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 ≤ 30°C to 2°C - 25°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

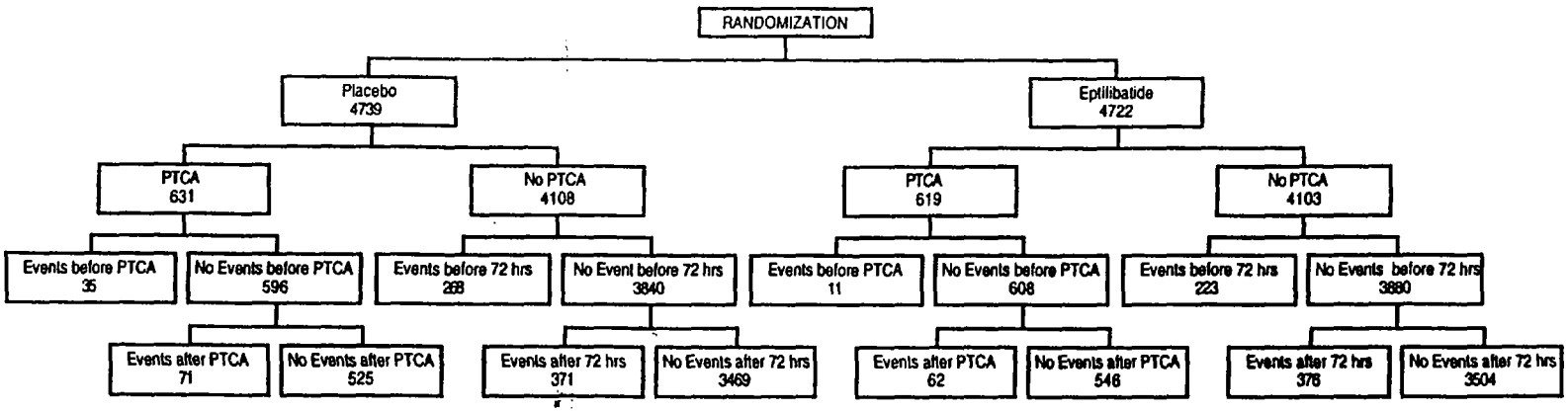
New Studies Included in submission

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 Integrilin 90 µg/kg Integrilin 135 µg/kg Integrilin 180 µg/kg	single dose 2 weeks washout between injections	12 12 12 12
I96-050 Mant U.K.	Completed (June to Sept. 1996)	Single-center open label rising single dose; infusion only	Total exposed to Integrilin Integrilin 0.5 µg/kg-min Integrilin 1.0 µg/kg-min Integrilin 2.0 µg/kg-min	24 hours 2 week washout between treatment	13 13 12 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) Placebo Integrilin 135 µg+0.75 µg/kg-min Integrilin 180 µg+2.05 µg/kg-min Integrilin 250 µg+3.0 µg/kg-min	24 - 72 hours, 30 day follow-up	 18 20 44 45
94-016A [PERIGEE] Tardiff, Jennings USA/Canada	Completed (Oct. 1994 to Feb. 1997)	multicenter, randomized, double-blind	Placebo Integrilin 180 g/kg+2.0 g/kg-min Integrilin 180 g/kg+1.3 g/kg-min*	72 hrs follow-up 30 days and 6 months	99 [all in main study
94-016 [Pre-PURSUIT] Topol, Califf (21 sites) USA	Terminated (July to November 1995)	multi-center randomized, double-blind	Placebo Integrilin 135 µg+1.0 µg/kg-min Integrilin 135 µg+1.25 µg/kg-min	72 hrs follow-up 30 days and 6 months	36 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 Integrilin 180 g/kg+1.3 g/kg-min * Integrilin 180 g/kg+2.0 g/kg-min	72 hrs follow-up 30 days and 6 months	4739 1487 4722

* = regimen discontinued during study

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

Appendix 9


RANDOMIZATION
Placebo
4739
Eptilibatide
4722
PTCA
631
No PTCA
4108
PTCA
619
No PTCA
4103
Events before PTCA
35
No Events before PTCA
596
Events before 72 hrs
268
No Event before 72 hrs
3840
Events before PTCA
11
No Events before PTCA
608
Events before 72 hrs
223
No Events before 72 hrs
3880
Events after PTCA
71
No Events after PTCA
525
Events after 72 hrs
371
No Events after 72 hrs
3469
Events after PTCA
62
No Events after PTCA
546
Events after 72 hrs
376
No Events after 72 hrs
3504

6) to determine the IC50 and IC80 for Integrilin in the setting of unstable angina/NQMI in comparison with historical controls obtained in patients with coronary heart disease undergoing coronary angioplasty.

The **patient population** was derived from those enrolled in the PURSUIT study (patients presenting with acute coronary syndrome of unstable angina/probable NQMI). All patients who were eligible for PURSUIT were also eligible for PERIGEE. For complete inclusion/exclusion criteria, see PURSUIT protocol.

The **substudy design** was multicenter (14 centers were used although 20 were planned), randomized, and placebo controlled. The **total sample size** was originally set at 150 but only 99 subjects were actually studied.

The 3 **dosing arms** were
-initial bolus and infusion placebo,
-initial bolus 180 ug/kg and infusion 1.3 ug/kg•min
-initial bolus 180 ug/kg and infusion 2.0 ug/kg•min

The duration of infusion was 72 hours. The lower dose of integrilin was discontinued after 2397 patients were enrolled into PURSUIT.

The **pharmacokinetic profile** of integrilin was to be determined by a total of 9 blood samples collected per patient. Samples were to be drawn prior to start of bolus of study drug and then at 5 minutes, and 1, 4, 24, 48, and 72 hours after drug administration.Specimens were assayed for

-Integrilin concentrations,
-ex vivo platelet aggregation and
-GP IIB/IIIa receptor occupancy.

Blood samples for the **pharmacodynamic parameters**, ADP- and TRAP-induced *ex vivo* platelet aggregation and *ex vivo* GP IIb/IIIa receptor occupancy, were drawn prior to start of bolus of study drug and then at 5 minutes, and 1, 4, 24, 48, and 72 hours after drug administration as well as at hours 4 and 8 after discontinuation of the infusion.

The **blind** was maintained by assigning a special code to each patient used for the purposes of this substudy.

RESULTS

Study patients: Of the 99 patients enrolled into PERIGREE, 50 received placebo, 1 received low dose (dose was prematurely terminated, see above), and 48 received high dose integrilin.

Pharmacokinetics

Discarded data points: data showing integrilin concentrations 3 times higher than the theoretical concentration at steady state (Css) --2 data points-- and post infusion timepoints for patients who did not received the complete 72 hour infusion --6 data points--were not utilized in the modeling of the pooled data. In addition, only 42 of the 48 patients who received the high dose had concentrations of integrilin above the lower limit of quantification (43.5 ng/ml). Data from the 1 patient who received the lower dose was not used in the PK analysis.

Not all patients had PK values at all time points. Therefore, concentration-time data from all subjects were analyzed using a population PK approach. The table below shows the estimated PK parameters for integrilin. Metabolites were not assayed.

PK parameters

	Integrilin high dose
Parameter (units)	Estimate (standard error)
Css (ng/ml)	2201 (^)
AUC0-∞ (ng•hr/ml)	161768 (^)
t1/2 alpha (hr)	0.267 (0.166)
CL (ml/min•kg)	0.909 (^)
Vdss (l/kg)	0.185 (^)

^Not calculated

Figure 1 shows the concentration-time profile for integrilin.

The report states that Css of integrilin for this study was higher than that obtained in normal volunteer studies.

Pharmacodynamics

The percent of study patients achieving ≥ **80% inhibition of platelet aggregation** was measured at various time points using both ADP- and TRAP-induced *ex vivo* platelet aggregation methods and PPACK as the anticoagulant. The results are shown in the table below for the high dose integrilin group only; the results for the placebo group were 0 at all time points.

Number and (percent) of patients+

Time relative to start of infusion/no. of patients	ADP agonist	TRAP agonist
5 min/29	24 (83)	2 (7)
1 hr/25	12 (48)	1 (4)
4 hr/13	7 (54)	0
24 hr/32	27 (84)	4 (13)
48 hr/16	16 (100)	3 (18)
72 hr/5	5 (100)	0

+A total of 48 patients received the high dose.
Table 4

The results from the ADP-induced aggregation showed that while 83% of patients achieved ≥ 80% inhibition of platelet aggregation during the bolus, this percent was not maintained at hours 1 and 4 of the constant infusion. By 24 hours of the infusion, all patients with data had achieved the target inhibition of platelet aggregation and this was maintained through 48 and 72 hours (only 5 patients had data at 72 hours). Figure 2 displays these findings.

The **concentration-response relationship** (measured as *ex vivo* platelet aggregation) using ADP as the agonist and PPACK as the anticoagulant is shown in Figure 3. Similarly shaped curves are obtained when TRAP is used. However, the IC50 and IC80 are different. These are shown

below.

Derived IC (95% limits)

	ADP induced platelet aggregation		TRAP induced platelet aggregation	
parameter	PPACK	Na citrate	PPACK	Na citrate
Total observations/n	143/35	43/31	144/35	42/30
IC50 ng/ml	557	431	1038	635
IC80 ng/ml	1107	785	3848	2147

The TRAP-induced aggregation showed a much lower percent of patients who achieved ≥ 80% inhibition of platelet aggregation at all time points. This is shown in Figure 4.

The percent of patients achieving ≥ 80% inhibition of platelet aggregation (ADP as the agonist) at 24 hours of infusion was 84% with the use of PPACK as the anticoagulant and 100% with sodium citrate as the anticoagulant. This is shown in Figure 5.

The fraction of patients showing ≥ 80% **GP IIb/IIIa receptor occupancy** with PPACK as the anticoagulant is shown in Figure 6. Using different anticoagulants affected the results: at 24 hours of infusion the percent occupancy was 67% with PPACK compared to 91% with sodium citrate.

There was a decline in the mean ADP induced platelet aggregation and receptor occupancy within 4 to 8 hours after the infusion was discontinued but the numbers of patients with data are small.

In summary,
-the Css is reported to be higher in patients than in normal volunteers
-the results of platelet aggregation and occupancy rates are dependent upon the agonist and anticoagulant used. All results, however, were in approximately the same range;
-there is a concentration-effect relationship for both platelet aggregation and receptor occupancy,
-there is a decline in the fraction of patients with ≥ 80% platelet GP IIb/IIIa receptor occupancy and in the fraction of patients with ≥ 80% inhibition of platelet aggregation at 1 and 4 hours post bolus and the start of the infusion. This may have implications regarding efficacy.

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Figure 1. Eptifibatide Plasma Concentration-Time Profile in Patients with Unstable Angina or NQMI After Administration of INTEGRILIN™ 180 µg/kg IV Bolus Immediately Followed by a Continuous 2.0 µg/kg•min IV Infusion for 72 Hours (Protocol 94-016A).

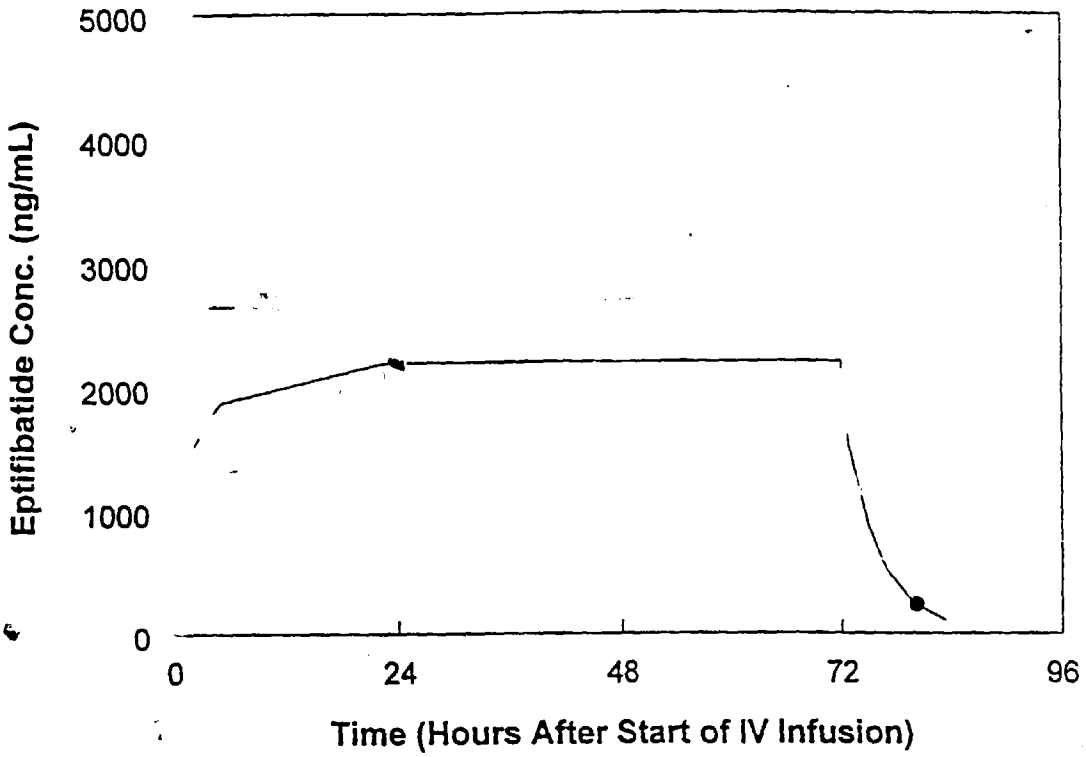

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Figure 2. Fraction of Patients with Unstable Angina or NQMI Which Achieved at Least 80% Inhibition of *Ex Vivo* Platelet Aggregation (Using PPACK-Collected Blood/ADP Agonist) After Administration of INTEGRILIN™ 180 µg/kg IV Bolus Immediately Followed by a Continuous 2.0 µg/kg•min IV Infusion for 72 Hours (Protocol 94-016A).

