institute Randomization Center (DCRIRC). The DCRIRC assigned a randomization sequence in blocks of nine (1:1:1 treatment ratios) to each center. Based on the next sequence of slot in the center's randomization sequence, a treatment was assigned to a patient by providing the investigator with a kit number for a given patient. Kits were identified by an arbitrary six digit number. The kit number became the patient's identification number. The randomization procedure did not permit verification of the randomization sequence because the kit numbers were not sequential.

Patient Disposition

The trial enrolled 10948 subjects; 4739 (43.29%) were randomized to placebo, 1487 (13.58%) to 180/1.3 dose, and 4722 (43.13%) to 180/2.0 dose. There were 875 centers from 27 countries. The number of centers per country ranged from 1 (El Salvadore, Guatemala, and Panama) to 364 from the United States of America. The integrilin 180/1.3 group was discontinued on 7/22/96 as permitted by the protocol. The last patient assignment to integrilin 180/1.3 group was on 7/25/96 (patient No. 312125). A summary of subject disposition is presented in Table R.1. Table R.1 describes several groups, all of which are subsets of the total randomized group. The "as treated" group was made up of subjects randomized to a treatment group and actually received the correct treatment. The "treated other than as randomized" group was made up of subjects randomized to a treatment group, but received the wrong dose or treatment. The "treated but not randomized" represents subjects who were meant to be randomized, but received treatment medication before they could be enrolled into study. The "number lost to follow-up" are subjects who did not have a 30 day follow-up visit. The "number not treated" represent patients enrolled and randomized into study but did not receive any study drug.

Table R.1 Patient Disposition

	Placebo	Integrilin (180/1.3)	Integrilin (180/2.0)	Total
Number Randomized	4739	1487	4722	10948
Number Not Treated	42 (0.9%)	15 (1.0%)	42 (0.9%)	99 (0.9%)
Number with No Follow-up Lost to Follow-up	8 (4.3%)	2 (3.8%)	12 (6.8%)	22 (5.3%)
Treated but not Randomized	1	0	2	3
Treated Other than As Randomized	8	2	8	18
"As Treated" Population	4696	1472	4679	10847

Data Source: Table 5.1 Vol 2.47 page 101

Treated but not randomized = patients that received study drug without undergoing the entry criteria check

Treated Other than As Randomized = Patients who were randomized into one group but received the wrong treatment

Demographics

The overall population had 7090 (64.77%) male and 3857 (35.23%) females; 9627 (88.11%) caucasians, 545 (4.99%) blacks, 44 (0.40%) asians, 627 (5.74%) hispanics, 25 (0.23%) American indians, 27(0.25%) Asiatic indians, and 31 (0.28%) were listed as other. The subjects were recruited from different regions; 1762 (16.09%) came from eastern Europe, 585 (5.34%) from Latin America, 4358 (39.81%) from North America, 4243 (38.76%) from western Europe. A summary of Demographic characteristics by treatment groups are listed in Table R.2.

Table R.2. Demographic Characteristics of Subjects in The Different Treatment Groups.

	Characteristic	Placebo (N= 4739)	Integrilin (180/1.3) (N=1487)	Integrilin (180/2.0) (N=4722)
Age (years)	Mean \pm S E	62.8 \pm 0.16	61.7 \pm 0.28	62.8 \pm 0.16
	Median	64	63	64
	Min: Max	23:94	26:93	20:92
Age Distribution (Years)	< 50	665 (14.0%)	240 (16.1%)	660 (14.0%)
	50 - 59	1076 (22.7%)	334 (22.5%)	1108 (23.5%)
	60 - 69	1562 (33.0%)	504 (33.9%)	1487 (31.5%)
	> 70	1436 (30.3%)	409 (27.5%)	1467 (31.1%)
Gender	Male	3028 (63.9%)	987 (66.4%)	3075 (65.1%)
	Female	1711 (36.1%)	500 (33.6%)	1646 (34.9%)
Ethnic Origin	Caucasian	4202 (88.9%)	1240 (83.5%)	4185 (88.8%)
	Black	237 (5.0%)	57 (3.8%)	251 (5.3%)
	Asian	17 (0.4%)	10 (0.7%)	17 (0.4%)
	Hispanic	230 (4.9%)	168 (11.3%)	229 (4.9%)
	American Indian	10 (0.2%)	6 (0.4%)	9 (0.2%)
	Asiatic Indian	14 (0.3%)	2 (0.1%)	11 (0.2%)
	Other	19 (0.4%)	2 (0.1%)	10 (0.2%)
	Missing	10	2	10

Primary Endpoint - Composite Endpoint of Death and Myocardial Infarction at 30 Days

The primary endpoint of the PURSUIT trial was the difference between treatments for the composite endpoint of all cause mortality and myocardial (re)infarction (MI) at 30 days. The definitions of death and MI were prespecified in the protocol. The CEC adjudicated events were the protocol specified accepted endpoint.

There was, however, a large difference between investigator determined myocardial (re)infarctions and CEC adjudicated MI events at 30 days. According to the study protocol certain items on the CRF were considered triggers which automatically referred a suspected case to the CEC for adjudication. The review of triggers were computerized. The CEC actually reviewed 5053 total cases identified by triggers. The remaining cases not triggered by the computerized review was considered, by default, as reviewed and found to be negative, as classified by the investigators. The list of automatic triggers are presented in **Appendix 1**. The frequency of reported myocardial infarction by the two groups (investigators and CEC committee) is reported below in Table R.3

Table R.3 Frequency of CEC and Investigator Myocardial Infarction at 30 days for All Randomized Subjects

		CEC		
		No	Yes	Total
Investigators	No	9373	817	10190(93.04)
	Yes	163	599	762(6.96)
Total		9536(87.07)	1416(12.93)	10952(100.0)

A Chi square test comparing the frequency of myocardial (re)infarction determinations by the two groups yielded a p-value 1×10^{-10} ($\chi^2 = 2572.79$ with a $df = 1$). Such a magnitude of difference between the two groups is a cause for concern. According to the data summarized in Table R.3 the investigators missed 817 (57.7%) of the adjudicated cases of myocardial infarctions that occurred in this study. Additional analyses to evaluate the difference between investigator and CEC events are ongoing.

The distribution of concordance between the CEC adjudicated MI's and investigator designated MI's are present by treatment groups in Table R.3.1. The concordance ratios were similar by treatment group.

Table R.3.1 Frequency of CEC and Investigator Designated Myocardial Infarction at 30 Days by Treatment Groups

		Placebo (n=4739)		Integrilin 180/2.0 (n=4722)	
		MI by Investigator		MI by Investigator	
		No	Yes	No	Yes
MI By CEC	No	3980(83.98)	75(1.58)	4033(85.41)	58(1.23)
	Yes	353(7.45)	289(6.10)	357(7.56)	232(4.91)

Analysis also show that despite the differences in diagnosing MI, the results obtained by the CEC and investigators, point towards a beneficial effect of integrilin on the primary endpoint. However, it the degree of certainty that is provided by the different data, which pose a problem.

The protocol did not state the specific statistical test to be used for evaluation of efficacy endpoints. The sponsor presented the results using the Chi square test which is acceptable for the objective tested. However, results of the Log rank test was also requested from the sponsor, because in one of the protocol amendments the sponsor discussed the use of time to event analysis.

The Chi Square test was performed with and without the low dose group. This was done because it was felt that the low dose group could provide useful information

about the effect of the study drug. The protocol specified that only the high dose group will be compared to the placebo group.

The overall Chi square test comparing 180/2.0 and placebo, (using the CEC adjudicated events) yielded a marginally significant p-value = 0.042 ($\chi^2 = 4.120$, df = 1). When the investigator identified events are used in determining the primary efficacy endpoint the overall significance improved drastically to p-value = 0.001 ($\chi^2 = 11.232$, df = 1). For the three groups (integrilin 180/2.0, integrilin 180/1.3 and placebo) the overall test statistic was statistically significant with a p-value = 0.038 ($\chi^2 = 6.549$, df = 2) for the CEC adjudicated primary efficacy endpoint. When the investigator designated events are used in the primary endpoint analysis, the test statistic was significant with a p-value of 0.003 ($\chi^2 = 11.587$, df = 2) The data is summarized in Table R 4. The primary endpoints categories are mutually exclusive.

Table R.4. Number of Patients With an MI and/or Death within 30 days for all Randomized Subjects

CEC Adjudicated Events				
	Placebo	Eptifibatide 180/2.0	Eptifibatide 180/1.3	p value
1° Endpoint	745 (15.72%)	672 (14.23%)	200 (13.45%)	0.042 ^A 0.038 ^B
Deaths	101	79	22	
MI	568	507	150	
Both	76	86	28	
Investigator Designated Events				
	Placebo	Eptifibatide 180/2.0	Eptifibatide 180/1.3	p value
1° Endpoint	475 (10.02%)	380 (8.05%)	128 (8.61%)	0.001 ^A 0.003 ^B
Deaths	107	89	25	
MI	298	215	78	
Both	70	76	25	

1° Endpoint = Death or MI

^A = Comparison of placebo vs 180/2.0

^B = Comparison of all three groups

Subgroup Efficacy Analyses

Age

The overall Chi square test comparing the primary efficacy endpoint by age showed that the frequency of primary efficacy endpoint increased with increasing age. The test was statistically significant with a p-value=0.001 ($\chi^2 = 151.52$, df=3) for CEC adjudicated events. The results were significant when investigator designated events were used, p-value=0.001 ($\chi^2 = 165.5$, df=3). Even within treatment groups there were statistically significant difference in the incidence of primary efficacy endpoint. The results are summarized in Table R.4a.

Table R.4a. Primary Efficacy Endpoint at 30 days for all Randomized Subjects by Age

CEC Adjudicated Primary Efficacy Endpoint				
	Less than 50 yrs (n=660)	50 - 59 yrs (n=1108)	60 - 69 yrs (n=1487)	70 yrs and Over (n=1467)
Placebo	64(9.62)	148(13.75)	235(15.04)	298(20.75)
Integrilin 180/2.0	58(8.79)	107(9.66)	212(14.26)	295(20.11)
Integrilin 180/1.3	14(5.83)	34(10.18)	69(13.69)	83(20.29)
Investigator Designated Primary Efficacy Endpoint				
	Less than 50 yrs (n=660)	50 - 59 yrs (n=1108)	60 - 69 yrs (n=1487)	70 yrs and Over (n=1467)
Placebo	28(4.21)	80(7.43)	160(10.24)	207(14.42)
Integrilin 180/2.0	27(4.09)	50(4.51)	112(7.53)	191(13.02)
Integrilin 180/1.3	6(2.50)	19(5.69)	50(9.92)	53(12.96)

Region:

The overall Chi square test comparing the primary efficacy endpoint by region resulted in a significant p-value = 0.001 ($\chi^2 = 44.28$, df = 3) using the CEC adjudicated events. The results remained statistically significant for investigator events with a p-value = 0.009 ($\chi^2 = 11.544$, df = 3). Further evaluation showed that the difference between placebo and integrilin is driven by a highly significant difference observed only in North America. In all other regions, the results were not significant, and in Eastern Europe and Latin American, the results show that there were more events in the integrilin group than in the placebo group. The results are summarized in Table R 5. A summary of the complete numbers by region can be found in **Appendix 2**.

Table R.5. Primary Efficacy Endpoint at 30 days for all Randomized Subjects by Region

CEC Adjudicated Primary Efficacy Endpoint				
	North America	West Europe	East Europe	Latin America
Placebo	288(15.0)	273(14.8)	153(19.7)	31(15.7)
Integrilin 180/2.0	224(11.7)	255(13.8)	161(21.0)	32(16.1)
Integrilin 180/1.3	71(13.4)	67(12.3)	35(15.8)	27(14.3)
Investigator Designated Primary Efficacy Endpoint				
	North America	West Europe	East Europe	Latin America
Placebo	180(9.4)	183(9.9)	89(11.5)	23(11.7)
Integrilin 180/2.0	129(6.8)	154(8.3)	78(10.2)	19(9.5)
Integrilin 180/1.3	39(7.3)	54(9.9)	19(8.6)	16(8.5)

Gender:

A comparison of the primary efficacy endpoint by gender between integrilin 180/2.0 and placebo was not statistically significant, p-value = 0.151 ($\chi^2 = 2.061$, df = 1) for CEC adjudicated events. The results were similar for the investigator designated events. A closer examination of the data, however, shows that there is an increased number of events in the integrilin treated group of females compared to the females in the placebo group. The results are summarized in Table R. 6.

Table R.6 Number of Patients With an MI and/or Death within 30 days for all Randomized Subjects by Gender.