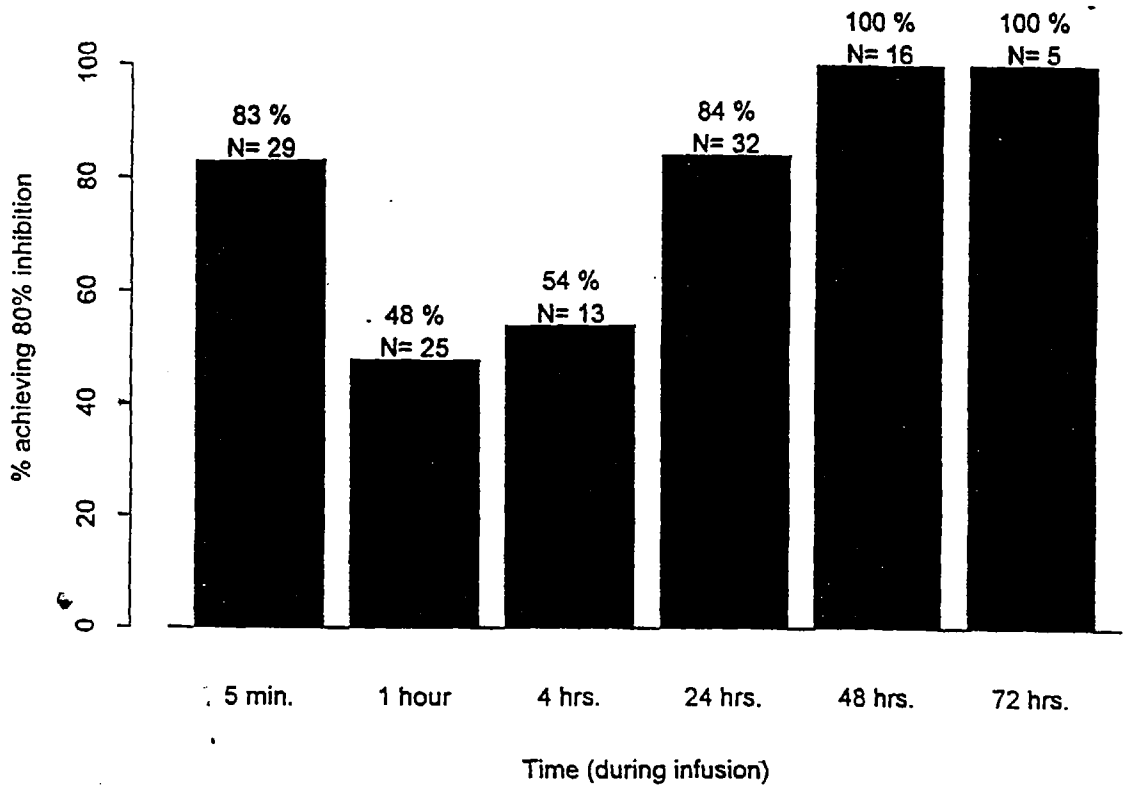

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Figure 10. Eptifibatide Plasma Concentration-Platelet Aggregation Response Relationship (Using PPACK-Collected Blood/ADP Agonist) in Patients with Unstable Angina or NQMI After Administration of INTEGRILIN™ 180 µg/kg IV Bolus Immediately Followed by a Continuous 2.0 µg/kg•min IV Infusion for 72 Hours (Protocol 94-016A).

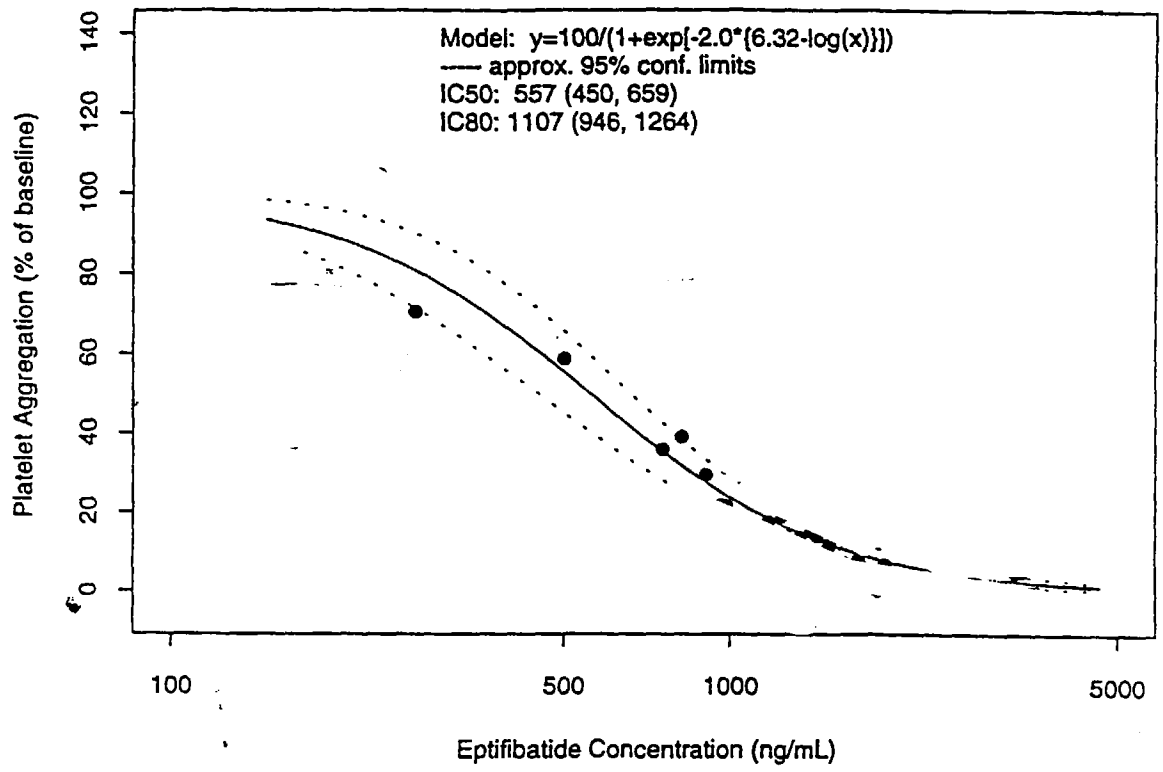

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Figure 5. Fraction of Patients with Unstable Angina or NQMI Which Achieved at Least 80% Inhibition of *Ex Vivo* Platelet Aggregation (Using PPACK-Collected Blood/TRAP Agonist) After Administration of INTEGRILIN™ 180 µg/kg IV Bolus Immediately Followed by a Continuous 2.0 µg/kg•min IV Infusion for 72 Hours (Protocol 94-016A).

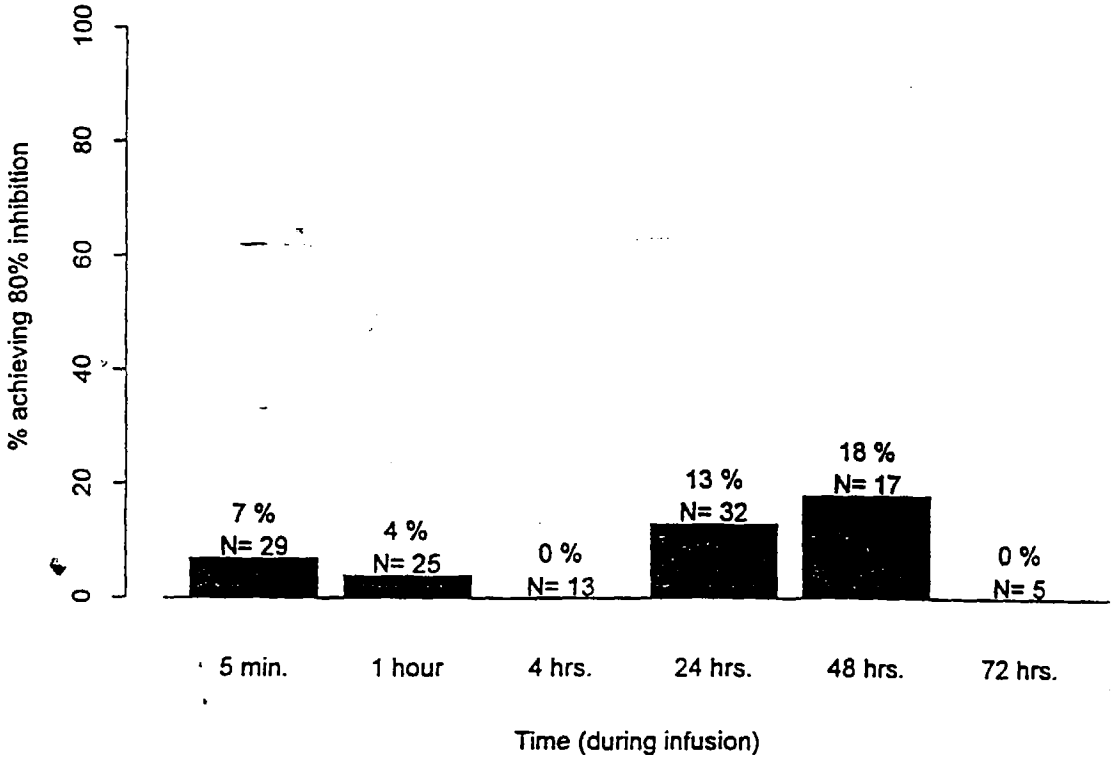

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Figure 15. Fraction of Patients with Unstable Angina or NQMI Which Achieved at Least 80% Inhibition of *Ex Vivo* Platelet Aggregation at 24 Hours After Administration of INTEGRILIN™ 180 µg/kg IV Bolus Immediately Followed by a Continuous 2.0 µg/kg•min IV Infusion (Protocol 94-016A).

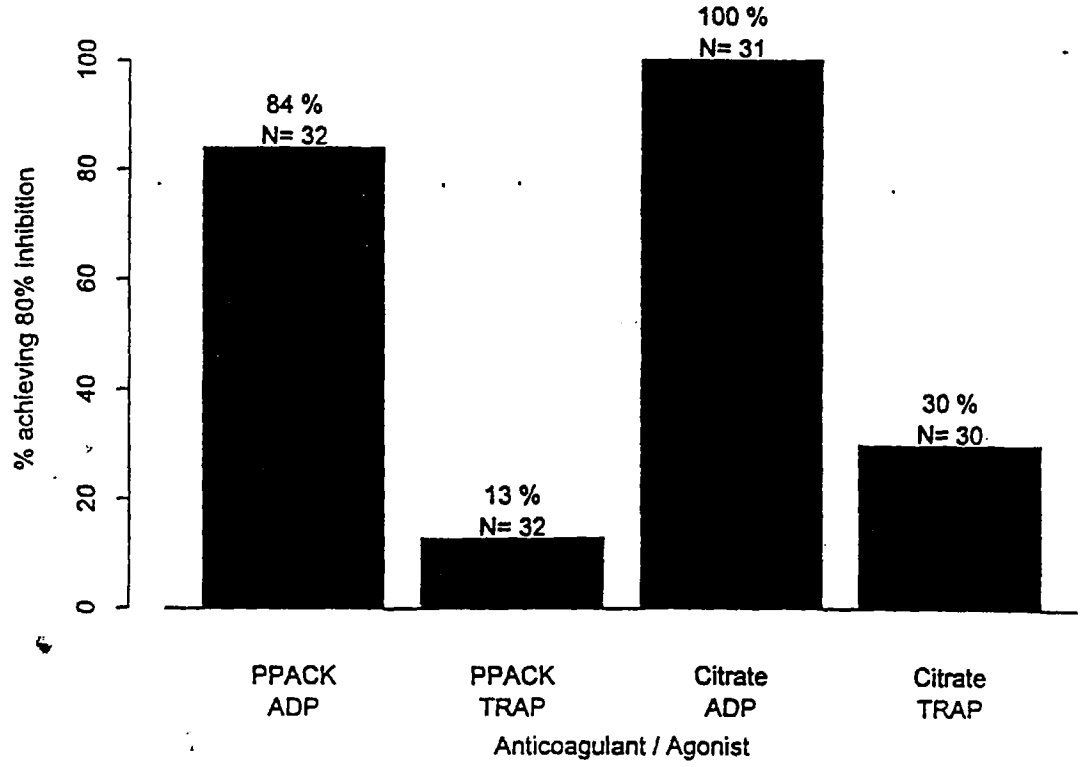

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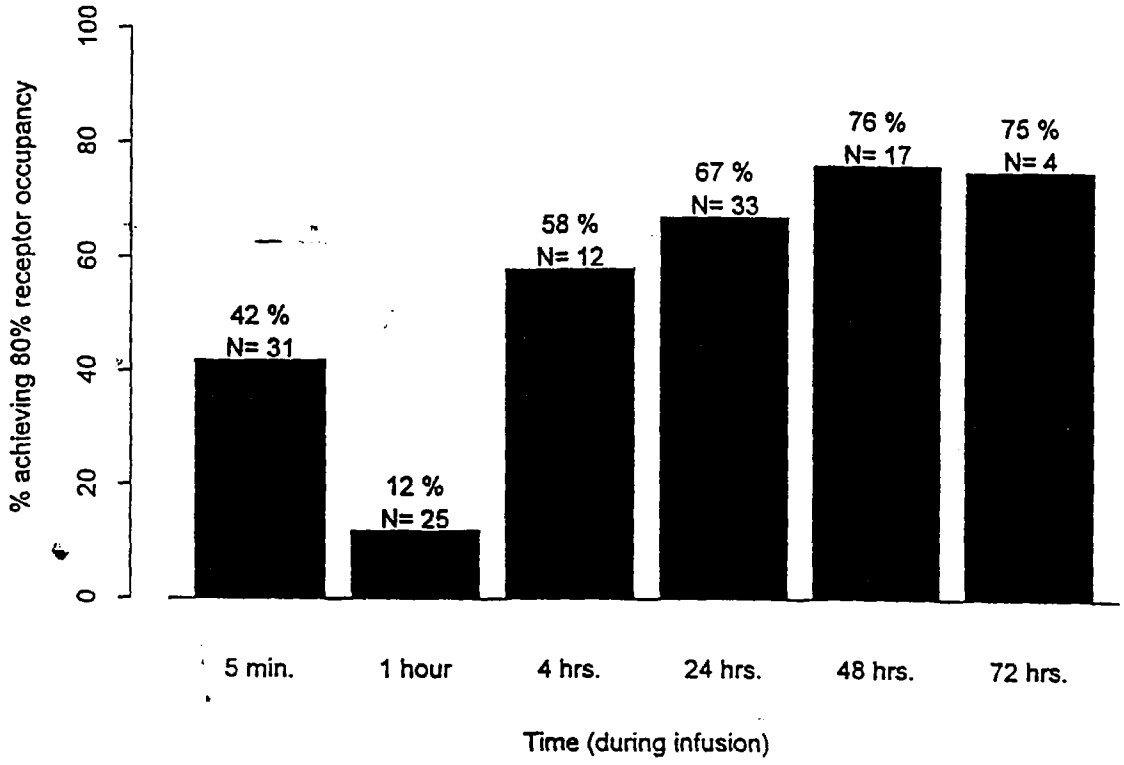
Figure 6. Fraction of Patients with Unstable Angina or NQMI Which Achieved at Least 80% Platelet GP IIb/IIIa Receptor Occupancy (Using PPACK-Collected Blood) After Administration of INTEGRILIN™ 180 µg/kg IV Bolus Immediately Followed by a Continuous 2.0 µg/kg•min IV Infusion (Protocol 94-016A).



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MEDICAL OFFICER REVIEW OF STUDY 96-023 (the PRIDE Study) FROM NDA 20718 (INTEGRILIN)

NDA: 20-718

NAME OF DRUG: Eptifibatide
TRADE NAME: Integrilin
FORMULATION: Injectable
PROPOSED INDICATIONS: Prevention of recurrent coronary events and death
SPONSOR/MONITORS: Cor Therapeutics Inc.

DATE OF SUBMISSION:
DATE RECEIVED BY FDA:
DATE ASSIGNED TO CURRENT REVIEWER: 11.7.97
DATE REVIEW COMPLETED: 1.9.98
DOCUMENTS USED FOR REVIEW: 1) NDA volumes 2.33, 2.34, 2.35, and 2.36.

REVIEWER: Douglas C. Throckmorton M.D.

1.0 Table of Contents

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2.0 Study Title: Protocol Number: 96-023 was a randomized evaluation of the pharmacodynamics and safety of a range of dosing regimens of Eptifibatide (Integrilin) versus placebo in patients undergoing coronary intervention. Also called the PRIDE (the platelet aggregation and receptor occupancy with Integrilin dynamic evaluation) Study.

4.0 Background

The PRIDE study was designed to examine the dose-response relationship of Integrilin to inhibition of *ex vivo* ADP-induced platelet aggregation and to GP IIb/IIIa receptor occupancy in the presence of a non-citrate anticoagulant in patients undergoing PTCA. The sponsor also states that this study was done following concerns about the pharmacodynamic effects of Integrilin noted in study 93-012, done using Integrilin without the concomitant use of a non-citrate anticoagulant. This method may have overestimated the effect of Integrilin on *ex vivo* platelet aggregation.

5.0 Study Design

Methods

The study was a randomized, placebo-controlled, multicenter study conducted in patients with coronary artery disease (CAD) undergoing percutaneous transluminal coronary angioplasty (PTCA). Blinding was maintained only while the subjects were in the catheterization laboratory.

Study Design

Enrolled subjects received a bolus of either Integrilin or placebo followed by a continuous intravenous infusion begun immediately before the start of the PTCA. The infusion continued for 24-72 hours after the completion of PTCA. Subjects also received 81-325 mg aspirin (ASA) 1-12 hours before starting the PTCA, and daily thereafter.

Both ASA (325 mg) and ticlopidine (250 mg BID) for one month were recommended to investigators for subjects who received intracoronary stent placement.

Heparin was also administered according to an algorithm, starting just prior to sheath placement. After the procedure it was recommended that the heparin be discontinued, and the sheaths removed within 4-6 hours. Heparin dose was adjusted with the aim of an activated clotting time (ACT) or 200-250 seconds during the PTCA in groups C and D (see below) and 300-350 in groups A and B. If thrombolytics were used, an intracoronary route of administration was suggested, with an upper dose of 10 mg tPA, 100,000 units of streptokinase, or 250,000 units of urokinase (≤10% of systemic doses).

Table 5.0.1 Treatment groups in the PRIDE study[a].

Dose Group	Patient Enrollment (Target)	Study Drug Bolus (μg/kg)	Study Drug Infusion (μg/kg-min)	Infusion Duration (hours)
A	20	Placebo	Placebo	24-72
B	20	135	0.75	24-72
C	40	180	2.0	24-72
D	40	250	3.0	24-72

a from NDA volume 2.33 page 16.

The protocol was amended twice. The first amendment stopped accrual into group B, the lowest Integrilin dose. The second amendment, dated 4.16.97, proposed a substudy adding a dosing regiment incorporating a second bolus for comparison with the dosing groups C and D. The results of this study are not available, but will be filed as a supplementary report.

5.1 Number of subjects/ randomization

The study was conducted at 14 sites.

127 subjects were enrolled in the four study groups. One subject did not receive study drug following randomization and so was eliminated from the data analysis.

5.2 Inclusion/ Exclusion Criteria

Inclusion Criteria

1. Male or female ≤75 years of age with known coronary artery disease (CAD) scheduled to undergo PTCA.
2. Premenopausal females should have a negative pregnancy test confirmed before enrollment.

5.2 Inclusion/ Exclusion Criteria (cont)

Exclusion Criteria

1. Contraindication to ASA therapy.
2. Current or anticipated use of another GP IIb/IIIa inhibitor.
3. History of clinically significant bleeding within past 30 days.
4. Severe hypertension (systolic BP >200 mmHg or diastolic BP >110 mmHg).
5. Major surgery within 6 weeks of treatment.
6. History of know hemorrhagic stroke at any time, or stroke of unknown etiology within past 2 years.
7. Increased risk of bleeding (PT > 1.2X normal, INR≥2.0, platelet count <100,000, hematocrit <30%).
8. Participation in an experimental protocol within past 30 days.
9. MI within past 48 hours.
10. Renal failure (creatinine ≥2.0 mg/dl or receiving maintenance dialysis).

5.3 Dosage/ Administration

Table 5.3.1 Dosing regimens in the PRIDE study[a].

Dose Group	Study Drug Bolus (μg/kg)	Study Drug Infusion (μg/kg-min)	Infusion Duration (hours)	Heparin Regimen	ASA Regimen
A	Placebo	Placebo	24-72	Standard. Target ACT 300-350 msec	81-325 mg/day
B	135	0.75	24-72	Standard. Target ACT 300-350 msec	81-325 mg/day
C	180	2.0	24-72	Low-dose. Target ACT 200-250 msec	81-325 mg/day
D	250	3.0	24-72	Low-dose. Target ACT 200-250 msec	81-325 mg/day

a. from NDA volume 2.33 page 21.

Other cardiac medications were used as clinically indicated.

5.4 Duration/ Adjustment of Therapy

The following conditions were grounds for discontinuation from study

1. Clinical deterioration requiring emergency or urgent cardiac surgery.
2. Unusual or excess bleeding (defined in Appendix A of the protocol).
3. Ischemic stroke or new significant neural deficit or change in mental status.
4. Development of a platelet count <50,000/mm^3.
5. Patient requirement for or receipt of a prohibited medication.
6. Serious adverse event possibly related to drug administration.
7. Serious adverse event which, in the view of the investigator, made it not in the best interests of the subject to continue.

5.5 Safety and Efficacy Endpoint Measured

Efficacy Assessment

1) Primary study efficacy endpoint

Assessment of the degree of ADP-induced platelet aggregation in blood samples collected using D-phenylalanyl-L-prolyl-L-arginine chloromethyl ketone (PPACK) as an anticoagulant.

2) Secondary study efficacy endpoints

a. Degree of inhibition of ADP-induced platelet aggregation in blood samples collected using sodium citrate anticoagulant.

b. Degree of inhibition of thrombin receptor agonist protein (TRAP)-induced platelet aggregation in blood samples collected using PPACK or sodium citrate anticoagulant.

c. Degree of receptor occupancy of platelets in blood samples collected using PPACK or sodium citrate as anticoagulants.

Clinical efficacy was also assessed using a composite endpoint of death, MI, and urgent/emergent coronary revascularization (CABG or angioplasty). The incidence of this endpoint and each of its components were assessed 24 hrs, 72 hrs, and 30 days after PTCA.

5.5 Safety and Efficacy Endpoint Measured (cont)

Safety Assessment

Safety evaluations included the following: 12-lead ECGs:. laboratory measurements, including the following: hematology; platelet counts; prothrombin times (PT); activated partial thromboplastin time (aPTT); serum chemistries: urinalysis; creatine kinase (CK); and CK MB isoenzymes. The table below shows the timing of testing.

Table Study flow chart for timing of safety assessment during protocol 96-023[c].

	Before enrollment	At enrollment	During Infusion					After Infusion			
			5 min	1 hr	8 hr	16 hr	24 hr	2 hr	4 hr	D/C	30 Day
Physical Exam		X									
Adverse event history										X	X
Electrocardiogram		X							X	X	X
PT	X										
aPTT	X										
ACT[b]		X	X								
CPK & CPK MB		X			X	X	X				
Serum Chemistries	X								X		
Hematology	X								X		X
Platelet Count	X				X	X	X		X		X
Urinalysis	X								X		
Integrilin levels		X	X	X	X		X	X	X		
Platelet aggregation		X	X	X	X		X	X	X		
Platelet receptor occupancy		X	X	X	X		X	X	X		

a. Pre-registration occurs when subject is planned for PTCA.
b. ACT = activated clotting time.
c. Data from NDA volume 2.33, Appendix A.

5.6 Statistical Considerations

No formal sample size calculations were performed for this phase II study. The study protocol specified a total of 120 subjects enrolled in a 1:1:2:2 ratio.

Demographics and baseline characteristics were compared using one-way analysis of variance for continuous variables, and with Cochran-Mantel-Haenszel chi-square or Fischer's exact test, where appropriate, for categorical variables.

For the platelet aggregation studies, differences between anticoagulants were determined using approximate t-tests based on a mixed model of platelet receptor occupancy, expressed as % of total receptors (see NDA volume 2.36, section 2.4.3 for details of the model).

6.0 Study Results

6.1 Patient Demographics & Baseline Characteristics

Details of patient population are in the study summary tables below. A total of 127 subjects (8 males, 16 females), with known CAD scheduled for PTCA, were enrolled, and 120 completed the study. Their ages were 38 to 59, with a median age of 52. There was no significant age difference among the four groups. Overall, the population was fairly typical for subjects undergoing PTCA, with no significant differences between the study groups noted.

Table 6.1 Patient demographics from the PRIDE study[b].

Demographic	Control group n=17	Integrilin 135/0.75 n=22	Integrilin 180/2.0 n=45	Integrilin 250/3.0 n=42	Total population n=126
Gender (#/ %male)	13 (76%)	18 (82%)	36 (80%)	33 (79%)	100 (79%)
Age (mean±sd)	59±16	63±22	59±45	57±42	59±
Race					
White	12 (71%)	18 (82%)	41 (91%)	37 (88%)	108 (86%)
Black	4 (24%)	2 (9%)	1 (2%)	4 (10%)	11 (9%)
Hispanic	1 (6%)	2 (9%)	2 (7%)	1 (2%)	7 (6%)
Height (cm)[a]	173	176	172	172	173
Weight (kg)[a]	80.6	88.0	87.0	90.3	87.4

a. Height & weight expressed as mean of all values.
b. Data from NDA volume 2.33, table 4.4.

6.1 Patient Demographics & Baseline Characteristics (cont)

Table 6.2 Concomitant medical conditions present at baseline in the PRIDE study[a].

Demographic Presence of:	Placebo n=17	Integrilin 135/0.75 n=22	Integrilin 180/2.0 n=45	Integrilin 250/3.0 n=42	Total population n=126
Hypertension	13 (76%)	13 (59%0	25 (56%)	28 (67%)	79 (63%)
Diabetes	6 (35%)	8 (36%0	12 (27%)	8 (19%0	34 (27%)
Hyperlipidemia	9 (53%)	14 (64%)	28 (63%)	24 (57%)	75 (60%)
Family Hx of CAD	7 (41%)	8 (36%)	24 (54%)	19 (45%)	58 (46%)
Cigarette use (former or current)	9 (53%)	11 (50%)	29 (64%)	30 (71%)	79 (63%)
COPD	1 (6%)	3 (14%)	7 (16%)	4 (10%)	15 (12%)
PVD	0 (0%)	1 (4%)	5 (11%)	4 (10%)	10 (8%)
Chronic renal failure	1 (6%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)
Cerebrovascular disease	0 (0%)	0 (0%)	1 (2%)	2 (5%)	2 (2%)
Previous TIA	0 (0%)	0 (0%)	0 (0%)	1 (2%)	1 (1%)
Previous Stroke	0 (0%)	0 (0%)	1 (2%)	1 (2%)	2 (2%)
History of angina	14 (82%)	20 (91%)	32 (73%)	29 (69%)	95 (76%)
History of MI	10 (59%)	13 (59%)	19 (42%)	22 (52%)	64 (51%)
History of CHF	4 (24%)	2 (9%)	3 (7%)	0 (0%)	9 (7%)
History of PTCA	6 (35%)	8 (36%)	18 (40%)	19 (45%)	51 (40%)
History of CABG	2 (12%)	4 (18%)	7 (16%)	4 (10%)	19 (14%)

a. Data from NDA volume 2.33, table 4.4.

Table 6.2 Concomitant medical conditions present at baseline in the PRIDE study (cont).

Baseline Cardiac Function & Coronary Anatomy	Placebo n=17	Integrilin 135/0.75 n=22	Integrilin 180/2.0 n=45	Integrilin 250/3.0 n=42	Total population n=126
LVEF[a] (mean ±sd)	53±15%	56±16	54±13	53±12	54±13
Index Artery[b]	17 (100%)	22 (100%)	45 (100%)	42 (100%)	126 (100%)
LAD	6 (35%)	4 (18%)	17 (38%0	14 (33%)	41 (33%)
LCX	4 (24%)	12 (55%)	11 (24%)	12 (29%)	39 (31%)
RCA	7 (41%)	5 (23%)	16 (36%)	16 (38%)	44 (35%)
Unknown	0 (0%)	1 (4%)	1 (2%)	0 (0%)	2 (2%)

a. LVEF: left ventricular ejection fraction (%).

b. Index artery refers to the coronary artery angioplastied. Greater than 90% of the index arteries were native in all groups (data not shown).

6.2 Disposition of Subjects

Table 6.2.1 Disposition of subjects in the PRIDE study[a].

Category	Placebo	Integrilin 135/7.0	Integrilin 180/2.0	Integrilin 250/3.0	Total
Randomized Subjects	18	22	45	42	127
Did not receive study drug	1	0	0	0	1
Treated subjects	17	22	45	42	126
<22 hours of infusion	2 (12%)	1 (46%)	6 (13%)	2 (5%)	11 (9%)
22 to <26 hours of infusion	14 (82%)	20 (91%)	38 (84%)	38 (91%)	110 (87%)
≥26 hours of infusion	1 (6%)	1 (4%)	1 (2%)	2 (5%)	5 (4%)
Study drug stopped <24 hours[b]	4	1	6	4	15
AE other than bleeding	1 (25%)	0 (0%)	1 (17%)	0 (0%)	2 (13%)
Accidental/IV problems	2 (50%)	0 (0%)	1 (17%)	0 (0%)	3 (20%)
Bleeding	0 (0%)	0 (0%)	0 (0%)	2 (50%)	2 (13%)
D/C'd by nurse on floor early	0 (0%)	0 (0%)	0 (0%)	1 (25%)	1 (7%)
PTCA unsuccessful	0 (0%)	0 (0%)	1 (17%)	0 (0%)	1 (7%)
Subject discharged	1 (25%)	1 (100%)	1 (17%)	1 (25%)	4 (27%)
Subject withdrew consent	0 (0%)	0 (0%)	1 (17%)	0 (0%)	1 (7%)
Ran out of study drug	0 (0%)	0 (0%)	1 (17%)	0 (0%)	1 (7%)
Subjects with 30 day follow-up	14	21	44	40	120

a. Data from NDA volume 2.33, table 4-1.

b. Refers to subjects who were discontinued before 24 hours after infusion and were identified by the investigators as having prematurely withdrawn from the study. Numbers are expressed as % of total subjects prematurely discontinued.

6.2b Protocol Violations & Deviations

Four subjects received bolus and infusion doses for a treatment group other than the treatment group assigned at randomization. All 4 subjects were assigned to the treatment actually received for analysis.

Eight other subjects were 'somewhat discrepant from the dosing regimens dictated by the treatment group to which they were analyzed' according to the sponsor (1 placebo, 7 Integrilin). These subjects were analyzed according to the study group to which they were assigned. An examination of these 'discrepancies' is found in NDA volume 2.33, table 4-2. All of the errors were either small decreases or increases (<10%) in the amount of study drug administered, relative to the dose calculated for the subject's weight.

Other protocol violations are included below. The most prevalent protocol violations reflected errors in the timing of ASA administration, accounting for 21/28 of the protocol violations reported. These occurred in 21/126 subjects (17%).