CEC Adjudicated Events						
	Placebo		Eptifibatide 180/2.0		Eptifibatide 180/1.3	
	Female	Male	Female	Male	Female	Male
1° Endpoint	234(13.7)	511(16.9)	245(14.9)	427(13.9)	76(15.2)	124(12.6)
Deaths	32	69	27	52	7	15
MI	174	394	179	328	59	91
Both	28	48	39	47	10	18
Investigator Designated Events						
	Placebo		Eptifibatide 180/2.0		Eptifibatide 180/1.3	
	Female	Male	Female	Male	Female	Male
1° Endpoint	146(8.5)	329(10.9)	144(8.7)	236(7.7)	44(8.8)	84(8.5)
Deaths	35	72	32	57	6	19
MI	86	212	78	137	27	51
Both	25	45	34	42	11	14

1° Endpoint = Death or MI

Ethnic Origin:

There were very few blacks, hispanic, Asians or ether ethnic minorities in the study population. Therefore, it is difficult to make any conclusions about the use of the integrilin in such groups. A comparison of the primary efficacy endpoint by ethnic origin between the two groups was not statistically significant, p-value = 0.139 ($\chi^2 = 9.685$, df = 6) for CEC events. Similar results were obtained for investigator events with p=0.109 ($\chi^2 = 10.402$, df = 6). The results are summarized in Table R. 7. For a complete summary of numbers see **Appendix 3**

Table R.7. Number of Primary Efficacy Endpoint at 30 days for all Randomized Subjects

CEC Adjudicated Primary Efficacy Endpoint			
	Caucasians	Blacks	Hispanics
Placebo	665(15.8)	30(12.7)	40(17.4)
Integrilin 180/2.0	615(14.7)	22(8.8)	30(13.1)
Integrilin 180/1.3	169(13.6)	6(10.5)	24(14.3)
Investigator Designated Primary Efficacy Endpoints			
	Caucasians	Blacks	Hispanics
Placebo	426(10.1)	15(6.3)	27(11.7)
Integrilin 180/2.0	351(8.4)	12(4.8)	16(7.0)
Integrilin 180/1.3	112(9.0)	4(7.0)	11(6.5)

Subjects Undergoing different Procedures

Among subjects who underwent CABG there was no statistical difference between the integrilin treated and placebo groups, p-value = 0.120 ($\chi^2 = 2.412$, df = 1). The events ratio go in the correct direction, but did not achieve statistical significance, most probably because of lack of power.

Among subjects who underwent PTCA there was a difference between the integrilin treated and placebo groups, p-value = 0.039 ($\chi^2 = 4.245$, df = 1). The data for subjects who underwent PTCA were analyzed by time to procedure. The cut off time of interest was 72 hours, so the data is presented in Figure R.1 showing the events in the different subgroups. It is important to note that this analysis was not part of the study protocol, and

that subjects were not randomized to PTCA versus no PTCA. So no statistical inference can be made from this analysis. For that reason, the differences observed was not tested for statistical significance on purpose. This analysis was done to determine if the data contained in this study support the marginal findings of the IMPACT II study. It was noted that integrilin appear to lower the incidence of primary endpoint among patients who underwent PTCA. This observation is more pronounced among those who underwent PTCA within 72 hours of randomization.

Among subjects who had balloon procedure there was no statistically significant difference between the two groups. The events were in the right direction, where those patients treated with integrilin had fewer events than those in the placebo group, but the difference did not achieve statistical significance, probably due to lack of power.

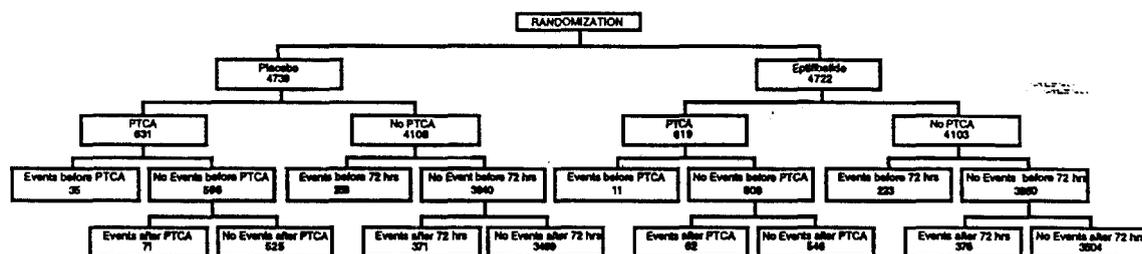
Among subjects who had a stent procedure there was no statistically significant difference between the two groups. The events were in the right direction, where those patients treated with integrilin had fewer events than those in the placebo group, but the difference did not achieve statistical significance, probably due to lack of power. The data is summarized in Table R.8. A complete summary of the numbers are provided in Appendix 4.

Table R.8. Primary Efficacy Endpoint at 30 days for all Randomized Subjects by Procedure

CEC Adjudicated Primary Efficacy Endpoint				
	CABG (n=1762)	PTCA (n=2888)	Balloon(n=2367)	Stent (n=1332)
Placebo	230/773(29.75)	210/1289(16.29)	169/1058(15.97)	98/595(16.47)
Integrilin 180/2.0	194/742(26.15)	166/1210(13.72)	141/985(14.31)	86/558(15.41)
Integrilin 180/1.3	60/247(24.29)	59/389(15.17)	50/324(15.43)	25/179(13.97)
Investigator Designated Primary Efficacy Endpoint				
	CABG (n=1762)	PTCA (n=2888)	Balloon(n=2367)	Stent (n=1332)
Placebo	114/773(14.75)	151/1289(11.71)	117/1058(11.06)	76/595(12.77)
Integrilin 180/2.0	90/742(12.13)	102/1210(8.43)	89/985(9.04)	54/558(9.68)
Integrilin 180/1.3	34/247(13.77)	39/389(10.03)	31/324(9.57)	18/179(10.06)

The balloon and stent groups are a sub population of all patients who were classified as having had PTCA.

Figure R.1. Patient Disposition By PTCA Within 72 Hours After Randomization



See Appendix 9 for an enlarged copy

Use of Aspirin and Heparin

Two hundred and thirteen (1.76%) subjects enrolled in the study did not receive aspirin. The aspirin doses used in the trial ranged from 10 mg to 1500 mg. The breakdown of those who did not receive aspirin by treatment group is as follows; 38 (1.28%) were from the 180/1.3 group, 83 (0.88%) were from the 180/2.0 group, and 92 (0.92%) were from the placebo group. There was no statistically significant difference in primary endpoint by the use of aspirin. The break down of primary efficacy events by treatment group is presented in Table R.9.

primary endpoint by the use of aspirin. The break down of primary efficacy events by treatment group is presented in Table R.9.

Table R.9 Primary Efficacy Endpoint at 30 days for all Randomized Subjects by Aspirin Use

CEC Adjudicated Primary Efficacy Endpoint			
	Placebo Events	Integrilin 180/2.0	Integrilin 180/1.3
No Aspirin	13 (14.13)	10 (12.05)	7 (18.42)
Aspirin	730 (15.76)	662 (14.32)	192 (13.31)
Investigator Designated Primary Efficacy Endpoint			
	Placebo Events	Integrilin 180/2.0	Integrilin 180/1.3
No Aspirin	10 (10.87)	8 (9.64)	5 (13.16)
Aspirin	464 (10.2)	372 (8.04)	122 (8.46)

One thousand, one hundred and sixty-four (10.60%) subjects enrolled in the study did not received heparin. The breakdown of subjects who did not receive heparin is as follows; 184(12.32) from the integrilin 180/1.3 group, 496(10.45) from the integrilin 180/2.0 group, and 485(10.20) from the placebo group. There were no statistical significant difference between those who received heparin and those who did not with regards to the primary efficacy endpoint. A summary of the primary efficacy events is presented in Table R.10.

Table R.10 Primary Efficacy Endpoint at 30 days for all Randomized Subjects by Heparin Use

CEC Adjudicated Primary Efficacy Endpoint			
	Placebo Events	Integrilin 180/2.0	Integrilin 180/1.3
No Heparin	394(15.11)	368(14.15)	109(13.10)
Heparin	352(16.47)	304(14.33)	91(13.89)
Investigator Designated Primary Efficacy Endpoint			
	Placebo Events	Integrilin 180/2.0	Integrilin 180/1.3
No Heparin	252(9.68)	208(7.98)	70(8.35)
Heparin	223(10.45)	172(8.13)	58(8.93)

Use of Thrombolytics

The use of thrombolytics did not have a significant effect of the primary efficacy endpoint. A summary of primary efficacy endpoint by thrombolytic therapy used is presented in Table R.11.

Table R.11 Primary Efficacy Endpoints at 30 Days for all Randomized Subjects by use of Thrombolytics

	t-PA	Urokinase	Streptokinase	APSAC	Other	Total
CEC	56(44.8)	21(50.0)	75(59.1)	0	1(33.3)	153(51.3)
Investigator	55(44.0)	15(35.7)	70 (55.12)	0	2(66.7)	142(47.7)
Total No.	125	42	127	1	3	298

Compliance

Other than the errors described above, this study was an acute or urgent treatment situation, so compliance was not a problem with subjects. However, compliance of the investigators with the study protocol will be evaluated by the clinical investigative branch of the agency.

SAFETY

Deaths

There were 420 deaths in the database, 392 of these deaths occurred during the first 30 days of follow-up. There was no statistically significant difference in deaths between the three groups. The results were similar when only the high dose was compared to the placebo group. The distribution of deaths by treatment group is provided in Table R.4.

The dataset "death" contain 420 deaths and cause of death. See **Appendix 5** for list of deaths with causes of death.

The primary causes of death occurring within 30 days after randomization is summarized in Table R.13.

Table R.13 Causes of Death within 30 Days of Randomization for all Treated Patients

Cause of Death	Placebo	Integrilin 180/2.0	Integrilin 180/1.3
Cardiovascular	121	98	28
Cardiogenic Shock	40	32	9
Myocardial Infarction/Ischemia	34	24	8
Heart Failure/Insufficiency	10	15	3
Congestive Heart Failure	9	3	1
Cardiac Arrest	8	13	1
Arrhythmia	8	3	3
Heart Rupture	6	1	0
Cardiac Disease/ Cause	2	3	1
Cardiac Procedure	4	1	0
Tamponade	0	1	0
Shock	0	1	1
Sudden Death	0	1	1
Noncardiovascular	19	22	8
Respiratory Failure/Distress	5	2	5
Pulmonary Embolism	5	1	0
Infection/Bacteremia/Sepsis	1	4	0
Hemorrhagic Stroke	1	1	1
Nonhemorrhagic Stroke	1	3	0
Undefined Stroke	1	2	0
Bleeding	2	3	0
Renal Failure	0	2	0
Medical Procedure	1	0	1
Anaphylactic Shock	1	0	0
Other	1	4	1
Unknown/Not Specified	38	44	12
Total Deaths	178	164	48

Bleeding

The most common adverse event observed in the trial was bleeding. The sponsor used two systems to describe the bleedings events observed in the trial. The first was the description of bleeding as major or minor using the TIMI criteria. The TIMI criteria as defined in the protocol is as follows;

- major bleeding: intracranial hemorrhage (primary hemorrhagic stroke or cerebral infarction with hemorrhagic conversion as defined by the CEC); or a decrease in hemoglobin concentration ≥ 5 g/dL (or hematocrit ≥ 15 percent points) – when calculating decrease in hemoglobin concentration (or hematocrit), a transfusion of one unit of whole blood or PRBC within 48 hours prior to determination of the nadir value was considered equivalent to a decrease of 1 g/dL (or 3 percent points)
- minor bleeding: (when calculating decrease in hemoglobin concentration [or hematocrit], the same rules for transfusion applied as for major bleeding): upper gastrointestinal bleeding; genitourinary bleeding; other observed blood loss associated with a decrease in hemoglobin concentration ≥ 3 g/dL (or hematocrit > 10 percent points); or if no bleeding site was identified, a decrease in hemoglobin concentration ≥ 4 g/dL (or hematocrit ≥ 12 percent points)
- insignificant or none: both bleeding data and hematology values were reported for the patient, but the patient was not classified as having either major or minor bleeding

The second system for describing bleeding was defined as follows:

- mild: did not require transfusion or result in hemodynamic compromise (e.g., subcutaneous bleeding, minor hematomas, oozing from puncture sites, trace guaiac-positive stool, microscopic hematuria);
- moderate: required transfusion of packed red blood cells (PRBC) or whole blood, but did not lead to hemodynamic compromise requiring intervention; and
- severe/life threatening: primary hemorrhagic stroke or cerebral infarction with hemorrhagic conversion; other bleeding that caused hemodynamic compromise (e.g., sustained hypotension, shock) requiring blood or fluid replacement, inotropic support, ventricular assist devices, surgical intervention, or cardiopulmonary resuscitation to maintain sufficient cardiac output.

Overall Bleeding Results

The incidence of bleeding according to the TIMI criteria is presented Table R.14 for patients treated with placebo or eptifibatide 180/2.0. The results show that the addition of eptifibatide 180/2.0 to standard antithrombotic therapy in this patient population caused a measurable increase in the risk of bleeding.

Table R.14 Incidence of Bleeding within 30 Days According to TIMI Criteria in Patients Treated With Placebo or Eptifibatide 180/2.0

TIMI Bleeding Status	Placebo (N=4696)	Eptifibatide (N=4679)
Major	425 (9.3%)	498 (10.8%)
Minor	347 (7.6%)	604 (13.1%)
Insignificant or None	3805 (83.1%)	3502 (76.1%)
Unresolved ^a	119	75

^a Insufficient information to make a determination. [Source: Appendix 13-1]

Bleeding Locations for Patients With TIMI Major or Minor Bleeding

In the PURSUIT study, the incidence of bleeding in patients who underwent CABG in both the placebo and eptifibatide treatment groups was similar. Therefore, bleeding in patients who did not undergo this procedure will be examined.

The incidence of major and minor bleeding in patients who did not undergo CABG during the 30 days after enrollment was approximately two to three times higher in the integrilin treated group. TIMI bleeding status in patients who did not have a CABG are presented in Table R.15.

Table R.15 Incidence of Bleeding within 30 Days According to TIMI Criteria in Patients Who Did Not Have CABG

TIMI Bleeding Status Excluding CABG Patients	Placebo (N=3954)	Eptifibatide (N=3973)
Major	50 (1.3%)	121 (3.1%)
Minor	190 (4.9%)	448 (11.5%)
Insignificant or None	3604 (93.8%)	3337 (85.4%)
Unresolved ^a	110	67

^a Insufficient information to make a determination.

[Source: Appendix 13-13]

Among patients who did not undergo CABG, the most common locations for major and minor bleeding were femoral artery access and upper and lower gastrointestinal. The incidence of retroperitoneal bleed was increase four times with the use of integrilin. In addition, genitourinary and oropharyngeal bleeds were common sites for minor bleeding. The results of major or minor bleeding according to the TIMI criteria are summarized in Tables R.16 - R.17. This table shows individual reports, of which there may have been more than one bleeding event per patient, whereas the TIMI criteria classify overall bleeding for a patient. Therefore, the sum of the individual reports will be greater than the total number of patients.

Table R.16 Location of Bleeding Events in Patients Who Did Not Have CABG and Who Had Major or Minor TIMI Bleeding Reported for 30 Days After Treatment Initiation

Location of Bleeding Event by TIMI Bleeding Classification Excluding CABG Patients*	Placebo (N=3954)	Eptifibatid (N=3973)
Major Bleeding	(N=50)	(N=121)
Femoral artery access	16	54
Brachial	2	3
Hemoglobin/Hematocrit ↓ Only	25	25
Oropharyngeal	4	12
Genitourinary	3	11
Gastrointestinal, Lower	3	23
Gastrointestinal, Upper	2	22
Unidentifiable Source Requiring Transfusion	4	9
Pulmonary	2	5
Retroperitoneal	2	8
Injection/Procedure Site	6	2
Intracranial Bleeding*	3	4
Post-Trauma Bleeding	0	0
Undefined Hemorrhage	1	2
Unknown	0	0

* CABG-related bleeding was reported for one patient in each group

* As adjudicated by the CEC [Source: Appendix 13-225]

Table R.16(Continued) Location of Bleeding Events in Patients Who Did Not Have CABG and Who Had Major or Minor TIMI Bleeding Reported for 30 Days After Treatment Initiation

Location of Bleeding Event by TIMI Bleeding Classification Excluding CABG Patients	Placebo (N=3954)	Eptifibatid (N=3973)
Minor Bleeding	(N=190)	(N=448)
CABG-Related	1	1
Femoral artery access	49	133
Brachial	7	20
Hemoglobin/Hematocrit ↓ Only	46	47
Oropharyngeal	9	123
Genitourinary	72	171
Gastrointestinal, Lower	8	50
Gastrointestinal, Upper	21	79
Unidentifiable Source Requiring Transfusion	1	8
Pulmonary	5	19
Retroperitoneal	3	3
Injection/Procedure Site	0	6
Post-Trauma Bleeding	0	1
Undefined Hemorrhage	2	7
Unknown	1	2

* CABG-related bleeding was reported for one patient in each group

* As adjudicated by the CEC [Source: Appendix 13-225]

Table R.17 Type, Location, or Indication of Bleeding Events Reported for 30 Days After Treatment Initiation in Patients Treated With Placebo or Eptifibatide and Who Had Major or Minor TIMI Bleeding

Type or Location of Bleeding Event by TIMI Bleeding Classification	Placebo (N=4696)	Eptifibatide (N=4679)
Major Bleeding	(N=425)	(N=498)
CABG-Related	317	308
femoral artery access	60	128
Brachial	6	15
Hemoglobin/Hematocrit ↓ Only	70	65
Oropharyngeal	11	76
Genitourinary	16	39
Gastrointestinal, Lower	12	38
Gastrointestinal, Upper	8	35
Unidentifiable Source Requiring Transfusion	11	19
Pulmonary	6	8
Retroperitoneal	2	11
Injection/Procedure Site	8	7
Intracranial Bleeding*	3	5
Post-Trauma Bleeding	1	1
Undefined Hemorrhage	1	3
Unknown	1	0

* As adjudicated by the CEC [Source: Appendix 13-198]

Table R.17 (Continued) Type, Location, or Indication of Bleeding Events Reported for 30 Days After Treatment Initiation in Patients Treated With Placebo or Eptifibatide and Who Had Major or Minor TIMI Bleeding

Type or Location of Bleeding Event by TIMI Bleeding Classification	Placebo (N=4696)	Eptifibatide (N=4679)
Minor Bleeding	(N=347)	(N=604)
CABG-Related	127	132
Groin	60	154
Brachial	9	22
Hemoglobin/Hematocrit ↓ Only	67	65
Oropharyngeal	13	140
Genitourinary	79	183
Gastrointestinal, Lower	11	53
Gastrointestinal, Upper	27	80
Unidentifiable Source Requiring Transfusion	1	9
Pulmonary	6	19
Retroperitoneal	3	3
Injection/Procedure Site	0	7
Post-Trauma Bleeding	0	1
Undefined Hemorrhage	3	8
Unknown	2	2

* As adjudicated by the CEC [Source: Appendix 13-198]

There was an increase in both major and minor bleeding with increasing age, and this increase with age was somewhat more pronounced in the eptifibatide treatment group. Within age categories, the greatest increment in major bleeding between the eptifibatide and placebo treatment groups was in the highest age group (>70 years old).

Females treated with eptifibatide experienced a greater incidence of minor bleeding than males. However, the incidence of major bleeding was slightly less in females than males, likely due to the lower use of interventions (CABG and percutaneous) in women worldwide.

There was an increase in major and minor bleeding in the eptifibatide group compared to the placebo treatment group in both Caucasians and Blacks, particularly in minor bleeding in Blacks.

In the placebo treatment group, the incidence of both major and minor bleeding was higher in the heaviest weight group, however, this was not true for the eptifibatide treatment group. The differences in bleeding between the different weight categories were minor.

The incidence of major bleeding increased with increasing aPTT value particularly in the eptifibatide treatment group. The incidence of major bleeding between groups was higher among eptifibatide-treated patients compared to placebo in both the therapeutic and suprathreshold ranges for maximal aPTT. TIMI bleeding classification of patients stratified by age, gender, ethnicity, weight and aPTT are summarized in Table R.18.

Table R.18 TIMI Bleeding Classification of Patients Treated With Placebo or eptifibatide Stratified by Age, Gender, Ethnicity, Weight, and aPTT

Subgroups ^a	Placebo (N=4696)		Eptifibatide (N=4679)	
	Major	Minor	Major	Minor
Age				
<50 y	44 (7.0%)	32 (5.1%)	38 (6.0%)	63 (9.9%)
50-59 y	94 (9.1%)	71 (6.9%)	111 (10.3%)	100 (9.3%)
60-69 y	149 (9.9%)	119 (7.9%)	163 (11.2%)	191 (13.1%)
≥70 y	138 (9.9%)	125 (8.9%)	186 (13.0%)	250 (17.5%)
Gender				
Male	310 (10.6%)	225 (7.7%)	337 (11.2%)	359 (12.0%)
Female	115 (7.0%)	122 (7.4%)	161 (10.0%)	245 (15.3%)
Ethnicity				
Caucasian	369 (9.1%)	309 (7.6%)	439 (10.7%)	532 (13.0%)
Black	20 (9.3%)	21 (9.7%)	27 (11.3%)	44 (18.3%)
Other	35 (12.2%)	17 (5.9%)	31 (11.7%)	28 (10.5%)
Weight				
All Patients				
<74 kg	139 (8.1%)	132 (7.7%)	198 (11.0%)	242 (13.5%)
74-95 kg	222 (9.7%)	156 (6.8%)	234 (10.7%)	280 (12.8%)
>95 kg	64 (11.2%)	59 (10.4%)	66 (10.6%)	82 (13.2%)
Maximal aPTT				
<50 sec	46 (7.1%)	34 (5.2%)	43 (6.4%)	73 (10.8%)
50-80 sec	119 (9.0%)	109 (8.3%)	150 (11.4%)	179 (13.6%)
≥ 80 sec	255 (10.9%)	192 (8.2%)	291 (12.5%)	325 (14.0%)

^a In each category, the denominator is the number of patients with TIMI bleeding status resolved. [Source: Appendices 13-53, 13-93, 13-103, 13-113 and 13-123]

The difference in bleeding between the treatments at the end of infusion established the difference eventually observed at the end of initial hospitalization and thereafter. The increase from 7.5% to 23.1% of patients in the placebo group is 15.6 absolute percentage points, compared with the increase of 11.9 absolute percentage points from 27.7% to 39.6% in the eptifibatide group. Thus, these results indicate that the identified risk of excess bleeding with eptifibatide occurred during the infusion period. Investigator-reported bleeding events during the infusion, initial hospitalization, and through 30 days after initiation of treatment are summarized in Table R.19.

Table R.19 Investigator-Reported Bleeding Events During Infusion, Initial hospitalization and the 30 Days After Initiation of Treatment in Patients Treated With Placebo or Eptifibatide

Bleeding	Placebo (N=4696)	Eptifibatide (N=4679)
Any Bleeding During Infusion	354 (7.5%)	1295 (27.7%)
Any Bleeding During Initial Hospitalization	1083 (23.1%)	1853 (39.6%)
Any Bleeding for 30 Days	1086 (23.1%)	1853 (39.6%)

[Source: Appendices 13-245 and 13-267]

Severe/life threatening bleeding was uncommon and occurred only slightly more frequently with eptifibatide compared to placebo. More bleeding events were reported with eptifibatide than with placebo, but, consistent with the results already noted for the evaluation according to TIMI criteria, most of the events were mild or moderate and occurred during the initial hospitalization. Investigator-reported bleeding by maximum severity during the 30 days after initiation of treatment is summarized in Table R.20 for patients who received placebo or eptifibatide 180/2.0.

Table R.20

Investigator-Reported Bleeding Events by Maximum Severity During the 30 Days After Initiation of Treatment in Patients Treated With Placebo or Eptifibatide

Bleeding	Placebo (N=4696)	Eptifibatide (N=4679)
Maximum Severity of Any Bleeding		
Severe/Life Threatening	52 (1.1%)	87 (1.9%)
Moderate	418 (8.9%)	521 (11.1%)
Mild	595 (12.7%)	1202 (25.7%)
Not Specified	21 (0.4%)	43 (0.9%)

[Source: Appendix 13-353]

TRANSFUSIONS

Packed red blood cells (PBRCs) were the most common type of transfusion, and were used more often by eptifibatide than placebo-treated patients. Transfusion of non-red cell elements, such as platelets, fresh-frozen plasma and cryoprecipitate, were generally similar in the placebo and eptifibatide treatment groups, although eptifibatide-treated groups experienced a small increase, particularly in RBC transfusions. The need for transfusion of blood elements is another indication of the severity of bleeding. Transfusions required for treated patients are summarized in Table R.21.

Table R.21 Patients Treated With Placebo or Eptifibatide Who Required Transfusion During the Initial Hospitalization

Transfusions	Placebo (N=4696)	Eptifibatide (N=4679)
Any During Infusion	19 (0.4%)	34 (0.7%)
Any During Hospitalization	490 (10.4%)	601 (12.8%)
Packed Red Blood Cells or Whole Blood	438 (9.3%)	550 (11.8%)
PRBC	401 (8.5%)	520 (11.1%)
Whole Blood	39 (0.8%)	33 (0.7%)
Platelets	104 (2.2%)	122 (2.6%)
Fresh-Frozen Plasma	117 (2.5%)	147 (3.1%)
Cryoprecipitate	14 (0.3%)	13 (0.3%)
Autotransfusion	60 (1.3%)	56 (1.2%)
Missing	1	1

[Source: Appendices 13-432 and 13-444]

The incidence of bleeding as reported by the investigator was increased within both of the eptifibatide groups compared to placebo. There is a dose response relationship between bleeding and increasing dose of eptifibatide. As seen in the TIMI bleeding results, there was an increase in bleeding as the dose increased from 180/1.3 to 180/2.0. Investigator-reported bleeding during the 30 days after initiation of treatment is summarized in Table R.22 for the contemporaneous group of patients who received placebo, eptifibatide 180/1.3, or eptifibatide 180/2.0.

Table R.22 Investigator-Reported Bleeding Events During the 30 Days After Initiation of Treatment in Patients Treated With Placebo, Eptifibatide 180/1.3, or Eptifibatide 180/2.0

Bleeding	Placebo (N=1462)	Eptifibatide 180/1.3 (N=1472)	Eptifibatide 180/2.0 (N=1482)
Any Bleeding During Infusion	109 (7.5%)	304 (20.7%)	394 (26.6%)
Any Bleeding During Initial Hospitalization	295 (20.2%)	484 (32.9%)	573 (38.7%)
Any Bleeding for 30 Days	297 (20.3%)	484 (32.9%)	573 (38.7%)

[Source: Appendices 13-257, 13-258, 13-279 and 13-280]

Serious Non-Bleeding Events

The effect of intergrilin on other body systems (as evaluated by blood chemistry) cannot be commented upon, because there was no blood chemistry evaluation as part of this study protocol. The absence of blood chemistry may have been by agreement between the Division of Gastrointestinal and Coagulation drug products and the sponsor. Also, this drug is to be used one time (given as a bolus followed by a 72 hour infusion, and stopped),

so that a long term effect of this drug on other body systems is unlikely. Except, of course, the effects on the hematologic system which has been evaluated in the study.