Table 6.2b.1 Protocol violations in the PRIDE study[a].

Category	Placebo	Integrilin 135/7.0	Integrilin 180/2.0	Integrilin 250/3.0	Total
Chronic renal insufficiency	1	0	0	0	1
ASA >24 hrs before PTCA	0	0	1	2	3
ASA <1 hr before PTCA	4	2	8	3	17
ASA not received before PTCA	0	1	0	0	1
PTCA not done	0	0	1	1	2
Discrepant dosing regimen	1	1	4	2	8
Total	6	3	11	8	28

a. Data from NDA volume 2.33, table 4-3.

6.2c Concomitant Therapies used after Trial Initiation

Heparin, ASA and ticlopidine were administered to subjects as discussed in section 5.0. All subjects received Heparin during the PTCA, which was discontinued after the procedure in all but 4 subjects per protocol. Subjects also received 81-325 mg aspirin (ASA) 1-12 hours before starting the PTCA, and daily thereafter. Both ASA (325 mg) and ticlopidine (250 mg BID) for one month were recommended to investigators for subjects who received intracoronary stent placement. Concomitant medications are summarized below.

Table 6.2c.1 Concomitant therapies used during the PRIDE trial[a].

Medication	24 hrs before infusion	During infusion	24 hrs after infusion	At time of discharge
Abciximab (Reo-Pro)	0 (0%)	0 (0%)	1 (0.8%)	0 (0%)
ACE inhibitors	38 (30.2%)	41 (32.5%)	30 (23.8%)	41 (32.5%)
Antiarrhythmics	2 (1.6%)	5 (4%)	2 (1.6%)	1 (0.8%)
Aspirin	125 (99.2%)	95 (75.4%)	67 (53.2%)	122 (96.8%)
Beta blockers	72 (57.1%)	55 (43.7%)	44 (34.9%)	75 (59.5%)
Calcium-channel blockers	42 (33.3%)	48 (38.1%)	22 (17.5%)	42 (33.3%)
Digoxin	4 (3.2%)	4 (3.2%)	4 (3.2%)	6 (4.8%)
Nitrates	60 (47.6%)	51 (40.5%)	31 (24.6%)	58 (46.0%)
Oral anticoagulants	0 (0%)	1 (0.8%)	1 (0.8%)	4 (3.2%)
Ticlopidine	12 (7.5%)	51 (40.5%)	36 (28.6%)	57 (45.2%)

a. Data from NDA volume 2.33, table 4-10.

6.3 Pharmacokinetics of Integrilin from the PRIDE Trial

Plasma eptifibatide concentrations from 101 of the 127 subjects enrolled in PRIDE who had measurable serum concentrations of eptifibatide. The subjects were also required to have plasma eptifibatide, platelet aggregation, and receptor occupancy data at each of the seven timepoint. The 17 placebo subjects did not have quantifiable eptifibatide levels, and were not included in this analysis.

Table 6.3.1 Subjects included in the pharmacokinetic analysis of PRIDE trial results[a].

Study Drug Infusion (µg/kg-min)	Infusion Duration (hours)	# of subjects included in analysis
135	0.75	20, total of 103 observations
180	2.0	42, total of 216 observations
250	3.0	39, total of 194 observations

a. Data from NDA volume 2.36, section 2.3.1.

6.3 Pharmacokinetics of Integrilin from the PRIDE Trial (cont)

The following table summarizes the pharmacokinetic parameters. The sponsor estimated that there is a linear relationship between the dose of Integrilin and the serum concentrations achieved over the range of doses studied.

Table 6.3.2 Summary of pharmacokinetic parameters of eptifibatide from the PRIDE study[a].

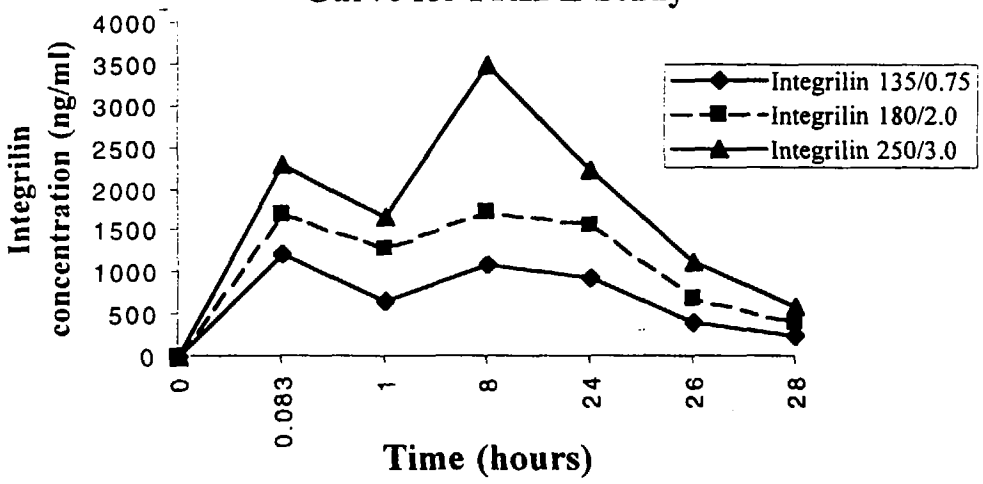
Parameter (mean ±sem)[b]	Eptifibatide 135/0.75	Eptifibatide 180/2.0	Eptifibatide 250/3.0
c_o (ng/ml)	1267±273	1503±133	2513±241
C_{ss} (ng/ml)	724±34	1499±48	2351±82
$t_{1/2}$ (hours)	2.48±0.51	2.81±0.52	2.58±0.44
AUC(I) (ng-hours/ml)	19546±932	38284±1210	59734±2063
CL (ml/min-kg)	1.04±0.049	1.33±0.042	1.27±0.044
V_d (l/kg)	0.201±0.025	0.259±0.027	0.238±0.025

a. Data from NDA volume 2.33, section 5.3.

b. C_o = estimated initial plasma concentration; Css = plasma concentration at steady state; Vdss = steady-state volume of distribution; t1/2 = elimination half-life; CL = total body clearance; AUC(I) = area under plasma concentration-time curve extrapolated to infinity.

The figure below shows the Integrilin concentration over time for the three doses of Integrilin. This is to be compared with the platelet inhibition and receptor occupancy time-curves in the pharmacodynamics section below. Note that the x axis is not to scale, and that only one time point is available between 1 hour and 24 hours (the end of the infusion). Also note that following the end of the infusion, Integrilin concentrations fall quickly (26 and 28 hours), consistent with the $t_{1/2}$ of approximately 2.5 hours.

Figure 6.3.3 Dose-Time-Concentration Curve for PRIDE Study



6.4 Pharmacodynamics of Integrilin from the PRIDE Trial

For purposes of reference, the dose used in the pivotal PURSUIT trial of Integrilin was 180 µg/kg bolus followed by 2.0 µg/kg infusion (the intermediate dose studied in the PRIDE Trial).

6.4.1 Platelet aggregation

The effect of Integrilin on ADP-induced and TRAP-induced platelet aggregation was studied on ex vivo platelets from test subjects. The results are summarized in the tables below. In general, there was an immediate inhibition of platelet aggregation after the bolus and start of infusion, followed by a small return towards baseline at one hour. There was a sustained inhibition of platelet aggregation detected between 8 and 24 hours. No information on the time-course of the effect of Integrilin on platelet aggregation between 1 and 8 hours is available. This effect to inhibit platelet aggregation was rapidly lost after discontinuation of the infusion, declining towards baseline within 4 hours after termination. This pattern was similar regardless of the method of harvesting the platelets (PPACK or citrate buffer) or of the aggregation stimulant (ADP or TRAP) used.

6.4.1 Platelet aggregation (cont)

Table 6.4.1.1 Mean ADP-induced platelet aggregation using PPACK-collected platelets in the PRIDE study[a]. Data is expressed as the % of baseline determination.

Time after start of infusion	Integrilin 135/7.0	Integrilin 180/2.0	Integrilin 250/3.0	Placebo
Baseline	100	100	100	100
5 minutes	21	10	3	103
1 hour	38	20	7	98
8 hours	30	11	3	98
24 hours	27	11	4	101
2 hours post-infusion	55	40	18	80
4 hours post-infusion	70	48	38	77

a. Data for these tables comes from NDA volume 2.36, tables 2-10.

Table 6.4.1.2 Mean ADP-induced platelet aggregation using citrate-collected platelets in the PRIDE study[a]. Data is expressed as the % of baseline determination.

Time after start of infusion	Integrilin 135/7.0	Integrilin 180/2.0	Integrilin 250/3.0	Placebo
Baseline	100	100	100	100
5 minutes	10	5	1	102
1 hour	16	5	2	97
8 hours	12	3	3	92
24 hours	14	3	4	79
2 hours post-infusion	45	23	9	83
4 hours post-infusion	62	43	22	82

a. Data for these tables comes from NDA volume 2.36, tables 2-10.

Table 6.4.1.3 Mean TRAP-induced platelet aggregation using PPACK-collected platelets in the PRIDE study[a]. Data is expressed as the % of baseline determination.

Time after start of infusion	Integrilin 135/7.0	Integrilin 180/2.0	Integrilin 250/3.0	Placebo
Baseline	100	100	100	100
5 minutes	49	34	24	93
1 hour	60	47	30	100
8 hours	52	36	22	90
24 hours	55	38	25	101
2 hours post-infusion	77	65	45	88
4 hours post-infusion	81	82	62	75

a. Data for these tables comes from NDA volume 2.36, tables 2-10.

Table 6.4.1.4 Mean TRAP-induced platelet aggregation using citrate-collected platelets in the PRIDE study[a]. Data is expressed as the % of baseline determination.

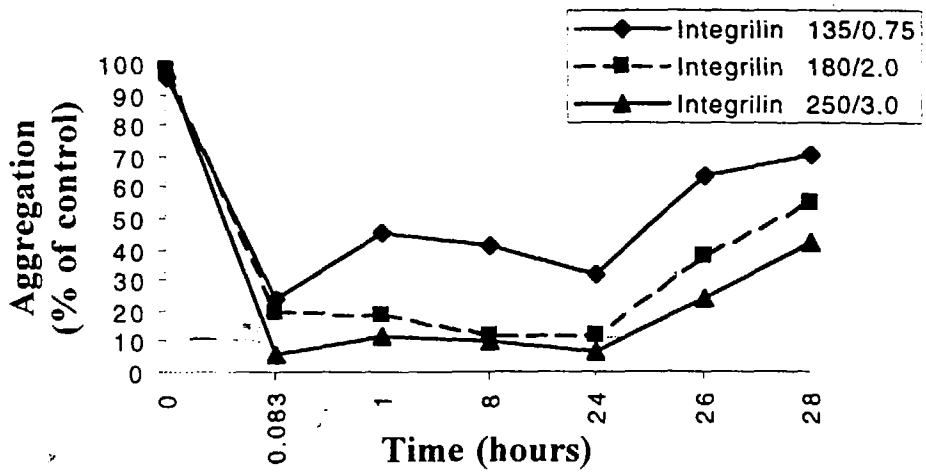
Time after start of infusion	Integrilin 135/7.0	Integrilin 180/2.0	Integrilin 250/3.0	Placebo
Baseline	100	100	100	100
5 minutes	26	24	20	108
1 hour	34	26	22	104
8 hours	27	25	22	101
24 hours	29	24	25	92
2 hours post-infusion	62	44	29	93
4 hours post-infusion	70	64	48	85

a. Data for these tables comes from NDA volume 2.36, tables 2-10.

6.4.1 Platelet aggregation (cont)

When the same data is looked at in graphic form (shown for ADP-induced aggregation using PPACK-buffered platelets), there is a small decline in the platelet aggregability shortly after the end of the bolus. This corresponds to the small decrease in serum Integrilin levels seen after 1 hour (see figure 6.3.3).

Figure 6.4.4 ADP-induced Platelet Aggregation in PRIDE Study



The sponsor aimed to achieve 80% inhibition of platelet aggregation *ex vivo*. Regardless of the aggregation stimulus or buffer used, less than 50% of the subjects who received the lowest dose of Integrilin achieved this level of inhibition. The table below summarizes the % of subjects who achieved at least 80% inhibition of platelet aggregation at 8 and 24 hours, from the two higher doses of Integrilin. Note that, regardless of the buffer system used, the two highest doses of Integrilin caused ≥80% inhibition in >75% of subjects for the ADP-induced platelet aggregation. In contrast, no dose of Integrilin studied induced >50% inhibition of TRAP-induced platelet aggregation, regardless of the buffer.

Table 6.4.1.5 Fraction of subjects who achieved ≥80% inhibition of platelet aggregation at the specified times from the PRIDE trial[a].

Conditions and Integrilin dose	1 hour	8 hours	24 hours
Integrilin 180/2.0 group			
ADP-induced in PPACK buffer	19/37 (51%)	30/36 (83%)	25/33 (76%)
ADP-induced in citrate buffer	35/36 (97%)	33/33 (100%)	31/31 (100%)
TRAP-induced in PPACK buffer	3/36 (8%)	5/34 (15%)	4/31 (13%)
TRAP-induced in citrate buffer	7/37 (19%)	9/34 (26%)	12/31 (39%)
Integrilin250/3.0 group			
ADP-induced in PPACK buffer	31/35 (89%)	34/34 (100%)	33/34 (97%)
ADP-induced in citrate buffer	32/32 (100%)	28/29 (97%)	29/30 (97%)
TRAP-induced in PPACK buffer	8/33 (24%)	16/33 (48%)	13/32 (41%)
TRAP-induced in citrate buffer	13/31 (42%)	9/28 (32%)	11/29 (38%)

a. Data from NDA volume 2.36, tables 6-10.

Using the concentration data and the data on the inhibition of platelet aggregation, the sponsor estimated that there was a strong relationship between plasma concentration and platelet aggregation: the IC_{50}= 811ng/ml for ADP-induced aggregation in PPACK; and IC_{50} = 504 ng/ml for ADP-induced aggregation in citrate.

There was also a strong correlation between Integrilin concentration an receptor occupancy (see NDA volume 2.36, Figure 25 and 26). For PPACK-collected platelets, the concentration of Integrilin necessary for 50% and 80% receptor occupancy (ROC_{50} and ROC_{80}) were 375 and 1723 ng/ml respectively. For citrate-buffered platelets, the concentrations necessary were 127 and 539 ng/ml respectively. These values are approximately 1/3 of the Integrilin serum concentration achieved at the doses used in the PRIDE trial (see figure 6.3.3 and table 6.3.2 above).

6.4.2 Platelet GP IIb/IIIa receptor occupancy

The sponsor also examined the fraction of IIb/IIIa receptors occupied by Integrilin in selected subjects receiving each of the three doses of Integrilin for platelets collected in PPACK and citrate-buffers. Receptor occupancy was consistently higher for the 250/3.0 dose of Integrilin than for the 180/2.0 and 135/7.0 doses. There also appeared to be a small decline in receptor occupancy at the end of one hour at under several of the doses and conditions studied.

Table 6.4.2.1 Mean GP IIb/IIIa receptor occupancy using PPACK-collected platelets in the PRIDE study[a]. Data is expressed as the % of baseline determination.

Time after start of infusion	Integrilin 135/7.0	Integrilin 180/2.0	Integrilin 250/3.0	Placebo
Baseline	0	0	0	0
5 minutes	76	81	85	0
1 hour	64	71	81	0
8 hours	67	74	85	0
24 hours	60	75	84	0
2 hours post-infusion	46	57	65	0
4 hours post-infusion	31	47	59	0

a. Data for these tables comes from NDA volume 2.36, tables 2-10.

Table 6.4.2.2 Mean GP IIb/IIIa receptor occupancy using citrate-collected platelets in the PRIDE study[a]. Data is expressed as the % of baseline determination.

Time after start of infusion	Integrilin 135/7.0	Integrilin 180/2.0	Integrilin 250/3.0	Placebo
Baseline	0	0	0	0
5 minutes	89	94	96	4
1 hour	85	89	90	8
8 hours	78	89	93	10
24 hours	80	87	94	4
2 hours post-infusion	69	76	86	8
4 hours post-infusion	56	66	83	8

a. Data for these tables comes from NDA volume 2.36, tables 2-10.

7.0 Safety Analyses of the PRIDE Trial Results

7.0.1 Clinical endpoints

While the PRIDE trial was not designed to assess the influence of Integrilin on clinical outcomes, these events were recorded during the trial. The table below summarizes these events. Statistical comparisons would not be meaningful given the small number of events.

Table 7.0.1.1 Clinical endpoints from the PRIDE trial at 24 hours and 30 days.

Endpoint	Placebo n=17	Integrilin 135/0.75 n=22	Integrilin 180/2.0 n=45	Integrilin 250/3.0 n=42	Integrilin Total n=109
Through 24 hours post-infusion					
Death	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Definite/Possible MI	1 (6%)	0 (0.0%)	1 (2.2%)	0 (0.0%)	1 (0.9%)
Definite/Possible Ischemia	3 (18%)	0 (0.0%)	5 (11.1%)	1 (2.4%)	6 (6%)
CABG					
Urgent or Elective	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Repeat PTCA	1 (5.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hemorrhagic Stroke	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Through 30 days post-infusion					
Death	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Definite/Possible MI	1 (6%)	0 (0.0%)	1 (2.2%)	0 (0.0%)	1 (0.9%)
Definite/Possible Ischemia	3 (18%)	0 (0.0%)	6 (14%)	1 (2.4%)	7 (6.4%)
CABG					
Urgent or Elective	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Repeat PTCA/atherectomy	2 (12%0	0 (0%)	1 (2.2%)	2 (5.1%)	3 (2.8%)
Hemorrhagic Stroke	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

7.0.2 Subject Deaths

There were no subject deaths during the trial.

7.0.3 Serious Adverse Events

Serious Bleeding Adverse Events

Events were called serious if they were identified as such by the investigator, resulted in prolonged hospitalization, were serious as judged by TIMI scale, or if they required transfusion.

Table 7.0.3.1 Serious bleeding events in the PRIDE trial[a].

Treatment Group	Patient Number	Gender, Age	Clinical Event, Notes
Placebo	104015	Male, 73	Major bleed (groin), pressure applied No transfusion
Placebo	8014	Female, 59	Drop in Hct without identified source Transfused
Integrilin 180/2.0	6015	Female, 58	Drop in Hct without identified source Transfused
Integrilin 180/2.0	103001	Male, 49	Decrease in Hct of 13.6 without identified source No transfusion
Integrilin 180/2.0	104002	Male, 61	Serious GI bleed per investigator Decrease in Hct 10.4 No transfusion
Integrilin 250/3.0	6012	Male, 61	Change in Hct 5.9 Transfused

a. Data from NDA volume 2.33, table 7-7, and volume 2.35, listings 22 and 23.

Serious Non-bleeding Adverse Events

Events were called serious if they were identified as such by the investigator, resulted in prolonged hospitalization. No obvious difference in either the rate or the type of serious adverse events between the placebo and Integrilin subjects was evident in this small subject population.

Table 7.0.3.1 Serious bleeding events in the PRIDE trial[a].

Treatment Group	Patient Number	Gender, Age	Clinical Event, Notes
Placebo	4001	Male, 60	Chest Pain, SAE per investigator
Placebo	8014	Female, 59	Abrupt closure, SAE per investigator
Placebo	104005	Male, 57	Pulmonary edema, SAE per investigator
Placebo	104021	Male, 73	Chest pain, SAE per investigator
Integrilin 135/0.75	104013	Male, 68	Chest pain, SAE per investigator
Integrilin 135/0.75	104022	Male, 75	Chest pain, SAE per investigator
Integrilin 180/2.0	12010	Male, 58	Hypotension, bradycardia, SAE per investigator
Integrilin 180/2.0	104004	Male, 48	Chest pain, SAE per investigator
Integrilin 180/2.0	104007	Male, 45	Chest pain, SAE per investigator
Integrilin 180/2.0	104020	Male, 56	Chest pain, SAE per investigator
Integrilin 250/3.0	6012	Male, 61	Aortic and right iliac aneurysm repair requiring hospitalization
Integrilin 250/3.0	104018	Male, 48	Chest pain, SAE per investigator

a. Data from NDA volume 2.33, table 7-8, and volume 2.35, listings 22 and 23.

7.0.4 Discontinuations Due to Adverse Events

Four subjects discontinued due to adverse events in the PRIDE Trial: one in the placebo group and three receiving eptifibatide.

Table 7.0.4.1 Subjects discontinued from the PRIDE trial due to adverse events[a].

Treatment Group	Patient Number	Event	Time from start of study drug to event (hrs)	Duration of study drug infusion (hrs)
Placebo	8014	Abrupt closure	4.9	3.2
Integrilin 180/2.0	12010	Hypotension/ bradycardia	2.33	3.5
Integrilin 250/3.0	1014	Spontaneous hemetemisis & gross hematuria	6.75	20.3
Integrilin 250/3.0	6004	Spontaneous hemetemisis	6.13	6.4

a. Data from NDA volume 2.33, table 7-6, and volume 2.35, listings 3, 22 and 26.

Patient narratives for discontinued subjects

1. Placebo: subject 8014 , a 59 year-old black female was hospitalize with angina. Study drug was halted after 3.2 hours due to abrupt closure of an LAD lesion 45 minutes after end of angioplasty. Subject was treated successfully with Reo-pro and the vessel was reopened.

2. Integrilin 180/2.0: subject 12010, a 38 year old white male was hospitalized with angina. The baseline BP was 132/68. After a 'mild' bleeding episode at the groin site, the subject developed hypotension and bradycardia (he was taking a beta-blocker), and had a cardiac ischemic episode. Subject was given atropine, demerol, and benadryl (!), and the bradycardia resolved immediately after discontinuation of the study medication. The hypotension resolved 50 minutes after stopping the study medication.

3. Integrilin 250/3.0: subject 1014, a 60 year old white male, was hospitalized with a history of prior PTCA and CABG. After starting the study drug and receiving heparin (ACT 295-316 secs), he developed spontaneous hematemesis 6.5 hours after starting the study drug, and gross hematuria 15 minutes later. After stopping the study drug, his hematocrit fell from 45% to 39% before returning to baseline levels without transfusion at the 30 day follow-up (47%).

4. Integrilin 250/3.0: subject 6004, a 59 year old white female, hospitalized for angina. After starting the study drug and receiving heparin (ACT 214 secs), she had two episodes of hematemisis approximately 6 hours later. Study drug was discontinued and subject recovered without transfusion.

7.0.5 Adverse Events in the PRIDE study

7.0.5.1 Bleeding Adverse Events

TIMI Scale Bleeding

The table below summarizes the bleeding AEs in the PRIDE trial according to the TIMI scale. No intracranial bleeding was reported. There was an increase in both minor and insignificant bleeding in the Integrilin groups, especially the highest Integrilin dose group.

Table 7.0.5.1.1 TIMI scale bleeding during hospitalization in the PRIDE trial[a].

Bleeding Classification	Placebo n=17	Integrilin 135/0.75 n=22	Integrilin 180/2.0 n=45	Integrilin 250/3.0 n=42	Total n=126
Major	1 (6%)	0 (0%)	1 (2%)	0 (0%)	2 (2%)
Minor	0 (0%)	0 (0%)	1 (2%)	4 (9.5%)	5 (4%)
Insignificant	3 (18%)	6 (27%)	13 (29%)	9 (21%)	31 (25%)
None	12 (70%)	15 (68%)	25 (56%)	27 (64%)	79 (63%)
No data	1 (6%)	1 (4%)	5 (11%)	2 (5%)	9 (7%)

a. Data from NDA volume 2.33, table 7-1.

Both subjects who were classified as having a major bleeding AE were due to changes in hematocrit, with no identified bleeding source.

1. Placebo subject 104015 had his hematocrit change from 50% to 43.5% 4 hours after the end of the infusion and 34.4% after 12 days. No transfusion was given.

2. Integrilin 180/2.0 subject 103001 had his hemoglobin decrease from 15.3 g/dl to 10.2 g/dl 6 hours after termination of the study drug infusion. No transfusion was given, and 30 day follow-up hemoglobin was 15.3.

7.0.5.1 Bleeding Adverse Events (cont)

Bleeding Sites (per investigator)

The investigators were asked to identify any bleeding site. No severe bleeding was identified from any site, and the femoral artery access site accounted for >75% of the reported bleeding sites. There was an increased incidence of groin bleeding, gross hematuria, hematemesis, oral bleeding, hemoptysis, and epistaxis identified in the Integrilin groups, relative to placebo, especially the highest dose group (250/3.0).

Table 7.0.5.1.2 Bleeding sites identified by the PRIDE study investigators[a].

Bleeding Classification	Placebo n=17	Integrilin 135/0.75 n=22	Integrilin 180/2.0 n=45	Integrilin 250/3.0 n=42	Total n=126
Groin	3 (18%)	4 (18%)	13 (29%)	10 (24%)	30 (24%)
Gross hematuria	0 (0%)	0 (0%)	0 (0%)	2 (5%)	2 (2%)
Hematemesis	0 (0%)	0 (0%)	1 (2%)	2 (5%)	2 (2%)
Gastrointestinal	0 (0%)	0 (0%)	0 (0%)	1 (2%)	1 (3%)
Oral	0 (0%)	0 (0%)	0 (0%)	2 (14%)	2 (2%)
Hct drop only	0 (0%)	1 (4%)	1 (7%)	0 (0%)	2 (2%)
Hemoptysis	0 (0%)	0 (0%)	0 (0%)	1 (2%)	1 (1%)
Epistaxis	0 (0%)	0 (0%)	0 (0%)	1 (2%)	1 (1%)

a. Data from NDA volume 2.33, table 7-2, expressed as % of total subjects with available data.

Transfusions

Three subjects received transfusions: one placebo subject (8014); one in the Integrilin 180/2.0 group (6015) and one in the Integrilin 250/3.0 group (6012).

7.0.5.2 Non-bleeding Adverse Events

Overall results for nonbleeding AEs are summarized below.

Table 7.0.5.2.1 Non-bleeding AEs in the PRIDE study[a].

Bleeding Classification	Placebo n=17	Integrilin 135/0.75 n=22	Integrilin 180/2.0 n=45	Integrilin 250/3.0 n=42	Total n=126
Number of subjects with at least one AE	12 (71%)	10 (45%)	26 (58%)	23 (55%)	71 (56%)
Number of AEs	21	13	52	39	124

a. Data from NDA volume 2.33, table 7-4. 8 of the events had an onset prior to start of study drug, and 18 occurred >24 hours after stop of infusion. A total of 108 occurred through 24 hours post-infusion and started after study drug.

The most common AEs are shown in the table below.

Table 7.0.5.2.2 Non-bleeding AEs reported by ≥5% of subjects in the PRIDE study[a].

Bleeding Classification	Placebo n=17	Integrilin 135/0.75 n=22	Integrilin 180/2.0 n=45	Integrilin 250/3.0 n=42	Integrilin Total n=109
Overall body system					
Back Pain	3 (18%)	3 (14%)	10 (22%)	9 (19%)	21 (19%)
Headache	1 (6%)	0 (0%)	1 (2%)	4 (10%)	5 (5%)
Injection site reaction	1 (6%)	0 (0%)	1 (2%)	5 (12%)	6 (6%)
Injection site pain	1 (6%)	1 (5%)	2 (4%)	2 (5%)	5 (5%)
Cardiovascular system					
Chest pain/ angina	5 (29%)	4 (18%)	12 (27%)	5 (12%)	21 (19%)
Digestive system					
Nausea/vomiting	1 (6%)	1 (5%)	7 (16%)	2 (5%)	10 (9%)

a. Data from NDA volume 2.33, table 7-5, and volume 2.35, listing 26.

Review of the individual AEs in volume 2.35, listing 26, revealed no rare or unusual AEs which could be linked to study drug administration.

7.0.5.3 Laboratory Adverse Events

The first table summarizes the changes in mean hematology values from baseline to 4 hours post-infusion. For most lab values, fewer than 10 subjects had pre- and post-infusion labs available, limiting the interpretation of these data.

Table 7.0.5.3.1 Mean change in hematology values from the PRIDE trial[a].

Laboratory measure	Placebo	Integrilin 135/0.75	Integrilin 180/2.0	Integrilin 250/3.0	Total
Hemoglobin (g/dl)	-0.7±1.2	-0.4±0.8	-0.9±0.9	-0.8±1.2	-0.8±1.0
WBC count (x10^9/l)	2.4±3.4	1.3±2.1	1.1±2.6	0.9±2.0	1.2±2.4
Platelet count (x10^9/l)	1.9±20	-9.6±23	-1.9±30	-4.9±36	-3.9±30

a. Data from NDA volume 2.33, section 7.6, and volume 2.35, listing 28-33. Data shown is the change in mean hematology values from baseline to 4 hours post-infusion for the subjects with available data.

No subject had a post-infusion platelet count of <100,000 or a WBC count of <1000.

Very few subjects had coagulation parameters collected post-infusion (<5 for all dose-groups), making any interpretation of these data difficult. In general, the median pre-infusion aPTT was 29.3 seconds. The lowest median aPTT in the Integrilin group was 27.5 in the Integrilin 135/0.75 group and the highest was 32.6 seconds in the 250/3.0 group.

The next table summarizes the changes in mean serum chemistries that occurred. For most lab values, between 10 and 30 subjects had pre- and post-infusion labs available (see NDA volume 2.33, table 7-12).

Table 7.0.5.3.2 Mean change in clinical chemistry values from the PRIDE trial[a].

Laboratory measure	Placebo	Integrilin 135/0.75	Integrilin 180/2.0	Integrilin 250/3.0	Total
SGOT (U/l)	-1.2±8.5	6.0±13	3.1±17	5.7±15	4.1±15
SGPT (U/l)	1.0±5	3.1±13	-1.4±8	-0.8±16	-0.1±12
Creatinine (mg/dl)	0.1±0.2	0.1±0.2	0.0±0.2	0.1±0.1	0.1±0.2

a. Data from NDA volume 2.33, section 7.6, and volume 2.35, listing 28-33. Data shown is the change in mean values from baseline to 4 hours post-infusion for the subjects with available data.