Serious bleeding was to be reported separately from serious non-bleeding events, but, in a very small number of instances, investigators entered bleeding events on the CRF or ancillary data collection forms as if they were non-bleeding in nature. These events were retained as "non-bleeding events" to be complete, but a detailed discussion of bleeding complications has been presented earlier, and the bleeding events recorded as non-bleeding will not be addressed in this section. The one instance of cerebral hemorrhage that was reported as a non-bleeding event was also captured in the previous bleeding section.

The PURSUIT study enrolled patients with significant cardiovascular disease. Serious non-bleeding adverse events were, however, not common in this population, and were reported for approximately 19% of the patients overall. Table R.23 Summarizes the results for the "most common" serious non-bleeding adverse events, those reported by at least 1% (after rounding) of the patients treated with either placebo or eptifibatide 180/2.0, and for thrombocytopenia reported by investigators. The most common events were reported for 2% to 7% of patients, without evidence of a difference between placebo and eptifibatide. Most common were events related to the underlying disease, such as atrial or ventricular fibrillation, ventricular tachycardia, congestive heart failure, hypotension, shock, and cardiac arrest. Thrombocytopenia was reported infrequently as a serious event for 0.06% (3/4696) of placebo-treated and 0.24% (11/4679) of eptifibatide-treated patients, the objective laboratory results showed overall proportions of patients with platelet counts <100,000/ μ L or <50,000/ μ L to be >0.24%, and with no real differences between treatment groups. No other event was reported more often for one group than for the other, and there was no other indication in these data of a discernible effect of eptifibatide compared with placebo.

Table R.23 Incidence of Common Serious Non-Bleeding Adverse Events Plus Thrombocytopenia Reported for Patients Treated With Placebo or Eptifibatide *

Body System/Organ Class and Individual Serious Adverse Events	Placebo (N=4696)	Eptifibatide (N=4679)
Any Serious Non-Bleeding Adverse Event	877 (19%)	890 (19%)
Cardiovascular System		
Atrial Fibrillation	301 (6%)	294 (6%)
Hypotension	290 (6%)	324 (7%)
Congestive Heart Failure	257 (5%)	240 (5%)
Cardiac Arrest	127 (3%)	109 (2%)
Shock	117 (2%)	120 (3%)
Phlebitis	69 (1%)	64 (1%)
Atrioventricular Block	61 (1%)	70 (1%)
Ventricular Fibrillation	65 (1%)	59 (1%)
Ventricular Tachycardia	54 (1%)	51 (1%)
Hemic/Lymphatic System		
Thrombocytopenia	3 (<1%)	11 (<1%)
Nervous System		
Cerebral Ischemia	24 (1%)	18 (<1%)

* "Common" means reported by at least 1% of the patients in either treatment group.

[Source: Appendix 13-578]

Other events that could be associated with bleeding were serious hypotension and shock. So evaluation of serious hypotension and shock, reports by the investigator, was carried out. The results indicate that the incidence of hypotension and shock were directly related to TIMI bleeding status, regardless of treatment, and suggest that there was a slight excess risk of these events in patients treated with eptifibatide. The clinical relevance of the latter finding is unknown; however, the incidences of serious hypotension or shock were higher in patients who received eptifibatide than in those who received placebo (≤ 0.7 percentage point). The results are summarized in Table R.24.

Table R.24 Incidence of Serious Hypotension and Shock Recorded Over 30 Days in Patients Treated With Placebo or Eptifibatide According to TIMI Bleeding Status

Adverse Event	Treatment	TIMI Bleeding Status		
		Insignificant or None	Minor	Major
Hypotension	Placebo	4.3% (162/3805)	11.5% (40/347)	18.8% (80/425)
	Eptifibatide	4.0% (140/3502)	12.6% (76/604)	21.9% (109/498)
Shock	Placebo	1.8% (68/3805)	4.0% (14/347)	7.1% (30/425)
	Eptifibatide	1.5% (52/3502)	3.6% (22/604)	9.2% (46/498)
Hypotension or Shock	Placebo	4.5% (172/3805)	11.8% (41/347)	19.5% (83/425)
	Eptifibatide	4.2% (146/3502)	12.9% (78/604)	22.5% (112/498)

* Patients with unresolved TIMI bleeding status are not included. [Source: Appendices 13-163, 13-173 and 13-183]

Strokes

The most serious adverse event occurring in conjunction with antithrombotic therapy is intracranial bleeding (hemorrhagic stroke). Information for each patient suspected of having a stroke was collected on the CRF, and detailed results of any diagnostic procedure (e.g., computed tomography) were collected and provided to the CEC for review and adjudication. Thus, as for MI, two interpretations of the occurrence of the event exist: one by the investigator at the site; and another by the CEC. Summaries of the results of both assessments are shown below, along with a summary of the differences in diagnoses. Overall, the results suggest no definable additional risk of stroke, particularly hemorrhagic stroke, with eptifibatide compared with placebo.

According to the CEC, there were 71 strokes within 30 days of the beginning of treatment, the overwhelming majority of which (60) were identified as cerebral infarctions, as shown in Table R.25.

Table R.25 Incidence of Strokes During the 30 Days After Initiation of Treatment With Placebo or Eptifibatide as Adjudicated by the CEC

Stroke	Placebo (N=4696)	Eptifibatide (N=4679)
Patients With Any Stroke	39 (0.8%)	32 (0.7%)
Total Number of Strokes	39	32
Stroke Type		
Primary Hemorrhagic	2 (<0.1%)	3 (0.1%)
Cerebral Infarction	33 (0.7%)	27 (0.6%)
Infarction With Hemorrhagic Conversion	1 (<0.1%)	2 (<0.1%)
Type Uncertain	3 (0.1%)	0

[Source: Appendix 13-618]

All hemorrhagic stroke -- primary hemorrhagic stroke and cerebral infarction with hemorrhagic conversion -- was rare in both treatment groups: 0.06% (3/4696) with placebo and 0.1% (5/4679) with eptifibatide 180/2.0. Although not directly comparable, the results for eptifibatide 180/1.3 were not noticeably different in character, and the incidence of hemorrhagic stroke -- 0.07% (1/1474) -- was comparable with those in the other two groups.

The incidence of identified hemorrhagic stroke was identical (0.1%) in the two groups; even if the two strokes of unknown etiology in the eptifibatide group were assumed to be hemorrhagic, the incidence would still be no greater than with placebo.

In terms of residual functional deficit, the numbers were too small to make meaningful comparisons. It is possible that a slightly greater proportion of placebo-treated than eptifibatide-treated patients who had strokes had no residual deficit (15.9% vs. 9.1%). Results according to the investigators were not noticeably different from those for the CEC in either number or character, as shown in Table R.26.

Table R.26 Incidence of Investigator-Reported Strokes and Assessment of Resulting Functional Deficit During the 30 Days After Initiation of Treatment With Placebo or Eptifibatide

Stroke	Placebo (N=4696)	Eptifibatide (N=4679)
Patients With Any Stroke	44 (0.9%)	33 (0.7%)
Total Number of Strokes	45	33
Stroke Type		
Hemorrhagic	5 (0.1%)	4 (0.1%)
Nonhemorrhagic	31 (0.7%)	27 (0.6%)
Type Unknown	7 (0.1%)	2 (<0.1%)
Missing ^a	2	0
Worst Functional Deficit per Patient Lasting Until Hospital Discharge or 30 Days	(N=44)	(N=33)
None	7 (15.9%)	3 (9.1%)
Minor	7 (15.9%)	9 (27.3%)
Moderate	11 (25.0%)	8 (24.2%)
Severe	8 (18.2%)	5 (15.2%)
Patient Died	9 (20.5%)	8 (24.2%)
Missing ^a	2	0

^a No information on CRF about diagnosis, including "type unknown". [Source: Appendix 13-638]

Discontinuation of intravenous infusion of integrilin due to Adverse Events

There were 3126 subjects whose infusion of integrilin were discontinued before the 72 hours. The discontinuations were disproportionately higher in the integrilin treated group compared to the placebo group. The difference in discontinuation rate was statistically significant with a p-value= 0.001 (= 29.210, df =2). The result is similar when only the integrilin high dose is compared to the placebo group, p-value = 0.001 (= 27.435, df=1). Table R.12 presents a summary of the discontinuations by treatment groups. Reasons for drug discontinuations are summarized in Table R.13. A list of patients whose drug infusion was discontinued for adverse events other than bleeding is provided in **Appendix 6**.

Table R.12 Rate of Discontinuation of Integrilin Infusion by Treatment Group

Integrilin Infusion	Placebo	Integrilin 180/2.0	Integrilin 180/1.3	Total
Discontinued	1238 (26.12)	1449 (30.69)	398 (26.77)	3085 (28.18)
Completed	3501 (73.88)	327 (69.31)	1089 (72.98)	7863(71.82)
Total	4739	4722	1487	10948

Table R.13 Reasons for Discontinuation of Integrilin Infusion by Treatment Group

Reasons	Placebo	Integrilin 180/2:0	Integrilin 180/1:3	Total
Bleeding	37	357	62	456
Need for CABG	201	193	55	449
Preference for Open label Dextra	1	0	2	3
Accidental IV Problems	87	93	34	214
Thrombocytopenia	15	30	8	53
Need for Thrombolytic Therapy	45	15	7	67
Other	55	61	9	125
Adverse Events other than Bleeding	52	48	15	115
Change of Diagnosis	95	80	32	207
Physician Preference	111	102	37	250
Patient Died	28	14	4	46
Patient Transferred	52	67	10	129
Patient Discharged	342	290	84	716
Major Exclusion Identified	14	18	8	40
Patient withdrew consent	40	40	22	102
Use of Alternative GP Therapy	63	41	9	113
Total	1238	1449	398	3085

Summary

There appears to be a beneficial effect of integrilin on the incidence of deaths and myocardial infarction. However, the overall effects seen are due to the effect of the drug observed in North America only. In western Europe the results were in the correct direction, indicating a beneficial effect of integrilin, but did not reach statistical significance. This provides some degree of comfort, because if the accepted notion that the practice of medicine in the two regions are similar, and the results of the findings in North America is to be believed, then the similarity of the results provide a basis for such a belief. Some of the possible explanations as to why the drug will be effective only in North America and no where else, may include;

1. Different medical practice norms in North America versus the rest of the world. Even though one would not expect big differences between western Europe and North America.
2. Differences in invasive procedures between North America and the rest of the world. Even though the bleeding risk was higher among those who did not undergo any procedure.
3. Lack of statistical power for detection of statistical differences in Latin America and eastern Europe. Only 585 (5.34%) of subjects came from Latin America, and 1762 (16.09%) of subjects came from eastern Europe.

Overall, the effects seen in the trial appear to occur in American, among caucasians and males.

The marginal p-value achieved by the trial data, appears to achieve statistical significance if we adjust the alpha level ($\alpha=0.05$) for the two interim analyses carried out by the sponsor during the study period. The significance level to achieve statistical significance becomes $\alpha=0.0478$. The results of the Chi square test of the primary efficacy endpoint gave a p-value=0.042. This raises another concern, as to what the alpha level for

testing the significance of the multiple secondary endpoints listed in the study protocol should be. Simulations and adjustments for multiple endpoints and comparisons will be carried out to answer this question.

The safety concerns identified in this review include;

- 1) Increased risk of bleeding among patients treated with integrilin. and
- 2) Increased rate of drug discontinuations among patients treated with integrilin.

A closer integration of the results show that the observed benefits of the drug seem to be negated the amount of excess bleeding observed in the treated group. The issue of blood transfusion contains some subtle nuances that need to be considered carefully.

Another concern, is the statistically significant difference in the diagnosis of myocardial infarction between the CEC and investigators. The blinded CEC diagnosed twice as many myocardial infarctions than the investigators at the site of study. One possible explanation may be that the investigators did not follow the protocol and the CEC did. Another possibility may be that the investigators used in the study were not trained in the diagnosis of myocardial infarction, or that the CEC were over zealous in their diagnosis of myocardial infarction. One cannot speculate as to the reason why the CEC will be over zealous.

There is a concern about the randomization process as carried out in this trial, because the process could not be independently verified.

The selection of the 180/2.0 dose had no supporting human data, prior to the PURSUIT trial. It was based entirely on in-vitro data and hypothesis. Given the excess bleeding observed in the treated group, one has to consider whether 180/2.0 is the correct dose of this drug. Perhaps a lower dose could have achieved the same efficacy results with less bleeding.