Examination of the individual subject lab values showed the following incidence of abnormally elevated LFTs (SGOT or SGPT).

Table 7.0.5.3.3 Individuals with abnormal post-study drug SGOT/SGPT who had normal baseline values[a].

Laboratory measure	Placebo	Integrilin 135/0.75	Integrilin 180/2.0	Integrilin 250/3.0	Integrilin Total
Elevated SGOT or SGPT	0/9 (0%)	2/13 (15.3%)	3/28 (10.7%)	1/22 (4.5%)	6/63 (9.5%)

a. Data from NDA volume 2.35, listing 31. Individuals who had an abnormal labs at baseline which worsened during therapy are not included.

A listing of these subjects and their LFTs at baseline and follow-up are listed below. No bilirubins were reported, and no follow-up lab SGOT/SGPT values are available.

Table 7.0.5.3.3 Abnormal SGOT and SGPT levels in the PRIDE study[a].

Treatment group/Patient #	Baseline/Peak SGOT (U/l)	Baseline/Peak SGPT (U/l)
Placebo		
No subjects		
Integrilin 130/7.5		
6019	**29/58 (h)**	**39/64 (h)**
6016	**31/50 (h)**	**35/53 (h)**
Integrilin 180/2.0		
6021	**16/55 (h)**	**11/35 (nl)**
104001	**22/76 (h)**	**32/33 (nl)**
104002	**16/58 (h)**	**15/20 (nl)**
Integrilin 250/3.0		
6022	**25/66 (h)**	**25/30 (nl)**

a. Data from NDA volume 2.33, table 7-14.

7.0.5.3 Laboratory Adverse Events (cont)

Mean creatine kinase (CK) levels rose in all of the treatment groups except the Integrilin 135/0.75 group. Six subjects had abnormal elevations in their CKs during the study, and are summarized below.

Table 7.0.5.3.3 Abnormal CK levels in the PRIDE study[a].

Treatment group/Patient #	Baseline/Peak CK (U/l)	Peak CK-MB (ng/ml)	Clinical Outcome
Placebo			
104008	58/838	13 (high)	None
Integrilin 180/2.0			
11003	167/278	17 (high)	None
104001	37/493	15.1 (high)	Abrupt closure of LAD, Dissection . Stent placement
104002	550/74 (entered with abnormal CK)	9.0 (high)	MI, IV NTG, heparin
Integrilin 250/3.0			
6012	308/8935	22.0 (high)	Abdominal aortic and iliac aneurysm repair
6022	78/2910	18.0 (normal)	CK attributed to pressure on groin by investigator

a. Data from NDA volume 2.33, table 7-14.

Urinalyses were also examined in the PRIDE trial, and the results are summarized below. First, the number of subjects who developed occult blood in their urine following study drug was examined. Note that the number of subjects with available data is very small. There was a trend towards the development of microscopic hematuria in all three Integrilin dose groups. This was supported by the examination of the sediment microscopically. An increase in the number of RBCs in the urine was seen in 4 subjects, all of whom received Integrilin.

Table 7.0.5.3.4 Development of dipstick-positive hematuria in the PRIDE trial[a].

Occult blood[b]	Placebo n=3	Integrilin 135/0.75 n=9	Integrilin 180/2.0 n=12	Integrilin 250/3.0 n=17	Total n=41
Change from baseline to 4 hours after infusion					
N-P	0 (0%)	2 (22%)	1 (8%)	2 (12%)	5 (12%)
N-N	3 (100%)	6 (67%)	8 (67%)	14 (82%)	31 (76%)
P-P	0 (0%)	0 (0%)	3 (25%)	1 (6%)	4 (10%)
P-N	0 (0%)	1 (11%)	0 (0%)	0 (0%)	1 (2%)

a. Data from NDA volume 2.33, section 7.6, and volume 2.35, listing 28-33. Data shown is the change in mean values from baseline to 4 hours post-infusion for the subjects with available data.

b. Shown is the pre- and post-infusion results. N=negative, P= positive.

One Integrilin-treated and one placebo subject had negative urine protein at baseline and were positive for protein at the 4 hour post-infusion time-point.

8.0 PRIDE Trial Efficacy Summary

Pharmacokinetics

1. Integrilin plasma concentrations appear dose-proportional over the range of doses studied.

2. Integrilin elimination $t_{1/2}$ was approximately 2.6 hours, with a total body clearance of 1.2 ml/min-kg and a volume of distribution of 0.22 l/kg in the study population.

Pharmacodynamics

1. Integrilin binds reversibly to the GP IIb/IIIa receptor on human platelets in a dose- and concentration dependent fashion. The dose of Integrilin necessary to achieve 80% occupancy of the GP IIb/IIIa receptor on human platelets was 1723 ng/ml for PPACK-buffered, and 539 ng/ml for citrate-buffered platelets. These serum concentrations are achieved using the Integrilin doses studied in this trial.

2. Integrilin causes dose- and concentration-dependent inhibition of human platelet aggregation *ex vivo*. The dose of Integrilin necessary to cause an 80% reduction of platelet aggregation (IC_{80}) *ex vivo* is dependent on the agonist and buffer system used. For ADP-induced platelet aggregation, the IC_{80} is 811 ng/ml for PPACK-buffered and 504 ng/ml for citrate-buffered platelets. This was the primary analysis proposed by the sponsor. For TRAP-induced platelet aggregation, the IC_{80} values are approximately 3 time higher, and are not reproducibly achieved using the Integrilin doses studied in this trial.

3. The times of maximal Integrilin concentration correlates with the maximal inhibition of platelet aggregation, and are achieved immediately after the bolus and at steady state (8 hours after start of infusion). Inhibition of platelet aggregation at one time point intermediate between bolus and steady state (1 hour) demonstrated a lower degree of inhibition of platelet aggregation.

4. Rapid reversal of inhibition of platelet aggregation and receptor occupancy occur rapidly after discontinuation of Integrilin infusion, with values returning towards baseline by 4 hours. These findings are consistent with the pharmacokinetics of Integrilin.

9.0 PRIDE Trial Safety Summary

1. Few clinical events (MI, death, urgent revascularization, stroke, recurrent ischemia) occurred in the 30 day follow-up of the PRIDE trial, precluding any meaningful statistical analysis of the effect of Integrilin on these event rate. There was a lower incidence rate for definite/possible cardiac ischemia in the combined Integrilin group (6.4%) than in the placebo (18%) at 30 days (see table 7.0.1.1). No other differences in the incidence rates of the clinical events listed were noted.

2. No subjects died during the PRIDE trial or during the 30 day follow-up of the subjects with available data.

3. Subjects receiving Integrilin did not have a higher rate of serious adverse events, and no unusual or rare adverse events were associated with Integrilin use.

4. Subjects receiving Integrilin did have a higher incidence of minor bleeding and discontinuation due to bleeding, particularly in the 250/3.0 dose group.

5. No intracranial bleeding was reported in any subject in the PRIDE trial.

6. Subjects receiving Integrilin did not have a higher rate of non-bleeding adverse events relative to the placebo group. No rare or unusual adverse events associated with Integrilin administration were identified.

7. No hematological abnormalities were associated with Integrilin administration. No thrombocytopenia or neutropenia was reported.

8. The database is inadequate to assess the effect of Integrilin on the coagulation parameters due to the small number of subjects with data.

9. There was a higher incidence of the development of abnormally elevated SGOT/SGPT in the Integrilin group when compared with placebo. No chronic or severe liver damage was reported. No bilirubin values were submitted in the database.

10. There was a higher incidence of microscopic hematuria in the Integrilin group when compared with placebo.

10.0 PRIDE Trial Reviewer's Conclusions

Integrilin has a dose- and time-dependent effect on platelet aggregation measured *ex vivo*, and occupies the GP IIb/IIIa receptor. Depending on the assay used to measure platelet aggregation, these effects of Integrilin take place at serum concentrations that are likely to be achieved using the proposed dose of Integrilin in a large fraction of subjects.

No serious safety issues were identified. There was an increase in minor bleeding in the Integrilin group, especially at the highest dose used (250/3.0). In the PURSUIT trial, the intermediate dose was used (180/2.0). There was also an association between Integrilin administration and an asymptomatic rise in SGOT and SGPT (especially SGOT). These safety issues have been forwarded to the primary Medical Reviewer for consideration.

Douglas C. Throckmorton, M.D.

cc:
ORIG: NDA 20-718
HFD-110 Division File
HFD-110/CSO Zelda McDonald
HFD-110/Medical Officer Douglas Throckmorton
HFD-110/Team Leader Charles Ganely

APPEARS THIS WAY
ON ORIGINAL

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
MEDICAL OFFICER'S REVIEW

NDA No.:	20-718
Sponsor:	COR Therapeutics, Inc. JAN 26 1997
Drug:	Integrilin™ (Intrifiban)
Class:	Antithrombotic Agent; Platelet GP IIA./IIIb inhibitor
Indications:	Adjunct Antithrombotic Therapy in PTCA
Date of NDA Submission:	4-1-1996
Date of Filing:	5-15-1996
Safety Update (4 month)	8- 2-1996
Amendment: Clinical/Statistical:	10-15-1996
Amendment: Clinical/:Statistical:	11-21-1996
Advisory Committee Briefing Document:	11-21-1996
Medical Reviewer:	Lilia Talarico, M.D.
Review Date:	12-13-1996

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BACKGROUND INFORMATION

Percutaneous transluminal coronary angioplasty (PTCA) is performed in more than 300.000 patients in the United States each year to restore coronary patency. Several methods of PTCA are currently used, including balloon angioplasty, atherectomy excimer laser, and rotational ablation angioplasty. Regardless of the method used, between 2 and 10% of patients will experience acute occlusion of the treated coronary artery during or within hours or days after the procedure. This major complication of PTCA, referred to as abrupt closure, leads to myocardial ischemia and can eventually cause death, MI, or the need for urgent repeat interventional revascularization, i.e. repeat PTCA, stent placement, or CABG surgery. The etiology of abrupt closure in individual cases remains unclear but complex plaque morphology and thrombus formation are two major factors.
All methods of angioplasty disrupt the vascular intima and expose thrombogenic surfaces onto which platelet activation/aggregation and thrombus formation occur. This results in a spectrum of thrombotic events ranging from asymptomatic platelet micro thrombi to abrupt closure of the dilated coronary by the thrombus or by the thrombotic extension of minor vessel dissection. In addition to abrupt closure, other pathological clinical events may occur in association with PTCA as a result of the thrombotic processes, including the sequelae of both peripheral and intra coronary emboli which are often associated with large catheters, prolonged procedures, or advanced patient age.

Clinical studies have demonstrated the efficacy of aspirin in the prevention of abrupt vessel closure. No randomized trials have been done with heparin, but observational studies indicate that the risk of abrupt closure is reduced when the activated clotting time (ACT) is over 300 seconds or the activated partial thromboplastin time (aPTT) is greater than three times control.
However, angioplasty performed with aspirin and heparin therapy still has a 2-10% incidence of abrupt closure of the treated vessel. In the 1985-1986 National Heart, Lung and Blood Institute PTCA Registry of 1,801 patients undergoing PTCA, the incidence of abrupt closure was 7%. The increasing complexity of lesions approached with percutaneous interventions has resulted in little change in the rate of abrupt vessel closure.
PTCA performed for acute, evolving MI, recent MI, and UA carry a still higher risk of post-procedural abrupt closure because these conditions are associated with both disrupted plaque architecture and ongoing thrombosis.
Efforts to reduce the risk of abrupt closure after coronary angioplasty have focused on pharmacologic manipulation of the coagulation system with new and more effective antiplatelet and antithrombin agents and on mechanical intervention with employment of intra coronary stents to prospectively improve revascularization or to bail-out the vessel once abrupt closure has occurred.

The final step in the process of platelet aggregation is the activation of the membrane receptor GPIIb/IIIa complex and the binding of fibrinogen and von Willebrand factor to this platelet membrane receptor. The GPIIb/IIIA-bound fibrinogen functions as a molecular bridge between platelets causing them to aggregate to each other. Inhibition of the platelet receptor GPIIb/IIIa and of the binding of fibrinogen to platelets can ultimately prevent platelet aggregation regardless of the aggregating agonist. Therefore, compounds that inhibit the platelet receptor GPIIb/IIIa are likely inhibit platelet aggregation more effectively than aspirin which inhibits only one of the pathways of platelet aggregation, the cyclo-oxygenase pathway of TX-A2 generation.
The clinical usefulness of GPIIb/IIIa inhibitors has been demonstrated in the EPIC study where the administration of c7E3, a chimeric monoclonal antibody-Fab fragment to GP IIb/IIIa, reduced ischemic complications of angioplasty in patients at high risk of abrupt closure.

Integrilin is a disulfide-linked cyclic heptapeptide that prevents the binding of fibrinogen and other ligands to GP IIb/IIA. receptor complex on the platelet membrane and, consequently, inhibits platelet aggregation. Integrilin has been developed by COR Therapeutics for prevention of ischemic complications of acute coronary syndromes.

Summary of Preclinical and Pharmacologic (PK/PD) Studies of Integrilin

Animal studies of Integrilin have shown that the drug was essentially devoid of ancillary pharmacologic actions other than the inhibition of platelet aggregation.
The safety profile reflected the primary pharmacodynamic action on platelets.
No unexplained significant toxic effects were observed in preclinical studies.
Despite the consistent antithrombotic effect in animals, there was no excessive bleeding at sites of surgery and no spontaneous bleeding.
Transient dose-related thrombocytopenia was recorded for rabbits immediately after infusion, and in baboons after 30 minutes of infusion of high doses of Integrilin, however, in studies of repeated-dose toxicity in rats and cynomolgus monkeys no thrombocytopenia was reported.
Addition of aspirin and heparin to Integrilin increased the bleeding time in baboons, an effect also noted in normal volunteers, although the results were variable.

In pregnant animals, Integrilin was found to cross the placental barrier slowly and maximum concentration in fetal tissue was more than an order of magnitude less than in maternal tissue. Studies of reproductive function in animals exposed to continuous intravenous infusion of Integrilin over appropriate periods revealed no evidence of a significant adverse effect on fertility or reproductivity, on the course

of pregnancy or viability or development of embryos and fetuses, or on development of the offspring. No evidence of mutagenicity was found in specific studies. Carcinogenicity was not studied as Integrilin is intended only for acute, short-term administration. There was no evidence of delayed-type hypersensitivity in mice or antigenicity in guinea pigs.

The pharmacokinetics of Integrilin have been evaluated in healthy subjects, subjects with impaired renal function, patients with ischemic heart disease, as well as in a population pharmacokinetic study in 1725 patients undergoing coronary angioplasty in the IMPACT II study. The pharmacokinetics of Integrilin appear to be linear in the dosing range of 0.5-1.5 ug/kg-min with evidence of extra-renal clearance. Integrilin has a short half-life in normal young subjects with no evidence of gender effect on pharmacokinetics. The plasma clearance of Integrilin in the population pharmacokinetic study varied directly with the patient's weight and creatinine clearance and inversely with age. Lower plasma clearance and longer plasma half-life were found in coronary patients compared to younger, healthy men.
The steady-state volume of distribution of Integrilin appears to be similar in the healthy subjects and patients with coronary heart disease. In the target population, i.e. patients with ischemic heart disease (usually elderly), the plasma half life of Integrilin is approximately 2 hours and the plasma clearance is 100-150 uL/kg-hr.