There is lack of internal consistence in the integrilin database, for example in the database called "AE" (for Adverse events) there are only 3 cases of thrombocytopenia are listed under the placebo group and 11 cases listed under Eptifibatide group (this data is supported by information from Appendix 13-578 as well). However, if we look under the database "drugadm" (for drug administration), there are 15 cases of thrombocytopenia listed for placebo and 30 cases listed for integrilin. There are several such inconsistencies found in the sas database. Different numbers are obtained depending on which variable and database one uses. This not only made the review difficult, but reduces the confidence one has in the information contained in the database submitted for review.

RECOMMENDED REGULATORY ACTION

The drug is not approvable based on the data contained in the PURSUIT trial alone.

However, consideration may be given to the data from the IMPACT II study, as to how and if the PURSUIT study supports the IMPACT II study, and if the data from the two studies support approval of the drug.

Isaac W. Hammond, M.D., Ph.D.

cc: orig.
HFD-110
HFD-110 / CSO / C. GANLEY / I. Hammond

Appendix 1.

CEC Triggers

CODE	FORM	PAGE & SECTION	TRIGGER FOR	DESCRIPTION
B	CRF	Page 2, Section 6	MI	Patient unblinded and reason for unblinding was need for urgent surgery/procedure/thrombolytic therapy
C	CRF	Page 3, Section 8	MI	Date of thrombolytic therapy entered on form
D (dropped after study started)	CRF	Page 4, Section 10	MI	Diagnostic catheterization was urgent or emergent
E	CRF	Page 4, Section 11	MI	Intervention/Repeat catheterization was urgent or emergent AND patient had recurrent ischemia on CRF page 6, section 15
F	CRF	Page 6, Section 14	STROKE	Date of stroke entered on form
G	CRF	Page 6, Section 15	MI	Post randomization MI answered YES OR post randomization shock answered YES (recurrent ischemia answered YES dropped after study start)
H	CRF	Page 7, Section 15	MI or STROKE	Acute mitral regurgitation answered YES, myocardial rupture/acute VSD answered YES, OR TIA answered YES
I	CRF	Page 7, Section 16	MI	CABG answered YES
J	CRF	Page 9, Section 19	MI	CK-MB > ULN AND prior CK-MB \geq 1.5X ULN AND prior CK-MB > ULN if no CK-MB, CPK \geq 2X ULN AND CPK \geq 1.25X previous CPK, CPK > 1.5X ULN AND CPK \geq (prior CPK+200)
L	Baseline Cardiac Episode	Page 1	MI	Date of recurrent chest pain entered AND episode description is indicated as myocardial infarction or ischemia with ST changes
M	30 Day Visit	Page 1, Section 5	MI or STROKE	Suspected or definite MI answered YES OR stroke answered YES
N	30 Day Rehospitalization	Page 1, Section 1	MI or STROKE	Discharge diagnosis is indicated as acute MI, ischemic heart disease, OR cerebrovascular disease
O	30 Day Rehospitalization	Page 2, Section 2	MI	Date of recurrent chest pain entered AND episode description is indicated as myocardial infarction or ischemia with ST changes
P	30 Day Rehospitalization	Page 3, Section 3	MI or STROKE	MI answered YES, 1st or 2nd angiogram type is urgent or emergent, CABG type is urgent or emergent, OR stroke answered YES
Q	30 Day Rehospitalization	Page 3, Section 4	MI	CK-MB > ULN, if no CK-MB, then CPK \geq 1.5X ULN
R	ECG Core Lab	Page 2	MI	Any ECG interpreted as infarction during

				hospitalization (after enrollment)
Y	Manual Trigger		MI or STROKE	A trigger identified by the reviewer and manually added to tracking database

APPENDIX 2

Number of Patients With an MI and/or Death within 30 days for all Randomized Subjects by Region

		Placebo			
		Composite	Deaths	MI	Both
North America	CEC	288(15.0)	40	220	28
	Investigators	180(9.4)	43	112	25
Western Europe	CEC	273(14.8)	34	206	33
	Investigators	183(9.9)	38	116	29
Eastern Europe	CEC	153(19.7)	19	123	11
	Investigators	89(11.5)	17	59	13
Latin America	CEC	31(15.7)	8	19	4
	Investigators	23(11.7)	9	11	3
		Integrilin 180/2.0 Events			
		Composite	Deaths	MI	Both
North America	CEC	224(11.7)	31	170	23
	Investigators	129(6.8)	36	75	18
Western Europe	CEC	255(13.8)	22	201	32
	Investigators	154(8.3)	25	100	29
Eastern Europe	CEC	161(21.0)	17	122	22
	Investigators	78(10.2)	16	39	23
Latin America	CEC	32(16.1)	9	14	9
	Investigators	19(9.5)	12	1	6
		Integrilin 180/1.3 Events			
		Composite	Deaths	MI	Both
North America	CEC	71(13.4)	8	57	6
	Investigators	39(7.3)	10	25	4
Western Europe	CEC	67(12.3)	7	49	11
	Investigators	54(9.9)	9	36	9
Eastern Europe	CEC	35(15.8)	2	27	6
	Investigators	19(8.6)	1	11	7
Latin America	CEC	27(14.3)	5	17	5
	Investigators	16(8.5)	5	6	5

APPENDIX 3

Number of Patients With an MI and/or Death within 30 days for all Randomized Subjects

		Placebo			
		Composite	Deaths	MI	Both
Caucasians	CEC	665(15.8)	93	510	62
	Investigators	426(10.1)	95	271	60
Blacks	CEC	30(12.7)	1	24	5
	Investigators	15(6.3)	4	9	2
Hispanics	CEC	40(17.4)	6	28	6
	Investigators	27(11.7)	6	15	6
		Integrilin 180/2.0 Events			
		Composite	Deaths	MI	Both
Caucasians	CEC	615(14.7)	69	469	77
	Investigators	351(8.4)	75	205	71
Blacks	CEC	22(8.8)	4	17	1
	Investigators	12(4.8)	4	7	1
Hispanics	CEC	30(13.1)	6	16	8
	Investigators	16(7.0)	10	2	4
		Integrilin 180/1.3 Events			
		Composite	Deaths	MI	Both
Caucasians	CEC	169(13.6)	17	128	24
	Investigators	112(9.0)	20	71	21
Blacks	CEC	6(10.5)	1	5	0
	Investigators	4(7.0)	1	3	0
Hispanics	CEC	24(14.3)	4	17	3
	Investigators	11(6.5)	4	4	3

APPENDIX 4

Number of Patients With an MI and/or Death within 30 days for all Randomized Subjects

		Placebo			
		Composite	Deaths	MI	Both
CABG (n=773)	CEC	230(29.75)	18	190	22
	Investigator	114(14.75)	22	74	18
PTCA (n=1425)	CEC	258(18.11)	12	225	21
	Investigator	194(13.61)	15	161	18
Balloon (n=1119)	CEC	188(16.80)	4	168	16
	Investigator	135(12.06)	7	115	13
Stent (n=607)	CEC	101(16.64)	2	91	8
	Investigator	78 (12.85)	4	68	6
		Integrilin 180/2.0 Events			
		Composite	Deaths	MI	Both
CABG (n=745)	CEC	195(26.17)	16	163	16
	Investigator	90 (12.08)	23	58	9
PTCA (n=1331)	CEC	202(15.15)	12	170	20
	Investigator	128(9.62)	16	96	16
Balloon (n=1026)	CEC	157(15.30)	10	132	15
	Investigator	100(9.75)	13	75	12
Stent (n=570)	CEC	90 (15.79)	3	81	6
	Investigator	58 (10.18)	4	49	3
		Integrilin 180/1.3 Events			
		Composite	Deaths	MI	Both
CABG	CEC	60 (24.19)	4	49	7
	Investigator	34 (13.71)	6	23	5
PTCA	CEC	78 (12.77)	3	69	6
	Investigator	58 (13.21)	4	49	5
Balloon	CEC	55 (16.13)	3	48	4
	Investigator	36 (10.56)	4	29	3
Stent	CEC	29 (15.68)	0	26	3
	Investigator	21 (11.35)	1	18	2

APPENDIX 5

List of Subjects who Died During Study with Cause of Death Where Provided

Obs	Patient ID	Treatment	Race	Sex	Age	Time	Cause
1	122205	180/1.3	3	F	60	252	
2	122613	180/2.0	3	M	64	446	Non hemorrhagic stroke
3	124053	180/1.3	3	F	71	16	Ongoing ischemia->v f resistant to therapy->cardiogenic shock
4	125833	Placebo	3	F	65	103	Cardiogenic shock post PTCA/STENT without success
5	128632	180/2.0	3	M	78	344	
6	128991	180/1.3	3	M	65	122	
7	130983	180/2.0	3	M	65	306	
8	131661	180/2.0	3	F	81	39	Cardiac arrest post during PTCA
9	134117	180/1.3	3	F	75	137	COPD aortic stenosis cad
10	134684	Placebo	3	F	54	127	
11	137710	180/1.3	3	F	74	266	Myocardial infarction
12	137894	180/1.3	3	I	71	50	
13	138049	180/1.3	3	F	70	130	Recurrent inferior myocardial infarction
14	138258	180/1.3	3	I	64	224	Cardiogenic shock
15	138388	Placebo	3	F	72	135	
16	139305	180/2.0	3	F	74	61	Cardiac arrest
17	139566	Placebo	3	M	77	312	Ventricular fibrillation
18	141846	180/2.0	3	M	63	94	Cardiogenic shock
19	141846	180/2.0	3	M	63	94	Cardiogenic shock
20	142117	180/1.3	6	F	53	257	Shock
21	142506	Placebo	3	F	71	465	
22	143764	180/1.3	3	M	73	255	
23	144134	180/2.0	6	F	68	639	Post operative CABG pump failure
24	144531	180/1.3	3	M	69	73	Cardiac cause
25	145359	180/2.0	3	M	47	158	Myocardial infarction
26	145962	180/2.0	6	M	68	43	Cardiogenic shock
27	146524	180/1.3	3	M	67	457	MI
28	147123	Placebo	4	M	66	655	
29	147218	Placebo	4	F	48	436	
30	147401	180/1.3	6	F	56	457	Cardiogenic shock
31	147533	180/1.3	6	M	58	446	Acute respiratory failure secondary to hemorrhagic necrotizing tracheitis because of orotracheal tube
32	147596	180/1.3	6	F	73	30	MI
33	148337	180/1.3	5	M	73	531	Cardiogenic shock
34	148944	180/1.3	3	M	75	366	
35	149185	Placebo	6	M	73	577	Severe mediastinal and pleural bleeding
36	149526	180/2.0	3	M	63	168	Myocardial infarction
37	149680	Placebo	6	M	50	628	
38	149688	180/2.0	3	M	67	126	Coronary artery disease aorta stenosis
39	166494	180/1.3	3	M	74	261	Cardiogenic shock
40	166605	180/1.3	3	M	72	201	Heart failure
41	167778	Placebo	3	F	64	16	Aortic and coronary art dissection
42	167837	180/1.3	3	M	53	244	Fibrillation ventricular asystole

Obs	Patient ID	Treatment	Race	Sex	Age	Time	Cause
43	168871	180/1.3	3	F	75	151	Shock Cardiogenic
44	170516	180/2.0	3	M	72	198	
45	172635	180/1.3	3	M	69	513	
46	173444	Placebo	3	F	74	542	Cardiogenic shock
47	174073	180/2.0	3	M	72	194	Unable to wean from Pump
48	174108	180/2.0	3	M	71	93	Sepsis questionable pulmonary embolism questionable
49	177231	180/2.0	6	F	74	431	Cardiogenic shock
50	177265	180/2.0	6	M	70	345	Low cardiac output renal insufficiency
51	179999	Placebo	6	M	46	28	Myocardial infarction
52	180122	Placebo	6	F	73	167	Acute myocardial infarction
53	183943	180/1.3	3	M	64	197	Sudden death
54	185137	180/2.0	3	M	72	684	Multi organ failure
55	185137	180/2.0	3	M	72	684	Multi organ failure
56	199072	180/2.0	3	F	68	90	Reinfarction myocardial
57	201338	Placebo	6	M	58	173	Cardiogenic shock
58	202860	180/2.0	4	M	45	103	
59	206666	Placebo	3	F	83	327	Cardiogenic shock/myocardial infarction
60	207902	Placebo	6	M	72	79	Bleeding post CABG myocardial rupture
61	207921	Placebo	3	M	55	560	
62	209119	Placebo	3	F	62	65	Acute heart failure
63	209798	Placebo	3	M	74	148	Cardiac failure
64	211227	180/1.3	4	M	70	48	Respiratory failure
65	211882	180/1.3	3	M	75	83	Cardiogenic shock failure to wear off bypass
66	218049	180/2.0	3	M	76	74	Asystole
67	219305	180/2.0	3	F	63	84	Myocardial infarction - Cardiogenic shock
68	220014	180/2.0	3	M	70	35	Myocardial infarction
69	222797	180/1.3	3	M	84	127	
70	225197	Placebo	3	M	64	78	Cardiac ischemia
71	233515	Placebo	3	M	48	14	Myocardial infarction
72	234536	180/1.3	3	M	58	291	
73	235139	180/2.0	6	M	47	276	
74	235228	180/2.0	3	M	56	295	Congestive heart failure
75	235252	Placebo	4	M	75	28	Cardiogenic shock
76	235537	180/2.0	3	M	75	34	
77	237451	Placebo	3	M	52	159	ventricular fibrillation
78	238723	180/2.0	3	M	54	124	Asystole
79	239156	180/2.0	3	M	84	443	
80	239893	Placebo	3	F	72	186	Cardiogenic shock
81	239908	180/1.3	3	M	68	468	
82	240508	Placebo	3	M	65	12	CHF and. Myocardial infarction
83	240617	180/2.0	3	M	54	42	Cardiac arrest due to myocardium
84	240737	180/2.0	3	F	82	94	Pump failure
85	241568	180/2.0	3	M	74	572	Massive pulmonary embolism
86	241816	180/2.0	3	M	87	55	Cardiogenic shock due to recent MI
87	241960	180/2.0	3	F	83	531	
88	242536	Placebo	3	F	75	236	Infarcted liver
89	244028	180/2.0	6	M	50	715	Gastrointestinal upper bleeding
90	244157	180/1.3	3	F	77	223	Cardiogenic shock