The pharmacodynamics of Integrilin were evaluated by correlating dose and plasma concentrations of Integrilin to Simplate bleeding time and inhibition of ADP-induced *ex vivo* platelet aggregation taken at various time points during and after the infusions. The administration of Integrilin, with or without heparin, had only a modest effect (up to approximately a three-fold increase) on Simplate bleeding time. The addition of aspirin caused a more profound, though quite variable, effect (up to five-fold increase).
A consistent and highly significant relationship was observed between plasma concentration of Integrilin and simultaneous determinations of inhibition of platelet aggregation. Greater than 80% inhibition of platelet aggregation was achieved with infusion rates of Integrilin of 1.0 ug/kg-min. Infusion rates of 1.5 ug/kg-min produced greater than 80% inhibition in most individuals. A rapid and profound inhibition occurred with the administration of an Integrilin bolus of 135 to 180 ug/kg. The effects of Integrilin on *ex vivo* platelet aggregation were rapidly reversible following termination of the infusion. Concurrent administration of aspirin or heparin did not appear to have an important effect on the inhibition of platelet aggregation produced by Integrilin administration.
In the population pharmacokinetic analysis of the IMPACT II study of patients undergoing angioplasty, none of 20 coadministered drugs were found to have an important effect on the plasma clearance of Integrilin, except for warfarin, for which insufficient data were available to make a definitive determination.

Patients undergoing elective coronary angioplasty were more susceptible to the platelet effect of Integrilin, whereas patients with Unstable Angina (UA) were more resistant to the effect of Integrilin by a factor of 2 to 3 relative to individuals of similar age but without UA.

Clinical Development Program of Integrilin

The clinical development of Integrilin as an antithrombotic agent for the prevention of ischemic complications in acute coronary syndromes was initiated in 1991. Following five Phase I studies, three Phase II/III clinical trials have evaluated the efficacy and safety of Integrilin as an adjunct in patients undergoing PTCA for the prevention of acute cardiac ischemic complications of coronary angioplasty.
Study 92-009, or IMPACT I (Integrilin to Manage Platelet Aggregation and Prevent Coronary Thrombosis), was the first of the three studies in patients undergoing PTCA. The study compared two Integrilin dose regimens consisting of a bolus dose of 90 ug/kg and two infusion durations of 4 or 12 hours, respectively, to placebo.
Study 93-012 (IMPACT High/Low study) assessed the PK and PD of various dose regimens of Integrilin with plasma levels, inhibition of *ex vivo* platelet aggregation, and of bleeding time, in order to select the dose regimen for the Phase III pivotal clinical trial, IMPACT II study.
Study 93-014 or IMPACT II compared the efficacy and safety of two Integrilin regimens, a bolus dose of 135 ug/kg followed by a 20-24 hour Integrilin infusion of either 0.5 or 0.75 ug/kg/min, to placebo in 4010 patients undergoing PTCA.

The assessment of Integrilin in the treatment Myocardial Infarction (MI) and of Non-Q-Wave MI (NQMI) and Unstable Angina (UA) is presently ongoing in a Phase II study of patients with MI treated with thrombolytics (#92-011) and in a Phase III clinical trial of NQMI/UA, the PURSUIT study (#94-016).

NDA 20-718: CLINICAL REVIEW

On 4-1-1996, COR Therapeutics submitted a New Drug Application (NDA 20-718) for the approval of Integrilin as adjunctive therapy to aspirin and heparin in patients undergoing percutaneous transluminal coronary angioplasty, atherectomy, excimer laser or rotoblator (PTCA) for the prevention of acute cardiac ischemic complications (death, MI, and need for urgent revascularization) related to abrupt closure of the treated vessel.

The NDA was based primarily on the efficacy and safety results of a single study, the IMPACT II trial. The data from IMPACT I and IMPACT High/Low were included

as supportive efficacy information since these studies were not designed to demonstrate statistical significance of efficacy in terms of clinical events. The IMPACT II study provides nearly 95% of the database in the NDA.

NDA 20-718 was submitted in electronic format (Computer Assisted NDA or CANDA). Electronic Case Report Forms (CRF) and Tabulations (CRT) were provided for all the patients in IMPACT I and IMPACT II studies. Study reports were provided in hard copy and in electronic format. The electronic format of the study report of IMPACT II was provided with hyperlink to all the data summary tables and summary listings.

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SUMMARIES OF THE CLINICAL TRIALS

Study 92-009/ IMPACT I (NDA vol.1.101-1.104)

Study Title: A Randomized, Double-Blind Trial of Integrilin, versus Placebo in the Setting of Coronary Angioplasty.

Study Objectives: The objectives of this clinical study were:

- to assess measures of biological efficacy of Integrilin in the treatment of arterial thrombosis
- to establish the safety profile of Integrilin in the setting of coronary angioplasty
- to develop preliminary estimates of treatment effects to be used in the design of a subsequent Phase III clinical study.

The study was also designed to provide measures of the pharmacokinetics, the effects on platelet aggregation and bleeding times, and the immunogenicity (by measurement of anti-Integrilin antibodies) of Integrilin in a subset of patients.

Investigational Plan: This was a multi- center, controlled, randomized, double-blind clinical study which compared two dosing regimens of Integrilin to placebo in patients undergoing angioplasty with a marketed device (balloon catheter, directional atherectomy, AIS excimer or Rotoblator).

This study was conducted at 15 investigational sites where 150 patients were enrolled in two groups of 75 patients each. Each group was randomly assigned in a 2:1 ratio to either Integrilin or matching placebo. Treatment in each group was initiated 30 minutes before the start of the angioplasty procedure, and was continued throughout the procedure and for 4 or 12 hours post-angioplasty. The study was blinded for Integrilin and placebo, but not for the two infusion durations. The bolus and the infusion doses were selected based on prior pharmacodynamic studies which had demonstrated 80-90% inhibition of platelet aggregation.

All study patients received aspirin prior to and following the angioplasty procedure. All patients also received a bolus and an infusion of heparin to an ACT of between 300" and 350" during the procedure and to an aPTT of 60" or two times baseline following the completion of the procedure.
Other cardiac medications were used as clinically indicated.

The study treatment regimens are summarized in the following table.

Treatment Regimen by Study Group

Treatment	Integrilin Dose and Duration		
	Bolus Dose	Infusion Rate	Infusion Duration Post-Angioplasty
Group A	Integrilin 90 ug/kg in 1-6 mL over 1-2 min	Integrilin 1.0 ug/kg-min	4 hours
	Placebo in 1-6 mL over 1-2 min	Placebo	4 hours
Group B	Integrilin 90 ug/kg in 1-6 mL over 1-2 min	Integrilin 1.0 ug/kg-min	12 hours
	Placebo in 1-6 mL over 1-2 min	Placebo	12 hours

Eligibility criteria included: angiographically documented coronary artery disease (>60% diameter stenosis in at least one epicardial vessel), anticipated PTCA of at least one coronary artery segment, age greater than 18 years, availability for follow-up studies for at least 30 days and for a phone interview for at least 6 months, ability to give informed consent, males, or females not of childbearing potential

Patients with hemorrhagic diathesis, severe hypertension, surgery within 6 weeks prior to enrollment, neurological abnormalities suggesting a structural intracranial disease, receiving warfarin or having a prothrombin time greater than 1.2 times control, hematocrit <30%, acute MI within 48 hours, women of childbearing potential, patients treated with thrombolytic therapy within 48 hours or within one week associated with fibrinogen levels <150 mg/dL or the presence of fibrin split products, gastrointestinal or urinary or genital bleeding within the past 30 days, patients unable to give informed consent, with platelet count <100,000, known hemorrhagic retinal disease, creatinine levels >4.0 mg/dL, patients who had participated in any other investigational drug study within 7 days prior to enrollment, and patients weighing more than 125 kg (limited by drug supply), were excluded from the study

Patients were withdrawn from the study for any of the following reasons:

- Patient withdrawal of informed consent
- Change in condition after screening and before treatment such that the patient no longer meets inclusion/exclusion criteria
- Use of warfarin

Patients had study drug discontinued for any of the following reasons:

- An adverse event resulting in an opinion by the investigator that it was not in the best interest of the patient to continue participation in the study
- Myocardial Infarction (MI)
- Clinical deterioration requiring emergency invasive procedures
- Unusual or excessive bleeding.

Patients withdrawn from the study could be replaced by the investigator to ensure enrollment and treatment of 150 subjects. Patients discontinued due to an adverse event were not replaced.

No formal sample size or power calculation for clinical efficacy were performed in this exploratory Phase II study. Based on Phase I data, the sample size was adequate to demonstrate an effect of treatment on bleeding time and platelet aggregation.

Efficacy Endpoints: The primary efficacy endpoint of the study was a composite of the following endpoints occurring within 30 days after angioplasty:

- death,
- myocardial infarction (MI) (including infarct extension and reinfarction), or
- need for urgent intervention [intra-aortic balloon pump, coronary artery bypass graft (CABG) surgery, urgent angioplasty or stent placement].

Patients who experienced at least a single occurrence of any of the endpoint events were counted once in the composite endpoint.
The secondary effectiveness endpoint was the composite incidence of death, MI and all interventions (urgent and non-urgent) at 6 months after PTCA.

The determination of elective versus urgent intervention was made by the Investigator for events within the 30-day follow-up and by a single-blinded sub-investigator for events occurring between 30 days and 6 months.

Pharmacodynamics (PD) and Pharmacokinetics (PK) Measurements: Special tests, including platelet aggregation, bleeding time, determination of anti-Integrilin antibodies, and pharmacokinetics were conducted in a subset of patients.

A summary of the clinical and laboratory assessment is shown in Table 3-2

Table 3-2
Schedule of Events

Evaluation	Assessments Before and After the Coronary Angioplasty Procedure											
	Hours Pre-procedure		Hours Post-procedure								Post-infusion	
	1-24	0.5	EOP[a]	1	1-4 hourly	6	12	18	24	Discharge	30 Days	6 Mos
Medical/Medication History	X									X	X	
Physical Examination	X									X	X	
Vital Signs[1]	X				X	X	X	X	X	X		
12 Lead ECG	X									X		
Hematology[2]	X									X	X	
Platelet Count[3]	X			X		X	X		X	X	X	
PT/aPTT[4]	X									X		
Serum Chemistry[5]	X									X		
CK/CK-MB	X					X	X		X	X		
Urinalysis[6]	X									X		
Angiographic Assessment	X		X									
Anti-Integrelin Antibodies[7]	X										X	
Survey on Major Outcomes[8]										X	X	X
Infusion Start		X										
Platelet Aggregometry[7]	X	X		X		X						
Simplate Bleeding Time[7,9]	X	X[9]	X		X[9]							
Integrelin Plasma Levels		X		X								

[a] EOP = immediately at end of angioplasty procedure.
[1] Including blood pressure, pulse, respiration, and temperature.
[2] Including hemoglobin, hematocrit, total and differential leukocyte count, red blood cell count. CBC was also done when clinically significant bleeding occurred.
[3] Platelet count was also done when clinically significant bleeding event occurred.
[4] Also done when clinically significant bleeding occurred.
[5] Including creatinine, BUN, alkaline phosphatase, SGOT, SGPT, glucose, sodium, potassium, chloride, bicarbonate.
[6] Including pH, specific gravity, protein/albumin, glucose, ketones, bilirubin, blood.
[7] Testing was to be performed in 28 patients at Duke University and Cleveland Clinic.
[8] Outcomes were assessed as they occurred or at discharge / 30 days / 6 months
[9] Collection times were changed for Simplate Bleeding Time in Amendment I to Supplement I-1hour into infusion was deleted, and post-infusion was changed from 15 to 60 minutes.

Protocol Amendments: There were two amendments to the Protocol and one supplement addressing supplemental tests and clarification of dosing schedule and definition of endpoint events (MI).

Analyses of Efficacy: Clinical benefit was assessed by comparing the 4-hour, the 12-hour, and the combined Integrilin groups to the placebo groups in all randomized patients. The two Integrilin groups were also examined for differences.

Evaluation of Safety: Safety was evaluated for all treated patients. All adverse events occurring during the study period, all events requiring hospitalization or medical care after hospital discharge were recorded in the CRF.
Information on specific bleeding events (i.e., intracranial hemorrhage, hematoma at access site, GI, GU bleeding, etc.) were requested in the CRFs and details of blood and blood products transfusions were recorded.

The severity of bleeding events was determined by two criteria: the investigator assessment and the TIMI criteria.
Bleeding, as assessed by the investigator, was defined as:

- Mild Bleeding: Of no clinical consequence, not requiring transfusion and less than a 250 cc blood loss.
- Moderate Bleeding: A 250-500 cc blood loss.
- Severe Bleeding: Greater than 500 cc blood loss requiring transfusion. Included in this category were life-threatening bleeding events (i.e., intracranial hemorrhage and other clinically serious bleeding).

The TIMI criteria of bleeding were defined as:

- Major bleeds: Intracranial bleeding or bleeding associated with a decrease in hemoglobin greater than 5 g/dL (or 15% hematocrit).
- Minor bleeds: 1) spontaneous bleeding as gross hematuria or hematemesis, 2) blood loss that was observed, spontaneously or non spontaneously, with drop in Hgb >3 g/dL (or drop in Hct $\geq 10\%$),
  3) a decrease in Hgb >4 g/dL (or 12% Hct) with no bleeding site identified.

The safety of Integrilin was also assessed by the following:

- Change in hemoglobin/hematocrit from pre-procedure to discharge
- Nadir hemoglobin/hematocrit from pre-procedure to discharge
- Units of packed red cells transfused to 30 days
- Bleeding index (Δ in Hgb [or 1/3 Δ in Hct] + number of units of packed RBC)

Two non-prespecified interim safety reviews were performed after the enrollment of 23 and 66 patients. The first review indicated groin bleeding leading to changes in sheaths insertion. The second review of 66 patients by the Sponsor and Principal Investigator indicated no safety concerns, and enrollment was completed.

RESULTS OF THE STUDY

Disposition of Patients: Patient enrollment and study completion status by treatment group is summarized in Table 4-1.

Table 4.1: Patient Accountability by Treatment Group- Randomization to Treatment

Category	Combined Integrilin	Combined Placebo	Integrilin 4 Hr	Integrilin 12 Hr	TOTAL
Patients who were randomized	101	49	5 2	49	150
Randomized Patients who did not receive study medication	3	3	2	1	6
Randomized, treated Patients	98	46	50	48	144
Randomized, treated patients, but medication was terminated	14	6	5	9	20
Patients who completed study drug infusion	84	40	45	39	124

Of the 150 randomized patients, all but six (4%) received study drug. Four of these six patients were disqualified prior to administration of study drug because of characteristics of their coronary artery lesions and two for unclear reasons. A total of 20 patients (14 Integrilin-, 6 placebo-treated) had study drug discontinued prior to completion of their randomized dosing. The reasons for early discontinuation of study drug are summarized in Table 4-2.