Obs	Patient ID	Treatment	Race	Sex	Age	Time	Cause
91	244391	180/2.0	6	F	89	134	Cardiogenic shock
92	244655	180/2.0	3	M	62	686	
93	245239	180/2.0	3	M	80	96	Cardiogenic shock
94	245278	180/1.3	3	M	75	434	Recurrent myocardial infarction pump failure
95	245349	180/1.3	3	F	67	124	Ischemic heart disease
96	245586	Placebo	3	F	66	635	
97	246016	180/2.0	3	M	77	478	Cardiac heart failure
98	247312	180/1.3	3	M	64	609	Myocardial ischemia, bradycardia
99	248354	Placebo	3	F	74	96	Intrathoracic bleeding due to surgical complication (bypass surgery)
100	248623	Placebo	3	M	64	488	
101	248786	180/1.3	6	M	39	171	Cardiogenic shock
102	248946	180/2.0	6	M	57	273	
103	249012	Placebo	3	M	73	66	MI
104	258613	Placebo	3	M	50	709	
105	258613	Placebo	3	M	50	709	
106	258719	Placebo	3	M	79	278	Cardiogenic shock post CABG made in emergency
107	260647	180/1.3	3	M	93	174	ARDS
108	261897	180/2.0	3	F	76	120	Kidney failure CHF
109	261944	180/2.0	3	M	55	14	Cardiac arrest
110	263007	Placebo	3	M	71	53	Increase hr due to increase CHF
111	264355	Placebo	3	M	67	397	Heart failure
112	264388	180/2.0	3	F	69	333	Pulmonary infection - septic shock
113	265164	180/2.0	6	M	60	479	
114	265535	Placebo	3	M	70	53	Recurrent myocardial infarction
115	265594	Placebo	3	M	79	63	Acute myocardial infarction, Cardiogenic shock
116	265695	Placebo	3	M	61	683	
117	265719	Placebo	3	F	75	164	Myocardial infarction proceeding to congestive heart failure
118	266251	180/1.3	3	M	74	401	Mesenteric thrombosis
119	266771	180/2.0	3	M	66	456	Myocardial infarction, pulmonary edema, shock
120	266819	Placebo	3	M	66	6	Lung acute edema CHF
121	266888	Placebo	3	M	73	50	Cardiogenic shock
122	267325	180/1.3	3	F	73	136	
123	267624	Placebo	3	M	76	160	Resp failure bradycardia asystole
124	268395	180/2.0	3	M	72	292	Exacerbation of COPD
125	268580	Placebo	3	M	56	537	
126	268987	180/1.3	3	M	74	198	
127	270483	Placebo	6	M	75	355	Thrombosis left main coronary post stent implanted
128	280423	Placebo	3	M	71	349	Ventricular fibrillation
129	282483	180/1.3	3	F	69	62	Intracerebral hemorrhage with herniation syndrome
130	282539	180/1.3	3	M	67	170	Congestive heart failure, second to severe artery disease
131	282546	Placebo	3	M	74	129	Cardiogenic pulmonary edema and shock
132	282856	180/2.0	3	F	88	685	
133	283785	180/2.0	3	F	70	565	
134	284868	180/2.0	3	F	69	529	Shock
135	286447	180/1.3	3	F	71	637	
136	286985	180/2.0	6	M	51	200	Cardiogenic shock

Obs.	Patient ID	Treatment	Race	Sex	Age	Time	Cause
137	287399	Placebo	3	M	70	70	Cardiac rupture and tamponade
138	288789	180/1.3	6	M	54	97	Ventricular fibrillation
139	288817	180/2.0	3	M	57	4	Antero septal myocardial infarction
140	288923	180/2.0	3	M	55	395	Cardiogenic shock 2 inferior MI
141	288931	180/1.3	6	F	71	57	Ventricular fibrillation
142	289425	180/1.3	3	M	68	244	Hypoxic encephalopathy life support withdrawn
143	290237	180/2.0	3	F	74	559	Sudden death, coronary insufficiency
144	290528	Placebo	3	M	76	82	Cardiogenic shock
145	290584	180/1.3	3	F	73	181	
146	291250	180/2.0	3	F	72	88	MI
147	292259	180/2.0	3	M	58	22	Myocardial infarction
148	292568	180/2.0	3	M	71	266	Cerebrovascular accident
149	292695	Placebo	3	M	62	126	Acute MI
150	294055	Placebo	3	M	78	63	Cardiogenic shock
151	294234	180/1.3	3	M	67	18	Recurrent myocardial infarction
152	294246	180/2.0	3	M	72	415	
153	294364	Placebo	3	M	63	435	Cardiogenic shock due to re-MI
154	294916	180/1.3	3	M	72	217	Low output state
155	295907	180/2.0	3	F	84	146	Myocardial infarction
156	296778	180/2.0	3	F	71	230	Ischemic stroke
157	297321	180/1.3	3	M	73	83	Pneumonia
158	297464	180/1.3	3	M	81	95	Heart failure
159	297814	180/2.0	3	F	63	103	BP continued to decrease and low CO state
160	298744	180/2.0	3	F	77	51	Hemorrhagic shock
161	299575	Placebo	3	M	78	28	Severe coronary artery disease
162	299635	180/2.0	3	F	80	439	Shock Cardiogenic
163	299784	180/1.3	3	M	81	129	Cardiac arrest
164	299904	180/1.3	3	F	69	104	Cardiogenic shock
165	300072	180/2.0	3	M	71	555	Cardiogenic shock
166	300423	Placebo	6	F	75	69	Cardiogenic shock
167	300684	180/2.0	3	M	63	210	Cardiac arrest
168	301326	180/2.0	3	M	73	60	Cardiac arrest
169	301717	Placebo	3	M	81	463	
170	302663	180/2.0	3	F	68	131	Infarction cardiac arrest
171	303033	180/2.0	3	F	54	323	Acute MI
172	303453	Placebo	3	M	69	242	Cardiogenic shock
173	304214	Placebo	3	M	82	23	Insufficiency of left ventricle
174	306714	180/2.0	6	F	85	419	
175	306722	180/2.0	6	F	56	229	Severe respiratory insufficiency
176	306791	180/2.0	6	F	73	222	Cardiogenic shock
177	306799	180/2.0	6	M	46	559	Choque neptico (? Septic Shock?)
178	307475	180/2.0	3	F	69	96	Cardiogenic shock due to myocardial infarction
179	307655	180/2.0	3	M	72	74	Coronary heart disease acute myocardial infarction left ventricular failure Cardiogenic shock
180	307864	180/2.0	3	M	74	160	Heart failure
181	307925	Placebo	3	F	69	253	
182	308288	Placebo	3	M	69	7	Left main coronary artery atherosclerotic occlusion, left dominant type

Obs.	Patient ID	Treatment	Race	Sex	Age	Time	Cause
183	308620	Placebo	3	M	58	57	CHF
184	308620	Placebo	3	M	58	57	CHF
185	308696	Placebo	3	M	58	420	
186	309030	180/2.0	3	F	75	466	Multisystem organ failure post MI & post CABG.
187	310217	180/2.0	3	M	79	479	
188	310286	Placebo	3	F	82	84	Cardiogenic shock with 3 vessel cad
189	310402	Placebo	3	F	63	276	Asystole
190	311867	180/2.0	3	F	76	98	Heart failure
191	313081	180/2.0	4	F	91	70	Arrhythmia
192	313462	Placebo	3	M	74	56	
193	314488	180/2.0	3	M	74	178	Cerebral infarction
194	314785	Placebo	3	F	68	261	Cardiogenic shock
195	315036	180/2.0	3	F	77	306	Cardiogenic shock
196	317198	Placebo	3	F	74	567	
197	317270	180/2.0	3	M	70	100	Progressive hypotension, bradycardia, pump failure
198	317520	180/2.0	3	M	75	208	CVA
199	317788	180/2.0	3	M	79	108	
200	317997	180/2.0	3	M	76	333	Myocardial infarction
201	318951	180/2.0	4	F	70	464	
202	319837	180/2.0	3	M	62	93	
203	320812	Placebo	3	F	73	433	Ventricular Arrhythmia
204	321192	180/2.0	3	F	70	390	Cardiovascular disease no detailed information
205	322130	180/2.0	3	M	64	323	Myocardial infarction complicated by cardiogenic shock
206	322442	Placebo	3	M	68	130	Cardiogenic shock
207	324330	180/2.0	3	F	70	681	Heart failure, hypostatic bronchopneumonia, pulmonary embolism
208	325189	Placebo	3	M	68	145	Complications from CABG
209	325290	Placebo	3	M	76	145	Cardiopulmonary arrest
210	325848	180/2.0	3	M	65	492	
211	326822	Placebo	3	M	90	319	
212	327043	Placebo	3	F	67	118	RV infarct with cardiogenic shock resultant renal failure and cerebral death
213	327507	Placebo	3	M	73	58	Complete heart block
214	327760	Placebo	3	F	82	392	Congestive heart failure
215	328489	Placebo	3	M	64	5	Pulseless electrical activity possible massive MI
216	329592	Placebo	3	M	79	683	
217	329826	Placebo	3	M	55	46	Anaphylactic shock
218	330641	Placebo	8	M	60	102	
219	330702	180/2.0	3	M	67	19	Cardiogenic shock
220	331215	180/2.0	3	M	75	625	Cachexia / neoplasm
221	331697	Placebo	3	F	70	44	Acute myocardial infarction
222	331887	Placebo	4	F	62	208	
223	333095	180/2.0	3	M	79	491	
224	334320	Placebo	3	F	81	171	Cardiac shock
225	334422	180/2.0	3	M	70	199	
226	334601	Placebo	3	F	64	73	Acute ischemic death most likely bypass occlusion
227	336222	180/2.0	3	F	79	396	
228	336266	Placebo	3	F	63	162	Acute myocardial infarction

Obs	Patient ID	Treatment	Race	Sex	Age	Time	Cause
229	338417	Placebo	3	F	69	292	Acute MI
230	340613	Placebo	3	F	61	658	
231	341467	Placebo	3	M	75	41	Cardiogenic shock
232	341650	Placebo	3	F	75	53	Main stem disease recurrent ischemia cardiogenic shock
233	341952	180/2.0	3	M	86	435	Acute renal failure
234	342298	Placebo	3	M	55	686	
235	342528	Placebo	3	M	73	288	Pump failure
236	342736	Placebo	3	M	67	146	Pulmonary embolism
237	345901	Placebo	3	M	66	177	
238	346094	180/2.0	3	M	80	58	Cardiac arrest
239	346309	180/2.0	3	F	69	372	Acute MI
240	346531	180/2.0	3	F	81	85	Left ventricle dysfunction
241	347668	Placebo	4	M	74	639	
242	348157	180/2.0	3	M	83	325	Cardiogenic shock
243	348212	180/2.0	3	F	70	146	Dissection of LMS during diagnostic cath
244	348268	180/2.0	3	M	73	706	
245	348721	180/2.0	3	F	79	444	
246	349204	Placebo	3	M	74	624	Shock septic
247	349362	180/2.0	3	M	87	294	Acute MI renal failure
248	349615	Placebo	3	M	79	2	Cardiogenic shock
249	349735	Placebo	3	F	74	128	Free wall rupture
250	349830	Placebo	3	F	76	701	
251	349838	180/2.0	3	M	75	609	
252	350853	180/2.0	3	M	72	21	
253	353657	180/2.0	3	F	74	215	Cardiogenic shock
254	353906	Placebo	3	F	78	124	Cardio pulm arrest
255	355419	Placebo	3	M	76	129	Cardiac failure during surgical intervention
256	355453	Placebo	3	F	84	448	Cardiogenic shock
257	355611	180/2.0	3	F	69	169	Acute MI
258	355945	180/2.0	3	F	73	158	Acute anterior wall MI with 2 cardiogenic shock
259	355991	Placebo	3	M	66	340	Cerebral infarct
260	357630	Placebo	3	M	80	48	
261	357996	Placebo	3	F	74	301	MI (reinfarction)
262	358245	Placebo	3	M	64	88	Acute myocardial infarction
263	358348	Placebo	3	M	65	121	Myocardial Infarction
264	358467	180/2.0	3	M	75	230	Cardiogenic shock
265	358609	180/2.0	3	M	64	466	
266	358704	Placebo	3	F	81	30	Rupture of left ventricular free wall
267	358984	180/2.0	3	M	61	660	
268	359001	180/2.0	3	F	54	136	Acute Myocardial Infarction
269	359041	Placebo	3	F	70	683	
270	361380	180/2.0	3	F	65	399	Cardiogenic shock
271	361622	180/2.0	3	F	80	187	Cardiogenic shock
272	361803	Placebo	6	M	32	147	Severe 3 vessel disease
273	362315	180/2.0	3	F	75	257	Myocardial infarction
274	362911	180/2.0	3	M	73	62	Cardiogenic shock
275	362924	Placebo	3	M	81	398	
276	363032	Placebo	9	M	71	210	Retroperitoneal hemorrhage