Table 4.2: Reasons for Early Discontinuation of Study Drug by Treatment

Reasons Study Drug Terminated	Combined Integrilin (n=98)	Combined Placebo (n=46)	Integrilin 4 Hr (n=50 treated)	Integrilin 12 Hr (n=48 treated)	TOTAL (n=144 treated)
Bleeding or Drop in Hg/Hct	5	0	2	3	5
Stent or Dextran	1	2	0	1	3
Hypotension	1	1	0	1	2
Shock, Death	0	1	0	0	1
Error/ IV problem	1	0	1	0	1
Need for CABG	3	1	1	2	4
Inability to cross lesion	2	2	0	2	4
Other:High Dose Thrombolytic Use	1	0	1	0	1
Total Discontinued	14	6	5	9	20

The most common reason for early discontinuation of study drug in the Integrilin-treated group was bleeding or drop in hematocrit/hemoglobin. This occurred in 5 patients including 3 patients assigned to the 12-hour infusion Integrilin group and 2 assigned to the 4-hour infusion Integrilin group. No patients in the placebo group were discontinued because of bleeding events.
Treatment was unblinded in six, five in the integrilin groups and one from the placebo group.

Of the 150 randomized patients; 124 completed the study: 40 placebo-treated patients and 84 Integrilin-treated patients.
Of the 148 patients followed to hospital discharge (two of the 150 randomized patients died before discharge), all were followed to the 30-day assessment and 137 were followed out to 6 months (Table 4.3).

Table 4-3 Patient Accountability by Treatment Group - Discharge to 6 Month Follow-up

Category	Treatment Group				
	Combined Integrelin	Combined Placebo	Integrelin 4 Hr	Integrelin 12 Hr	TOTAL
Patients followed to hospital discharge [2 of 150 randomized patients died before hospital discharge]	100	48	51	49	148
Patients followed to 30-day assessment*	100	48	51	49	148
Patients eligible for 6 month follow-up	100	48	51	49	148
Patients followed to 6 month follow-up	92	45	46	46	137
Reasons not followed to 6 month follow-up					
Unable to locate and no other data available on rehospitalization	3	2	2	1	5
Patient refusal	1	0	1	0	1
Reason missing and no other data available on rehospitalization	2	1	1	1	3
Patients eligible for adjudications by cardiologist at 6 month**					
Patient rehospitalization	45	9	21	24	54
Cardiac catheterization	19	8	11	8	27
Died	1	1	0	1	2

[Source: Table A-1A]
* 148 patients available for 30-day assessment; 120 had required hematology labs drawn.
** Defined by rehospitalization, cardiac catheterization or death as adjudicated by a sub-investigator (see Section 9.4).

By the 6-month follow-up, 45/100 or 45% in the integrilin group compared with 9/48 or 18.8% in the placebo group were re-hospitalized. Nine of the 45 re-hospitalizations in the Integrilin group were due to non-cardiac reasons and 11 occurred in patients who had experienced a prior clinical efficacy endpoint.
Two of the re-hospitalizations in the combined placebo group were for non-cardiac indications, and none had experienced a previous efficacy endpoint.

Demographics and Medical History: Seventy-five percent of the study patients were male, 96.0% were Caucasian, the mean age was 59.8 years.
The baseline characteristics of patients randomized in the study were reasonably balanced between the treatment groups.

Indications for Revascularization and Characteristics of Coronary Lesions: The reasons for the index angioplasty procedure are presented in Table 4-5.

Table 4.5: Reasons for Revascularization at Pre-Treatment

Category	Combined Integrilin	Combined Placebo	Integrilin 4 Hr	Integrilin 12 Hr	TOTAL
Recent MI	17 (16.8)	8 (16.7)	10 (20.4)	7 (13.5)	25 (16.8)
Unstable Angina	62 (61.4)	25 (52.1)	29 (59.2)	33 (63.5)	87 (58.4)
Stable Angina	12 (11.9)	10 (20.8)	7 (14.3)	5 (9.6)	22 (14.8)
Asymptomatic with Positive Functional Study	10 (9.9)	5 (10.4)	3 (6.1)	7 (13.5)	15 (10.1)
Total	101 (100.0)	48 (100.0)	49 (100.0)	52 (100.0)	149 (100.0)

A slightly greater number of high risk patients (unstable angina) was seen in the combined Integrilin groups compared to the placebo group.
The largest number of coronary artery lesions were in the proximal and medial left anterior descending coronary artery [59/197 (29.9%)]. Approximately 86% of patients in both treatment groups underwent balloon angioplasty.
Dissections were more frequent in the combined placebo-treated group (21/60 or 35%) than in the combined Integrilin-treated group (22/130 or 17%) ($p=0.006$). Thrombus was more common in placebo patients (7/61 lesions or 11.5%) compared with Integrilin patients (8/135 lesions or 5.9%).

Pre-Study and Concomitant Medications: A total of 76.5% of the combined Integrilin group and 65.2% of the combined placebo group received aspirin prior to angioplasty. The use of cardiac drugs was similar for the Integrilin and placebo groups. The combined Integrilin group was on heparin at randomization more frequently than the combined placebo group (20.4% compared with 10.9%), possibly due to the larger number of patients with UA in the Integrilin group. Heparin was given to 94-95% of patients during angioplasty; the mean dose was similar for all treatment groups.

Within 24 hours of angioplasty, there were no major differences in administration of concomitant medications between the Integrilin and placebo groups.

EFFICACY RESULTS

Clinical Efficacy

30-Day Assessment: The combined treatment with Integrilin reduced the incidence of death, non-fatal MI, urgent CABG, urgent PTCA or stent placement by 43% when compared with patients in the combined placebo group. The composite of events in the combined placebo and Integrilin groups was 6/49 (12.2%) and 7/101 (6.9%), respectively. The composite of events decreased with the increased length of infusion, demonstrating a dose-response relationship between the 4- and 12-hour Integrilin groups [5/52 (9.6%) and 2/49 (4.1%), respectively].
Two deaths occurred, 1 in the 4-hour placebo and 1 in the 4-hour Integrilin group.

6-Month Assessment: At 6 months, the composite endpoint of death, MI and urgent intervention was similar between the Integrilin and placebo groups: 18/101 or 17.8% and 7/49 or 14.3%, respectively. More patients the Integrilin group (52/101 or 51.5%) than in the placebo group (10/49 or 20.4%) underwent elective procedures or experienced MI (9/101 or 8.9% versus 1/49 or 2.0%) between 1 and 6 months after enrollment .

The occurrence of clinical outcomes following study treatment, assessed at 30 days and at 6 months, is summarized in Table 5-1.

Table 5.1: Incidence (%) of Death or Major Cardiovascular Procedures within 30 days of Treatment (ITT Analysis) and at 6 months follow-up

Endpoint Event at 30 days	Combined Integrilin (N=101)	Combined Placebo (N=49)	Integrilin 4 Hr (N=52)	Integrilin 12 Hr (N=52)
Death	1 (1.0)	1 (2.0)	1 (1.9)	0
MI	2 (2.0)	1 (2.0)	1 (1.9)	1 (2.0)
Urgent Angioplasty	2 (2.0)	1 (2.0)	2 (3.8)	0
Urgent CABG	2 (2.0)	1 (2.0)	1 (1.9)	1 (2.0)
Urgent Stent	0	2 (4.1)	0	0
Composite Endpoint	7 (6.9)	6 (12.2)	5 (9.6)	2 (4.1)
Composite Endpoints at 6 Months				
Composite Endpoints with Urgent Events	18 (17.8)	7 (14.3)	10 (19.2)	8 (16.3)
Composite Endpoint with Urgent and non-urgent Events	52 (51.5)	10 (20.4)	30 (57.7)	22 (44.9)

SAFETY EVALUATIONS

The safety analysis included a total of 144 treated patients: 99 received Integrilin and 44 received placebo. A total of 58 of the 144 patients had at least one adverse event recorded: 15 (32.6%) patients reported 34 events in the combined placebo group, 20 (40.0%) patients reported 55 events in the 4-hour Integrilin group, and 23 (47.9%) patients reported 50 events in the 12-hour Integrilin group.

Nausea, back pain and transient hypotension were the most frequently reported adverse events. All three were more frequent in Integrilin-treated than in placebo-treated patients. Hypotension was most likely secondary to a bleeding event. Back pain was attributed to prolonged bed rest due to bleeding from access site.

Common Adverse Events (Non-Ischemic, Non-Bleeding): The number of patients in each treatment group experiencing one or more events is shown in table 6.1.

Table 6.1 Incidence of Patients with Adverse Events within 30 Days of Enrollment by Treatment Group

Patients with Complications	Treatment Group Combined			
	Integrilin		Placebo	
Number of Patients	N=98	100%	N=46	100 %
Hemorrhagic Stroke	1	1.0%	0	
Altered Mental Status	1	1.0%	0	
Respiratory Failure/Pulmonary Edema	4	4.1%	2	4.1%
Renal Insufficiency/Renal Dialysis	3	3.0%	0	
Vascular Repair	2	2.0%	0	
Arrhythmia: 3 AV block	0		1	2.2%
Arrhythmia (VT) >30"/VF	3	3.0%	3	6.2%
Arrhythmia Atrial Fib/Flutter, PAT	2	2.0%	0	
Arrhythmia Severe Sinus Bradycardia	6	6.1%	1	2.2%
Transient Hypotension	17	17.3%	2	4.3%
Sustained Hypotension	1	1.0%	1	2.2%
Nausea/Vomiting	27	27.5%	9	19.5%
Back Pain	16	16.3%	5	10.9%
Fever	3	3.1%	2	4.2%
Headache	3	3.1%	3	6.5%
Other	8	8.2%	4	8.7%
Any one of the Above	43	43.9%	15	32.6%

Bleeding Events and Severity rating by TIMI Criteria and by Investigators Criteria:
The incidence rates for any bleeding event and severity are presented in the following table.

Patients with Bleeding Events and Severity of bleeding

Patients with Bleeding Complications	Treatment Group Combined			
	Combined Integrilin		Combined Placebo	
	N=99	%	N=44	%
TIMI CRITERIA Patients with Any Bleeding Events	44	44.9	9	20.5
Patients with Minor Bleeding Events	12	12.2	1	2.2
Patients with Major Bleeding Events	5	5.1	4	9.0
INVESTIGATORS CRITERIA Patients with Mild Bleeding	31	31.6	5	10.9
Patients with Moderate Bleeding	5	5.1	2	4.3
Patients with Severe Bleeding	8	8.2	2	4.3

Major bleeding occurred mostly at the femoral access site. One patient in the Integrilin 4 hour group had fatal intracranial bleeding. Patients with more than one bleeding event were counted as separate events. The incidence of bleeding events by treatment group is summarized in the following table. In this table, the incidence of events by severity is expressed as percentage of total events.

Bleeding events

Overall Incidence of Bleeding Events by Severity	Treatment Group Combined			
	Combined Integrilin		Combined Placebo	
	N=98	%	N=46	%
Patients with Any Bleeding Events	44	44.9	9	19.6
Total Events	62	100.0	10	100.0
Mild Bleeding Events	48	77.4	6	60.0
Moderate Bleeding Events	6	9.7	2	20.0
Severe Bleeding Events	8	12.9	2	20.0

The majority of events were mild in both the combined Integrilin-treated group and the combined placebo-treated group. Patients in the combined Integrilin group experienced more than twice total bleeding events than the placebo group. The incidence of moderate or severe bleeding events were also more common in Integrilin patients. There was no clear trend observed in bleeding events in the 4-hour compared with the 12-hour Integrilin-treated groups.

Of the three severe bleeding events in the 4-hour Integrilin group, one was an intracranial bleed, one occurred at the access site, and one was associated with CABG surgery. Of the five severe bleeding events among the 12-hour Integrilin-treated patients, three occurred at the access site (groin) and two were associated with CABG surgery. In the placebo-treated group, one patient had severe bleeding at the access site (groin), and one patient had severe bleeding with CABG surgery.

Transfusions: Ten of the 144 (6.9%) patients received transfusions: 2 of 46 (4.3%) in the combined placebo group compared with 8 of 98 patients (8.2%) in the combined Integrilin group (three in the Integrilin 4-hour and five in the Integrilin 12-hour infusion group).
Four patients received transfusions during CABG surgery: one patient had received placebo, one had received the 4-hour Integrilin infusion and two had received the 12-hour Integrilin infusion. Groin bleeding required transfusion in four patients.
Four patients received platelet transfusions. One of these patients (#08001) had developed thrombocytopenia in conjunction with CABG surgery.

Deaths: Two deaths occurred during the 30 day follow-up period after randomization. One occurred in the 4-hour Integrilin-treated group, the second occurred in the 4-hour placebo-treated group. The patient in the Integrilin-treated group died from complications of an intracranial bleed. The patient was also receiving concomitant heparin with aPTT greater than 150 seconds after the angioplasty procedure and 92 seconds five hours prior to the onset of symptoms. This death was considered possibly drug-related by the investigator.
The patient in the placebo-treated group died after developing a refractory ventricular tachycardia shortly after the coronary angioplasty procedure. This death was not considered drug-related by the investigator, but considered a result of abrupt closure.

Serious Adverse Events: Eleven serious adverse events occurred in Integrilin treated patients: 1 death; 4 major bleeding events, and 5 discontinuations due to adverse events.
One patient was discontinued due to a major bleeding event.

Discontinuations: Study drug was discontinued in 20 patients, including 14 in the Integrilin group (5 in the 4-hour group, and 9 in the 12-hour group) and 6 in the placebo group. The reasons for discontinuation is displayed in the following table. The determinations were made by the investigators while blinded to treatment assignment.

Discontinuation of Study Drug Infusion (including deaths) by Reason and Treatment Group

	Combined Integrilin	Combined Placebo
Randomized Patients Receiving Treatment	98	46
Patients Discontinued	14	6
Discontinuation Due to Angioplasty Failure Stent/Dextran required Need for CABG Could not Access Lesion	6 (6%) 1 3 2	5(11%) 2 1 2
Discontinuations Due to Adverse Events Bleeding or Drop in Hgb/Hct Hypotension Shock/Death	6 (6%) 5 1 0	1 (2%) 0 0 1
Other (difficult intravenous access, cardiac instability)	2	0

Discontinuations due to Adverse Events: The six discontinuations due to adverse events are summarized in the following table. The events were either directly or, in one patient, indirectly attributed to bleeding events. The only discontinuation due to an adverse event in the placebo group was death due to cardiogenic shock.
The death in the Integrilin group occurred after completion of the drug infusion.

Discontinuation of Study Drug Infusion due to Adverse

Patient Number and Treatment Group	Adverse Event
02002 Integrilin/4 hour	Severe Sinus Bradycardia, Hypotension, Moderate groin bleed
10004 Integrilin/4 hour	Vomiting, Mild groin bleed, Transient Hypotension
01010 Integrilin/12 hours	Severe groin bleed, Moderate GI bleed, Nausea, Vomiting, Respiratory failure
03013 Integrilin/12 hour	Mild groin bleed
13001 Integrilin/12 hour	Groin bleed
02024 Integrilin/12 hour	Groin bleed (major)