Obs	Patient ID	Treatment	Race	Sex	Age	Time	Cause
277	363591	180/2.0	3	M	80	10	Myocardial infarction
278	363758	Placebo	3	M	68	220	Acute coronary insufficiency
279	363921	180/2.0	3	M	77	274	
280	364173	180/2.0	3	M	83	96	Acute myocardial infarction
281	364239	Placebo	3	M	72	26	Cardiogenic shock
282	364983	180/2.0	3	M	64	80	
283	365277	180/2.0	3	M	78	32	V fib cardiogenic shock
284	365731	180/2.0	3	M	60	249	
285	368167	180/2.0	3	M	65	98	Cardiogenic shock
286	368565	Placebo	6	M	54	271	MI
287	368859	180/2.0	3	F	82	624	
288	369163	Placebo	3	M	65	82	Myocardial ischemia pulmonary edema
289	370730	Placebo	3	M	90	238	
290	370799	Placebo	3	M	83	96	Congestive heart failure
291	371219	180/2.0	3	F	80	234	CHF
292	371503	Placebo	3	M	68	179	Myocardial infarction
293	372252	180/2.0	3	M	71	100	Cardiogenic shock/heart failure
294	372598	Placebo	3	F	70	107	Congestive heart failure
295	373315	Placebo	6	M	76	47	MI
296	374346	180/2.0	3	F	69	702	Subtentorial bleeding
297	374553	Placebo	3	M	57	413	Cardiogenic shock
298	375007	Placebo	3	F	71	285	CHF
299	375007	Placebo	3	F	71	285	CHF
300	375233	Placebo	3	F	86	52	Acute anterior myocardial infarction
301	376017	180/2.0	3	F	84	162	Cardiac arrest
302	376552	Placebo	3	M	68	595	Cardiogenic shock
303	377467	180/2.0	3	M	57	211	Cardiac shock
304	378304	Placebo	3	M	67	73	Resp. Failure
305	380178	Placebo	3	F	71	495	Cardiogenic shock
306	380284	Placebo	3	M	75	14	Pulmonary edema myocardial infarction
307	380537	180/2.0	3	F	75	106	Heart rupture
308	380537	180/2.0	3	F	75	106	Heart rupture
309	381653	180/2.0	3	M	69	224	Multiple reinfarctions on the anterior & post walls
310	381746	180/2.0	3	M	85	174	Acute myocardial infarction
311	382239	Placebo	3	M	72	129	Massive pulmonary embolism
312	382908	Placebo	3	M	79	269	MI
313	383150	180/2.0	3	M	70	485	Cardiac arrest
314	383186	Placebo	3	M	54	423	
315	383794	180/2.0	3	F	44	469	
316	383814	Placebo	6	F	78	89	Respiratory arrest
317	384038	Placebo	3	M	64	103	Heart failure
318	385524	180/2.0	3	F	67	191	Cardiogenic shock
319	385850	Placebo	3	M	62	212	Cardiac arrest
320	386031	180/2.0	3	M	83	51	Cardiogenic shock and ventricular fib
321	386250	Placebo	3	M	73	10	Acute MI
322	386770	180/2.0	3	M	69	310	Heart failure
323	386961	180/2.0	3	M	77	163	
324	388657	180/2.0	3	F	74	45	Cardiogenic shock

Obs	Patient ID	Treatment	Race	Sex	Age	Time	Cause
325	389005	180/2.0	3	M	66	124	Heart failure
326	389291	180/2.0	3	F	76	183	Cardiac arrest
327	389585	Placebo	3	M	75	27	
328	390001	180/2.0	3	F	74	54	Cardiogenic shock
329	391184	Placebo	3	M	78	47	Arrhythmia related to acute MI
330	392263	Placebo	3	F	83	138	Myocardial infarction
331	392792	Placebo	3	F	71	169	MI
332	394429	Placebo	3	M	71	50	Cardiogenic shock
333	394513	180/2.0	3	M	64	88	Infarct myocardial
334	394622	Placebo	3	M	74	519	Cardiogenic shock
335	394803	180/2.0	3	M	70	100	Cardiogenic shock
336	395662	180/2.0	3	F	77	112	Respiratory failure
337	396514	Placebo	3	M	61	27	Acute myocardial infarction (cardiogenic shock)
338	397480	Placebo	3	F	83	133	Cardiogenic shock
339	397800	180/2.0	3	F	65	156	
340	398182	Placebo	3	M	63	155	Massive pulmonary embolism
341	398321	Placebo	3	M	83	143	Cardiogenic shock
342	398794	Placebo	3	F	75	369	Post CABG cardiogenic shock probable RV infarction
343	400257	Placebo	3	M	69	53	MI
344	400415	Placebo	3	M	69	37	Pulmonary edema
345	400577	Placebo	3	M	77	133	CVA plus aspiration pneumonia
346	401072	Placebo	4	F	49	465	
347	401476	Placebo	3	M	71	22	Ventricular tachycardia fibrillation
348	401615	Placebo	3	F	79	137	Cardiogenic shock
349	401652	180/2.0	3	M	61	131	
350	402338	Placebo	3	M	84	396	
351	402982	Placebo	3	F	71	66	Cardiogenic shock
352	403050	Placebo	3	M	77	122	Complication due to PTCA
353	403589	180/2.0	3	M	67	423	Cardiac tamponade with mediastinal hemorrhage
354	403834	180/2.0	3	M	90	295	
355	404130	180/2.0	3	F	76	179	Acute myocardial infarction-cardiogenic shock.
356	404199	Placebo	3	M	75	218	Myocardial infarction rupture left ventricle
357	404357	Placebo	3	M	69	185	Respiratory arrest
358	404442	180/2.0	3	F	69	46	Reinfarction myocardial
359	404715	180/2.0	3	F	74	178	Reinfarction myocardial
360	404773	180/2.0	3	M	65	566	
361	406948	180/2.0	3	M	61	16	MI
362	407534	180/2.0	3	F	64	518	MI
363	411020	180/2.0	3	M	72	51	Severe cardiac disease
364	411033	180/2.0	4	F	50	248	Acute MI with heart failure.
365	411624	180/2.0	3	F	73	439	
366	412967	Placebo	3	F	84	80	Cardiac ischemia
367	414445	Placebo	3	F	76	6	Acute MI lateral and posteroinferior
368	415100	Placebo	3	F	88	135	Left ventricular failure
369	416749	180/2.0	3	F	66	48	Myocardial infarction and heart failure
370	417184	180/2.0	3	M	74	462	Ischemia small intestine
371	417323	Placebo	3	F	68	394	Acute myocardial infarct
372	418254	Placebo	3	F	73	325	Cardiogenic shock

Obs	Patient ID	Treatment	Race	Sex	Age	Time	Cause
373	418561	Placebo	9	M	66	152	Acute MI
374	419539	180/2.0	3	M	82	73	Intra-cerebral hemorrhage
375	420062	Placebo	3	M	63	23	Cardiac arrest
376	421586	180/2.0	3	M	77	336	Sepsis
377	422625	Placebo	3	M	53	167	Pulmonary embolism
378	422907	180/2.0	3	F	92	321	
379	425900	Placebo	3	F	76	9	Cardiogenic shock
380	427273	Placebo	3	M	66	492	Heart failure due to pulmonary embolism
381	427565	Placebo	3	F	74	11	Myocardial infarction
382	429017	Placebo	3	M	63	320	Acute anterior myocardial infarction, VSD acute renal failure sepsis
383	432150	180/2.0	3	M	83	14	Unstable angina tachyarrhythmia acute pulmonary edema
384	432449	Placebo	3	M	68	517	
385	434162	Placebo	3	M	71	179	Cardiogenic shock
386	434660	Placebo	3	M	79	309	
387	435251	Placebo	3	M	64	230	Cardiogenic shock
388	436090	Placebo	3	M	68	268	Surgical complications including cerebral anoxia and hemorrhage.
389	437045	Placebo	7	M	82	181	Ischemic cardiomyopathy with V. Fib arrest
390	437857	180/2.0	4	M	74	372	
391	438128	Placebo	3	M	68	255	Unknown
392	438364	Placebo	3	M	77	289	Pulmonary edema ventricular fibrillation
393	439688	180/2.0	3	M	61	480	Bacteremia
394	441206	Placebo	3	M	82	558	
395	444689	Placebo	3	F	80	40	Asystole
396	445469	Placebo	3	M	51	230	Arrhythmia
397	447861	Placebo	3	F	41	121	Resuscitation/CABG after MI
398	452064	Placebo	3	M	74	400	Intracerebral hemorrhage

Race: 3=Caucasian; 4=Black; 5=Asian; 6=Hispanic; 7=American Indian;
8=Asiatic Indian; 9=Other

APPENDIX 6

List of Patient Whose Drug Infusion was Discontinued for Adverse Events Other Than Bleeding

Number	Study Number	Treatment Group	Reason
1	117630	Low Dose	Frequent Nausea, Emesis
2	122932	Low Dose	Rash
3	134186	Placebo	Stroke Symptoms
4	138049	Low Dose	Myocardial Infarction
5	140341	Placebo	Possible Phlebitis
6	141142	Low Dose	Thromboectomy Left Arm
7	141724	Placebo	Cardiac Arrest + Head Injury
8	142476	Placebo	Hypotension, + Violent Headache
9	144309	Placebo	Headache
10	144531	Low Dose	Hypotension + TCK APTT = 122
11	145501	Low Dose	Severe Arm Pain Bilaterally
12	146288	Placebo	Episode of "Retrovragy"
13	167000	High Dose	Headache and Nose Bleeds
14	178048	Placebo	Acute Psychic Disorder
15	190165	Low Dose	Perforation of the Stomach
16	197843	High Dose	High Fever (40 degrees Celsius)
17	206718	High Dose	Bradycardia, Hypotension
18	226301	High Dose	Cardiac Arrest
19	243472	Low Dose	Psychotic Reaction
20	244345	High Dose	Cardiogenic Shock
21	246339	High Dose	Hematocrit Drop
22	249441	High Dose	Creatinine Too High
23	264355	Placebo	Aphasia, Weakness Right Arm
24	266036	Low Dose	Phlebitis
25	268339	High Dose	Pain at Infusion Site
26	268899	High Dose	Increased Liver Enzymes/ Renal Insuff.
27	268987	Low Dose	Patient Becomes Confused
28	284710	High Dose	
29	285237	Placebo	Severe Headache
30	285249	High Dose	Hallucinations, excitability, aggression
31	286102	Placebo	TIA, Cerebral Infarction
32	286201	Low Dose	Serious Decrease in Hemoglobin
33	287734	High Dose	Hypotension
34	287892	Placebo	Abnormal Liver Function Tests
35	290528	Placebo	Heart Failure, Respiratory Arrest
36	291402	Low Dose	Severe Headache
37	293538	High Dose	Anaphylaxis
38	294376	Low Dose	Increase Creatinine
39	295879	Low Dose	Anaphylaxis
40	296778	High Dose	Susp. Intracerebral Hemorrhage
41	297321	Low Dose	Shock
42	298190	High Dose	Phlebitis
43	299062	High Dose	Creatinine Rise to 2.1 mg/dl
44	300423	Placebo	Acute Dyspnea, Severe Hypotension

Number	Study Number	Treatment Group	Reason
45	301305	High Dose	Confusion
46	303564	Placebo	Increased AST, ALT
47	306128	Placebo	Hypertension, 240/120 mm Hg.
48	307391	Placebo	Suspected Stroke
49	307734	Placebo	TIA
50	308620	Placebo	Stroke
51	314343	Placebo	Acute Hepatitis and Renal Injury
52	314800	High Dose	Patient Confused, pulled IV out
53	317520	High Dose	TIA
54	317613	High Dose	Fever
55	325189	Placebo	Burning at IV Site
56	326553	Placebo	Superficial Phlebitis
57	327368	High Dose	APTT > 120 secs.
58	331035	Placebo	Hypotension and Renal Failure
59	331094	Placebo	Suspected MI,
60	331991	Placebo	Decreased Platelets (103)
61	33062	High Dose	Hemoglobin (3 gm)
62	333308	High Dose	Increased LFT's
63	333809	High Dose	Patient Felt Throat Swelling
64	334050	High Dose	Hypotension
65	338816	High Dose	Myocarditis
66	340356	Placebo	Shaking Chill, Fever
67	341467	Placebo	Cardiogenic Shock
68	342477	High Dose	Confusion
69	344244	High Dose	Suspected Stroke
70	345353	High Dose	Hypotension, Rigors, Nausea
71	348542	High Dose	Elevated Blood Pressure
72	350075	Placebo	Agitation, Psychiatric
73	350387	Placebo	Confusion
74	351297	Placebo	Embolitic CVA
75	353906	Placebo	R/O CVA, Lethargic & Fell, Syncope
76	355386	High Dose	Anemia
77	355453	Placebo	Cardiogenic Shock
78	357225	High Dose	Perforated Coronary Artery
79	357534	Placebo	Anemia
80	358704	Placebo	Cardiac Wall Rupture
81	359985	High Dose	Anaphylaxis
82	360608	Placebo	Nausea and Vomiting
83	361217	High Dose	Increased Creatinine
84	364323	Placebo	CPR During CA
85	365222	High Dose	Increased Confusion
86	367720	Placebo	Fever, Headache, Flushed Face
87	373091	High Dose	Decreased BP, Fever
88	374117	Placebo	Burning IV site, Light Headedness
89	376499	High Dose	Fever
90	377737	Placebo	Acute Psychosis
91	378578	High Dose	Psychotic Syndrome

Number	Study Number	Treatment Group	Reason
92	378718	Placebo	Hypotension
93	381052	High Dose	Epileptic seizures
94	383339	Placebo	Rash
95	384038	Placebo	Disorientation, Confusion
96	394341	Placebo	Increased Creatinine, Anemia
97	395356	High Dose	Complications in Cath. Lab
98	397592	High Dose	Allergic Reaction - Wheals & Erythema
99	398779	High Dose	Hypotensive Episode
100	399223	Placebo	Increased Creatinine
101	400577	Placebo	CVA
102	403050	Placebo	Disorientation
103	403878	High Dose	Increased Creatinine
104	408266	Placebo	Thrombocytopenia
105	410943	High Dose	Hypotension
106	412135	Placebo	Confusion, Removed IV
107	414445	Placebo	Acute MI
108	419539	High Dose	Stroke
109	419718	High Dose	Confusion
110	423581	High Dose	Aortic Dissection
111	428926	Placebo	Cerebral Infarct
112	433710	High Dose	Development of Hives
113	434289	High Dose	Thrombocytopenia
114	435804	Placebo	Fever
115	435921	Placebo	Anemia
116	436707	Placebo	Psychotic Episode
117	437639	High Dose	Anemia

Appendix 7
Summary of Protocol Amendments

Protocol Amendment #1 (submitted 3-37-95)

On March 27, 1995 the following changes were made in the protocol.

1. Change in medical monitor from Todd Lorenz, M.D., to Michael Kitt, M.D.
2. Change in inclusion criteria; page 10, section 4.2.b to read:
Patients must have either transient ST segment elevation > 0.5 mm or transient or persistent ST segment depression of > 0.5 mm or definitive T wave inversion of > 1.0 mm during or within 12 hours of an episode of chest pain. Transient ST segment elevation is defined as of < 30 minutes duration and not treated with thrombolytics or direct PTCA.
3. Change in exclusion criteria; page 10, section 4.3.e to read:
A history of known hemorrhagic strokes at any time, or stroke of any etiology within 30 days prior to study enrollment.
4. Change in study drug administration; page 16, section 6.2 to read:
Each kit will contain 1 vial for the bolus dose and 9 vials for the infusion of blinded study drug material. On the day of treatment, study medication will be prepared for the patient to be treated according to the kit number assigned by the randomization center personnel. The pharmacist or nurse will dispense each patient's medication labeled with the patient's number, assignment kit number and initials. The bolus dose and infusion rate to be delivered will be transcribed on the syringe for bolus administration and on the vials for infusion administration.
5. Change in discontinuation of study drug; page 16, section 6.3 to read:
Study drug should be continued for up to 72 hours. Study drug infusion may be terminated prematurely (before 72 hours) if there is a clear clinical indication such as early resolution of the unstable syndrome and early discharge. In addition, study drug may be terminated prematurely for treatment failure, adverse event, significant bleeding, or if cardiac surgery is performed. For patients who are transferred to another hospital during the course of the infusion, the infusion timing begins after initiation of the infusion and should be continued for up to 72 hours. As with any clinical trial, if at any time there is a conflict between continuing the trial protocol and providing optimal patient care, optimal care should be considered a priority.
6. Change in anginal medications; page 22, section 7.3.1 to read:
Calcium channel antagonists may be added at the discretion of the treating physician and are encouraged for patients with systolic hypertension (SBP > 150 mm Hg).
7. Change in secondary endpoints; page 24, section 8.2 to read:
Secondary endpoints for all randomized patients will include:
 - Cost
 - Quality of life
8. Change in heparin infusion adjustment nomogram; page 36, Appendix D1
9. Change in heparin adjustment nomogram during coronary angioplasty; page 37, Appendix D2
10. Change in timing of ECGs and lab draws for aPTT, hemoglobin, hematocrit and platelet count.

Protocol Amendment # 2 (submitted 9-25-95)

On September 25, 1995 the following changes were made in the protocol.

1. Dose change:- changing the dose from 135 µg/kg bolus plus 1.0 or 1.25 µg/kg-min to 180 µg/kg plus 1.3 or 2.0 µg/kg-min.
2. Changed the primary efficacy endpoint analyses from a pooled comparison of two dosing regimens to placebo to a pairwise comparison of the single-dose arm evaluated for the duration of the study to placebo (pages 9 and 61 of IND Amendment # 132).
3. Specified that patients enrolled under the previous version would be analyzed separately from the main study (pages 7 and 44 of IND Amendment #132).

4. Provided for discontinuation of the 180/1.3 arm if an early interim evaluation by the DSMB showed no substantial difference between the bleeding and stroke profiles of 180/1.3 and 180/2.0 (page 45 of IND Amendment # 132)
5. Provided for interim analyses of efficacy with the potential for discontinuing the study early if there was overwhelming evidence of benefit or lack of benefit with eptifibatide compared with the control (pages 11 and 45 on Amendment # 132).
6. Limited the age of patients to ≤ 75 years until an early interim analysis to establish safety of these regimens in terms of bleeding and strokes were conducted.
7. Allowed for the inclusion of patients with appropriate symptoms of UA/NQMI and increased levels of CK-MB (above the upper limit) but who lacked documenting ECG evidence.
8. Expanded the study to a worldwide basis.

Protocol Amendment # 3 (submitted 10-9-95)

On October 9, 1995 the following changes were made in the protocol. These changes were considered by the sponsor as minor and therefore not submitted to the agency.

1. Addition of Schering-Plough Research Institute (SPRI) as the sponsor for the trial outside Canada and US.
2. Change in name of the medical monitor from Michael Kitt, M.D., to Don Gretler, M.D. and Michael Bergman, M.D..

Protocol Amendment # 4 (submitted 2-12-96)

On February 12, 1996 the following changes were made in the protocol.

1. Clarification of the desire to study only the 180/2.0 regimen to completion and to discontinue the 180/1.3 regimen, unless there was a bleeding/stroke problem with the 180/2.0 regimen.
2. Change in storage temperature from $\leq 30^{\circ}\text{C}$ to $2^{\circ}\text{C} - 25^{\circ}\text{C}$.
3. Deletion of the recommendation to wait for diagnostic catheterization or PTCA until 24 to 48 hours after enrollment if the patient was stable because this did not reflect typical clinical care in patients with UA/NQMI
4. Deletion of two secondary efficacy endpoints.
5. Change in the definition of peri-operative MI - delete "new regional wall motion abnormalities" from the definition of MI associated with CABG surgery because cardiac imaging is obtained in only a small number of selected patients (this did not affect the remaining definitions dealing with increase in CK-MB or appearance of new significant Q waves in the ECG).
6. Addition of collection of non-serious adverse events
7. Miscellaneous administrative changes

Protocol Amendment # 5 (submitted 6-26-96, IND Amendment # 167)

On June 26, 1996 the following changes were made in the protocol.

1. Allowed for enrollment of patients older than 75 years, so long as they weighed more than 50 kg (because of a perceived greater risk of bleeding in lighter weight patients).
2. Allowed for the enrollment of patients with persistent ST-segment elevation > 0.5 mm but not requiring reperfusion therapy because of a small ischemic area.
3. Deleted the requirement that qualifying changes on the ECG be recorded within 12 hours of an episode of chest pain.
4. Clarified that total CK and CK-MB levels were to be collected immediately before and 8 and 16 hours after cardiac surgery, just as for percutaneous coronary revascularization, and that CK-MB should always be measured in instances of suspected ischemia, regardless of total CK level.
5. Deleted the recommendation not to re-start infusion of study drug if it had been interrupted for ≥ 1 hour.
6. To minimize the risk of bleeding while maintaining therapeutic effect, changed the recommended dosing for concomitant heparin from an absolute to a weight-adjusted basis for

patients weighing < 70 kg, and provided an adjustment nomogram for all patients to achieve an aPTT of 50 to 70 seconds, rather than the original 50 to 80 seconds.

7. Deleted the provision for adjudication of the 6 months efficacy data by the CEC.

Protocol Amendment # 6 (submitted 7-19-96, Amendment # 169) "**Final Protocol no subject was treated under this protocol**"

On July 19, 1996 the following changes were made in the protocol.

1. The data safety monitoring committee to review safety data and make one of 3 choices;
 - a) Select the 2.0 µg/kg-min dose for continued evaluation if no untoward safety risks have been observed,
 - b) Select the 1.3 µg/kg-min infusion dose as a result of observing untoward safety risk at the high dose, or
 - c) Elect to continue both Integrilin dosing regimens for the entire study.
2. The study synopsis was changed to reflect change number 1.
3. The statistical procedures and data analysis was changed to allow for change number 1.
4. The randomization assignment was changed to permit randomization into one Integrilin group or placebo. In stead of two Integrilin dosage groups and placebo.
5. Sample size calculations revised to allow for changes that might result from change number 1 and interim looks at the data.
6. Editorial changes in the section on statistical analyses.
7. Interim analyses was changed to allow for change number 1.
8. Dosing regimen was changed to reflect change number 1.
9. Interim analysis procedure was changed to reflect change number 1.
10. Efficacy analyses was changed to reflect change number 1.
11. Data safety monitoring committee section was changed to incorporate change number 1.

Protocol Amendment # 7 (submitted 7-22-97, Amendment # 213)

On July 22, 1997 the following changes were made in the protocol.

1. Addition of secondary endpoint - evaluation of the primary composite endpoint and its individual components at 6 months as well as at the currently prescribed endpoints of 96 hours, 7 days and 30 days after enrollment.
2. Addition of safety and efficacy analysis of Integrilin in the subgroup of patients undergoing coronary angioplasty while on study therapy.

Appendix 8

New Studies Included in submission

Protocol / Investigator/ Country	Status (Dates of Study)	Design	Treatment/Dose (Bolus + Infusion)	Duration	# Of Subj.
C96-047 Cohen USA	Completed (March to April 1996)	Single-center Open label Single bolus Injection	14C-Integrilin 135 µg/kg	single dose	8
I96-049 Mant U.K.	Completed (May to July 1996)	Single-center Open label rising single dose bolus injection only	Total exposed to Integrilin	single dose	12
			Integrilin 90 µg/kg	2 weeks washout	12
			Integrilin 135 µg/kg Integrilin 180 µg/kg	between injections	12
I96-050 Mant U.K.	Completed (June to Sept. 1996)	Single-center open label rising single dose; infusion only	Total exposed to Integrilin	24 hours 2 week washout	13
			Integrilin 0.5 µg/kg-min Integrilin 1.0 µg/kg-min	between treatment	13 12
			Integrilin 2.0 µg/kg-min		12
96-023 [PRIDE] Tcheng (15 sites) USA	Completed (Sept. 1996 to January 1997)	multicenter randomized, blinded while in catheterization laboratory	Four groups received aspirin 81-325 mg, weight adjusted heparin, and Integrilin IV bolus+infusion, or aspirin and heparin alone (Placebo)	24 - 72 hours, 30 day follow-up	
			Placebo		18
			Integrilin 135 µg+0.75 µg/kg-min		20
			Integrilin 180 µg+2.05 µg/kg-min Integrilin 250 µg+3.0 µg/kg-min		44 45
94-016A [PERIGEE] Tardiff, Jennings USA/Canada	Completed (Oct. 1994 to Feb. 1997)	multicenter, randomized, double-blind	Placebo	72 hrs	99 [all in main study]
			Integrilin 180 g/kg+2.0 g/kg-min Integrilin 180 g/kg+1.3 g/kg-min*	follow-up 30 days and 6 months	
94-016 [Pre-PURSUIT] Topol, Califf (21 sites) USA	Terminated (July to November 1995)	multi-center randomized, double-blind	Placebo	72 hrs	36
			Integrilin 135 µg+1.0 µg/kg-min Integrilin 135 µg+1.25 µg/kg-min	follow-up 30 days and 6 months	42 40
94-016 [PURSUIT] Topol, Califf, Simoons (726 sites) USA, Canada, Latin America Eastern/Western Europe	Completed (July, 1995 to Jan. 1997)	multi-center, randomized, double-blind	Placebo	72 hrs	4739
			Integrilin 180 g/kg+1.3 g/kg-min * Integrilin 180 g/kg+2.0 g/kg-min	follow-up 30 days and 6 months	1487 4722

* = regimen discontinued during study

Data Source: Table 1-1, pages 120-131, vol 2.24

Appendix 9

